Protocol number: VAR-2024-01

Varian ProBeam360 Proton Therapy System China Clinical Trial (Wuhan)

Name of the medical device for investigation	Proton therapy system	
Model	ProBeam360 2.0	
Management categories for investigational medical devices	Class III medical devices	
Class III medical devices subject to clinical trial approval		Yes□ No☑
Similar products in China		Yes☑ No□
Protocol version number and date	Version number: 1.0, Version date: 2024.01.12	
Clinical trial institution	Huazhong University of Science and Technology Tongji Medical College Affiliated Union Hospital	
Sponsor	Varian Medical Systems Trading (Beijing) Co., Ltd	
NCT number	NCT06347731	

Directory

List of abbreviations

Abbreviations	Full spelling in English	Chinese translation
3DCRT	3-Dimensional Conformal Radiation Therapy	3D conformal radiation therapy
ADL	Activities of Daily Living	Daily activities
AE	Adverse Events	Bad Incident
WHITE	Serum Albumin	Serum albumin
OLD	Alanine Aminotransferase	Alanine aminotransferase
APTT	Activated Partial Thromboplastin Time	Activation of partial thromboplastin time
AST	Aspartate Aminotransferase	Glutamate aminotransferase
GOOD	Blood Urea Nitrogen	Urea nitrogen
Ccr	Endogenous Creatinine Clearance Rate	Creatinine clearance
CFDA	China Food and Drug Administration	State Food and Drug Administration
CH	Chordoma	Chordoma
CK-MB	Creatine Kinase Isoenzymes-MB	Creatine kinase isoenzymes
CP	Child-Pugh	-
CR	Complete Response	Complete remission
CRA	Clinical Research Associate	Clinical monitor
CRF	Case Report Form	Case report form
CTCAE	Common Terminology Criteria for Adverse Events	Common terminology criteria for adverse events
cTn	Cardiac Troponin	Troponin
CTV	Clinical Target Volume	Clinical targets
DART	Dynamic Adaptive Radiation Therapy	Dynamically adapted radiotherapy techniques
DIPS	Digital Imaging Positioning System	Digital image positioning system
DOR	Duration of Response	Duration of mitigation
DRR	Digitally Reconstruction Radiograph	Digitally reconstructed radiography
DVH	Dose Volume Histogram	Volume dose histogram
EC	Ethics Committee	Ethics Committee
ECOG	Eastern Cooperative Oncology Group	Eastern U.S. Oncology Collaborative Group
eCRF	Electronic Case Report Form	Electronic case report form

Abbreviations	Full spelling in English	Chinese translation
EDC	Electronic Data Capture System	Electronic data collection systems
ERA	Erythrocyte	Urine red blood cell count
FAS	Full Analysis Set	Full analysis set
FPG	Fasting Plasma Glucose	Fasting blood sugar
GCP	Good Clinical Practice	Good Clinical Trial Management Practice for Medical Devices
GLU	Glucose	Urine sugar
GTV	Gross Tumor Volume	Gross tumor area
HBV	Hepatitis Virus B	Hepatitis B virus
HCG	Human Chorionic Gonadotropin	Blood pregnancy test
HCV	Hepatitis Virus C	Hepatitis C virus
HGB	Hemoglobin	haemoglobin
HIV	Human Immunodeficiency Virus	Human immunodeficiency virus
ICF	Informed Consent Form	Informed consent
IGRT	Image-Guided Radiation Therapy	Image-guided radiation therapy
IMPT	Intensity Modulated Proton Therapy	Conformal intensity-modulated proton therapy
IMRT	Intensity Modulated Radiation Therapy	Conformal intensity-modulated radiation therapy
INR	International Normalized Ratio	International standardized ratio
LET	Linear Energy Transfer	Linear energy transfer
LEU	Leucocyte	Urine white blood cell count
LGG	Low-Grade Glioma	Low-grade glioma
LVEF	Left Ventricular Ejection Fractions	Left ventricular ejection fraction
Mb	Myoglobin	myoglobin
NEUT	Neutrophil	Neutrophils
NMPA	National Medical Products Administration	State Drug Administration
NPC	Nasopharyngeal Carcinoma	Nasopharyngeal carcinoma
NSCLC	Non-Small-Cell Lung Cancer	Non-small cell lung cancer
NYHA	New York Heart Association	New York Heart Society
OAR	Organ at Risk	Endangers organs

Abbreviations	Full spelling in English	Chinese translation
WHETHER	Occult Blood Test	Occult blood test
OIS	Oncology Information System	Radiation therapy management software
OPC	Oropharyngeal Cancer	Oropharyngeal cancer
ORR	Objective Response Rate	Objective response rate
THE	Overall Survival	Overall lifetime
PBS	Pencil Beam Scanning	Pen beam scanning
PD	Progressive Disease	Disease progression
PFS	Progression-free Survival	Progression-free survival
PLT	Platelet	platelet
PPS	Per-Protocol Set	Conforms to the scenario set
PR	Partial Response	Partial remission
FOR	Protein	Urine protein
PRV	Planning Organ-at-Risk Volume	Plan to endanger organs
PSA	Prostate Specific Antigen	Prostate-specific antigen
PSI	Paul Scherrer Institute	Paul Scheller Institute, Switzerland
PT	Prothrombin Time	Prothrombin time
PTC	Proton Treatment Console	Proton therapy console
PTV	Planning Target Volume	Plan the target
QA	Quality Assurance	quality assurance
QOL	Quality-of-Life	Quality of life assessment
RBC	Red Blood Cell	erythrocyte
RBE	Relative Biological Effectiveness	Relative biological effects
RECIST 1.1	Response Evaluation Criteria in Solid Tumors RECIST Version 1.1	Tumor efficacy evaluation criteria version 1.1
RVR	Remaining Volume at Risk	Remaining danger areas
SAE	Serious Adverse Events	Serious adverse events
SBRT	Stereotactic Body Radiation Therapy	Stereotactic radiosurgery
SCIC	Second Channel Integrity Check	Second integrity check
SCLC	Small Cell Lung Cancer	Small cell lung cancer

Abbreviations	Full spelling in English	Chinese translation
Scr	Serum Creatinine	creatinine
SD	Stable Disease	The disease is stable
SDV	Source Data Validation	Raw data verification
SLD	Sum of Longest Diameter	The sum of the longest diameters of the tumor
SOBP	Spread-out Bragg Peak	Extend Bragg Peak
SOP	Standard Operating Procedure	Standard operating procedures
SS	Safety Set	Security datasets
ETC	Serum Total Bilirubin	Total serum bilirubin
TV	Treated Volume	Treatment area
ULN	Upper Limit of Normal	Upper limit of normal value
VMAT	Volumetric-Modulated Arc Therapy	Volumetric rotational intensity-modulated radiotherapy
WBC	White Blood Cell	white blood cell
WHO	World Health Organization	World Health Organization

Protocol summary

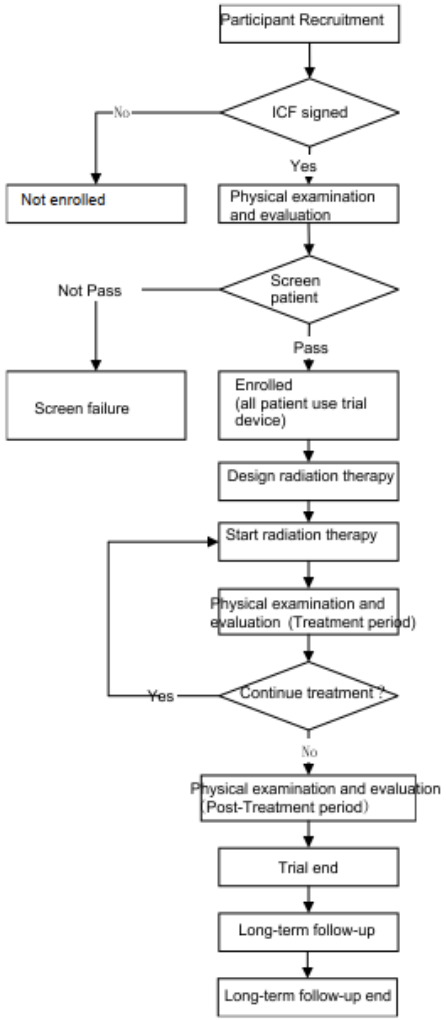
The name of the experiment	Varian ProBeam360 Proton Therapy System China Clinical Trial (Wuhan).
Device name	proton therapy system (hereinafter referred to as ProBeam360).
Manage categories	Class III (classification: 05 radiotherapy equipment--01 radiotherapy equipment--02 medical light ion therapy system).
Scope of application	Proton therapy system provide precision radiation therapy protons for lesions, tumors, and conditions in the patient's body that require radiation therapy.
Scope of the test	Cancer patients, including tumors of intracranial, head and neck, chest, abdomen, spine, pelvis, limbs, etc
Trial design	Prospective, open-label, single-centered, single-group target value method
Trial and long-term follow-up purposes	Clinical trial (screening-short-term follow-up): The data obtained by using Proton Beam system (ProBeam360) for radiation therapy in tumor patients compared with the target value to evaluate the effectiveness and safety of ProBeam360 for radiation therapy in tumor patients to provide clinical basis for product registration application. Long-term follow-up: The long-term efficacy and safety of ProBeam360 for radiation therapy in cancer patients were evaluated by using the long-term follow-up data of ProBeam360 for radiation therapy in cancer patients.
Sample size	At least 47 participants are enrolled in this trial. Assuming the expected primary efficacy evaluation indicator (3-month tumor local control rate) is 95%, the target value is 80%, the bilateral significance level is 0.05, and the confidence level is 80%, data from 42 participants are required at the end of the 3-month observation period. Considering the expected dropout rate of 10% during short-term follow-up of clinical trials, 47 subjects are required to be enrolled. (1) The number of cases of tumors in the intracranial, head and neck, chest, abdomen, spine, pelvic cavity, and limbs should be evenly distributed as much as possible. (2) The Intensity Modulated Proton Therapy (IMPT) technology and exercise management system should be used and validated in this study.
clinical trial Number of institutions	1 site
The expected duration of the participant's participation	The screening period from signing the informed consent form to enrollment is expected to be 4 weeks, the treatment period is 1~8 weeks, and the follow-up after the last treatment are divided into short-term follow-up and long-term follow-up, and the maximum duration of expected participation of each subject from screening to the end of short-term follow-up is 12 weeks +3 months. Long-term follow-up continued after the end of the short-term follow-up until the fifth year after the end of the last radiotherapy. (After a 3-month follow-up after the last treatment, a "Medical Device Clinical Trial Report" will be issued for the registration of this trial

	product Declaration.)
Expected overall duration of clinical trials and long-term follow-up	The first subject is expected to be enrolled in June 2024, and the clinical trial institution expects to enroll 12 subjects per month, for a total enrollment time of about 4 months, and the last subject ends the trial (short-term follow-up) is In April 2025. The last subject to end long-term follow-up in Janurary 2030.
Primary effectiveness Evaluation indicators	Disease Control Rate (DCR). Evaluation time: 3 months ± 7 days after the last treatment. Definition of indicators: Complete Response (CR), Partial Response (PR), Stable Disease (SD) for disease control. Proportion of participants who developed disease control three months after the end of the last radiotherapy. Evaluation methodology: Response Evaluation Criteria in Solid Tumors RECIST Version 1.1 (RECIST 1.1) by an independent imaging review team in tumour CT or MRI imaging before and after treatment were assessed. Participants who discontinued the trial for any reason (except loss to follow-up) before the end of radiation therapy were considered to have not controlled.
The main safety evaluation index	(1) Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 toxicity ratio Evaluation time: 3 months ± 7 days after the end of the last treatment. Indicator definition: Proportion of subjects with grade 3 toxicity during the trial cycle. Evaluation methodology: Investigators recorded AEs that occurred during the clinical trial cycle and graded them according to CTCAE V5.0. (2) CTCAE grade 4 and 5 toxicity ratio Evaluation time: the entire clinical trial cycle. Indicator definition: Proportion of subjects with toxicity of grade 4 and 5 during the trial cycle. Evaluation methodology: Investigators recorded AEs that occurred during the clinical trial cycle and graded them according to CTCAE V5.0.
Secondary effectiveness Evaluation indicators	(1) Objective Response Rate (ORR) (three days,1 month± 7 days, 2 months, ± 7 days, 3 months, ± 7 days after the end of the last treatment). (2) DCR (three days,1 month± 7 days, 2 months ± 7 days) after the end of the last treatment (3) Tumor markers (if required) (three days, 1 month ± 7 days, 2 months± 7 days, 3 months±7 after the end of the last treatment days). (4) Tumor-specific symptoms (screening period, 1 month ± 7 days, 2 months± 7 days, 3 months±7 days). (5) Product usability evaluation (ProBeam360 system, radiotherapy management software (Aria), radiotherapy planning software (Eclipse)) (the day of completion of the last treatment).
Secondary	(1) CTCAE grade 1 and 2 toxicity ratio (3 months ± 7 days after the end of the last

safety Evaluation indicators	treatment). (2) Laboratory tests [3 days after the end of the last treatment, 1 Months ±7 days, 2 months ±7 days, 3 months ±7 days]. (3) Eastern Cooperative Oncology Group (ECOG) physical status grading [3 days after the end of the last treatment, 1 month± 7 days, 2 months±7 days, 3 months ±7 days]. (4) Incidence of adverse events (AEs) (3 months ± 7 days after the end of the last treatment). (5) The incidence of Serious Adverse Events (SAEs) (3 months ± 7 days after the end of the last treatment). (6) Incidence of device defects (after last treatment)
Eligibility criteria	Inclusion Criteria (Major Criteria): (1) 18≤ age≤ 80 years, Gender is not limited; (2) Patients diagnosed clinically as benign or malignant intracranial tumors, as well as malignant solid tumors in the head and neck, chest, abdomen, spine, pelvic cavity, and limbs, based on cellular or histopathological diagnosis and/or evidence from imaging, laboratory tests, etc. (recurrent patients may only have evidence from imaging, laboratory tests, etc.); (3) The target lesion is a measurable solid tumor, and the longest diameter of the lesion should be ≥ 10mm; (5) According to the researchers' assessment, the expected survival time exceeds 6 months; (6) ECOG physical condition is graded as 0 to 2; (7) Women of childbearing had negative results in the blood pregnancy test (Human Chorionic Gonadotropin, HCG) 7 days prior to the first treatment; (8) The subject or subject's guardian is able to understand the purpose of the study, demonstrate sufficient compliance with the protocol and sign informed consent form. Exclusion Criteria (Major Criteria): (1) The subject with radiotherapy contraindications, including the known genetic tendencies that increase the sensitivity of normal tissue radiotherapy or the accompanying diseases that lead to hypersensitivity to radiotherapy; (2) The subject with other uncontrolled tumors except that to be treated according to medical history or the investigator's estimation, or with other malignant tumors within five years prior to enrollment; (3) Implanted pacemakers or other metal prosthesis within the scope of proton therapy; (4) Other situations that investigator determines not suitable for enrollment.
Specifications for the use of investigational medical device	All subjects used the investigational medical device: ProBeam360 for radiation therapy.

Statistical analysis	Statistical analysis with SAS 9.4 software. **All data are described statistically,** including baseline data, all efficacy measures, and all safety data. The measurement data give the mean, standard deviation, minimum, maximum, median, 25th quantile and 75th quantile; The counting data gives the frequency and composition ratio. **Effectiveness analysis** DCR was calculated and the Clopper-Pearson method was used to calculate the 95% confidence interval for tumor disease control. ORR was calculated and the Clopper-Pearson method was used to calculate the objective response rate 95% confidence interval. Descriptive statistics on the percentage change from baseline of the measurable sum of the longest diameter (SLD). The Waterfall Chart was made by the maximum percentage reduction in SLD per participant compared to the screening period. The *Kaplan-Meier* method was used to calculate the median duration of response, median progression-free survival, median survival, and overall survival, and plotted *K-M* curves (long-term follow-up data). **Safey analysis** Descriptive statistics were used to classify organ systems in MedDRA medical terms, and the incidence, occurrence, and severity of adverse events, adverse reactions, and serious adverse events were summarized. Laboratory indicators, ECOG physical status grading and other safety-related indicators were compared and evaluated before and after treatment, and clinical evaluation [no clinical significance, clinically significant (tends to normal), clinically significant (tends to be abnormal), not checked], CTCAE grade evaluation before and after treatment cross-tab. The central effect is considered in the analysis process, and the general linear model is used for the measurement data and CMH for the counting data. The baseline data analysis was performed using the Full Analysis Set (FAS); Effectiveness analysis uses FAS and Per Protocol Set (PPS); Security analysis uses the Safety Set (SS).

Trial flowchart



The body of the protocol

1 Sponsor information

1.1 Name of the sponsor

Varian Medical Systems Trading (Beijing) Co., Ltd

1.2 Sponsor address

No. 8 Yuncheng Street, Beijing Economic and Technological Development Zone, Beijing, 2nd floor, area B, 3rd floor

1.3 The name, address, contact information and relevant qualification documents of the agent

NA

2 Purpose and content of clinical trial

2.1 Objective

Clinical trial (screening-short-term follow-up): The data obtained by using Proton Beam equipment (ProBeam360) for radiation therapy in tumor patients compared with the target value to evaluate the effectiveness and safety of ProBeam360 for radiation therapy in tumor patients to provide clinical basis for product registration application.

Long-term follow-up: The long-term efficacy and safety of ProBeam360 for radiation therapy in cancer patients were evaluated by using the long-term follow-up data of ProBeam360 for radiation therapy in cancer patients.

2.2 content

This clinical trial is a prospective study, carried out in 1 clinical trial institutions, and 47 patients with tumors of intracranial, head and neck, chest, abdomen, spine, pelvis, limbs and other tumors were selected as study subjects, all using investigational medical devices, and designed for a single group of target values. The research device involved in this trial is the proton therapy device (ProBeam360), a medical device for investigation. Short-term follow-up is: 1 visit during the screening period (within 4 weeks before the first treatment), 2~9 visits during the treatment period according to the length of treatment weeks (1~8 weeks), and 3 after the last treatment 3 visits within a month; Long-term follow-up was 11 visits over a period of 3~5 months after the end of the last treatment. The main efficacy evaluation index was DCR 3 months after the end of the last treatment, and the main safety evaluation index was the proportion of CTCAE grade 3 toxicity in the entire short-term follow-up clinical trial cycle and CTCAE grade 4 & 5 toxicity reactions in the entire short-term follow-up clinical trial cycle. The collected data were analyzed and compared with the target values, and the effectiveness and safety of ProBeam360 in proton radiation therapy for patients with tumors such as intracranial, head and neck, chest, abdomen, spine, pelvis, and extremities were evaluated.

3 Overall design

3.1 Trial design

3.1.1 Trial and long-term follow-up purposes

3.1.1.1 Main purpose

To evaluate whether the main efficacy evaluation index of ProBeam360 in radiotherapy for cancer patients reached the target value 3 months after the end of the last treatment. The main safety evaluation index: whether the proportion of CTCAE grade 3 toxicity is lower than the acceptable value, and whether CTCAE grade 4 and 5 toxic reactions occur.

3.1.1.2 Secondary purposes

When evaluating the use of ProBeam in radiation therapy for tumor patients, the secondary effectiveness evaluation indicators ORR, DCR, tumor markers (if necessary), tumor-specific symptoms, and product usability evaluation are actually the actual situation.

When evaluating the use of ProBeam in radiation therapy in tumor patients, the proportion of secondary safety evaluation indicators CTCAE grade 1 and 2 toxicity, laboratory tests, ECOG physical status grade, adverse event rate, serious adverse event rate, The actual situation of the incidence of device defects.

3.1.2 Choice of trial method and justification

This trial was designed using the prospective, two-center, single-group target value method.

(1) Prospective study: Adopt a research approach that traces from the present to the future. Prospective studies can establish cause and effect; There are unified diagnosis, detection and evaluation standards for the obtained data, so the data processing is controllable.

(2) Single centers: Select 1 clinical trial institution to carry out the clinical trial.

(3) Single-group target value method: Because the same device of the experimental medical device is radioactive and difficult to obtain, the existing treatment method is not feasible due to objective conditions, so the single-group target value method is adopted. Moreover, the applicable population and main evaluation indicators of experimental medical devices can be fully defined and relatively stable; The main evaluation index adopts the effective rate mentioned in the "Guidelines for the Technical Review of Clinical Evaluation of Proton Carbon Ion Therapy System" (CFDA Circular No. 4 [2018]), which is relatively objective and reproducible. According to the Guidelines for the Technical Review of Clinical Evaluation of Proton Carbon Ion Therapy Systems, the target value of therapeutic response rate for

experimental medical devices should be at least 80%, and the expected value should be 95%. Among them, the effective definition is: CR+PR+SD (complete response CR, partial response PR, disease stable SD), which is basically consistent with the definition of tumor disease control rate in this clinical trial. Therefore, no control group was set up in this clinical trial, and the single-group target value method was used to evaluate whether the tumor disease control rate reached the target value (80%) and the main safety evaluation index CTCAE 3 when ProBeam was used in radiotherapy for tumor patients Whether the proportion of grade toxicities is less than acceptable (5%) and whether the proportion of CTCAE grade 4 and 5 toxicities is acceptable (0%).

3.1.3 Diagnostic and therapeutic methods of medical devices for investigation

All subjects used ProBeam, an investigational medical device. The investigator formulated an individualized radiotherapy plan according to the actual clinical situation of the subjects, and the use of experimental medical devices is detailed in the product manual.

The specific treatment process is: preoperative assessment to determine the indications (radiotherapist)→ signing of the informed consent form for radiotherapy (radiotherapist)→ selection and production of postural immobilization devices (radiotherapist, radiotherapist, physicist) → CT/MRI Simulation positioning (radiotherapist, radiotherapist, physicist)→ target and normal organ delineation (radiotherapist)→ radiotherapy plan design (physicist)→ radiotherapy plan review and authorization for executable plans (radiotherapist, physicist), → treatment plan validation (physicist), → proton radiation therapy (radiotherapist). First treatment, radiotherapist and physicist are present) → post-treatment efficacy evaluation (radiotherapist, independent imaging review team) → follow-up (radiotherapist).

Subjects will receive radiotherapy with reference to the dose and segmentation prescribed by the trial, and the expected radiotherapy cycle of each subject is 1~8 weeks.

3.1.3.1 Enrollment time

The investigators obtained the informed consent of the participants and signed the ICF, which was then screened according to the inclusion criteria. If the patient meets all the inclusion criteria of this trial and does not meet any of the exclusion criteria, the case is included in this trial, and the time of enrollment of the subject is used as the treatment on the day of the first treatment, and a unique enrollment number is obtained in the order of enrollment.

3.1.3.2 The number of subjects required for the clinical trial

After screening according to the inclusion criteria, it is expected that a total of 47 subjects will be included in this clinical trial, all of whom will be treated with investigational medical devices.

3.1.4 Effectiveness evaluation methods

If it is not possible to follow up at the clinical trial center according to the visit arrangement due to the epidemic, the clinical examination can be examined by other tertiary hospitals, and the test results will be transmitted back to the clinical trial center for evaluation; The carrier of imaging data in the outer hospital is not limited, and it is necessary to ensure that the imaging department of the center can be opened and read.

3.1.4.1 The main effectiveness evaluation indicators and the methods and time selection of their evaluation, recording and analysis

(1) Tumor disease control rate (DCR).

Reason for selection: According to the clinical trial effectiveness evaluation in the "Guidelines for the Review of Clinical Evaluation Technologies of Proton Carbon Ion Therapy System" (CFDA Circular No. 4 [2018]): "In view of the local characteristics of radiotherapy, it is recommended that the efficacy evaluation should be based on local control, and according to

the different diseases, the common standards in clinical research, such as the efficacy evaluation criteria for solid tumors, should be reasonably adopted RECIST. The efficacy evaluation can be divided into complete response CR, partial response PR, disease stable SD, disease progression PD, and the effective definition is: "CR+PR+SD." ”； Due to the particularity of the disease, the evaluation method recommended in the relevant diagnosis and treatment guidelines is selected. The tumor disease control rate was selected as the main effectiveness evaluation index, which was relatively objective and reproducible, and adopted the common standard in clinical research, which was widely recognized and applied by clinicians.

Definition of indicators: the occurrence of CR, PR and SD after the end of treatment is disease control; No biochemical recurrence at the end of prostate cancer treatment, no regional lymph nodes or distant metastases, considered disease control. Proportion of participants who developed disease control three months after the end of the last radiotherapy.

Metric type: Qualitative.

Data collection time: screening period, 3 months ± 7 days after the end of the last treatment.

Evaluation time: 3 months ± 7 days after the end of the last treatment.

Site of evaluation: Tumor receiving radiation therapy.

Evaluation method: The changes in tumor CT or MRI imaging before and after treatment were evaluated by an independent imaging review panel according to RECIST 1.1. At 3 months of radiographic evaluation, if PD is found, PET-CT is required to confirm it.

Calculation formula: DCR = number of disease control subjects / total number of subjects× 100%.

Criteria: See RECIST 1.1 for details. At the time of 3-month imaging evaluation, if the patient is found to have PD, PET-CT examination is required to confirm it, if progress is confirmed, it is recorded as PD, if progress cannot be confirmed, it may

be false progression, and it is recorded as SD. If prostate cancer does not have biochemical recurrence, PET-CT examination is not required, and there is no metastasis by default, which is regarded as tumor control, and if biochemical recurrence occurs, it is regarded as tumor not controlled, and PET-CT is required to confirm tumor metastasis.

Note: Participants who aborted the trial for any reason (except loss to follow-up) before the end of the last radiation therapy were considered to have disease progression (PD) or were not controlled. Disease site evaluation uses the same approach as baseline, including consistent contrasted/non-contrast scans and prompt scanning. If changes are needed, the case must be discussed with a radiologist to determine whether an alternative approach is possible. If not, the objective situation in the future is unclear.

3.1.4.2 Secondary effectiveness evaluation indicators and their methods and timing of evaluation, recording, analysis

(1) Objective response rate (ORR).

Reason for selection: The Guidelines for the Review of Clinical Evaluation Technologies of Proton Carbon Ion Therapy Systems (CFDA Circular No. 4 [2018]) recommends the use of the latest version of the commonly used evaluation criteria for radiation oncology as the clinical trial evaluation criteria, so RECIST 1.1 is used Relevant indicators as effectiveness evaluation criteria; Due to the particularity of the disease, the evaluation method recommended in the relevant diagnosis and treatment guidelines is selected. All of them can directly measure the effect of radiotherapy and are widely recognized and applied by clinicians.

Definition of indicators: CR or PR after the end of treatment is considered objective remission, prostate cancer has no biochemical recurrence at the end of the last treatment, and no regional lymph nodes or distant metastasis are considered objective remission. Proportion of participants who experienced objective remission at each time point after the end of the last treatment.

Metric type: Qualitative.

Data collection time: screen period,3 days, 1 month± 7 days, 2 months, ± 7 days , 3 months, ± 7 days after the end of the last treatment.

Evaluation time: 3 days, 1 month± 7 days, 2 months, ± 7 days, 3 months, ± 7 days after the last treatment.

Site of evaluation: Tumor receiving radiation therapy.

Evaluation method: The changes in tumor CT or MRI imaging before and after treatment were evaluated by an independent imaging review panel according to RECIST 1.1. At 3 months of radiographic evaluation, if PD is found, PET-CT is required to confirm it.

Calculation formula: ORR = number of subjects in objective response / total number of subjects × 100%.

Criteria: See RECIST 1.1 for details. At the time of 3-month imaging evaluation, if the patient is found to have PD, PET-CT examination is required to confirm it, if progress is confirmed, it is recorded as PD, if progress cannot be confirmed, it may be false progression, and it is recorded as SD. If prostate cancer does not have biochemical recurrence, PET-CT examination is not required, and there is no metastasis by default, which is regarded as objective remission, and if biochemical recurrence occurs, it is regarded as not objectively remission, and PET-CT is required to confirm tumor metastasis.

Note: Participants who aborted the trial for any reason (other than loss to follow-up) before the end of the last radiotherapy were considered to have not responded objectively. Disease site evaluation uses the same approach as baseline, including consistent contrasted/non-contrast scans and prompt scanning. If changes are needed, the case must be discussed with a radiologist to determine whether an alternative approach is possible. If not, the objective situation in the future is unclear.

(2) Tumor disease control rate (DCR).

Reason for selection: DCR 3 months after the end of the last treatment was the primary evaluation index, and DCR at other follow-up time was used as a secondary evaluation index.

Definition of indicators: the occurrence of CR, PR and SD after the end of treatment is disease control; No biochemical recurrence at the end of prostate cancer treatment, no regional lymph nodes or distant metastases, considered disease control. Proportion of participants who developed disease control at one month after the end of the last treatment.

Metric type: Qualitative.

Data collection time: screen period, 3 days , 1 month ± 7 days, 2 month ± 7 days after the end of the last treatment.

Evaluation time: 3 days, 1 month ± 7 days, 2 month ± 7 days after the last treatment.

Site of evaluation: Tumor receiving radiation therapy.

Evaluation method: The changes in tumor CT or MRI imaging before and after treatment were evaluated by an independent imaging review panel according to RECIST 1.1. At 3 months of radiographic evaluation, if PD is found, PET-CT is required to confirm it.

Calculation formula: DCR = number of disease control subjects / total number of subjects × 100%.

Criteria: See RECIST 1.1 for details. At the time of 3-month imaging evaluation, if the patient is found to have PD, PET-CT examination is required to confirm it, if progress is confirmed, it is recorded as PD, if progress cannot be confirmed, it may be false progression, and it is recorded as SD. If prostate cancer does not have biochemical recurrence, PET-CT examination is not required, and there is no metastasis by default, which is regarded as tumor control, and if biochemical recurrence occurs, it is regarded as tumor not controlled, and PET-CT is required to confirm tumor metastasis.

Note: Participants who aborted the trial for any reason (other than loss to follow-up) before the end of the last radiotherapy were considered to have PD or was uncontrolled. Disease site evaluation uses the same approach as baseline, including consistent contrasted/non-contrast scans and prompt scanning. If changes are needed, the case must be discussed with a radiologist to determine whether an alternative approach is possible. If not, the objective situation in the future is unclear.

(3) Tumor markers (if needed)

Reason for selection: The Guidelines for the Review of Clinical Evaluation Technologies of Proton Carbon Ion Therapy System (CFDA Circular No. 4, 2018) suggests that changes in tumor markers and functional imaging parameters should be used as reference factors for effectiveness evaluation.

Data collection and evaluation time: screen period, 3 days, 1 month ± 7 days, 2 months± 7 days, 3 months±7 months after the end of the last treatment Sky.

Evaluation method: tumor marker examination is performed, and the investigator judges that the tumor marker (before and after radiotherapy) is reported as clinically significant changes.

Note: Researchers choose relevant indicators according to the disease, and the scheme is not uniformly stipulated.

(4) Product usability evaluation (ProBeam360 system, radiotherapy management software (Aria), radiotherapy planning software (Eclipse)).

Reason for selection: Routine effectiveness indicators of medical device clinical trials.

Indicator type: quantitative, open-ended question.

Data collection and evaluation time: the day the last treatment was completed.

Evaluation method: Researchers using the corresponding function scored according to the Likrt scale and collected open-ended questions to evaluate the overall feeling of ease of use during treatment.

3.1.5 Safety evaluation methods

If it is not possible to follow up at the clinical trial center according to the visit arrangement due to the epidemic, the clinical examination can be examined by other tertiary hospitals, and the test results will be transmitted back to the clinical trial center for evaluation; The carrier of imaging data in the outer hospital is not limited, and it is necessary to ensure that the imaging department of the center can be opened and read.

3.1.5.1 The main safety evaluation indicators and the methods and time selection of their evaluation, recording and analysis

(1) CTCAE 3 toxicity ratio

Reason for selection: According to the Guidelines for the Technical Review of Clinical Evaluation of Proton Carbon Ion Therapy System (CFDA Circular No. 4 of 2018), if the proportion of CTCAE grade 3 acute toxic reactions exceeds 5%, it is considered as a clinical trial failure, so it is selected The proportion of CTCAE grade 3 toxicity is used as the main safety evaluation index, and CTCAE is a commonly used safety evaluation standard in radiation oncology, which is widely recognized and applied by clinicians.

Indicator definition: Proportion of subjects with grade 3 toxicity during the trial cycle.

Metric type: Qualitative.

Data collection time: the entire clinical trial cycle.

Evaluation time: 3 months ± 7 days after the last treatment.

Evaluation methodology: Investigators recorded AEs that occurred during the clinical trial cycle and graded them according to CTCAE V5.0.

Calculation formula: proportion of CTCAE grade 3 toxicities = (number of subjects with CTCAE grade 3 toxicity in the test cycle) / total number of subjects × 100%.

Judging criteria: See CTCAE V5.0 for details.

(2) CTCAE Grade 4 and 5 toxicity ratio

Reason for selection: According to the Guidelines for the Review of Clinical Evaluation Technologies of Proton Carbon Ion Therapy System (CFDA Circular No. 4 of 2018), CTCAE grade 4 and 5 toxicities are considered to be clinical trial failures, so 4 is selected The proportion of grade 5 and grade 5 toxicity reactions is used as a safety evaluation index, and CTCAE is a commonly used safety evaluation standard in radiation oncology, which is widely recognized and applied by clinicians.

Indicator definition: Proportion of subjects with toxicity of grade 4 and 5 during the trial cycle.

Metric type: Qualitative.

Data collection time: the entire clinical trial cycle.

Evaluation time: 3 months ± 7 days after the last treatment.

Evaluation methodology: Investigators recorded AEs that occurred during the clinical trial cycle and graded them according to CTCAE V5.0.

Formula: Proportion of CTCAE grade 4 and 5 toxicities = (number of subjects with CTCAE grade 4 and 5 reactions in the test cycle) / total number of subjects × 100%

Judging criteria: See CTCAE V5.0 for details.

3.1.5.2 Secondary safety evaluation indicators and their methods and time selection for evaluation, recording and analysis

(1) CTCAE grade 1 and 2 toxicity ratio

Reason for selection: The proportion of CTCAE grade 3~5 toxicity reactions 3 months after the end of the last treatment was the main safety evaluation index, and the proportion of CTCAE grade 1 and grade 2 toxicity reactions was used as a secondary safety evaluation index for auxiliary evaluation.

Indicator definition: Proportion of subjects with grade 1 and 2 toxicity during the trial cycle.

Metric type: Qualitative.

Data collection time: the entire clinical trial cycle.

Evaluation time: 3 months ± 7 days after the last treatment.

Evaluation methodology: Investigators recorded AEs that occurred during the clinical trial cycle and graded them according to CTCAE V5.0.

Calculation formula: proportion of CTCAE grade 1 and 2 toxicities = (number of subjects with CTCAE grade 1 and 2 toxicities in the test cycle) / Total number of participants× 100%.

Judging criteria: See CTCAE V5.0 for details.

(2) Laboratory tests

Reason for selection: According to the Guidelines for Technical Review of Clinical Evaluation of Proton Carbon Ion Therapy System (CFDA Circular No. 4 of 2018), changes in clinical symptoms and signs should be recorded for clinical manifestations, tumor improvement (imaging examinations, laboratory test data), etc., and comprehensive analysis should be carried out. At the same time, it is a routine safety monitoring index for medical device clinical trials.

Data collection and evaluation time: screening period, treatment period 1st day per week (Monday to Sunday is regarded as 1 calendar week, each natural week on the day of the first treatment), before treatment or -1 day (blood count only), 3 days after the end of the last treatment, 1 month ± 7 days (except coagulation routine), 2 months± 7 days (except coagulation routine), 3 months, ± 7 days (except coagulation routine). 。

Evaluation items: blood routine, coagulation routine, urine routine, liver function, kidney function.

Evaluation method: Laboratory tests are performed and the investigator judges clinically significant changes in laboratory indicators (before and after radiotherapy).

(3) ECOG grading of physical status

Reason for selection: According to the Guidelines for the Review of Clinical Evaluation Technologies of Proton Carbon Ion Therapy System (CFDA Circular No. 4 of 2018), the follow-up of subjects should include safety and efficacy evaluation. The general condition of the subjects is recommended to be evaluated using the internationally accepted scoring method.

Data collection time and evaluation time: screening period, treatment period on the first day of each week (every Monday to Sunday is regarded as 1 calendar week, each natural week on the day of the first treatment) before treatment or -1 day, 3 days after the end of the last treatment, 1 month ± 7 days, 2 months± 7 days, 3 months, ± 7 days.

Evaluation method: ECOG physical performance status was graded and reported by the investigator to report clinically significant changes in the test results (before and after radiotherapy).

(4) Adverse event rate

Reason for selection: Routine safety monitoring indicators for clinical trials of medical devices.

Indicator definition: Adverse events are adverse medical events that occur during clinical trials, whether or not related to a device.

Metric type: Qualitative.

Data collection time: the entire clinical trial cycle.

Evaluation time: 3 months ± 7 days after the last treatment.

Evaluation method: The investigator recorded all AEs that occurred.

Calculation formula: adverse event rate = number of subjects with adverse events in this group / total number of subjects in this group× 100%.

(5) Serious adverse event rate

Reason for selection: Routine safety monitoring indicators for clinical trials of medical devices.

Definition: Serious adverse events are those that occur in the course of a clinical trial that result in death or serious deterioration of health, including fatal illness or injury, permanent defects in body structure or function, requiring hospitalization or prolonged hospital stay, or requiring medical or surgical intervention to avoid permanent defects in body structure or body function; Events that lead to fetal distress, fetal death, or congenital anomalies or birth defects.

Metric type: Qualitative.

Data collection time: the entire clinical trial cycle.

Evaluation time: 3 months ± 7 days after the last treatment.

Evaluation methodology: The investigator recorded all SAEs that occurred.

Calculation formula: Serious adverse event rate = number of subjects with serious adverse events in this group / total number of subjects in this group× 100%.

(6) Incidence of device defects

Reason for selection: Routine safety monitoring indicators for clinical trials of medical devices.

Definition of indicators: refers to the unreasonable risk that medical devices may endanger human health and life safety under normal use during clinical trials, such as crash.

Metric type: Qualitative.

Time of data collection: during treatment.

Evaluation time: After the last treatment was completed.

Evaluation methodology: The investigator recorded all device defects that occurred.

Calculation formula: incidence of device defects = number of occurrences of device defects / number of times of device use × 100%.

4 Statistical considerations

4.1 Statistical design, methods, and analytical protocols

This study was a prospective, single-center, single-group target value trial.

All statistical analysis methods are described in detail in the statistical analysis plan. A first draft of the statistical analysis plan is formed after the protocol and eCRF are finalized and will be finalized prior to database locking.

4.2 Sample size calculation

4.2.1 Total sample size

This clinical trial intends to enroll 47 subjects. The sample size determination process is as follows:

This clinical study is designed for clinical verification of a single group of target values, and the tumor disease control rate, the main effectiveness evaluation index, is used as the basis for sample size estimation. According to the Guidelines for the Review of Clinical Evaluation Technologies of Proton Carbon Ion Therapy System (CFDA Circular No. 4 of 2018), the target value is set at 80%, and the bilateral significance level is 0.05, and the power degree 80%, applying the sample size estimation professional software PASS 15.0, calculated by the above parameters, the test group needs a sample size of at least 42 cases. Considering that about 10% of cases may be dropped or lost to follow-up during clinical validation, the sample size of the experimental group was expanded to 47 cases.

4.3 The level of significance and power of clinical trials

The significance level α (bilateral) = 0.05, and the power was 80%.

4.4 Expected shedding rate

In the sample size estimation process, the expected shedding rate is 10%.

This dropout rate refers to the proportion of participants who ultimately could not be included in the primary analysis. Shedding subjects are subjects who have been identified by the investigator as having serious protocol deviations. May include, but is not limited to, the following: the subject violates the inclusion criteria; Participants were not treated with experimental devices; Participants used concomitant medications/devices that are prohibited by the protocol; lack of data on key evaluation indicators; Participants did not obtain any data, etc.

4.5 Criteria for passing/failing clinical trial results

The target value of the main effectiveness evaluation index (tumor disease control rate) of the trial was 80%, and if the lower limit of the 95% confidence interval of the test results was greater than 80%, the tumor disease control rate of the experimental group reached the target.

If the main safety evaluation index of the trial (the proportion of CTCAE grade 3 toxic reactions) is greater than 5%, the clinical trial fails.

If the trial has CTCAE grade 4 and 5 toxicity, the clinical trial fails.

4.6 Criteria and reasons for terminating trials on statistical grounds

No interim analysis was performed in this study and therefore criteria for termination of the trial for statistical reasons were not established.

4.7 Statistical methods of data, together with methods of dealing with missing, unused or erroneous data and irrational data

4.7.1 Data statistical methods

Statistical analysis with SAS 9.4 software.

All data are described statistically, including demographics, baselines, all efficacy measures, and all safety data. The measurement data give the mean, standard deviation, minimum, maximum, median, 25th quantile and 75th quantile; The counting data gives the frequency and the corresponding percentage.

Effectiveness Analysis:

The number and percentage of cases achieving DCR were calculated, and the Clopper-Pearson method was used to calculate the 95% confidence interval for tumor disease control rate. ORR was calculated and the Clopper-Pearson method was used to calculate the objective response rate 95% confidence interval. Descriptive statistics on the percentage change from baseline of the sum of the longest diameter (SLD) of the measurable tumor. The Waterfall Chart was made by the maximum percentage reduction in SLD per patient compared to the screening period.

The *Kaplan-Meier* method was used to calculate the median duration of response, median progression-free survival, median survival, and overall survival, and plotted *K-M* curves (long-term follow-up data).

For tumor markers, compare and evaluate the changes before and after treatment, and give clinical evaluation [no clinical significance, clinically significant (tend to normal), clinically significant (tend to be abnormal), not checked].

Safety Analysis:

Descriptive statistics were used to classify organ systems in MedDRA medical terms, and the incidence, occurrence, and severity of adverse events, adverse reactions, and serious adverse events were summarized.

Laboratory indicators, ECOG physical status classification and other safety-related indicators were compared and evaluated before and after treatment, and clinical evaluation ([no clinical significance, clinically significant (tending to normal), clinically significant (tending to abnormal), not checked], CTCAE grade evaluation before and after treatment cross-table.

4.7.2 Missing, unused, or erroneous data (including mid-exit and evacuation) and unreasonable data

All missing, unused or erroneous data (including mid-exit and withdrawal) and unreasonable data will be discussed and finalized by investigators and

biostatisticians during the blinding review phase. The basic statistical principles of these data processing are as follows:

(1) Describe the details of each shedding case;

(2) Missing data from baseline, which can not be estimated;

(3) The missing values of DCR and primary safety evaluation indicators (proportion of CTCAE grade 3 toxicities, proportion of CTCAE grade 4 and 5 toxicities) at 3 months after the end of treatment can be estimated using worst-case scenarios.

(4) The missing values of qualitative secondary effectiveness evaluation indicators ORR, DCR and long-term follow-up effectiveness evaluation indicators can be estimated using worst-case scenarios;

(5) The missing values of quantitative secondary efficacy evaluation indicators DOR, tumor markers, product ease assessment and long-term follow-up effectiveness evaluation indicators were not estimated.

(6) Erroneous, unreasonable data (out-of-range data and data that contradicts other data or indicators of the study protocol) can be treated as missing values;

(7) Worst-case estimates are used for missing values for all minor safety indicators;

(8) The sensitivity analysis of the main effectiveness evaluation indicators and main safety evaluation indicators after treatment was carried out in the whole analysis center.

(9) The sensitivity analysis of all secondary effectiveness evaluation indicators after treatment was carried out in the whole analysis center.

(10) For all secondary safety evaluation indicators after treatment, sensitivity analysis was carried out in the security dataset.

4.8 Procedures for reporting deviations from the original statistical plan

Under normal circumstances, only the statistical analysis content agreed in advance included in the statistical analysis plan can be presented in the clinical trial report of this trial. The increased demand for statistical analysis for various uncertain reasons is only exploratory analysis.

4.9 Selection criteria and rationale for participants included in the analysis

Full Analysis Set (FAS): All subjects who received at least 1 investigational device treatment and at least one post-baseline observation data will be enrolled in FAS, according to the basic principles of intention-to-heart analysis. FAS will be used as the primary population for baseline data and sensitivity analysis for validity evaluation. Participants may only be excluded in very limited circumstances, including when important inclusion criteria are violated and no observational data are available after enrollment.

Compliant protocol set (PPS): is a subset of FAS, defined as subjects who have measurable lesions at baseline and have completed at least one assessment of primary efficacy indicators after baseline. PPS will be the primary population for the effectiveness evaluation of this study.

Safety dataset (SS): all participants who received at least 1 study device treatment and at least one safety assessment. SS will be the primary population for safety analysis in this study.

The assessment of baseline characteristics will use the full set of analyses; The evaluation of effectiveness will use both the full analysis set and the conforming protocol set; Security analysis uses security datasets.

4.10 Covariate and subgroup analysis

Subgroup analysis as necessary was not precluded. Subgroups include, but are not limited to:

(1) Tumor sites (tumors of the nervous system, head and neck, chest, abdomen, spine, pelvis, extremities, etc.).