March 2020

Ph.D. project plan

Ph.D.-student

Nicklas Juel Spindler, MD

Title:

Immuno-radiotherapy for metastatic castration-resistant prostate cancer

Principal supervisor

-Gitte Persson, MD, Ph.D., Clinical Associate Professor

Co-supervisors from Department of Oncology, Herlev and Gentofte Hospital, Copenhagen, Denmark:

-Dorte Nielsen, Professor, DMSc

-Henriette Lindberg, MD, Ph.D.

-Rikke Løvendahl Eefsen, MD, Ph.D.

Co-supervisor from the Danish Technical University (DTU), Biotherapeutic engineering and drug targeting, DTU Health Tech

-Thomas Andersen, professor, DTU Health Tech

-Anders E. Hansen, DVM, Senior Researcher, Ph.D.

Table of Contents

1 Problem statements and theoretic basis

Immunotherapy has improved patient survival for several types of cancers significantly. In general, clinical responses to immunotherapy are only observed in up to 30% of patients with solid cancers.

Prostate cancer is one of the malignancies that so far does not respond to immunotherapy, as it is considered a non-immunogenic tumor, i.e., a "cold tumor." It is believed that to change a cold tumor into a hot tumor, an increase in tumor-infiltrating lymphocytes, and a higher level of tumor antigen presentation is warranted. Stereotactic body radiation therapy (SBRT) induces cell death, and together with checkpoint inhibitors (CPI, immunotherapy), it is suggested to induce an immune response that leads to immunogenic cell death of the cancer cells.

So far, biomarkers have failed to identify patients who respond to immunotherapy, and sophisticated patient selection is needed critically. Pre-clinical studies have constructed and identified cancer models that can accurately mirror the differences in tumor antigen presentation and immune cell infiltration observed in patients. These studies will provide mechanistic information on immune-radiotherapeutic strategies that aim to improve immune cell infiltration and antigen activation and test new local immunogenic drugs.

Perspective

Metastatic castration-resistant prostate cancer is incurable, and new treatments are needed. This study will test if immunotherapy with or without stereotactic body radiation therapy will improve survival and quality of life for metastatic castration resistant prostate cancer patients and hopefully benefit patients with no further treatment options. Furthermore, new immunologic drugs are needed for treating solid cancers, and the latter proposed method could be a new way to overcome the low response rates in immunotherapy.

2 Background and rationale

Prostate cancer (PC) is the most frequent cancer in men in western countries and the second leading cause of cancer-related death among men (1). PC is dependent on testosterone, and the primary treatment for metastatic PC (mPC) is lifelong castration alone or for patients with high tumor burden in combination with either docetaxel (2,3) or abiraterone (4,5). In virtually all patients with

mPC, the disease progresses to metastatic castration-resistant (mCRPC) despite suppressed testosterone levels. Immunotherapy has not yet been approved for patients with mCRPC. Prostate cancer has low immunogenicity, mirrored by a "cold" tumor microenvironment (TME) with a high number of immunosuppressive cells and a low number of CD8+ tumor-infiltrating lymphocytes. This is considered as one of the major reasons for unresponsiveness to single-agent immune CPI (6). In mCRPC, immunotherapy with the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor ipilimumab has been explored in two phase 3 trials. However, no improved median OS was observed in these studies (7), although one study found a significantly increased progression-free survival (8). In mCRPC, a recent study reported that 31% of cases had PD-L1 expression (>1%), indicating a possible role for CPI in mCRPC. A blockade of both CTLA-4 and programmed cell death-1 (PD-1) appears to be more effective, as CTLA-4 works in the early activation of T cells, whereas PD-1 function during the later effector phase of the T cells (9).

Ionizing radiation may increase the immunogenicity of the TME through activation of the innate immune response and the recruitment and activation of tumor-antigen specific T-cells locally on the irradiated tumor. It may also improve anti-cancer immune response outside the irradiated field, causing an abscopal effect, a *de novo* systemic tumor-specific immune response (10) and is suggested to serve as an '*in situ*' vaccine (11).

Another proposed method of transforming the TME to a T-cell inflamed phenotype is by injecting immune-stimulating drugs into the primary tumor or metastasis, i.e., localized treatment, supplementing the systemic CPI treatment, and/or radiotherapy. Several new drugs have been proposed, and the vital tumor suppressor cytokine, transforming growth factor-beta (TGF-β), is known to enhance tumor survival and modulate the immune response by reducing the tumor-infiltrating T-cells when the TGF-β pathway is dysregulated (12). Blocking TGF-beta has been shown to increase the infiltration of T-cells and natural killer cells and restore the cell-mediated immune response to the tumor cells (13). Another way is by stimulating the innate immune system through the Toll-like receptors (TLR), which play a crucial role in the recognition and immune response of pathogens. Stimulation of specific TLRs leads to increased inflammation and antigen presentation, and studies of TLR-7 show an increased release of pro-inflammatory cytokines and activation of dendritic cells, causing "hot" TME (14). Please see figure 1. The combination of a topical TLR-7 agonist and radiotherapy has been shown to induce a potent anti-tumor immunologic response in breast cancer, i.e., an in situ tumor vaccine (15).

The main purpose of this study is to investigate how to induce a systemic immunogenic anti-tumor response in patients with metastatic castration-resistant prostate cancer (mCRPC) and identify

biomarkers and novel combinations of immunological stimulating drugs with radiotherapy in a murine mouse model.

We have initiated the phase II trial: ”**Randomized phase 2 trial of stereotactic body radiation therapy, SBRT of a soft tissue metastasis in combination with checkpoint inhibitors in metastatic castration-resistant prostate cancer** (termed CheckPRO)” at Herlev Gentofte Hospital.

The Ph.D. project seeks to answer the following three questions:

1. Can intratumoral injected TLR-7 and TGFβ increase the immunological response in a murine mouse model?
2. Could immunotherapy with or without radiotherapy be a promising and safe treatment option for patients with mCRPC ?
3. What characterize the mCRPC patients who will benefit from immunotherapy or immune-radiotherapy?

This project is based on a pre-clinical mouse-trial and a clinical phase II trial. Patients with metastatic castration-resistant prostate cancer are given immunotherapy with ipilimumab and nivolumab with or without stereotactic radiation therapy on a soft tissue metastasis. In case of promising results, there will be a basis for new projects for further identification of patients who respond to immunotherapy and/or for the investigation of new treatment combinations to get a more pronounced tumor shrinkage response.

3 Objective, hypothesis, and endpoints

This Ph.D. project is divided into three sub-projects:

Mouse trial – Part 1
Objective: To polarize and maintain the tumor microenvironment towards a T-cell inflamed phenotype and study abscopal effects using radiation therapy, immunotherapy, and intratumoral injected immune-stimulating drugs.

Hypothesis: Converting the intratumoral microenvironment to a T cell inflamed type using intratumoral sustained-release ImmunoGels (TLR-7 and TGFβ) potentiates the effect of radioimmunotherapy using PD1 checkpoint inhibitors in non-T cell inflamed and low immunogenicity cancers

Primary endpoint: Overall response rates, volume of tumors, changes in tumor and lymph node immune microenvironment, response to re-challenge of cancer cell lines.

CheckPro trial – Part 2
Objective: Evaluate the clinical benefit rate (CBR) and safety of immune checkpoint inhibition (ipilimumab and nivolumab) with and without stereotactic body radiation to a soft tissue metastasis.

Hypothesis: Immunotherapy with or without radiotherapy have a promising CBR in treating mCRPC with an acceptable safety profile.

Primary endpoint:

Clinical benefit rate (CBR) as defined by RECIST 1.1 (Stable disease for ≥ 6 months, partial response and complete response).

Secondary endpoints:

Safety data (adverse effect etc.), progression-free survival (PFS) per RECIST 1.1 and iRECIST, overall response rate (ORR) by iRECIST, duration of response (DoR), PFS rate, and overall survival (OS) rate at six months and one year and overall OS, Quality of Life using EORTC QLQ-C30

CheckPro trial – Part 3

Objective: To describe changes in tumor tissue and blood before, during and after immunotherapy and immune related predictive biomarkers.

Hypothesis: Response to therapy can be predicted by the changes in tumor tissue and blod.

Exploratory endpoints:

- Immunological changes in tumor and blood
- Association between biomarker levels and outcome
- Investigate the association between biomarkers in blood and tumor tissue and outcome, such as CBR, ORR, OS and PFS.

4 Methods and time schedule

MOUSE TRIAL – PART 1

The mouse trial will be conducted at the Panum Institute, University of Copenhagen, with the scientist group from Biotherapeutic engineering and drug targeting, DTU Health Tech.

We have selected four cancer cell lines representing murine melanoma with high/low antigenicity (AG) and +/-T cell inflamed.

Cancer models

- Model DT4: murine melanoma, "low antigenicity, non-T cell inflamed"
- Model DT4-0: murine melanoma, "high antigenicity, non-T cell inflamed
- Model DT2; murine melanoma, "low antigenicity, T cell inflamed"
- Model DT1: murine melanoma, "high antigenicity, T cell inflamed"

Therapeutic intervention:

- Radiotherapy – 8 Gray 3 fractions (1Gy/min, 320kV)
- Anti-PD1 therapy
- Intratumoral ImmunoGel (sustained-releasing depot of TLR7 agonist and TGF-b inhibitor)

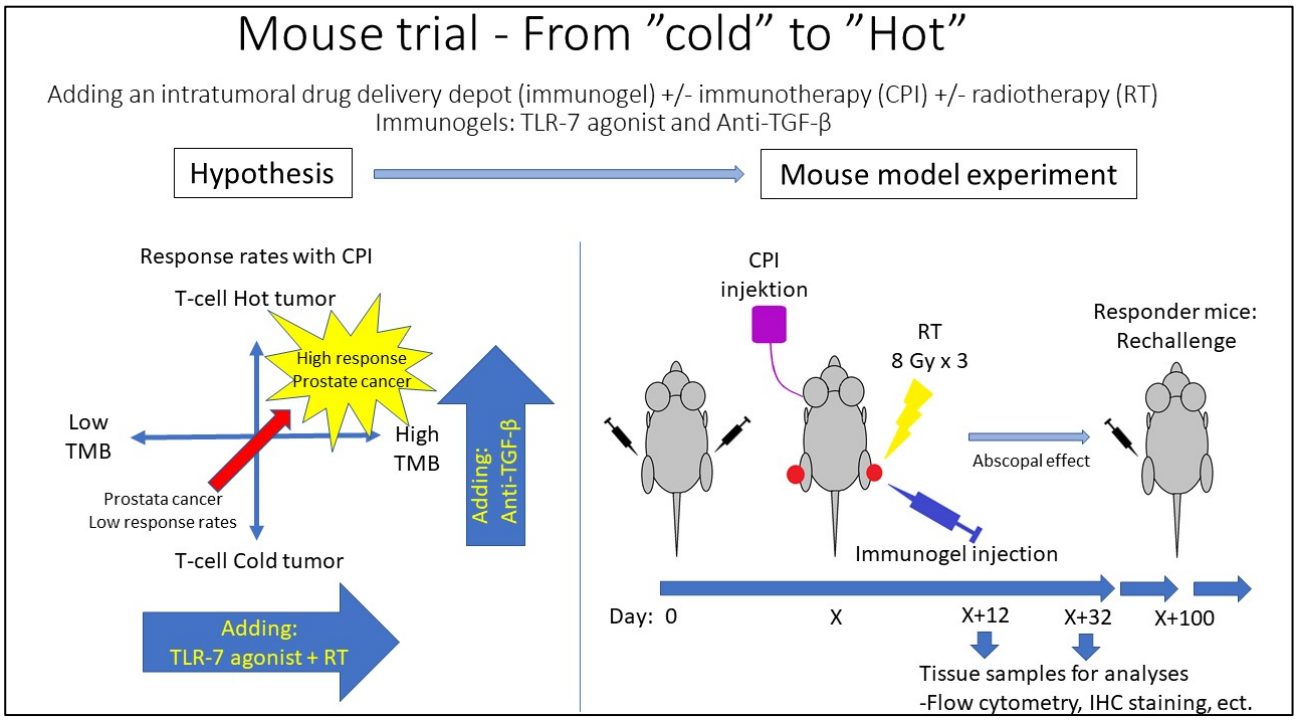
Groups (identical for all four cancer cell lines):

- Untreated controls
- Radiotherapy
- Radiotherapy + ImmunoGel
- Radiotherapy + ImmunoGel + anti-PD1
- Radiotherapy + anti-PD1
- ImmunoGel+anti-PD1

Mice are size dependently randomized to a treatment group by standard procedures
The tumor cell lines will be inoculated and injected into both flanks of each mice. One of the injected tumors will represent the primary tumor, which will receive localized treatment (radiotherapy and/or anti-TGF-β/TLR-7 injections combined with systemic immunotherapy), and the other tumor will represent a "metastasis." If the metastasis responds (decrease in size), an abscopal effect is achieved (systemic immunological response). If the mouse has a complete

response, it will be re-challenged with the same cell line to test if the mouse has reached a long-lasting immunological response. Please see Table 1 and Figure 1.

Figure 1



Mechanistic evaluation:

- At two time points (X+12 and X+32), tumors and tumor-draining lymph nodes are collected, and flow cytometry is performed to investigate myeloid and lymphoid immune cell infiltration and polarization.
- Mice are followed by three weekly tumor size measurements (digital caliper) and weight recorded.
- Single-cell suspension and cell staining are performed using standard procedures.
- Flow cytometric panels and design are under development (5th laser being installed, and this will provide additional flexibility).

Tumor tissue from responder and non-responder mice will be analyzed by immunohistochemistry for the following parameters:

- CD40 expression (in biopsy taken before the first dose in tumors)
- Tumor infiltrating T-cells
  - Effector memory cells
    - CD8+

  - CD45RO+
- Regulatory T cells
  - Foxp3+
  - CD4+
- PD-L1 and LAG-3 expression on tumor cells and immune cells
- Tumor-associated macrophages (TAMs)
- A Disintegrin and Metalloproteinases (ADAMs)
- More markers are to be determined

Time schedule
This subproject is expected to start in fall 2020 and is expected to end in fall 2021.

Table 1

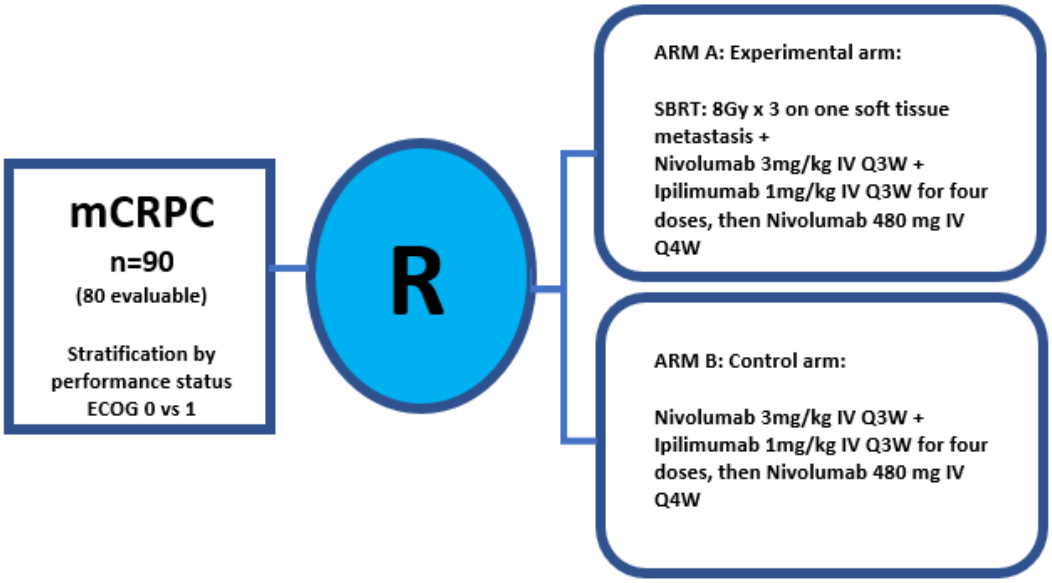
Day	0	X *	X+2	X+5	X+7	X+14	X+21	X+100
Inoculation of cancer cells lines	0							
Radiation therapy (8Gy)		0	0	0				
ImmunoGel intra-tumoral injection		0			0	0	0	
i.v. anti-PD1		0					0	
Re-challenge complete responders								0

*Mean tumor volume 100-150 mm^3

CheckPRO TRIAL – Part 2 and 3

This trial is a single-center study that involves the Department of Oncology, Copenhagen University Hospital of Herlev and Gentofte, Denmark. The trial is designed as an investigator-initiated prospective randomized, open-label phase 2 study in patients with metastatic mCRPC, who have progressed after treatment with one next-generation androgen receptor (AR)-targeted therapy and one line of taxane-based chemotherapy. Experimental therapy will be given to determine the efficacy and safety of nivolumab plus ipilimumab (Arm B) administered concurrently with or without SBRT to a soft tissue metastasis. The study is expected to randomize approximately 90 (80 evaluable) subjects with mCRPC. Subjects will be randomized 1:1 and stratified by performance PS (0 vs 1). The CheckPRO trail started including patients in November 2019, and 6 patients are enrolled so far.

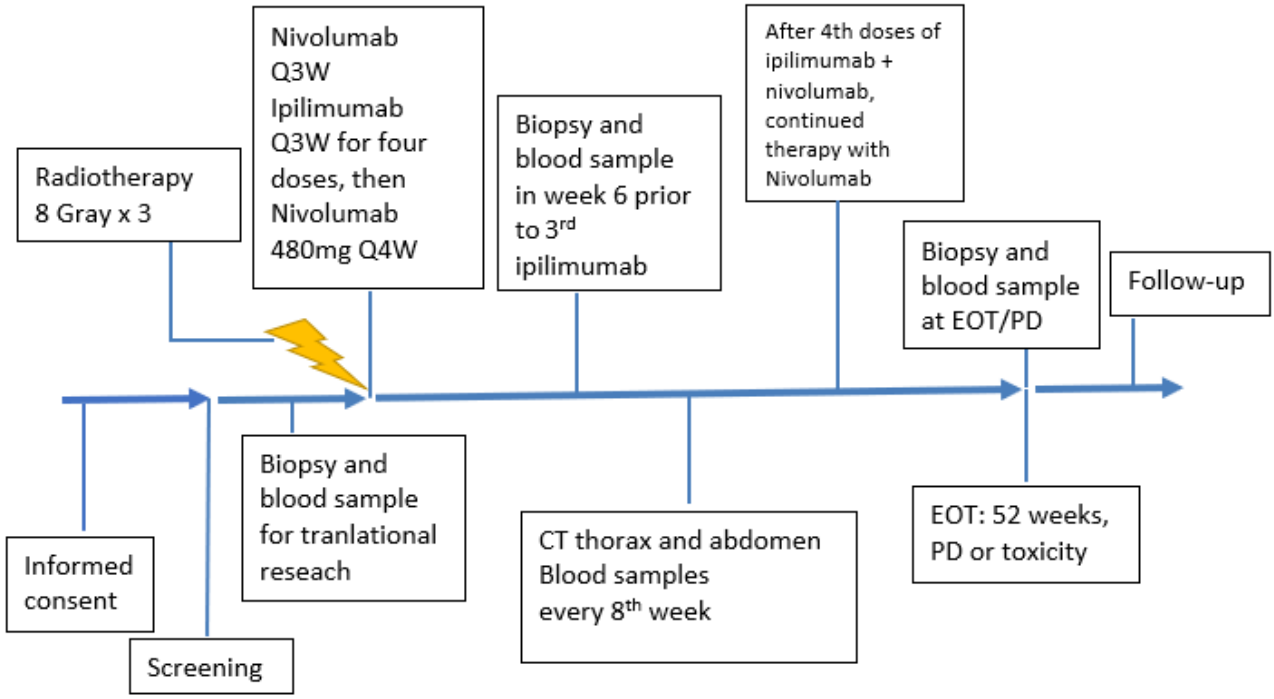
Figure 2 – Study design



- Prior to therapy, patients will be screened with a medical history, physical examination, computed tomography, and blood samples.
- Arm A: SBRT 8 Gray x 3 on a soft tissue metastasis within the first week plus nivolumab and ipilimumab Q3W for four doses, then nivolumab Q4W
- Arm B: nivolumab plus ipilimumab Q3W for four doses, then nivolumab Q4W

- Patients randomized to arm A will receive 8 Gray x 3 to a soft tissue metastasis within the first week of treatment. A highly conformal dose distribution to the metastasis will be delivered using a 6 Mega Volt LINAC with Rapid Arc treatment application
- Patients in both arm A and B will receive nivolumab 3mg/kg every third week plus ipilimumab 1 mg/kg every third week for four doses, then nivolumab 480mg IV every fourth week, q4w, for a maximum of 52 weeks or until disease progression (PD), unacceptable toxicity, withdrawal of consent or investigator's judgment.
- Two fresh biopsies will be acquired from the intended RT lesion (only in Arm A) and a non-RT target lesion (Arm A and Arm B) three times: before therapy begins, before the third dose of ipilimumab, and if possible at the time of PD. If possible, the biopsies will be collected from the same sites before and during therapy. Blood samples for translational research will be collected before and during therapy at the same time as biopsies and every eight weeks during therapy.
- Patients will have routine blood tests and adverse events registration at each visit.
- Tumor assessments will be performed by NAF-PET-CT scans every 8 weeks from treatment start. Patients who receive therapy for 52 weeks without progression of the disease, will have a follow-up with CT scans every eight weeks

Figure 3 - Patient flow-chart



TRANSLATIONAL RESEARCH

BIOMARKER TESTING AND RESEARCH BIOBANK

A new research biobank will be formed for this protocol, including blood and tissue from prostate cancer patients enrolled in this protocol. The key objective of the biomarker blood sampling is to identify specific biomarkers that are predictive of response to the combination of checkpoint inhibition and RT. Whether cell-free DNA in blood samples can serve as a "liquid biopsy" to monitor disease burden, response to treatment, and disease outcome will also be investigated.

Biomarker blood sampling is mandatory.

Blood samples for cell-free DNA and other translational biomarker analyses are collected prospectively together with the routine blood tests as part of their treatment:

- Before treatment start
- In week six before the 3rd treatment cycle
- At the time of each CT evaluation (including time point of progression of the disease)

Nucleic acids extracted from blood will be used for normal genome (if needed) and circulating tumor nucleic acid profiling. The collection of a blood sample upon disease recurrence is highly recommended as it may provide essential data on drug resistance mechanisms. Methodologies for circulating tumor nucleic acid identification may include but are not limited to DNA profiling or targeted gene sequencing, as informed by emerging data and methodologies.

Furthermore, blood samples will be analyzed for gene-, SNPs, RNA, and microRNA arrays profiling, and proteomics and metabolomics will be investigated. The transferred material will be administrated according to the local law. The project blood samples will be anonymized and stored at the Department of Oncology, Herlev & Gentofte University Hospital and destructed when the study is completed, at the latest August 1st, 2036.

In addition, a part of the tissue will be analyzed for DNA mutations according to standard diagnostic procedures at the Department of Pathology, headed by professor Estrid Høgdall. Tissue samples will be taken according to the regional standard diagnostic procedure and stored in the Bio- and Genome Bank (Danish Cancer Biobank). Written consent will be achieved from the patients to participate in the trial, which will be registered in Danish Cancer Biobank. The samples in the Danish Cancer Biobank can be permitted for approved research projects if enough tissue material is left for diagnostic purposes at present time and in the future. Samples for the research project will

be transferred to the research biobank of this trial. From gene profiling, the mutational load will be assessed. We will use the Oncomine comprehensive DNA mutation analysis panel that examines 142 genes related to cancer development and related to the effect or side effects of cancer treatment. The analysis used is the Oncomine Comprehensive gene analysis combined with a Thermo Fischer gene panel analysis, where sequencing is performed for hot-spot areas of cancer-specific tumor-oncogenes and all coding areas of tumor suppressor genes. Therefore, only genes of relevance for cancer diseases will be analyzed. For the next-generation sequencing, the Ion Torrent S5XL platform is used, and the Ion Reporter is used as the bioinformatic tool. The reading depth is planned to be about 250x for somatic gene variants to ensure consistent and reproducible results. Raw data will be stored in a back-up server RAID6 for ten years, a local procedure for Oncomine gene analyses from patients in the experimental cancer therapy unit. It is expected that gene variants found by coincidence will be very, very rare as only cancer-related genes are analyzed. All gene analyses are reported in a multidisciplinary forum, where molecular oncologists, pathologists, and molecular biologists discuss gene findings and how to handle those in the clinical setting. In case of a finding of coincident variant, the patients will be referred to counseling at Rigshospitalet.

Immune Blood Analyses
Analyses will primarily focus on the evaluation of treatment-induced quantitative changes in T-cells. They will include quantitative and qualitative analyses of blood T cells measuring concentration and phenotypic stage of T-cells by flow cytometry using surface markers CD3, CD4, CD8, CD28, CD95, CCR7, and CD45RA. Furthermore, regulatory T cells, myeloid-derived suppressor cells (MDSC), NK cells, NKT cells, dendritic cells, and monocytes will be quantitated by flow cytometry. ELISPOT IFN-γ analyses and new advanced technologies, including combinatorial coding flow cytometry, will be employed for the quantification of tumor antigen-specific T-cells.

Immune Tissue Analyses
Tumor tissue biopsies will be evaluated by immunohistochemistry for immune cell infiltrates also adding macrophages and neutrophils to the panel.

Two core needle biopsies will be taken from (intended) radiated (only in Arm A) and non-radiated (both Arm A and Arm B) tumors under local anesthesia using 18 gauge needles at the time points listed in Table 11. The biopsies taken from non-radiated tumors should preferably be taken from a tumor located in a minimum 2 cm distance from the radiated tumor at the investigator's discretion.

Tumor biopsy time points

- Before treatment start (- 14 days)
- Before third ipilimumab administration (-3 days)
- At the time of progression, if possible

The tumor biopsies will be taken from an assessable site at the discretion of the investigator. Ultrasound or CT may be used to guide the biopsies. Each tumor biopsy will be divided into two parts; one part will be evaluated for immunohistochemistry analysis in the Center for Cancer Immune Therapy (CCIT) at Herlev and Gentofte Hospital, and the other part will be placed in RNA stabilizing solution research biobank at the Oncology department, Herlev and Gentofte Hospital.

Analysis by Immunohistochemistry
Biopsy material will be analyzed by immunohistochemistry for the following parameters:

- CD40 expression (in biopsy taken before the first dose of immunotherapy)
- Tumor-infiltrating T-cells
  - Effector memory cells
    - CD8+
    - CD45RO+
  - Regulatory T cells
    - Foxp3+
    - CD4+
  - PD-L1 and LAG-3 expression on tumor cells and immune cells
  - Tumor-associated macrophages (TAMs)
  - A Disintegrin and Metalloproteinases (ADAMs)

The biopsy material will be coded (i.e., the samples will have the same patient number as allocated in the clinical study). PD-L1 expression on tumor cells will be determined using Monoclonal Rabbit Anti-PD-L1, Clone 28-8 in formalin-fixed, paraffin-embedded (FFPE) tissue. PD-L1 protein expression is defined as the percentage of tumor cells exhibiting positive membrane staining at any intensity. Furthermore, digital pathology by a multiplex technique will be applied for evaluation of the tumor microenvironment, including tumor cells and stromal cells, such as T cells and fibroblasts.

TIME SCHEDULE

Patient accrual starts November 25th, 2019, and ends November 25th, 2021. Follow-up will continue to November 25th, 2023 (last patient last visit).

5 Methods - considerations

Mouse Trial: From previous studies on mouse models, we expect a response rate at the primary tumor-site of a maximum of 5 % in the arm treated with CPI alone compared to an expected effect of 60% when combining radiotherapy and CPI. In total, ten mice are needed in each group (240 mice in total).

CheckPRO statistical considerations: The sample size calculation is based on a two-stage design for randomized phase II trials with two experimental treatment arms (no control arm). To date, response rates of about 10% for single-agent checkpoint inhibitor (CPI) for mCRPC have been observed. Overall, within each arm, a sample size of 40 is required to confirm that the clinical benefit ratio (CBR) is ≥ 30% in arm A with 80% probability given the CBR is < 10% when only treating with immunotherapy. A total of45 patients will be included in both arms to ensure that at least 40 patients can be evaluated and included in the analysis.

6 Facilities and laboratory

The clinical phase 2 study of the project will take place at Clinic 5, Herlev Gentofte Hospital, Department of Oncology (former name: Clinic for Experimental treatment). Resources including staff, logistics, modern equipment, and patients are on site already. The drugs ipilimumab and nivolumab are sponsored by the pharmaceutical company Bristol-Myers Squibb. In return, Bristol-Myers Squibb will receive safety data from this trial but are not a part of the clinical or translational studies. This is an investigator-initiated study, and Bristol-Myers Squibb will not be included in the execution, analyses, interpretations, or publication of these studies.
The experimental mouse trial will be in close collaboration with scientists from the Danish Technical University (DTU), Biotherapeutic engineering and drug targeting, DTU Health Tech with Prof. Thomas L. Andresen and Senior Researcher Anders E. Hansen. Laboratory equipment, staff, and facilities are available at both sites.

7 Ethical considerations

The CheckPro protocol has been approved by the Danish Health authorities as well as the Danish Medical Ethics Committee and follows the Helsinki Declaration and in accordance with Good Clinical Practice (GCP). All included patients must receive oral and written information about this study and provide written informed consent to be enrolled in this study. At any time, the patient can withdraw their consent, in which case standard treatment will be offered. The experimental mouse trial will be performed in close collaboration with scientists from the Danish Technical University. Approval from The Danish Animal Experimentation Council will be obtained before initiating the mouse trial. Experienced personal of animal nurses and veterinarians will assist the experiment.

8 Publication Strategy

Data and results from the study belong to the sponsor and principal investigator. Bristol Meyers Squib (BMS), who has sponsored the CPI drugs, has no influence over the analysis, interpretation, or publication of results. Within one year of the last patient's last visit of the primary study endpoint, study results will be disclosed on clinicaltrials.gov. After completing each part of the project (clinical and biomarkers sub-studies), the results, both positive and negative, and inconclusive, will be presented and published in peer-reviewed international journals.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. januar 2018;68(1):7–30.

2. Sweeney CJ, Chen Y-H, Carducci M, Liu G, Jarrard DF, Eisenberger M, m.fl. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 20. august 2015;373(8):737–46.

3. James ND, Spears MR, Clarke NW, Dearnaley DP, De Bono JS, Gale J, m.fl. Survival with Newly Diagnosed Metastatic Prostate Cancer in the "Docetaxel Era": Data from 917 Patients in the Control Arm of the STAMPEDE Trial (MRC PR08, CRUK/06/019). Eur Urol. juni 2015;67(6):1028–38.

4. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, m.fl. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 27 2017;377(4):352–60.

5. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, m.fl. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 27 2017;377(4):338–51.

6. Sharma P, Allison JP. The future of immune checkpoint therapy. Science. 3. april 2015;348(6230):56–61.

7. Kwon ED, Drake CG, Scher HI, Fizazi K, Bossi A, van den Eertwegh AJM, m.fl. Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial. Lancet Oncol. juni 2014;15(7):700–12.

8. Beer TM, Kwon ED, Drake CG, Fizazi K, Logothetis C, Gravis G, m.fl. Randomized, Double-Blind, Phase III Trial of Ipilimumab Versus Placebo in Asymptomatic or Minimally Symptomatic Patients With Metastatic Chemotherapy-Naive Castration-Resistant Prostate Cancer. J Clin Oncol Off J Am Soc Clin Oncol. januar 2017;35(1):40–7.

9. Haffner MC, Guner G, Taheri D, Netto GJ, Palsgrove DN, Zheng Q, m.fl. Comprehensive Evaluation of Programmed Death-Ligand 1 Expression in Primary and Metastatic Prostate Cancer. Am J Pathol. 1. juni 2018;188(6):1478–85.

10. Kaur P, Asea A. Radiation-induced effects and the immune system in cancer. Front Oncol. 2012;2:191.

11. Finkelstein SE, Salenius S, Mantz CA, Shore ND, Fernandez EB, Shulman J, m.fl. Combining immunotherapy and radiation for prostate cancer. Clin Genitourin Cancer. februar 2015;13(1):1–9.

12. Fabregat I, Fernando J, Mainez J, Sancho P. TGF-beta Signaling in Cancer Treatment [Internet]. 2014 [henvist 19. december 2019]. Tilgængelig hos: https://www.ingentaconnect.com/content/ben/cpd/2014/00000020/00000017/art00012

13. Teicher BA. Transforming Growth Factor-β and the Immune Response to Malignant Disease. Clin Cancer Res. 1. november 2007;13(21):6247–51.

14. Schön MP, Schön M. TLR7 and TLR8 as targets in cancer therapy. Oncogene. januar 2008;27(2):190–9.

15. Demaria S, Vanpouille-Box C, Formenti SC, Adams S. The TLR7 agonist imiquimod as an adjuvant for radiotherapy-elicited in situ vaccination against breast cancer. OncoImmunology. 1. oktober 2013;2(10):e25997.