## 1. Title and project group

English title: Can *TMPRSS2:ERG* gene-fusion predict resistance to PARP inhibitors in mCRPC patients

Dansk titel: Kan *TMPRSS2:ERG* gen-fusion forudsige resistens mod PARP hæmmere hos patienter med mCRPC


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Abbreviations

| | |
|---|---|
| PC | Prostate cancer |
| ADT | Androgen deprivation therapy |
| ctDNA | circulating tumor DNA |
| ETS | E26 transformation-specific |
| FFPE | Formalin-Fixed Paraffin-Embedded |
| HRR | Homologous Recombination Repair |
| mCRPC | metastatic castration-resistant PC |
| NGS | Next Generation Sequencing |
| PARP | poly (ADP-ribose) polymerase |
| OS | overall survival |

## 1. Introduction

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]. Androgen deprivation therapy (ADT) is well established as a backbone treatment option in case of metastatic disease[2]. Although the primary response rate following initiation of ADT is high, the disease will eventually progress despite levels of serum testosterone being in the castrate range. At this stage, metastatic castration-resistant PC (mCRPC) the prognosis is poor with a median overall survival (OS) of around 24-30 months[3].

Treatment options in mCRPC include androgen receptor pathway inhibitors (abiraterone[4], enzalutamide[5]), chemotherapy (docetaxel[6], cabazitaxel[7]) and radionuclides (radium-223[8], lutetium-177 PSMA[9]). In addition, 5-10% of patients with mCRPC have somatic or germline *BRCA1/BRCA2* mutations[10,11] making them eligible for treatment with a PARP inhibitor (i.e. olaparib), either alone[12] or in combination with abiraterone[13]. Although response rates to such targeted therapy are encouraging, only a limited number of patients benefit from treatment with PARP inhibitors. Further studies are therefore needed to improve treatment outcomes in this patient population.

In a recent retrospective study, we evaluated tumor samples from patients with mCRPC using next generation sequencing (NGS). Our results showed that a *TMPRSS2-ERG* gene-fusion was present in patients not benefitting from treatment with PARP inhibitor (PARPi), despite these patients having a mutation in one or more genes involved in DNA damage repair mechanisms, including *BRCA1/BRCA2*[14]. The response rate in patients with *BRCA1/BRCA2* is only 45%-55%, when exposed to PARP inhibitor-based therapy. A frequent (40-50%) characteristic feature of prostate cancer (PC) is the occurrence of genomic rearrangement that affects the transmembrane protease serine 2 (TMPRSS2) and E26 transformation-specific (ETS)- transcription factor-related gene (ERG).

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In this study we will investigate whether *TMPPRSS2-ERG* fusion and alterations in other genes of the ~~E26 transformation-specific (~~ETS~~)~~ transcription factor family (*ETV1*, *ETV4*, and *ETV5*)[15]~~,~~ when present in can predict resistance to PARPi in patients with mC~~P~~RPC and *BRCA1/BRCA2* mutations. The hypothesis is that the two groups of mCRPC (Gene-fusion positive) vs (Gene-fusion negative) will show different Response Rate (RR) towards PARPi using RECIST Criteria.

### *1.1 Aims and hypothesis*

The aim of this study is to assess the value of a specific gene-fusion to predict response to PARPi in patients with defects in their DNA damage repair mechanisms (*BRCA1* gene or *BRCA2* gene). Secondary aim is to validate if it is possible to detect the gene-fusion in a blood sample. The hypothesis is that the present of a gene-fusion in *TMPRSS2:ERG* in patients with a defect *BRCA1* gene or *BRCA2* gene will not respond less well to treatment with a PARPi. -The project involves two sub studies:

1) **A retrospective** analysis including patients with mCRPC who received treatment with olaparib as standard therapy between December 2020 and June~~April~~ 2025 at the Department of Oncology, Herlev and Gentofte Hospital. In this study all patients have already been identified with a pathogenic or likely pathogenic variant in the *BRCA1* gene or *BRCA2* gene, as part of the routine diagnostic investigation. The patients are already informed about any hereditary findings in the *BRCA1* and *BRCA2* genes as part of the standard routine procedure by the Department of Oncology. The patient will be identified through patient journal at Department of Oncology. In this sub study we will investigate whether a gene-fusion of the ETS transcription factor family is present in archived tumor samples. For the analyses one tissue slide of 10µm is needed from the FFPE tissue block stored at the Department of Pathology. Furthermore, clinical benefit will be evaluated using individual patient data from patient records including *BRCA1/2* gene mutation, Age, Gleason Score, prior treatment for PC / treatment history, metastatic sites, ECOG Performance Status, PSA, Hemoglobin, Alkaline phosphatase, LDH, treatment duration (PARPi), treatment response, reason for discontinuation, treatment for PC post PARPi. Clinical information for the retrospective part of the study will be withdrawn from patients record.

2) **A prospective** study including patients with mCRPC initiating treatment with olaparib, or another PARPi, either alone or in combination with an androgen receptor pathway inhibitor from June~~April~~ 2025 and onwards at the Department of Oncology, Herlev and Gentofte Hospital. In this study all patients have already been identified with a pathogenic or likely pathogenic variant in the *BRCA1* gene or *BRCA2* gene, as part of the routine diagnostic investigation. The patients have or will be informed about any hereditary findings in the *BRCA1* and *BRCA2* genes as part of the standard routine procedure by the Department of Oncology. Patients whom accept the

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PARPi treatment during their ~~will be identified through first~~ visit at Department of Oncology, will also be~~. At this visit the oncologist will talk with the patient and~~ invited to participate in this study by give information, written and oral, about the study. The oncologist will also make it clear that this study is not part of the patient's treatment plan. A delegation agreement between oncologists and PI are assigned. -All information will be in a silent room with no disturbances. At the information the patient will be informed about the possibility to have co-sitter with, and if relevant a new appointment will be arranged. There will be consideration period for the study up to surgery, several days. Again, we will investigate whether a gene-fusion of the ETS transcription factor family is present in archived tumor samples. For the analyses one tissue slide of 10µm is needed from the FFPE tissue block stored at the Department of Pathology. Additionally, gen-fusion status will be evaluated in ctDNA from archived blood samples. Clinical benefit will be assessed using a prostate cancer working group modified response evaluation criteria in solid tumors (RECIST) 1.1, based on the scans performed during the treatment course also with patient data including *BRCA1/2* gene mutation, Age, Gleason Score, prior treatment for PC / treatment history, metastatic sites, ECOG Performance Status, PSA, Hemoglobin, Alkaline phosphatase, LDH, treatment duration (PARPi), reason for discontinuation, treatment for PC post PARPi. The consent of the trial participant gives the trial manager direct access to obtain information about health conditions in the patient record when necessary, as part of the implementation of the research project, including as part of quality control and monitoring, which the trial manager is obliged to carry out.

### *1.2 Endpoints*

#### Primary endpoints

- Identification of gene-fusion of the ETS transcription factor family in tumor samples ~~tumor tissue and blood from~~for patients with mCRPC harboring defects in the *BRCA1/BRCA2* genes and measuring the ~~-~~Response Rate (RR) difference in the two groups (Gene-fusion positive) vs (Gene-fusion negative), by using RECIST Criteria.

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#### Secondary endpoints:

- Evaluation of clinical benefit (RR) following treatment with PARPi in patients with defects in the *BRCA1/BRCA2* genes with- or without the presence of gene-fusion of the ETS transcription factor family, measured in blood samples and compared to findings in tissue.
- Clinical benefit (RR) in patients treated with PARPi, who have a monoallelic versus biallelic loss in the *BRCA1/2* genes.

## 2. Methods

### *2.1 Study details*

The study contains a retrospective (sub study 1) and a prospective part (sub study 2) involving patients with mCRPC receiving standard treatment with PARPi at the Department of Oncology, Herlev and Gentofte Hospital.

### *2.2 Sample material*

The sample material (sub study 1 and sub study 2) is ~~either~~ stored ~~DNA (preferred material if available),~~ blood (8 mL) and~~,~~ 1 slide of formalin fixed paraffin embedded (FFPE) tumor samples ~~or fresh frozen tumor~~. A sufficient tumor content (>20%) in the analyzed material is secured by selection of a significant tumor area by a pathologist. ~~The use of ctDNA require 0.1% tumor DNA to ensure valid results.~~

### ~~*2.3*~~ *2.3 Next Generation Sequencing, ~~DNA Oncomine™ BRCA Research Assay and~~ RNA Oncomine Comprehensive v3*

Next generation sequencing using ~~gene panel Oncomine ™ *BRCA* Research Assay for DNA analysis of tissue and ctDNA and~~ the Oncomine™ Comprehensive v3 RNA which includes the ETS transcription factor family genes *ERG*, *ETV1*, *ETV4*, and *ETV5* for RNA gene-fusion analysis. All library preparations will be conducted on RNA ~~and DNA~~ according to manufacturer's instructions. ~~The Oncomine ™ *BRCA* Research Assay covering the full length *BRCA1* and *BRCA2* genes and is designed to work with a low input of partly degraded DNA from FFPE.~~ The assay is already used in the routine diagnostic workflow at our facility.

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## 3. Statistics

The total size of both sub study cohorts (n=80, retrospective study n=30, prospective study n=50) is sufficient to validate our initial results, showing that a *TMPRSS2:ERG* fusion is present in patients not benefitting from PARP inhibition, despite these patients having a mutation in the *BRCA1* gene or the *BRCA2* gene~~one or more genes involved in DNA damage repair pathways~~.

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The data will be presented as a comparison between clinical benefit (defined as: 1. at least 16 weeks treatment with PARPi, 2. 50% PSA reduction at 4 months or 3. progression free survival) in patients harboring gene-fusion (gene-fusion positive) and defects in the *BRCA1/2* genes versus patients only having defects in the *BRCA1/2* genes (gene-fusion negative).

The response to PARP therapy in prostate cancer patients is measured at 4 months comparing those with positive- and no fusion transcript all with mutations detected in *BRCA1/2* genes. The

statistical analysis will be done testing the response rate between the two groups using Chi-square test for homogeneity. Further analysis will include a multivariate analysis of response including relevant clinical variables using logistic regression modelling the probability for response.

Analysis of time to progression (biochemical, radiographic and/or clinical) will be done using the Cox proportional Hazards model~~. Exact tests will be used if assumptions are not met.~~ The level of significance is set to 5% and results will be presented with 95% confidence limits.

This is a retrospective/prospective study including 8~~6~~0 patients with *BRCA1/2* mutated prostate cancer with an estimation of ~~75~~50% of patient being presented with fusion transcript. This results in approximately 80% power to detect 33~~40~~% difference in response rates at the 5% significance level (2-sided).

## 4. Study Subjects

The study includes patients with mCRPC treated with standard therapy at the department of oncology from December 2020 and onwards. Patients will be included retrospectively and prospectively in sub study 1 and 2, respectively.

### *4.1 Inclusion and Exclusion Criteria*

Inclusion criteria

- Patients with mCRPC treated with olaparib or another PARPi.

Exclusion criteria

- Patients registered in ”Vævsanvendelsesregisteret”.

## 5. Risk Assessment and exemption from informed consent

*For study 1 (retrospective study)*:

We apply for exemption from informed consent from the patients involved in this study for the following reasons:

No additional sample material is required from the patients, and they are therefore not subjected to any additional harm or risk. Patients have before the diagnostic routine analyses consented to genomic analyses.

The patient samples (tissue and blood) have already been subjected to genomic analysis as part

of the ***standard diagnostic workflow*** preceding potential treatment with a PARPi. As such, there is only a minor risk of any additional significant genomic findings. Results from the extended gene analysis will not affect the treatment course with olaparib. The finding of a gene fusions will not change the choice of treatment as olaparib is approved for prostate cancer patients having a BRCA1/2 mutation. Unfortunately, most of the patients included in sub-study 1 have passed away due to the poor prognosis following mCRPC.

*For study 2 (prospective study):*

No additional biological material will be collected as the patient samples for study 2 (tissue and blood) have already been subjected to genomic analysis as part of the ***standard diagnostic workflow*** preceding potential treatment with a PARPi.

We will achieve oral and written patient consent before inclusion in the prospective study and no registration of data will be performed before consent is achieved. Patient consent will be registered in the patient journal for documentation (SP, Medie) and will in addition be stored by PI safe behind of two lockers at the hospital. Findings of a gene fusion will not change the treatment course with olaparib.

## 6. Collection of Biological Samples from Existing Biobanks

Available remaining ~~DNA, RNA,~~ blood and FFPE tissue from previous standard diagnostic samples are retrieved from the clinical biobank at the Department of Pathology, Herlev Hospital.

If diagnostic ~~DNA, RNA, or~~ FFPE tissue from the local pathology biobank is not available or insufficient for analysis, then relevant tumor material~~/DNA/RNA~~ will be requested from Bio- and GenomeBank, Denmark (RBGB).

Before any use of biological material, it will be ensured that patients are not registered in "Vævsanvendelsesregisteret".

There will not be generated a research biobank as analyses will be performed within one week, in case of potential excess of tissue and blood sample after the analyses described in the study, the remaining material will be destroyed.

## 7. Information from patient journals

The following clinicopathological parameters are collected from medical records.

- Previously genomic DNA and/or RNA testing results, clinical molecular diagnostic results, diagnosis, and histological subtype of tumor
- Information regarding the disease course including age, treatment history (PC),

relevant biochemistry (eg. prostate-specific antigen; PSA) and metastatic sites

- Treatment outcomes following treatment with PARPi
- Subsequent oncological treatments received following disease progression.

## 8. Handling of sensitive personal data:

Raw data analysis and other sensitive personal data (Patient ID and previous diagnostic results) will be handled locally on Herlev Hospital. Data will only be presented in an aggregated manner to ensure the anonymity of the study subjects.

Data will be processed in accordance with the data security guidelines from the Capital Region of Denmark to ensure compliance with the GDPR and the Data Protection Act will be complied.

## 9. Economy:

The study is initiated by Estrid Høgdall, Tim Svenstrup Poulsen, and Per Kongsted.
The study is fully financed internal by Department of Pathology.

## 10. Dissemination of study results

Results, positive as well as negative, will be published in a scientific peer reviewed international journal. The study group and other relevant participants will be co-authors if they meet the Vancouver criteria.

## 11. Ethical considerations and perspective

The project does not cause any harm to the participants and there is no risk of adverse findings as the patients have already been subjected to molecular genetic analyses in the routine diagnostic workup. The results of the study can be significant as gene-fusions are commonly known genetic rearrangement in mCRPC and occurs in about 50–75% of patients. This study is not covered by patient compensation or other compensation schemes, as only biological material that has already been taken is used and the analysis results have no therapeutic consequences.

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