Universitätsklinikum Tübingen

Department of Radiation Oncology
Medical Director
Prof. Dr. Dipl.-Phys. Karim-Maximilian Niyazi
Tel. 07071 29-82165
Fax 07071 29-5026
roinfo@med.uni-tuebingen.de

Medical
Medical center, MVZ
Specialty: Radiation Oncology
Medical Director:
Prof. Dr. med. Cihan Gani

Application for review of a research project involving humans by the Ethics Committee of the Medical Faculty

TEST PLAN

Project title:

Single-arm phase(II) study on the role of primary and metastasis-directed PSMA PET/CT-guided local ablative stereotactic radiotherapy in patients with oligometastatic prostate cancer with incomplete PSA decline on systemic therapy
(Radiotherapy in primarily metastasized prostate cancer - Image-guided local AbLaTion of prostate and Oligoresidual disease)

Internal Study Code
RIALTO study

Date of application:
July 25, 2025

Version V2 dated: October 17, 2025

Registration with the German Clinical Trials Register in accordance with Article 35 of the Declaration of Helsinki is requested

Information on the responsible persons/study directors:

Principal Investigator: Dr. Elgin Hoffmann
Co-Principal Investigator: Prof. Dr. Dipl.-Phys. Karim-Maximilian Niyazi

Investigators in radiation oncology (including PI/Co-PI above): Dr.
Frank Paulsen, Dr. Barbara Gehler, Dr. Hathal Haddad, Prof. Dr. Cihan Gani, Dr. Simon Böke, Dr. Vlatko Potkrajcic, Dr. David Baumann, Dr. Monica LoRusso, Evgeny Zharov

University Hospital for Radiation Oncology/Medical Care Center, Hoppe-Seyler-Str. 3, 72076 Tübingen

Study Director: Dr. Elgin Hoffmann, Tel: 07071-29 82165, Fax: 07071-29 5026.
Email: elgin.hoffmann@med.uni-tuebingen.de

Head of the clinic: Prof. Dr. Dipl.-Phys. Karim-Maximilian Niyazi, Tel: 07071-29 82165, Fax: 07071-29 5026.

Email: maximilian.niyazi@med.uni-tuebingen.de

Cooperation partners at the University Hospital of Tübingen:
Prof. Dr. Christian La Fougère, Dr. Ying Zhang, Department of Nuclear Medicine; Prof. Dr. Igor Tsaur, Prof. Dr. Steffen Rausch, University Clinic for Urology; Prof. Dr. Daniela Thorwarth, Research Section Biomedical Physics; Prof. Dr. Konstantinos Nikolaou, PD Dr. Andreas Brendlin, University Clinic for Diagnostic and Interventional Radiology

Cooperation partner Ludwig-Maximilians-University Munich:
Prof. Dr. Nina-Sophie Schmidt-Hegemann, Clinic for Radiation Oncology and Radiotherapy
Dr. Paul Rogowski, Clinic for Radiation Oncology and Radiotherapy
Prof. Dr. Rudolf Werner, University Clinic for Nuclear Medicine

Cooperation partner University Hospital Dresden:
PD Dr. Tobias Hölscher, Clinic for Radiation Oncology and Radiotherapy

Cooperation partner University Hospital Freiburg: PD Dr.
Simon Spohn, Department of Radiation Oncology and Radiotherapy

Cooperation partner University Hospital Giessen: Prof. Daniel Habermehl, Clinic for Radiation Oncology and Radiotherapy

Study Director
Principal Investigator Dr. Elgin Hoffmann _____ Date

Declaration of consent from the clinic director

The undersigned has read the test plan and agrees with its contents.

Institute Director
Co-Principal Investigator Prof. Dr. Dipl.-Phys. K.-M. Niyazi _____ Date

Contents

1. Synopsis

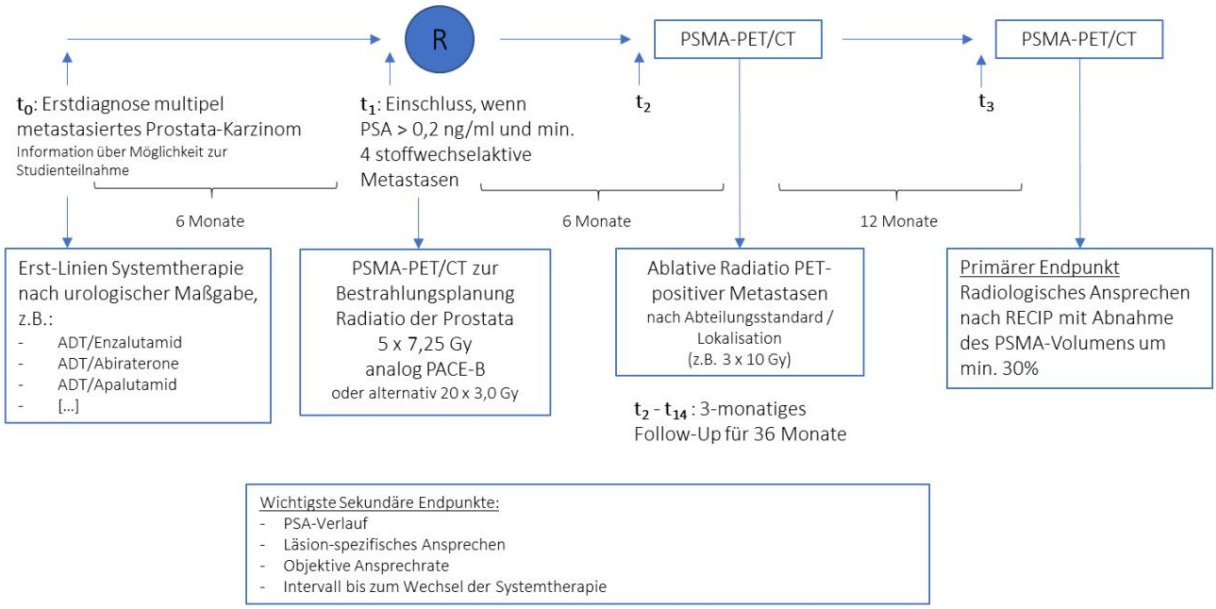
sponsor	University Hospital Tübingen, Medical Director: Prof. Dr. med. J. Maschmann Administrative Director: Dr. D. Harsch
Title	**Radiotherapy in primarily metastatic prostate cancer - Image-guided local AbLaTion of prostate and Oligoresidual disease**
Short Title	RIALTO study
EudraCT number	Not required
Internal Study Code	AKF application no. 1030-0-0 Report submitted to DKRS
Coordinating Investigator (Head of Clinical Examination, according to § 4 German Drug Law (AMG)	Dr. Elgin Hoffmann, Specialist in Radiation Therapy; University Hospital for Radiation Oncology and Radiation Therapy Tübingen Prof. Dr. med. Dipl.-Phys. Maximilian Niyazi
Indication	Primary osseous +/- lymphogenous oligo-/polymetastatic prostate cancer carcinoma
Number of Patients	27 patients
Inclusion Criteria	- Present declaration of consent - ECOG 0-2 - Ages 18-85 years - Acinar adenocarcinoma of the prostate, histologically secured - De novo oligo-/polymetastatic prostate cancer (min. 4 bone metastases) without visceral metastasis, lymph node metastasis possible - First-line therapy with antihormonal therapy (AHT) + X (X = e.g., enzalutamide / abiraterone / apalutamide, etc.) according to urological guidelines as per the S3 guideline for a minimum of 6 Months - Present staging at the time of ED with Multimetastasis, but exclusion of visceral metastases Metastases - PSA not below the limits after 6 months of systemic therapy Threshold value lowered from 0.2 ng/ml - ÿ 15 active osseous lesions in response assessment using PSMA-PET/CT after 6 months of systemic therapy
Exclusion Criteria	- PSA < 0.2 ng/ml after at least 6 months of systemic therapy - M1c (visceral metastases)

	- other active tumor disease in the last 2 years (except basal cell carcinoma of the skin/melanoma in remission) - Zn TUR-P or HIFU less than 6 months before RT start, Zn surgical resection of the prostate - Pre-irradiation in the pelvic area - Serious pre-existing conditions affecting the bladder or rectum (e.g., active fistula, chronic inflammatory bowel disease) - Presence of a tumor predisposition syndrome - serious pre-existing urological conditions - Contraindications to performing a PSMA-PET/CT scan - Contraindications to performing a Radiation - Pre-irradiation, which involves ablative irradiation of the Metastases prevented - In T4 stage: Persistent infiltration of the rectum- Mucosa after 6 months of systemic therapy; in Bladder infiltration: critical evaluation - Rising PSA level between initial diagnosis and Study screening - Indication to change systemic therapy or Initiation of chemotherapy before the start of the study
Description of the Medical Product/Medical Device	-
Study Design:	**Current:** Pilot study (single-arm phase II study, Fleming design) Therapeutic intervention: 1. Stereotactic radiation of the primarius (5 x 7.25 Gy, Alternatively, moderate according to departmental standard Hypofractionation with 20 x 3.0 Gy or 6 x 6.0 Gy analogously Stampede possible) 2. Stereotactic radiotherapy during systemic therapy continuing metabolically active metastases (residual) Metabolic activity in PSMA-PET/CT; ablative radiotherapy (stereotactic or normofractionated) in patients with primarily non-visceral metastatic adenocarcinoma of the prostate Anti-androgen systemic therapy following urological Standard of Care
Length of study/ Timelines	Total trial duration: 36 months

	Duration for individual patient: Study treatment: 2 to 6 weeks Follow-up: 36 months Number of visits: 15 visits FSI (First Subject In): 12/2025 LSI (Last Subject In): 12/2026 LSO (Last Subject Out): 06/2027 DBL (Data Base Lock): 03/2029 (primary endpoint) 06/2030 (secondary endpoints (QoL, side effects)) Statistical Analyzes Completed: 06/2029 Trial Report Completed (primary endpoint): 12/2029
Aim of the Study	Pilot study on radiological response after RECIP in PSMA-PET/CT in patients with primary metastatic prostate cancer Carcinoma, which occurs after 6 months in cases of oligopersistence Systemic therapy administered as part of local ablative radiotherapy can be. If the primary endpoint is reached, a multicenter study is planned, with an application for external funding (e.g., cancer support).
Objectives/Endpoints • Primary Objective/Endpoint • Secondary Objective/Endpoints • Exploratory Objective	Primary endpoint: Response in PSMA-PET/CT after RECIP with a decrease in PSMA volume of at least 30%. Secondary endpoints and parameters collected: • PSA progression • Lesion-specific response of the irradiated area Lesions on PSMA-PET/CT • Objective response rate ORR) • Interval until change of systemic therapy • Overall Survival (OS) • Failure-free survival (FFS) as any disease-specific Event • Progression-free survival (PFS)

	• Distant metastasis-free survival (MFS) • Disease-specific survival (prostate cancer specific survival, PCS) Exploratory endpoints: • Reason for changing systemic therapy • Choice of the next systemic therapy line • Side effects (according to CTCAEV5 and RTOG), Quality of life (EORTC QLQ-C30 prostate, QLQ-PR25, EQ-D5), assessment of organ function (gastrointestinal and urogenital: IPSS score, ICIQ score, NCI-PRO-CTCAE, IIEF)
Statistics, Safety Variables and Stopping Rules	Study design: Single-arm phase II study using the Fleming design Number of cases: 27 patients Statistical estimation: Significance level p=0.05; Null hypothesis: Success rate <15%, effectiveness of the intervention is certain if success rate >40%, Power 90%. Stopping rules: CTCAE grade 4 and 5 attributable to the therapy performed; persistent grade 3 adverse events > 90 days after radiation therapy in >50% of patients.
Database	Database: REDCap Biometrics: IKEaB, Prof. Martus
Participating Centres and Investigators	External: Dr. Paul Rogowski, PD Dr. Nina-Sophie Schmidt-Hegemann, Department of Radiation Therapy and Radio-Oncology, Ludwig-Maximilians-University Munich Intern: Prof. Dr. Christian la Fougère, University Clinic for Nuclear Medicine; Prof. Dr. Steffen Rausch, Prof. Dr. Igor Tsaur, University Clinic for Urology. Cooperations with the university hospitals of Dresden and Cologne, Freiburg and Augsburg are being considered.
Study Type Please select	ÿ AMG MPG X No-AMG/No-MPG (according to professional regulations)
Competent Regulatory Authorities Please select	ÿ BfArM and EK ÿ PEI and EK ÿ DIMDI

	X Only EK, notification to the BfS at fixed interval of planned PSMA-PET/CT examinations has been submitted, the opinion of the DEGRO expert commission regarding the classification of the planned irradiation as a therapeutic radiation application within the framework of medicine is available (in the appendix).
Monitoring according to GCP	Study conducted according to professional regulations, therefore no monitoring required.



A. Flowchart representation of the planned study intervention

	ADT + ARPI	PSMA-PET/CT	Therapie	Follow-Up												
Studienvisite	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
				1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	15 Mo.	18 Mo.	21 Mo.	24 Mo.	27 Mo.	30 Mo.	33 Mo.	36 Mo.
Intervention			SBRT Prostata			SBRT Met.										
Prüfung Ein- und Ausschlusskriterien		x														
Aufklärung und Einverständnis		x														
Registrierung		x														
Patientendatendokumentation		x														
Erhebung PSA-Wert	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
PSMA-PET/CT		x				x				x						
Dokumentation Lebensqualität		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dokumentation Nebenwirkungen			x	x	x	x	x	x	x	x	x	x	x	x	x	x

Note: The first study visit will only take place after the patient has been informed and given written consent. Patients.

B. Overview of study visits

2. Introduction, Background & State of Research

2.1 Oligometastatic prostate cancer

Prostate cancer is the most common non-cutaneous malignant tumor in men [1]. In 17% of patients, distant metastases are already present at the time of diagnosis (metastatic prostate cancer, MPC) [2].
The standard treatment according to the German S3 guideline [3] in this situation is the combination of antihormonal therapy (AHT) with androgen receptor pathway inhibitors (ARPIs); in cases of visceral metastasis, also in combination with docetaxel-containing chemotherapy. PSA response rates of up to 91% are achieved with this treatment [4].

However, in approximately one-third of MPC patients undergoing systemic therapy, PSA levels either decline insufficiently or progress within the first 3 years [5, 6]. Insufficient PSA decline is associated with poorer progression-free survival (PFS) and overall survival (OS) [7]. The inevitable castration resistance appears to be caused by the clonal selection of refractory tumor cells [8]. If the imaging correlate of the detectable PSA level during systemic therapy is limited to a small number of progressive or residual metastases, these could be amenable to local ablative therapy [9, 10]. In the case of oligometastatic prostate cancer (OMPC), studies have been published in recent years supporting such local therapeutic approaches in this situation.

2.2 Radiotherapy for oligometastatic prostate cancer

In the randomized phase 3 STAMPEDE trial, **primary-directed radiotherapy** (PDT) in addition to standard systemic therapy in patients with de novo OMPC and a limited number of metastases improved overall survival (OS) at 3 years from 73% to 81% [11] with comparable toxicity. The PEACE-1 trial demonstrated a benefit in progression-free survival (PFS) and OS from intensifying therapy by combining abiraterone with PDT in patients with a low metastatic burden [12, 13]. Therefore, European and German guidelines recommend PDT in patients with OMPC with a low metastatic burden (usually 3 bone metastases) [3, 14].

Several phase 2 trials also demonstrate the effectiveness of **metastasis-directed radiotherapy.**
(Metastasis-directed therapy, **MDT)** in OMPC. In the SABR-COMET trial, a survival benefit was found for stereotactic body radiotherapy (SBRT) of oligometastases in addition to standard systemic therapy [15]. In this trial, 27% of patients

an OMPC. In the ORIOLE study, MDT improved the biochemical status in patients with OMPC.
Progression-free survival and prolonged distant metastasis-free survival in a subgroup where all PSMA-PET/CT-positive lesions were treated with SBRT [16]. In the STOMP trial, MDT in patients with oligometastatic recurrence after primary therapy also significantly prolonged the time to initiation of systemic therapy [17]. In the SABR-COMET trial, three grade 5 toxicities occurred in the treatment arm, but only after SBRT of lung and adrenal metastases. The remaining toxicity in all three trials was moderate (< grade 3). The effect on PFS and OS of combining primary tumor-directed radiotherapy with ablative radiotherapy of metabolically active lesions, along with intensified androgen blockade, has not yet been investigated. Based on the aforementioned evidence, a further survival benefit from such combination therapy is assumed, which was systematically investigated in the present study.

to be investigated.

2.3 PSMA-PET for assessing treatment response and further treatment planning

Prerequisites for targeted ablative treatment are the accurate detection of metastatic lesions and, in the case of prior systemic therapy, a reliable assessment of the response at the level of individual lesions. PSMA-PET/CT has proven to be a promising molecular imaging modality in this regard. It is superior to conventional imaging modalities for primary staging [18, 19] and also appears to have higher sensitivity than CT and CT scans in the case of biochemical recurrence after primary therapy [20].

The presented study aims to assess the viability and volume of metastatic tumor manifestations using established methods (Response Evaluation Criteria in PSMA-PET/CT, RECIP 1.0, and, if applicable, Prostate Cancer Molecular Imaging Evaluation, Second Version, PROMISE V2) [21, 22]. These methods have already been validated for assessing treatment response after PSMA-targeted radioligand therapy. PSMA-PET/CT will be used to identify those metastatic lesions that exhibit residual tumor activity or progression under systemic therapy and should therefore be treated with local ablative therapy.

2.4 Preliminary work and current clinical practice

The design of the presented study is based on the cited publications, which report a benefit of local therapeutic procedures for OMPC. Both treatment methods—radiation of the primary tumor (PDT) and radiation of the metastases (MDT)—are already routinely performed in patients with low disease burden or clinical indications (e.g., risk of fracture). In suitable patients, a combination of PDT and MDT is already used as part of an individualized, maximum-treatment approach.

In a study of 80 patients with OMPC who underwent normofractionated or stereotactic MDT, some with radiation to the prostate (12.5%) or prostatic bed (26.3%), **good local control of the irradiated bone metastases** was observed —with local recurrence occurring in only 4.4% of cases—and progression-free survival (PFS) was improved: 40% of patients were recurrence-free 2 years after MDT [23]. The most common recurrence pattern was the appearance of new bone metastases in limited numbers (<5 metastases), for which repeat MDT was performed in 50% of cases. The therapy was well tolerated, and no grade 3 adverse events occurred.

Toxicity effects.

Building on the good control rates and the prolongation of progression-free survival (PFS) in the aforementioned analysis, the present study aims to investigate the combination of photodynamic therapy (PDT) with metabolic therapy (MDT) in patients with a limited number of metabolically active metastases. This is already performed as an individualized maximum therapy, but has not yet been systematically investigated. Upon achievement of the primary endpoint of radiological response, the investigated combination therapy will be routinely offered to patients with a limited number of metabolically active metastases as an evidence-based treatment intensification to improve prognosis.

3. Study Objectives

3.1 Primary Endpoint

The primary endpoint of the study is the radiological response after RECIP, corresponding to a PSMA volume reduction of at least 30% through the study intervention (radiation of the prostate and metabolically active metastases) in the area of the initially PSMA-expressing lesions. This should
The study intervention was achieved in 40% of patients.

3.2 Secondary endpoints

- PSA progression
- Lesion-specific response of irradiated lesions in PSMA-PET/CT
- Objective response rate (ORR)
- Interval until changing systemic therapy
- Overall Survival (OS)
- Failure-free survival (FFS) as the primary outcome of any disease specific event
- Progression-free survival (PFS)
- Metastasis-free survival (MFS)
- Disease-specific survival (prostate cancer specific survival, PCS)

Exploratory endpoints:

- Reason for changing systemic therapy
- Choice of the next systemic therapy line
- Side effects (according to CTCAEV5 and RTOG), quality of life (EORTC QLQ-C30 prostate, QLQ-PR25, EQ-D5), assessment of organ function (gastrointestinal and urogenital: IPSS score, ICIQ-Score, NCI-PRO-CTCAE, IIEF)

3.3 In summary, the RIALTO study has the following objectives:

1. Systematic *investigation of the imaging response in PSMA-PET/ CT* according to validated diagnostic criteria (RECIP or PROMISE V2) after ablative irradiation of all PSMA-PET/CT positive tumor manifestations while continuing antiandrogen therapy.
2. *Investigation of the influence of therapy on oncological parameters for all metabolically active manifestations,* as this should prolong the interval for changing systemic therapy and thus positively influence PSA levels, progression-free survival and overall survival.
3. *Assessment of the quality of life and potential side effects of radiotherapy in metastatic cancer patients* to assess the burden of the planned therapeutic intervention.
   to be able to estimate this patient cohort.
4. *In a broader sense, this study, with its research questions, prepares the ground for a randomized phase II trial for patients with unfavorable prognostic parameters, which is planned upon achievement of the primary endpoint.*

4. Description of the clinical study

4.1 Study design and rationale

This study is a non-randomized, single-stage phase II trial with a Fleming design. No control group is included because both ablative radiotherapy of metastases and (ultra-)hypofractionated radiotherapy of the prostate are standard treatment in curative and limited metastatic disease settings and have been validated in independent studies [11, 12, 24].

Several studies have demonstrated the benefit of MDT even in cases of polymetastatic disease, with a well-tolerated side effect profile [15, 16, 23, 25]. In a single-center series where patients with bone metastases, with and without prior prostate therapy, received ablative MDT plus antiandrogen therapy, a 2-year progression-free survival (PFS) was achieved in 40% of patients. Three-quarters of patients who experienced recurrent bone metastases received MDT again, thus delaying the need to switch systemic therapy. No high-grade adverse events (CTCAE grade 3 or higher) were observed with MDT.

The ultrahypofractionated radiotherapy of the prostate in this study is planned analogously to the PACE-B trial. In that trial, non-metastatic patients received primary radiotherapy of the prostate with 36.25 Gy/40.0 Gy to the PTV/CTV in five fractions with a single dose of 7.25 Gy/8.0 Gy. The 5-year toxicity analysis showed no increase in side effects with ultrahypofractionation in primary radiotherapy of the prostate compared to the normofractionated standard of care with 78 Gy [26]. Furthermore, the present study omits the administration of a prostate boost, thus limiting the single dose to 7.25 Gy and the total dose to 36.25 Gy. As an alternative treatment regimen (in case of technical or medical contraindication to ultrahypofractionation, radiation therapy with moderate hypofractionation with 20 x 3 Gy single dose (analogous to the CHHiP trial [27]) or radiation therapy according to departmental standard, e.g. analogous to the STAMPEDE study with 6 x 6.0 Gy) is performed.

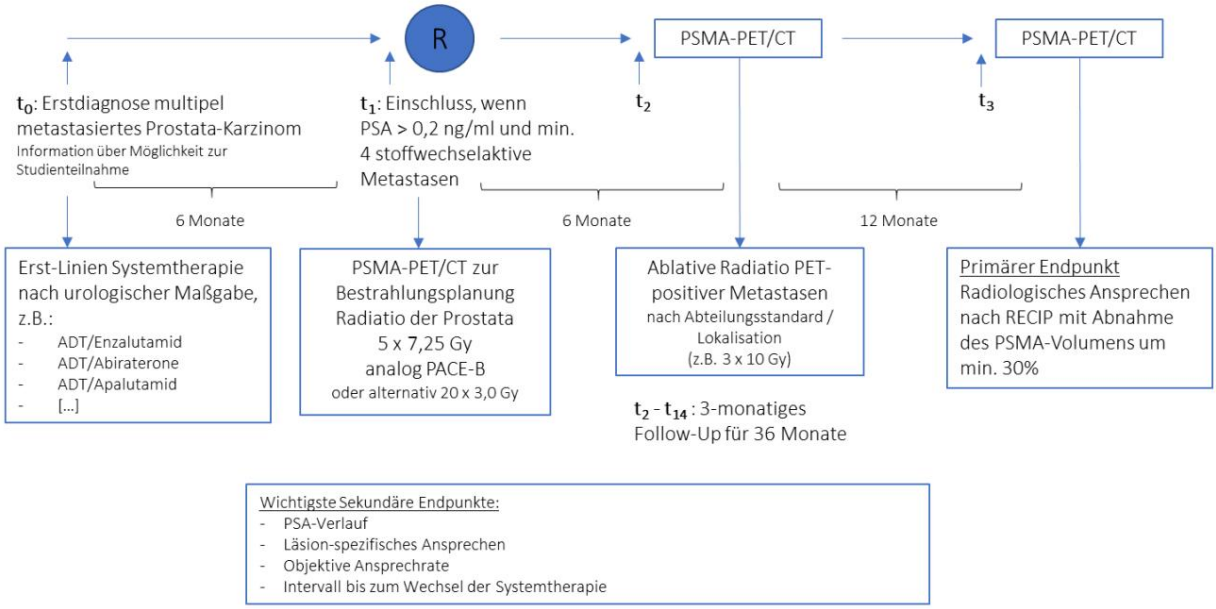
The STAMPEDE study, which investigated the effect of PDT in combination with standard-of-care therapy in patients with primary metastatic disease, demonstrated a benefit in overall survival from local therapy of the prostate in cases of limited metastasis [11].

No positive effect on overall survival in the polymetastatic situation was observed in this study; however, in this case, there was no complete androgen blockade and no radiation of the existing metastases, but only of the prostate.

Unlike previous studies mentioned above, the study presented here combines for the first time both established and validated treatment approaches – PDT with ultrahypofractionated radiation therapy of the primary tumor and MDT with stereotactic ablative radiation therapy of residual metabolically active tumors.

Metastases – in patients with oligoresidual disease that does not fully respond to systemic therapy. Since both PDT and MDT have been shown to have a positive effect on overall survival on their own, a further improvement in disease control is expected from combining both methods.

4.2 Overview of the study interventions



A graphical overview of the planned study interventions and the study procedure is shown in Figure 1. In summary, the prostate will be irradiated using MRI-guided, ultra-hypofractionated radiotherapy analogous to the PACE-B trial with 5 x 7.25 Gy on alternating days (or moderately hypofractionated with 20 x 3.0 Gy on five days/week or analogous to the department's internal standard, e.g., 6 x 6.0 Gy analogous to the STAMPEDE trial), followed six months later by ablative radiotherapy of all remaining metabolically active lymph node and bone metastases. In addition, a total of three PSMA-PET/CT scans are planned for radiotherapy planning and for assessing the radiological response according to RECIP (primary endpoint). Should a PSA increase occur during follow-up according to Phoenix criteria, the planned PSMA-PET scan will be performed earlier. In the case of isolated findings, repeat stereotactic radiotherapy will be considered. In the event of systemic progression and/or the occurrence of visceral metastases, the patient will be presented to the tumor board and the systemic therapy will be changed according to the recommendation made.

A risk-benefit assessment of the planned investigations and interventions is detailed below.

4.3 Risk-benefit assessment of the implemented measures

4.3.1 PSMA-PET/CT:

Planned Examination: A total of three PSMA-PET/CT scans are planned. For the respective radiation treatment planning (radiation of the prostate and metabolically active metastases), a PSMA-PET/CT scan will be performed at t1 and t2, 6 months apart. In addition to providing the PET data for radiation treatment planning, these PSMA-PET/CT scans will also be evaluated according to RECIP. To assess the primary endpoint – imaging response as seen in the PSMA-PET/CT scan – another PSMA-PET/CT scan will be performed 18 months after prostate radiation treatment.

Rationale: According to the S3 guideline, performing a PSMA-PET/CT scan is indicated for radiation therapy planning and for monitoring the treatment response during ongoing systemic therapy in metastatic disease.

Situation [3]. The results of several studies support the use of PSMA-PET/CT for radiotherapy planning, as it achieves higher specificity and sensitivity than the combination of CT and whole-body bone scintigraphy [19, 21, 28]. PSMA-PET/CT is also approved for assessing treatment response to systemic therapy, as is the case in the patient cohort studied here. The RECIP criteria have been validated as a standardized evaluation method for assessing response to radioligand therapy in the polymetastatic setting.

Procedure and specific risks: During a PET/CT scan, a radioactive tracer that selectively binds to PSMA and can therefore identify prostate cancer cell metastases with high specificity is injected. The scan lasts a maximum of two to three hours, during which the patient should lie still in the scanner. Specific risks for the patient, which occur rarely to very rarely, include local vein injury with hematoma formation due to phlebotomy when establishing venous access, infections at the injection site, allergic reaction to the tracer and/or contrast agent, general skin, tissue, or nerve damage due to positioning and immobilization, extravasation of the tracer with local tissue reaction, panic attack in patients with claustrophobia, and deterioration of kidney function and triggering of hyperthyroidism due to CT contrast agents. During a PET/MRI scan, exposure to the magnetic field can, in rare cases, cause overheating, headaches,

Ringing in the ears or tinnitus may occur. MRI scans should not be performed on patients with a pacemaker or other contraindications to an MRI examination.

Benefits of PSMA-PET/CT: PSMA-PET/CT enables the specific identification of prostate cancer metastases. It is superior to a combination of whole-body CT and whole-body scintigraphy in terms of specificity and sensitivity. This ensures the precise identification of metastases that can be treated with local ablative therapy. Furthermore, PET/CT provides additional diagnostic information that supports radiation therapy planning and, particularly in stereotactic radiotherapy, allows for more precise target volume definition. This typically allows the radiation volume to be reduced, thereby minimizing the risk of side effects. In monitoring disease progression during ongoing systemic therapy and assessing treatment response, PSMA-PET/CT offers important information about the location of metabolically active lesions and the response to treatment at the lesion level, compared to PSA levels alone, which can indicate disease activity.

4.3.2 Radiation therapy of the prostate and metastases:

Planned therapy: The first radiation therapy is planned to be ultrahypofractionated prostate irradiation with 5 x 7.5 Gy on alternating days, analogous to the PACE-B trial [26], but without dose escalation to the CTV. Alternatively, if ultrahypofractionation is not possible (e.g., due to organ-risk exposure), moderate hypofractionated prostate irradiation with 20 x 3.0 Gy, analogous to the CHHiP trial [27], 20 x 2.75 Gy, or 6 x 6 Gy, analogous to STAMPEDE, can be performed.

Six months after radiation therapy to the prostate (calculated from the first day of radiation therapy), an ablative Radiation therapy for residual metabolically active metastases, preferably as stereotactic

Radiation therapy according to departmental standard (e.g., 3 x 10 Gy, 5 x 6 Gy) is planned. Alternatively, radiation therapy according to departmental standard can be performed moderately hypofractionated or normofractionated.

Procedure: In preparation for radiation therapy, an informational consultation is conducted, followed by a planning CT and planning MRI scan without contrast agent for treatment planning (two appointments on different days). After these preparatory examinations, radiation therapy is scheduled to begin within a maximum of 10 working days; in the meantime, treatment planning is carried out according to study guidelines.

Ultrahypofractionated prostate radiation therapy is performed under MRI guidance using an MRI/linear accelerator hybrid system, which allows for more precise soft tissue imaging than CT-guided radiation therapy. Furthermore, online adaptation of the treatment plan to the current anatomical conditions and monitoring of organ movement during radiation are possible. This allows for more precise determination of the position of organs at risk and adaptation to enable the selection of smaller safety margins (compensating for motion uncertainty as well as intra- and interfractional positioning uncertainty). This results in a lower dose to organs at risk and thus a reduction in long-term side effects. Imaging, plan adjustment, and radiation delivery take place over approximately 30 minutes.

45 minutes per radiation treatment. A total of 5 treatments of 7.25 Gy each are planned on alternating days, corresponding to a very short total treatment time of 2 weeks.

If MR-guided ultra-hypofractionated radiotherapy of the prostate is not possible, moderately hypofractionated radiotherapy with 20 x 3.0 Gy fractions or according to departmental standards (e.g., 6 x 6.0 Gy analogous to the STAMPEDE trial) can be performed. Due to the lower fractional dose, this is administered as CT-guided IGRT with daily cone-beam CT monitoring and a treatment duration of 10–20 minutes. The radiotherapy is administered daily on weekdays, corresponding to a total treatment duration of four weeks.

The treatment planning for metastases is carried out analogously (CT-guided radiation therapy; MRI-guided radiation therapy is also possible for lymph node metastases); two appointments are scheduled for patient education and treatment planning. If possible, metastases should be treated stereotactically with 3-5 treatment sessions. There are no dose or fractionation guidelines; the prescription for metastases is based on the department's internal standard. If stereotactic radiation therapy is not possible due to normal tissue tolerance, normofractionation is performed.

Specific side effects of radiation therapy: In preparation for each radiation fraction, it is important to adhere to a fluid intake protocol with a target bladder volume of 200-250 mL for the radiation treatment. If the rectal ampulla is very full, an enema should be administered. During the MRI examination (for radiation planning/radiation), in rare cases, overheating, ringing in the ears, and tinnitus may occur. In very rare cases, hearing damage may occur if hearing protection is not fitted correctly, or headaches may develop.
Patients with a pacemaker or other contraindications to an MRI examination should not undergo an MRI scan.

The possible acute and long-term side effects correspond to the general side effects of radiation therapy to the pelvic region: pollakiuria, irritation of the bladder and/or urethra with irritation during urination. In the long term, a slight increase in urinary frequency and softer stool consistency may occur. Rarely, a slight deterioration in continence, more frequent urge to defecate with the occurrence of diarrhea or rectal mucus discharge may occur. In very rare cases, rectal bleeding, urinary retention with the possible need for the use of alpha-blockers with specific side effects or the need for indwelling catheterization, urethral stenosis, and, in extremely rare cases, the formation of a fistula or necrosis of the intestinal mucosa, requiring endoscopic or surgical intervention, may occur. The induction of a second malignancy cannot be ruled out (incidence of 1:100 to 1:1000 after 10 to 30 years), however, this already low risk is negligible in light of the polymetastatic prostate cancer disease.

Specific burdens of metastasis radiotherapy: Radiotherapy of metastases is associated with additional time commitment for appointments (3-5 for stereotactic radiotherapy; up to 25 for normofractionated radiotherapy). Depending on the number of metastases being treated, the duration of each radiotherapy session can be up to one hour. Depending on the location of the metastases, corresponding side effects from the radiotherapy may occur; however, the normal tissue constraints are chosen so that the risk of long-term side effects is 1-2%, and the focus is on maximum sparing of normal tissue. Furthermore, only metabolically active and therefore therapy-resistant metastases are treated, where further growth and thus potential complications due to local progression would be expected if no local radiotherapy or a change in systemic therapy were performed.

Benefit of the therapy (radiation of the prostate and metastases): The planned short-term ablative radiation therapy of metabolically active lesions, with a favorable side effect profile, aims to eliminate system therapy-resistant tumor cells in oligoresidual disease with a poor oncological prognosis. It is assumed that resistance to system therapy is driven by these resistant tumor cells. The targeted elimination of these therapy-resistant tumor cells should delay the development of resistance to system therapy, thereby extending progression-free survival and ultimately overall survival.

4.3.3 Accompanying examinations:

Planned measures: These will take place at the time of study enrollment/before the start of radiation therapy, in parallel with radiation therapy, at the time of completion of radiation therapy and during the follow-up.
Study visits.

Implementation: Follow-up visits are planned for the following times:
1. Pre-therapeutic for study inclusion and status assessment before the start of therapy (radiation of the prostate and metastases); six (up to a maximum of 9 months) after initiation of systemic therapy with evidence of a PSA value of >0.2 ng/ml.

2. At the time of completion of therapy (radiation of the prostate and metastases).
3rd month 1, 3, 6, 9, 12, 15, 18, 21 and 24 after study enrollment.

4. Subsequently, follow-up examinations are conducted as personal visits every 3 months to 18 months after completion of metastasis-directed therapy to record PSA levels, quality of life and to inquire about possible side effects.

Specific burdens: Attending study visits involves a time commitment, including travel to and from the study center and the visit itself, which lasts approximately 30-45 minutes. If the PSA level is checked in the patient's outpatient setting at the time of visits not related to the discussion of PSMA-PET findings, the questionnaires can be sent by mail. In this case, approximately 30 minutes should be allocated for completing the questionnaires per visit. The PSA level is checked via blood draw, which involves venipuncture. Theoretically, this procedure carries a risk of bleeding, infection, or tissue injury. However, blood draws with PSA level checks every 3 months are already part of routine urological therapy monitoring and are not an additional measure within the study.

Benefit: Regular study visits ensure close monitoring with consistent, frequent check-ups of PSA levels, a surrogate parameter for cancer progression. If PSA levels rise, appropriate diagnostic procedures can be initiated immediately, and any new findings can be investigated and treated. Medical consultations and assessments of quality of life allow for the initiation of appropriate therapy in cases of quality of life limitations or the occurrence of side effects. Furthermore, patients have reported that they appreciate and value a consistent connection to their treatment center.

4.4 Sample Size Estimation and Recruitment Period

Based on existing publications regarding PSA response to complete androgen blockade and irradiation of bone metastases, a radiological response after RECIP with a PSMA volume reduction of at least 30% is expected to be achieved in 40% of patients through the study intervention. If the success rate remains below 15%, it is assumed that the therapy provides no benefit. The study hypothesis will be rejected with a sample size of 27 patients (power of 90%, one-sided significance level ÿ=0.05) if >5/27 patients do not show a response after RECIP 12 months following metastasis-directed therapy.

At the urological center in Tübingen, approximately one patient per week with a new diagnosis of primary bone metastases in prostate cancer is presented to the tumor board. Considering the expected inadequate treatment response in approximately 20-30% of cases and adhering to the inclusion and exclusion criteria, a realistic number of 5-10 patients per center could be enrolled within one year. Therefore, a recruitment period of 12 months was chosen for the target of 6 centers.

4.5 Participating trial centers and investigators

The study will be conducted as a multicenter trial. A collaboration with Ludwig Maximilian University of Munich already exists; collaborations with the following study centers are planned: University Hospital Freiburg, University Hospital Augsburg, Carl Gustav Carus University

Dresden and the University Hospital of Cologne. A principal investigator and a deputy will be appointed for each site. The study protocol presented here will be submitted to the ethics committees of the cooperating centers as soon as an unconditional ethics opinion has been received from the Ethics Committee of the Medical Faculty of Tübingen. Patient recruitment will take place at the respective sites after a positive ethics opinion from the local ethics committee.

5. Patient selection

5.1 Recruitment

Patients for the study are referred to the outpatient clinic of the University Hospital for Urology, the urological tumor board, and their primary treating urologists to the outpatient clinic of the University Hospital for Radiation Oncology (or the cooperating radiation therapy centers) for an initial consultation and screening for potential study participation. During this consultation, patients are first informed about the guideline-based therapy – i.e., monotherapy with MDT in the event of symptoms (pain, risk of postural instability, etc.). All patients of the University Hospital for Radiation Oncology in Tübingen who meet the inclusion criteria are offered participation in the study.

The procedure, possible additional burdens caused by radiation therapy, any side effects, and the potential benefits for the patient are explained in detail.

It is specifically pointed out that participation in the study is voluntary and that consent can be withdrawn at any time before or after therapy. However, for radiobiological reasons, radiation therapy should ideally not be interrupted once started; this is possible, however, if the patient explicitly requests it after receiving appropriate information. It is also emphasized that guideline-compliant follow-up care and any potential re-irradiation in the event of symptomatic metastasis would be affected by a possible discontinuation of the RIALTO study.

becomes.

5.2 Inclusion criteria

- Present declaration of consent
- ECOG 0-2
- Ages 18-85
- Acinar adenocarcinoma of the prostate, histologically confirmed
- De novo oligo-/polymetastatic prostate cancer (min. 4 bone metastases) without Visceral and lymph node metastases are possible.
- First-line therapy with antihormonal therapy (AHT) + X (X = e.g., enzalutamide / abiraterone / apalutamide, etc.) according to urological guidelines as per S3 guideline for at least 6 months
- Present staging at the time of ED with multimetastasis, but exclusion of visceral metastases
- PSA not below the threshold of 0.2 ng/ml after 6 months of systemic therapy sunk
- ÿ 15 active osseous lesions in response assessment using PSMA-PET/CT after 6 months Systemic therapy

5.3 Exclusion criteria

- PSA after at least 6 months of systemic therapy < 0.2 ng/ml
- M1c (visceral metastases)
- other active tumor disease in the last 2 years (except basal cell carcinoma of the skin/melanoma in remission)

- Zn TUR-P or HIFU less than 6 months before RT start, Zn surgical resection of the prostate
- Pre-irradiation in the pelvic area
- Serious pre-existing conditions affecting the bladder or rectum (e.g., active fistula, chronic inflammatory bowel disease)

- Presence of a tumor predisposition syndrome
- serious pre-existing urological conditions
- Contraindications to performing a PSMA-PET/CT scan
- Contraindications to performing radiation therapy
- Pre-irradiation, which prevents ablative irradiation of the metastases
- In T4 stage: Persistent infiltration of the rectal mucosa after 6 months

  Systemic therapy; critical evaluation in case of bladder infiltration
- Rising PSA level: Indication to change systemic therapy or initiate a

  Chemotherapy before the start of the study

5.4 Necessary examinations and management prior to study enrollment:

- Histological confirmation of the tumor, preferably with Gleason score classification and indication of positive core needle biopsies (%); histological confirmation from a metastasis is possible, but not necessary.

- PSA level at the time of initial diagnosis and 6 months after initiation of combined therapy

  Systemic therapy at the time of study screening
- Imaging evidence of bone metastases at the time of initial diagnosis (preferably whole-body CT + whole-body bone scintigraphy, but at least one of the two examinations mentioned); optionally, a PSMA-PET/CT or PET/MRI may also have been performed at the time of initial diagnosis (if a PET/CT or PET/MRI was performed, a bone scintigraphy is not required)

- If any prior radiation therapy records exist, radiation therapy outside the pelvis should have been performed that is not related to the prostate cancer

  (Exception: radiation-induced gynecomastia prophylaxis during initiation of long-term ADT)
- Physical examination
- Documentation of the combined systemic therapy performed to date
- Contact and consultation with the primary treating urologist
- Tumor board decision
- Bone metastases that threaten structural stability, neurological deficits due to metastasis, stabilization of bone metastases by the introduction of

  metal

5.5 Patient discharge

Patients included in the study can withdraw from the study at any time at their own request and without giving reasons, and without affecting any future treatment or regular follow-up care after radiation therapy.

Exclusion from the study may occur at the discretion of the study physician for reasons of health risk (for example, if a serious comorbidity is present or if the planned radiation therapy is not possible due to prior radiation treatment). In the event of withdrawal from the study, the reason will be documented in the respective patient file and in the eCRF (CRF Drop-Out).

All patients who prematurely withdraw from the study after having already undergone a study intervention should receive a final examination immediately upon withdrawal, which should be documented in the eCRF (CRF Follow-Up). Furthermore, they should be offered a connection to the center as part of their regular radiotherapy follow-up care.

If consent to participate in the study is withdrawn, no further clinical data will be collected and no further study visits will be conducted. If a study intervention has already taken place, continued contact with the center for routine follow-up care after radiotherapy will be offered; no study data will be collected during this follow-up, only routine radiotherapy follow-up care will be provided. All data collected up to this point will be anonymized immediately, unless a request for complete data deletion is received. Treatment plans for treatments already administered within the study must be retained for 30 years in accordance with radiation protection regulations.

A cancellation of the planned study measures may become necessary for the following reasons:

- Disease progression necessitating the initiation of chemotherapy (e.g. Occurrence of visceral metastasis).
- Deterioration of general health, which precludes the continuation of the planned Measures prevented.
- An increase or doubling of the PSA level compared to baseline that is not attributable to a lesion requiring local therapy and necessitates a change in systemic therapy. If PSA progression according to Phoenix criteria is present, the next scheduled PSMA-PET scan is prioritized, and if isolated metastases are found, stereotactic radiotherapy is performed again. In cases of diffuse progression or the presence of visceral metastases, the therapy is adjusted according to the tumor board of the respective center. • An increase in metabolically active lesions on PSMA imaging to a degree that

  prevents the implementation of local therapeutic measures.
- Acute toxicity CTCAE grade 4, showing no improvement. • PSA doubling time < 6 months without imaging correlation.

If PSA levels rise during follow-up visits, the planned PSMA-PET/CT imaging for diagnostic purposes should be brought forward, and the study outpatient clinic should be consulted to determine whether newly occurring lesions should be treated with further local therapy.

5.6 Analysis of possible unforeseen severe side effects

An interim analysis to evaluate potential high-grade side effects 30 days after completion of radiation therapy is planned once a minimum of 9 patients have been enrolled (30 days after radiation therapy to the prostate and 30 days after radiation therapy to metastases). If there is a significantly increased number of CTCAE 3 adverse events (>25%), the course of the adverse events will be monitored after 90 days (assessment by two clinically experienced specialists from the study center); at this time, a resolution of acute post-radiation adverse events is expected. The study will continue if, 90 days after completion of radiation therapy, there is a significant improvement (to a maximum of CTCAE 2) in the acute adverse events in the majority of patients. If CTCAE 4 or CTCAE 5 toxicity occurs, patient recruitment will be stopped and a safety analysis will be conducted.
The study will only be resumed if a connection between the radiation therapy (SBRT of the prostate and metastases) and the toxicity that occurred can be ruled out.

5.7 Interruption and termination of the study

If a grade 3 or higher adverse event occurs, radiation therapy will be paused and appropriate supportive care initiated. The study team will be informed immediately, and the principal investigator will be consulted regarding the possible continuation of radiation therapy.

Should a grade 4 toxicity occur during treatment within the study, irrespective of the planned interim analysis regarding adverse events, and which cannot be controlled with supportive measures, then the study intervention must be interrupted until the observed toxicity subsides. The toxicity must be documented as a serious adverse event (SAE). The principal investigator is entitled to terminate the clinical trial prematurely for relevant medical/administrative reasons if

- Serious, irreversible adverse events (toxicity grade 4 or 5) occur that are clearly related to the study intervention under investigation (i.e., radiation of the prostate and metastases).

- the targeted patient recruitment does not take place within a reasonable timeframe • the research question under investigation becomes obsolete during the study due to new scientific findings and no longer serves the scientific purpose

  should meet the standard
- serious data quality problems should occur that cannot be resolved
  can
- unforeseen circumstances arise at the individual center that prevent the continuation of the
  Do not allow clinical trial
- in the event of relevant and serious violations of the study protocol
- Compliance with legal or ethical regulations cannot be guaranteed
  can.

The reasons for discontinuing the study will be documented in detail. Patients still undergoing treatment at the time of discontinuation will receive a final examination, which will be documented in the eCRF. If a study physician raises ethical concerns regarding the continuation of the study, these concerns must be reported to the principal investigator immediately. The principal investigator, in consultation with the co-principals, will decide on the discontinuation of the study.

5.8 Patient Registration

Patients are registered after receiving information and giving their informed consent to participate in the study. Their data is then pseudonymized, and prospectively documented on standardized data collection forms (eCRF - REDCap). Once a patient has been enrolled in the study, they must provide feedback to the study center in Tübingen within 24 hours so that central registration can be completed.

6. Guidelines for radiotherapy

6.1 Specifications for systemic therapy (antihormonal therapy according to guidelines)

In accordance with the S3 guideline, the initiation of systemic antihormonal therapy is started six months prior to study screening by the treating urologists (either at a center or in private practice). This involves complete androgen blockade through a combination of ADT and NHT (e.g., apalutamide, enzalutamide, or others, as determined by the primary treating urologist). The choice of drug and NHT is determined by the tumor board or the primary treating urologist, in accordance with the S3 guideline. This is the standard therapy and not part of the study protocol presented here. When initiating long-term hormone therapy, each patient is offered radiation gynecomastia prophylaxis according to departmental standards. Systemic therapy should be initiated at least six months prior to study enrollment and the PSMA-PET/CT scan.

If the PSA level does not fall completely to <0.2 ng/ml and thus the study inclusion criteria are met, systemic therapy will be continued until a significant PSA increase occurs (doubling of the baseline value or PSA doubling time of < 6 months).

6.2 Guidelines for radiotherapy

The study involves irradiation using two irradiation schemes.
planned (the applied scheme is recorded in the CRF):

1) Radiation therapy of the prostate

- 5 x 7.25 Gy up to a total dose of 36.25 Gy (MRI-guided on the MR-Linac once daily, 2-3 days per week)
- If the conditions for ultra-hypofractionated radiation therapy (MR-guided radiation therapy) are not guaranteed at the respective center, radiation therapy can be performed according to the respective departmental standard, e.g. analogous to the STAMPEDE study with e.g. 6 x 6.0 Gy or moderately hypofractionated analogous to the CHHiP protocol with 20 x 3.0 Gy up to a total dose of 60.0 Gy.

2) Radiation therapy for bone and lymph node metastases

- Analogous to department-internal standard, e.g. 3 x 9.0-10.0 Gy or 5 x 6.0-7.0 Gy at
  Lymph nodes (bulks) (once daily, 2-3 days per week)
- Alternatively, in cases of multiple lesions or large central venous extent, fractionation with, for example, [methods] is possible.
  5 x 6.0 Gy, dosed to the 80% isodose, is recommended.
- If stereotactic radiotherapy of the metastases is not possible due to anatomical proximity to OARs, metastasis size, or proximity to any previous irradiations, moderately hypofractionated radiotherapy of the metastases can be performed according to an established standard of the respective center.

The decision regarding the fractionation scheme rests with the treating center and its established standard. SBRT (e.g., 3 x 9.0–10.0 Gy) should be preferred over moderate hypofractionation. Whether this is feasible is determined based on the anatomical location, the size of the metastases, any potential risk to the patient's statics, and the expected normal tissue exposure. Stereotactic radiotherapy is only possible if the limits for organs at risk are not exceeded (see Section 6.3 Treatment Planning).

The radiation therapy should be administered as IMRT with daily IGRT.

6.3 Radiation therapy planning

6.3.1 Planning CT

Radiation therapy planning is performed using a planning CT scan, which is carried out in a reproducible patient position. For this purpose, moderate bladder filling and a rectum that is as empty as possible should be ensured for prostate radiation planning. The scan area for prostate radiation should extend caudally to the lesser tubercle and encompass the entire pelvis up to the cranial border of L2/3.

Depending on clinical necessity, individual aids can be adapted – particularly for planning the radiation therapy of metastases (vacuum mattress, abdominal belt, respiratory gating, custom mask). The slice thickness should be 1 mm for planning prostate radiation therapy and 1–2 mm for radiation therapy of metastases. For prostate radiation therapy, depending on the established workflow at the respective center, MRI-guided treatment planning can also be performed.

6.3.2 Treatment planning

All radiation treatment plans applied within the study and the PSMA-PET/CT or PSMA-PET/MRI images used for treatment planning are transmitted and stored electronically in pseudonymized form in the database at the study center. The evaluation of the PSMA-PET/CT scans according to RECIP criteria or PROMISE V2 is performed centrally by the Department of Nuclear Medicine Tübingen.

6.3.3 Planning prerequisites

For radiation therapy planning, pre-therapeutic diagnostics should be rigorously documented. If possible, the PSMA-PET data should be loaded into the radiation therapy planning system. Radiation therapy planning is performed using the planning system established at the respective location. For target volumes that move with respiration, radiation therapy planning is based on a 4D CT scan or a CT scan with respiratory gating, according to the respective center's established standard.

6.3.4 Documentation of irradiation parameters

The documentation of the irradiation parameters is done in the eCRF using REDCap.

6.4 Organs at Risk In

principle, all organs that are clearly distinguishable and located in anatomical relation to the target volume (distance to the PTV border <5 cm) should be contoured as organs at risk (OARs).

6.4.1 Pelvic organs at risk during prostate irradiation

The following OARs should be contoured for planning prostate radiation therapy:

OAR	**CT/MRI**	**definition**
bubble	CT/MRI	Bladder in CT scan (including outer wall)
rectum	CT/MRI	Analog RTOG (starting from the lowest level of the ischial tuberosity, cranial end in the region of the rectosigmoid junction, penile bulb (part of the
Bulbus	CT/MRI (T2w)	spongiosum bulb) under the urogenital diaphragm [29] best visualized in mpMRI (T2w)
right femoral head	CT	Right femoral head
left femoral head	CT	Left femoral head
pubis	CT	symphysis and pubic bone
Colon	CT	Contour the colon, provided the colon is 2cm above the The highest axial PTV layer is included
Small intestine	CT scan, possibly with MRI	Contour the small intestine if the small intestine is contained 2 cm above the highest axial PTV layer.
urethra	MRI (T2w)	Prostatic urethra from the upper surface of the urethra bulb to the junction with the prostate gland and its opening into the bladder (in mpMRI)

* in anatomical positional relationships

6.4.2 Organs at risk during radiotherapy for metastases

The following organs, considered at risk for planning metastasis radiation therapy, should be contoured using CT scans based on their anatomical relationship (as shown):

- Entire bone affected by metastasis; adjacent bones • In the case of vertebral body metastases: Separately, vertebral body and vertebral arch
- Brain
- Cerebellum
- Pituitary gland
- Right and left eye
- Right and left lacrimal glands
- right and left optic nerve
- Chiasma
- right and left inner ear

- Brainstem
- Spinal cord
- Brachial plexus and sacral plexus
- Thyroid gland
- Trachea
- Right and left lungs
- Right and left main bronchus
- Aorta, vena cava, pulmonary artery and vein
- Heart
- Esophagus
- Stomach
- Duodenum
- Liver (entire body) •

Colon

- Pancreas
- Right and left kidney
- Right and left ureter
- Rectum
- Bladder
- Left and right femoral head

6.5 Image-guided radiotherapy

Since SBRT is being performed, daily imaging should be carried out before each fraction delivery, using the best available image guidance (ideally cone-beam CT). For prostate irradiation, daily image guidance is performed using cone-beam CT or MRI. Deviations from the isocenter greater than 0.5 mm are corrected by repositioning the treatment table.

6.6 Target volume definition

6.6.1 Target volume definition for ultrahypofractionated prostate irradiation:

The target volume definition for ultrahypofractionated radiotherapy of the prostate is analogous to the PACE-B study, taking into account the current recommendation of ESTRO-ACROP [30].

Clinical target volume (CTV)

CTV_3625	Prostate + any extracapsular tumor
CTV_3000*	CTV_3625 plus seminal vesicles

* if T3b or T4 stage with seminal vesicle involvement

Planning target volume (PTV)

PTV_3625	CTV_3625 + 3 mm all around
PTV_3000	(CTV_3625 + CTV_3000) + 3 mm on all sides

6.6.2 Target volume definition for moderately hypofractionated radiotherapy of the prostate:

The target volume definition for moderately hypofractionated radiotherapy of the prostate is analogous to the CHHiP trial, taking into account the current ESTRO-ACROP recommendation [27, 30]. If radiotherapy is chosen according to the respective departmental standard (e.g., analogous to the STAMPEDE study), the prescriptions and dose constraints of the respective department apply.

Clinical target volume (CTV)

CTV_6000	Prostate + any extracapsular tumor
CTV_5700+SB*	CTV_6000 + SB

* if T3b or T4 stage with seminal vesicle involvement

Planning target volume (PTV)

PTV_6000	CTV_6000 + 6 mm/5 mm dorsal (rectum)
PTV_5700+SB*	(CTV_6000 + SB) + 6mm/5 mm dorsally (rectum)

In the RIALTO study – unlike the CHHiP trial, which used 3D conformal radiation therapy with three weekly position checks based on the bony structures of the pelvis – IGRT with daily verification (CBCT with prostate position check) and the prescription of normal tissue constraints as part of IMRT. Therefore, bowel distension staging analogous to CHHiP is not required for radiation therapy in the present study, as the settings are verified daily and adjusted based on IGRT position.

6.6.3 Target volume definition for stereotactic radiotherapy of metastases:

Pre-therapeutic imaging (at least CT of the PSMA-PET/CT, and if possible also PET) should be fused with the planning CT for target volume definition. Target volume definition is performed according to the recommendations of ICRU Report 62 [31], the ESTRO guideline for stereotactic radiotherapy of spinal metastases [32], the consensus guidelines for postoperative radiotherapy of spinal metastases, and the recommendations for target volume definition for stereotactic radiotherapy of non-spinal bone metastases [33]. Metastases requiring postoperative radiotherapy or those stabilized with metal will be treated outside the study protocol according to departmental standard.

GTV_X*	Extent of metastasis on CT scan (+/- PET)
CTV_X*	GTV + 2 mm all around; adaptation to anatomical boundaries
PTV_X*	CTV + 3 mm all around to compensate for movement and intra-/interfractional positioning uncertainty; if necessary, adaptation of the margin according to proximity to risk structures or possibility of intrafractional position control (center-specific)

*Name the target volume according to its anatomical location, e.g., 5th rib_right

6.6.4 Target volume definition for moderately hypofractionated/normofractionated metastasis radiotherapy

If stereotactic radiotherapy is not possible due to the size of the tumor or its anatomical proximity to risk structures, moderately hypofractionated or normofractionated radiotherapy can be performed according to departmental standards. Pre-therapeutic imaging (at least CT or PSMA-PET/CT, 28

If possible, PET should be fused with the planning CT scan for target volume definition. Target volume definition is performed according to the recommendations of ICRU Report 62 [31]. A BED of 100 Gy should be achieved if possible. Deviations should be documented in the CRF.

GTV_X*	Extent of metastasis on CT scan (+/- PET)
CTV_X*	GTV + 3 mm all around; adaptation to anatomical boundaries
PTV_X*	CTV + 3-7 mm all around (depending on departmental standard and method of position control) to compensate for movement and intra-/interfractional storage uncertainty; margin adjustment if necessary. proximity to risk structures

6.7 Dosage prescription and dose limits

6.7.1 Dosage Prescription

Target volume	**Dose prescription**
Prostate UHF	PTV_3625: 36.25 Gy in 7 Gy per fraction; D98% (PTV_3625) ÿ 33.25 Gy, D99% (CTV_3625) ÿ 34.5 Gy; D50% ÿ 35 Gy PTV_3000: 30 Gy in 6 Gy per fraction; D98% (PTV_3000) ÿ 28.5 Gy; D99% (CTV_3000) ÿ 28.5 Gy; D50% ÿ 30 Gy
Prostate MHF	PTV_6000: 60 Gy in 3 Gy per fraction; D99% (PTV_6000) ÿ 5 Gy, D98% (CTV_6000) ÿ 57 Gy; D1% ÿ 63 Gy; D50 = 60 Gy + 1% PTV_5700: 57 Gy in 2.85 Gy per fraction; D98% (PTV_5700) ÿ 51.3 Gy, D98% (CTV_5700) ÿ 54.15 Gy
Metastases SBRT	PTV min. 80% of the prescribed dose. GTV recorded at min. 95% of the prescribed dose; the maximum should be 120%. The prescribed dose should not be exceeded.
Metastases NF or MHF PTV D98% -	90% of the prescribed dose, D2% <107%, CTV D98% - 95% of the prescribed dose, D2% < 110%. Global maximum <115%.

6.7.2 Normal tissue constraints for ultrahypofractionated prostate radiotherapy:

The irradiation regimen used in this study is derived from the PACE-B trial, which involved fractionation of 5 x 7.25 Gy up to a total dose of 36.25 Gy (however, with a boost to the prostate (=CTV) of 5 x 8.0 Gy up to a total dose of 40.0 Gy, [26]. The dose prescription and normal tissue constraints were therefore adopted from the PACE-B trial. Since no intraprostatic boost is applied in our study, a lower dose to normal tissues is expected compared to the PACE-B trial [26, 34].

Risk body	**Normal tissue constraints**
rectum	V18.1 Gy < 50%, V 29 Gy < 20%, V 36% < 1cc, V 38.5 Gy < 0.2cc
bubble	V 18.1 Gy < 40%, V 37 Gy < 10 cc, optimum: V 37 Gy < 5 cc
Small intestine	V 18.1 Gy < 5cc, V 30 Gy < 0.01 cc
Urethra (Pars prostatica)	Avoidance of central hotspots, Dmax <37.5 Gy, D50% <36 Gy
PRV Urethra	urethra + 2 mm; D0.1cc < 41 Gy; D0.2cc < 37.5 Gy
Femoral heads	V 14.5 Gy < 5%
Bulbus penis	V 29.5 < 50%

Adapted and modified from [26].

6.7.3 Normal tissue constraints for moderately hypofractionated radiotherapy of the prostate:

The irradiation regimen used in this study is based on the CHHiP trial, in which fractionation of 20 x 3.0 Gy up to a total dose of 60.0 Gy was performed [27]. The dose prescription and normal tissue constraints were therefore taken from the constraints of the CHHiP trial [35, 36].

Risk body	**Normal tissue constraints** V60
rectum	Gy ÿ 0.01%, V57 Gy ÿ 15%, V40 ÿ 60%; Circumference Dmax <30 Gy
bubble	V60 ÿ 5%, V48 ÿ25%, V40 ÿ 50%
Small intestine	V0.01 cm³ < 52.7 Gy
Urethra (Pars prostatica)	V40 ÿ 50%, Dmax 61 Gy
Femoral heads	V40 ÿ 50%
Bulbus penis	V40 ÿ 50%

Adapted and modified from [35].

6.7.4 Normal tissue constraints for SBRT of metastases

The constraints for stereotactic radiotherapy are based on the guidelines for normal tissue exposure in stereotactic procedures and depend on the dose per fraction. Therefore, radiotherapy within the study is performed according to the standard of the respective site.

6.7.5 Normal tissue constraints for normofractionated/moderately hypofractionated radiotherapy of metastases

For moderately hypofractionated and normofractionated radiotherapy, department-specific standards also exist, which are based on volume, location, and possible pre-existing conditions and which must be adhered to when irradiating metastases.

Deviations
should be recorded in the eCRF.

7. Clinical examinations (visits)

7.1 Overview of the accompanying investigations

The following CRF plan, Fig. 2, provides an overview of the accompanying investigations (study visits, PSA follow-up, QoL questionnaires, toxicity assessment, etc.):

	ADT + ARPI	PSMA-PET/CT	Therapie	Follow-Up												
Studienvisite	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
				1 Mo.	3 Mo.	6 Mo.	9 Mo.	12 Mo.	15 Mo.	18 Mo.	21 Mo.	24 Mo.	27 Mo.	30 Mo.	33 Mo.	36 Mo.
Intervention			SBRT Prostata			SBRT Met.										
Prüfung Ein- und Ausschlusskriterien		x														
Aufklärung und Einverständnis		x														
Registrierung		x														
Patientendatendokumentation		x														
Erhebung PSA-Wert	x	x		x	x	x	x	x	x	x	x	x	x	x	x	x
PSMA-PET/CT		x				x				x						
Dokumentation Lebensqualität		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dokumentation Nebenwirkungen			x	x	x	x	x	x	x	x	x	x	x	x	x	x

Fig. 2: Schedule of study-specific examinations. Study visits take place at the beginning of the radiation therapy, during the radiation therapy itself, and at the end of the radiation therapy.

7.2 Study visits conducted

Specifically, the following parameters will be collected:

1) Examination at study enrollment: PSA level (current and trend), biopsies, staging examinations performed, and previously initiated systemic therapy. Assessment of baseline symptoms according to CTCAE v.5, EPIC, IPSS, and IIEF-5, as well as completion of the quality-of-life questionnaires (EORTC QLQ-C30, QLQ-PR25, and EQ-D5). Performance of a PSMA-PET/CT scan.
2) Weekly regular doctor consultations will be conducted concurrently with radiation therapy. At the start and end of radiation therapy, side effects will be assessed according to CTCAE v.5, EPIC-26, IPSS and IIEF-5, as well as quality of life (patient-reported: EORTC QLQ-C30 Prostate, QLQ-PR25, EQ-D5).

3) PSA levels should be monitored every 3 months via blood test until 30 months after completion of the last radiotherapy for metastases. This can be done at the center or in an outpatient setting, but due to potentially different underlying testing methods, it should preferably always be performed by the same provider, i.e., either at the center during the study visit or by the treating urologist/general practitioner.

   In addition, quality of life (patient-reported: EORTC QLQ-C30 prostate, QLQ-PR25, EQ-D5) and possible side effects according to CTCAE v.5, EPIC-26, IPSS and IIEF-5 are recorded quarterly.

7.3. PSMA-PET/CT

At study enrollment, a PSMA-PET/CT scan is performed to identify metabolically active lesions and for radiotherapy planning. The PSMA-PET/CT scan is evaluated using standardized criteria based on RECIP [21] or PROMISE V2 [22]. Six months after prostate irradiation, metabolically active lesions are again identified using PSMA-PET/CT. The imaging response after prostate irradiation and of metabolically active metastases is monitored with a repeat PSMA-PET/CT scan 18 months after completion of prostate irradiation. If the PSA levels rise above 2 ng/ml or the PSA doubling time is less than 6 months, this PSMA-PET/CT scan is performed earlier. If individual metastases suitable for radiotherapy are identified, they are treated according to the study protocol.

8. Biometrics

8.1 Data Management The data

collected for the studies (patient and disease-related data, imaging and laboratory data, radiation treatment planning parameters) are recorded and processed electronically (eCRFs – REDCap). In the event of withdrawal from the study, the data already collected may be used for analysis unless an explicit revocation of consent has been received.

All patient data is collected pseudonymously. Each patient is assigned an individual identification number, and only the participating personnel at the study center have access.

The list containing the mapping of full names to identification numbers is stored. This list is treated with strict confidentiality and retained for 10 years after the study's completion. All data entered into the database is pseudonymized. The completed PSMA-PET/CT scans and radiation treatment plans are also sent pseudonymized to the study center in Tübingen.

The principal investigators at each site are obligated to ensure compliance with legal and radiation protection regulations during the study and to uphold the principles of good scientific and clinical practice. Furthermore, they must ensure the correct and complete entry of data into the eCRFs.

The data collected as part of the study must be entered into the eCRFs by authorized and designated personnel. Authorization for this is granted after appropriate training and a written agreement and designation in the Delegation Log. Only trained, registered, and authorized personnel will have access to the eCRF database.

The data in the RED-Cap database are subjected to queries so that the persons responsible for the database at the study center (study nurse or study physician) can check the entries for discrepancies and correct them if necessary.

8.2 Evaluation Populations

Statistical analysis is planned according to intent-to-treat (ITT) and per-protocol (PP) data. **The intent-to-treat population** comprises all patients enrolled in the study who received at least one treatment and for whom some data (baseline questionnaires) are available. The **per-protocol population** comprises all patients in whom the planned therapy was fully completed according to the study protocol and for whom all relevant data are complete and documented.

8.3 Statistical Analysis

All planned analyses will be performed for both the ITT and PP populations. A descriptive analysis of the primary and secondary endpoints will be conducted by determining relevant statistical parameters (including mean, median, standard deviation, minimum, maximum, absolute and relative frequencies, qualitative assessment of quality of life and side effects) and calculating the corresponding 95% confidence intervals. Furthermore, a descriptive analysis of the radiation treatment plans is planned. Endpoints collected at different time points (including side effects, quality of life, and PSA levels) will be described for each time point, and their temporal progression will be visualized graphically.

For endpoints that represent an interval until an event (progression-free survival, time to change of systemic therapy, overall survival), an evaluation is also performed using Kaplan-Meier curves and log-rank tests. In addition, a Cox regression analysis is conducted to investigate potential influencing factors on the respective analyzed endpoints.

If indicated by the patients, the reasons for premature discontinuation of therapy will be investigated. In addition, the reasons for withdrawal from the program documented by the center will be reviewed.

Study and loss-to-follow-up analyzed.

8.4 Interim evaluation

An interim evaluation of the study results is not planned. An analysis of the side effect profile will be conducted after one-third of the treated patients have been reached (see section 5.6).

9. Ethics and legal requirements

9.1 Ethics Committee Review The study will be conducted in accordance with the principles of the current version of the Declaration of Helsinki [37, 38]. The study protocol presented here is being submitted for review by the Ethics Committee of the Medical Faculty of Tübingen. The patient information leaflet and the informed consent form for the study presented here will also be submitted separately for this purpose. Any future changes to the study protocol will be communicated to the responsible Ethics Committee immediately. Before patient recruitment begins at cooperating sites, the study protocol will also be submitted to the respective Ethics Committees at those sites for review. The Tübingen Ethics Committee will also be informed of the completion of the study and its results. The principal investigator and the principal investigators of the clinical trial have at least two years of experience in clinical trials. All members of the research team must have completed at least the basic course of the GCP investigator course no later than the start of the study.

9.2 Good clinical and scientific practice

The guidelines for good clinical and scientific practice must be followed during the study and in all contact with patients. Participating investigators are required to provide proof of attendance at relevant courses upon request. Study leaders must have at least two years of experience in conducting clinical trials.

present.

9.3 Legal radiation protection requirements

The requirements of radiation protection according to the Radiation Protection Ordinance and the Radiation Protection Act must be observed at all times during the diagnostic and therapeutic procedure.
This also includes the obligation to provide aftercare.

The diagnostic and therapeutic measures planned in the study have been validated in studies and are performed in routine clinical practice. Furthermore, in a position paper, the German Society for Radiation Oncology (DEGRO) has defined hypofractionated radiotherapy for prostate cancer as a medical procedure, provided certain conditions are met. This definition also includes the irradiation of patients with metastatic disease. These conditions are met. Moreover, the study protocol has been submitted to the DEGRO expert committee. The DEGRO expert committee's statement classifying the procedure as a therapeutic radiation application within the scope of medical practice is included with the study protocol (see appendix). Therefore, the study does not involve the application of ionizing radiation to humans for the purpose of medical research as defined in Section 31 of the German Radiation Protection Act (StrSchG), and consequently, no application needs to be submitted to the Federal Office for Radiation Protection (BfS). Since the PSMA-

PET/CT examinations are performed at defined times; the planned PSMA-PET/CT examinations are reported to the BfS.

9.4 Patient Information and Consent Form Before enrollment in the prospective study, each patient is informed that participation is voluntary and that withdrawal during the observation phase is possible at any time without explanation and without any negative impact on further care and therapy. In this case, therapy will continue as standard treatment without further modifications.

Before the start of the study, participants will be informed about the planned radiation therapy and possible radiation-induced side effects. In addition, they will receive comprehensive information about the study's research question and the scope of the therapeutic measures beyond standard therapy in the (oligo-(Beyond the metastatic situation): PDT in high-volume OMPC and stereotactic radiotherapy of the prostate instead of moderate hypofractionation as in the STAMPEDE and PEACE-1 trials. The nature, significance, scope, expected benefits, and potential additional burdens and risks of the study are explained. Sufficient time for reflection and the opportunity to ask questions are provided before study enrollment. Furthermore, the patient is given a "Patient Information" form (see attachment) which contains all important information again in written form. The patient's written consent must be obtained before the start of the study.
Patient representatives were involved in the development of the informed consent form. The consent form is provided in duplicate (one copy for the study center and one for the patient). It is only valid after the consent form has been signed, and only then can the patient be included in the study, provided they meet the inclusion and exclusion criteria. By signing the consent form, the patient also agrees to the recording of their medical data in pseudonymized form as part of the clinical trial. The physician confirms by signing the respective patient information form that an individual consultation has taken place and that a signed consent form has been received from the patient.

9.5 Data Protection and Confidentiality All patient-related data are collected in pseudonymized form. Each patient is assigned an individual patient number upon recruitment. The principal investigator maintains a confidential patient list documenting clinical and personal data. Only individuals directly involved in the study, who are bound by confidentiality, have access to this list. Access is logged electronically. All findings collected during the clinical trial are stored in paper form and on electronic data carriers and treated with strict confidentiality. In the event of publication of study results, publication is anonymized and cannot be traced, thus ensuring the confidentiality of personal data.

9.6 Retention of Study Documents The originals of all study documents (patient identification list, signed informed consent forms, etc.) and the general study documentation (protocol, amendments, correspondence with the ethics committee) will be stored for 10 years after completion or termination of the study.

stored in the study secretariats of the participating clinics and after this period

They have been deleted. They are protected against unauthorized access and are treated confidentially at all times.
Clinical data and treatment plans must be kept for 30 years according to the Radiation Protection Ordinance (radiation or X-ray treatment according to § 72 para. 1 no. 2b in conjunction with § 85 para. 2 no. 1 StrlSchG).

9.7 Publication of personal data

When analyzing study data and presenting and publishing study results, medical confidentiality and data protection regulations are strictly observed. All patients are informed upon study enrollment that their collected data will be stored in pseudonymized form, forwarded to the study center in Tübingen, and used for scientific evaluations (publications, follow-up applications, conference presentations). Access to the original data and medical records by third parties is restricted to the Tübingen study center or authorized representatives of government agencies (supervisory authorities). All individuals involved in data review are bound by confidentiality and applicable data protection regulations.

If a patient withdraws from the study, they will be contacted to determine whether they consent to the analysis of the data already collected. Data and treatment plans will not be destroyed due to applicable radiation protection legislation. The principal investigator at the respective study center must ensure that the patient's withdrawal from the study is promptly reported to the study center in Tübingen. The data sets will remain locally, or data already forwarded will be stored centrally. These data may continue to be used for data analysis (e.g., meta-analyses regarding recurrence or side effects) in other studies, provided the patient has not objected to this further use of their data in their informed consent form.

10. Administrative guidelines

10.1 Financing

The University Clinic for Radiation Oncology and Radiotherapy at the University Hospital of Tübingen is covering the costs of the clinical trial and the biometric analysis. Furthermore, a
Funding has been approved under the intramural AKF funding program (see attachment).

Participation in this study will not incur any additional costs for patients compared to standard therapy. The diagnostic and therapeutic measures presented in this study protocol are validated procedures and are therefore covered by health insurance. Reimbursement of transportation costs can be requested through the health insurance provider; insurance coverage is in place for every treated patient. No financial compensation will be provided. All individuals involved in conducting this study declare that there is no conflict of interest related to the study's execution and analysis.

10.2 Compliance with the Protocol and Protocol Amendments

All responsible parties involved are obligated to comply with the study protocol. In case of ambiguities or possible protocol violations, the study center must be consulted.

Tübingen. Any deviation from the diagnostic and/or therapeutic measures specified herein, including any postponement, must be documented and justified in writing, as determined by the investigators. Except in emergencies, the study center should be consulted. Amendments to this protocol can only be initiated and authorized by the study directors and must be approved by the

The ethics committee of Tübingen and the ethics committees of the participating centers must be approved.

10.3 Publication

For national and international publication of the study results, the study will be registered with the relevant registration authorities (registration with the German Oncology Association has already been applied for, registration with the German Clinical Trials Register has been applied for and registration with www.clinicaltrials.gov). is planned).

The results of the analysis following the completion of the study will be published under the responsibility of the study directors. Until then, all information relating to the study must be treated confidentially by the participating study centers. Publication of the primary and secondary endpoints is planned after the study is completed. All participating centers will be listed as co-authors in the study, provided there is no limit to the number of possible co-authors.

11. Participating testing centers

The following centers and their respective examining physicians are planned to participate:

University Hospital of the Ludwig-Maximilian University of Munich
Prof. Dr. Nina-Sophie Schmidt-Hegemann, Dr. Paul Rogowski
Department of Radiation Therapy and Radio-Oncology
Telephone: +49 (0)89 / 4400 - 73770

12. List of abbreviations

AHT	-	Antihormonal therapy
ARPI	-	Androgen Receptor Pathway Inhibitors
ATP	-	adapt to position
ATS	-	adapt to shape
BED	-	Biologically effective dose
BfS	-	Federal Office for Radiation Protection
CT	-	Computed tomography
CTC	-	Common Toxicity Criteria
CTV	-	Clinical target volume
DRU	-	Digital rectal examination
EQD2	-	2 Gy equivalent dose
Fx	-	Fractionation
GI	-	gastrointestinal
GKS	-	Whole-body bone scintigraphy
GTV	-	Gross tumor volume

GU	-	genitourinary = urogenital
Gy	-	Gray
IGRT	-	Image-guided radiotherapy
IMRT	-	Intensity-modulated radiotherapy
KU	-	Physical examination
MDT	-	Metastasis-directed ablative radiotherapy
MPC	-	Metastatic prostate cancer
mpMRI	-	multiparametric magnetic resonance imaging/mpMRI
OMPC	-	Oligo-metastatic prostate cancer
OS	-	Overall survival
PSA	-	Prostate-specific antigen
PSMA	-	Prostate-specific membrane antigen
PFS	-	Progression-free survival; progression-free survival
PDT	-	Primary-directed therapy, Radiation of the Primarius
PROMISE V2	-	Prostate Cancer Molecular Imaging Evaluation, Second Version
PTV	-	Planning target volume
RECIST	-	Response Evaluation Criteria In Solid Tumors
RECIP	-	Response Evaluation Criteria in PSMA-PET/CT stereotactic
SBRT	-	body radiotherapy, stereotactic extracerebral radiation
UHF	-	Ultrahypofractionation of the prostate
WHO	-	World Health Organisation
ZV	-	Target volume
ZVD	-	Target volume definition

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