

# *Kan en Gen-fusion forudsige resistens mod PARP hæmmer hos patienter med prostata kræft*

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## *Baggrund*

Prostata cancer (PC) hyppigste cancerform hos mænd i vestlige lande

Anden hyppigste årsag til cancer relateret død hos mænd

Androgen deprivation therapy (ADT) vel etableret behandling ved metastatisk sygdom

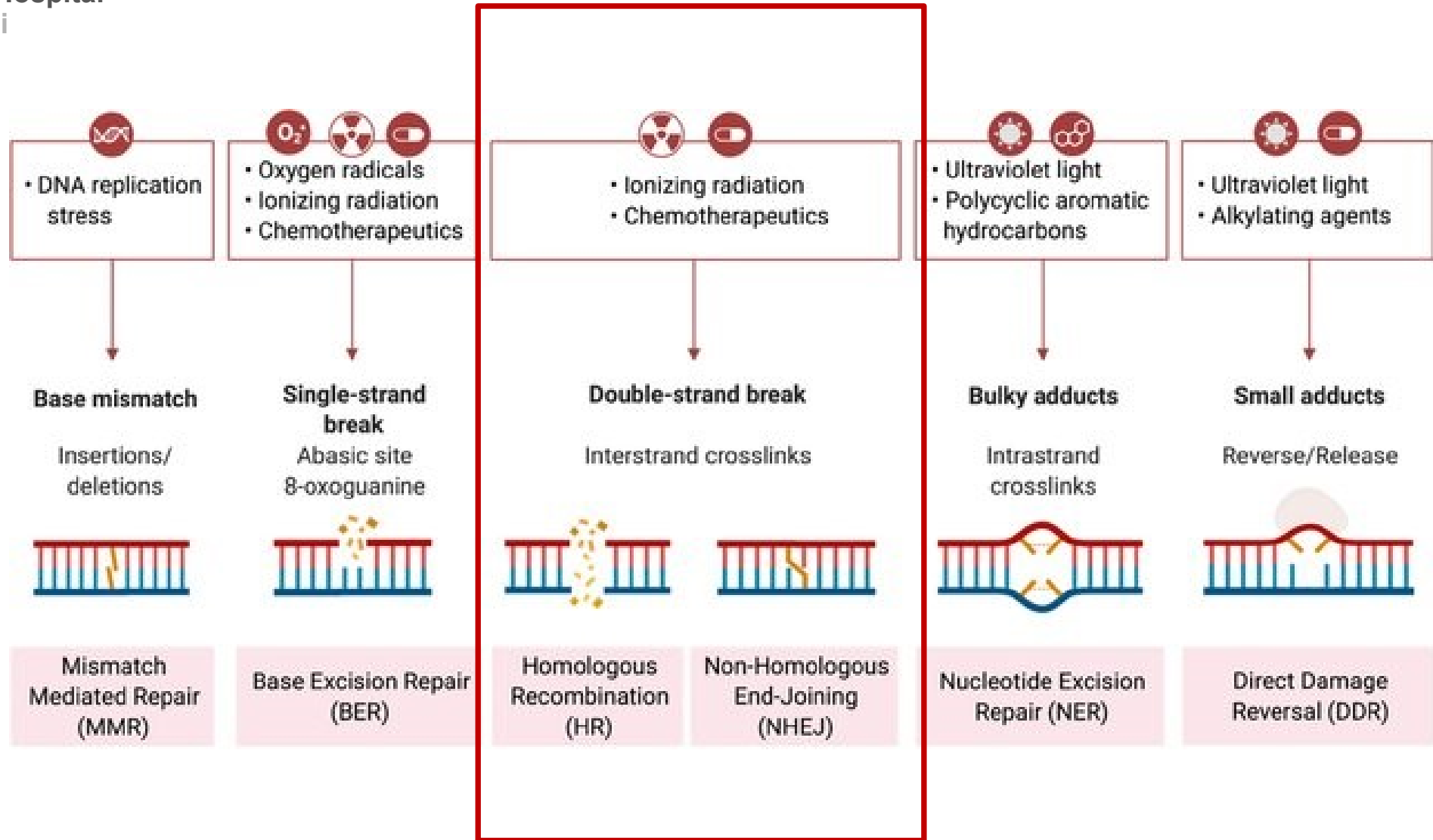
Selv om det primære behandlingsrespons er højt, vil sygdommen over tid progrediere

Prognosen for metastatisk castration-resistant PC (mCRPC) dårlig med en median overall survival (OS) på 24-30 måneder.

Approximately 5-10% of patients with mCRPC have somatic or germline *BRCA1/BRCA2* mutations - eligible for PARP inhibitor treatment (i.e. olaparib) - alone or in combination with abiraterone.

Limited number (approximately 50%) of patients benefit from treatment with PARP inhibitors.

**Er der et mønster som kan forudsige hvem der vil have respons?**



# Explorativt studie med brug af allerede eksisterende data

- Totalt 114 mCRPC patienter henvist til Fase 1 (eksperimentel behandling) i perioden 2015-2021 dvs. opbrugt alle standard behandlings muligheder
- Ialt 8 mCRPC patienter der har fået eksperimentel behandling på baggrund af en genomisk DNA repair defekt
- Sammenholdt deres genomiske profiler, både DNA og RNA med kliniske data og deres response af eksperimentelle terapi (PARP hæmmer).

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## ***TPR2:ERG Gene Fusion Might Predict Resistance to PARP Inhibitors in Metastatic Castration-resistant Prostate Cancer***

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**Abstract.** Background/Aim: The emergence of novel DNA damage repair (DDR) pathways in molecular-target therapy drugs (MTD) has shown promising outcomes in treating patients with metastatic castration-resistant prostate cancer (mCRPC). About 25% of mCRPC patients have actionable deleterious aberrations in DDR genes, primarily in the homologous recombination (HR) pathway. However, the response rate in patients with BRCA1/2 or mutations in HR-related genes is only 45%-55% when exposed to poly ADP ribose polymerase (PARP) inhibitor-based therapy (PARPi). A frequent characteristic feature of prostate cancer (PC) is the occurrence of genomic rearrangement that affects the transmembrane protease serine 2 (TPRSS2) and E26 transformation-specific (ETS) transcription factor-related gene (ERG). Materials and Methods: In this study, a total of 114 patients with mCRPC had their RNA and DNA sequenced using next-generation sequencing. Results: Based on their genetic profile of deleterious gene alterations of BRCA1/2 or ATM, six patients were selected for PARPi. Patients with TPRSS2:ERG gene fusion and homozygous alteration in ATM or BRCA2 (n=2) or heterozygous alterations (BRCA1 or BRCA2) and lack of TPRSS2:ERG gene fusion (n=2) did not

show clinical benefit from PARPi (treatment duration <16 weeks). In contrast, patients (n=2) without TPRSS2:ERG gene fusion and homozygous deleterious alterations in ATM or BRCA2 all had clinical benefit from PARPi (treatment duration ≥16 weeks). Conclusion: The TPRSS2:ERG transcript product might be used as a PARPi resistance biomarker.

Prostate cancer (PC) accounts for a high number of cancer-related deaths in men worldwide. In the USA, the PC incidence rate was 110.5 per 100,000 men during 2014-2018, while the death rate was 18.9 per 100,000 men during 2015-2019 (1). These figures are comparable to those observed in the Danish population.

A hallmark of PC is the high dependency on the androgen receptor (AR) for growth and survival (2). Androgen deprivation therapy (ADT) remains the backbone of systemic therapy in patients with localized and advanced disease. In addition, novel AR-targeting agents such as abiraterone acetate and enzalutamide are now administered in patients with metastatic castration-resistant PC (mCRPC) (3). Abiraterone acetate inhibits CYP17A1 (both 17 $\alpha$ -hydroxylase and 17,20-lyase), which is responsible for androgen biosynthesis, whereas enzalutamide binds to the androgen receptor, reduces the efficiency of its nuclear translocation, and impairs both DNA binding to androgen response elements and recruitment of coactivators (4, 5). Treatment options in mCRPC also include the use of taxanes (docetaxel and cabazitaxel), which inhibit mitosis by stabilizing microtubules, but also AR nuclear translocation, thereby reducing AR signaling (2). Although the introduction of radiopharmaceuticals such as Radium-223 and Lutetium-177-PSMA-617 has further expanded available treatment options, overall survival in patients with mCRPC remains poor (6).

**Key Words:** Prostate cancer, targeted therapeutics, next-generation sequencing, gene fusion, DNA repair gene, PARPi, ATR1, resistance.

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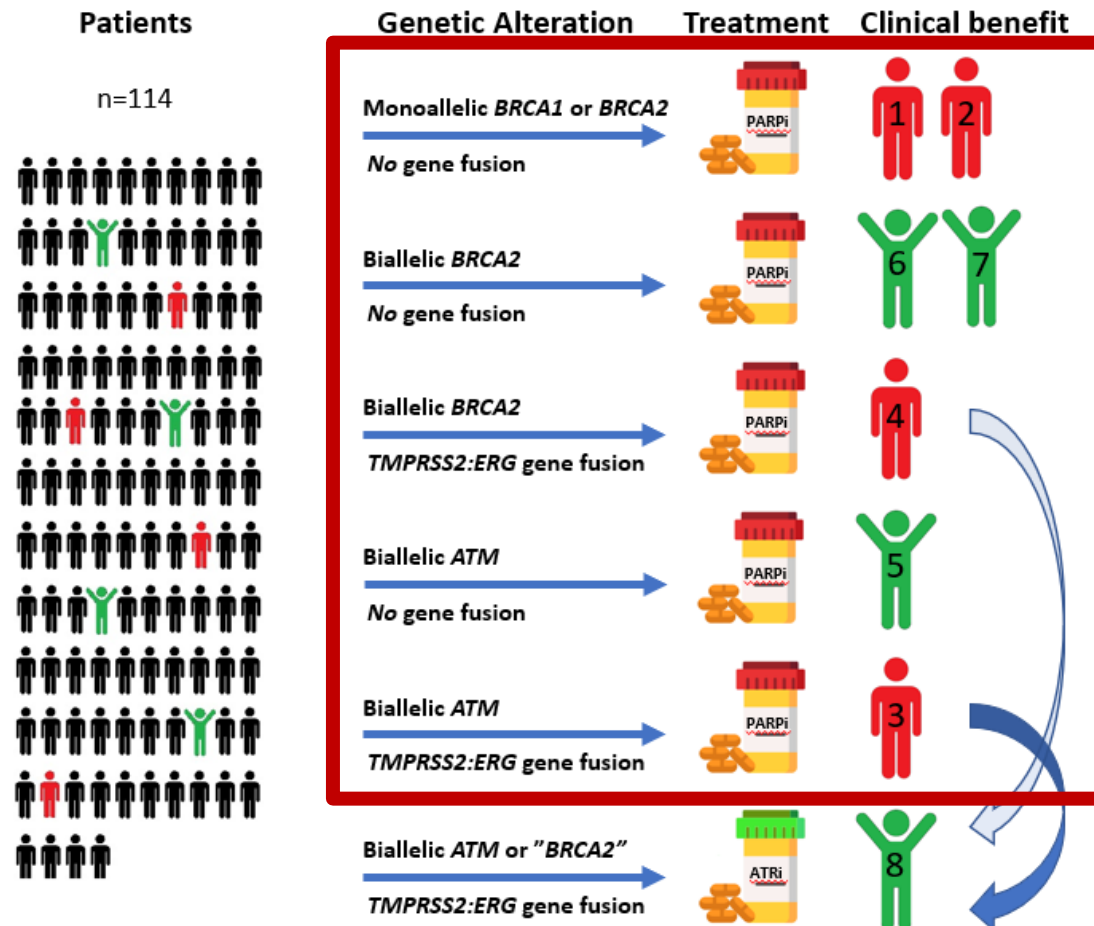
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# Resultater

- 10% af mCRPC patienter har ændringer i DNA repair gener især (*BRCA1/2* og *ATM* generne)
- Litteratur viser at cirka halvdelen (45-55%) respondere på PARP-hæmmer baserede terapi (n= 3/7)
- Arvelig ændring er grundlæggende ikke nok
- Biologisk er det velkendt at cirka 50% af alle PC har en specifik genændring (gen fusion *TMPRSS2:ERG*)
- PARP-hæmmer baserede terapi er godkendt som standard behandling
- ATR-hæmmer er stadigvæk eksperimentel (pt 8)



# Clinical protocol

Retrospective analysis on mCRPC  
received PARPi

and

**PROTOKOL GODKENDT den 13.10.2026 og vi er i gang**

prospective study on mCRPPC  
Receiving PARPi either alone or  
in combination with ADT.

To validate if *TMPRSS:ERG* gene-  
Fusion can predict effect of PARPi

## 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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**The aim** is to assess the value of ETS transcription factor family specific gene-fusion to predict response to PARPi.

**The hypothesis** is that the subtype of mCRPC patients with a biallelic pathogenic or likely pathogenic defect in genes involved in homologous recombination repair (HRR) will not respond to treatment with a PARPi, if also an ETS transcription factor family gene-fusion is present in the tumor tissue.

- 1) A retrospective analysis including patients with mCRPC who received treatment with olaparib as standard therapy between December 2020 and July 2025 at the Department of Oncology, Herlev and Gentofte Hospital.
- 2) we will investigate whether a gene-fusion of the ETS transcription factor family is present in archived tumor samples.
- 3) DoR and ORR will be evaluated using individual patient data from patient records including diagnosis and subtype, genomic data (DNA and/or RNA), 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.

DoR: Duration of response

ORR: Objective response rate

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 July 2025 and onwards at the Department of Oncology, Herlev and Gentofte Hospital.

Patients will be invited to participate in this study.

In this sub-study, we will investigate whether a gene-fusion of the ETS transcription factor family is present in archived tumor samples.

DoR 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 diagnosis and subtype, genomic data (DNA and/or RNA), 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.

# Spørgsmål ?

## PROSTATE CANCER

