A Review on Potential of PARP Inhibitors in the Treatment of Prostate Cancer

By

Saidul Islam
18146010

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
Brac University
May, 2022

Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

Student's Full Name & Signature:

Saidul Islam
18146010

Approval

The project titled "A Review on Potential of PARP Inhibitors in the treatment of prostate cancer" submitted by Saidul Islam (18146010) of Spring, 2018 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on 22th May, 2022.

Examining Committee:

Supervisor:
(Member)

_____

Dr. Shahana Sharmin
Assistant Professor, School of Pharmacy
Brac University

Program Coordinator:
(Member)

_____

Namara Mariam Chowdhury
Lecturer, School of Pharmacy
Brac University

Deputy Chairperson:
(Member)

_____

Dr. Hasina Yasmin
Professor, School of Pharmacy
Brac University

Departmental Head:
(Dean)

_____

Dr. Eva Rahman Kabir
Professor and Dean, School of Pharmacy
Brac University

Ethics Statement

No animal or human trial was conducted during this study

Abstract

Prostate cancer is still a fatal disease at metastatic castration resistance stage (mCRPC) in spite of pursuing advancements in patient survival, indicating the necessity of therapeutic approaches. A significant number of individuals having advanced prostate cancer, most of whom have a poor prognosis, have germinal and/or somatic mutations in their DNA damage response genes. These kinds of mutations lead to a reliance on the Poly (adenosine diphosphate ribose) polymerase for repairing single-strand breaks, indicating the necessity of Poly ADP Ribose Polymerase (PARP) inhibitors. Olaparib was the first FDA approved PARP inhibitor to demonstrate the improved overall survival in mCRPC patients having homologous recombination repair defects. Despite the fact that this is a significant step forward, there are still a number of questions regarding PARP inhibitors. This paper aims to discuss the significance and efficacy of PARP inhibitors mentioning the associated challenges and their future in the treatment of prostate cancer.

Keywords: Prostate cancer, therapeutic approaches, mCRPC, PARP Inhibitors, Olaparib.

Dedication

Dedicated to my beloved parents and my instructors

Acknowledgement

First of all, I would like to express my sincere gratitude to almighty Allah for granting me with countless blessings and opportunity to be able to complete this project.

Besides, I'd like to express my heartiest gratitude to my project supervisor Dr. Shahana Sharmin (Assistant Professor, School of Pharmacy, BRAC University) for providing me with the excellent opportunity to work on this fantastic project, which also allowed me to perform a lot of research and learn a lot of new things. I will be grateful to her for being so patient and sharing all those expert, valuable and sincere guidance throughout the entire phase which allowed me to accomplish this study.

I would also like to express my cordial gratitude to all the faculty members of school of Pharmacy for being a constant source of knowledge and inspiration throughout this whole four years which will definitely help me in the future while pursuing my dream.

Last but not the least, the guidance and support received from my parents and my friends helped me a lot finishing this project.

Table of Contents

List of Tables

List of Figures

List of Acronyms

PARPi	Poly ADP ribose inhibitor
AR	Androgen receptors
HRPC	Hormone-refractory prostate cancer
MAPK	Mitogen activated protein kinase
PIP2	Phosphatidylinositol (4,5)-bisphosphate
PIP3	Phosphatidylinositol (3,4,5)-trisphosphate
DDR	DNA damage response
BER	Base excision repair
NER	Nucleotide excision repair
NHEJ	Non-homologous end joining
HR	Homologous recombination
BRCA	Breast cancer gene
DSB	DNA double strand break
PC	Prostate cancer
PH	Prostatic hyperplasia
CRPC	Castration-Resistant Prostate Cancer
mCRPC	Metastatic Castration-Resistant Prostate Cancer
nmCRPC	Non-Metastatic Castration-Resistant Prostate Cancer

mHSPC	Metastatic Hormone-Sensitive Prostate Cancer
PSA	Prostate specific antigen
DRE	Digital rectal examination
TSM	Tumor Nodes and Metastasis
SSBs	Single stranded DNA breaks
NAD	Nicotinamide adenine dinucleotide
PARG	Poly (ADP-ribose) glycohydrolase
HRR	Homologous recombination repair
MMR	DNA mismatch repair
PCCR	Prostate cancer cluster region
OB1	Oligonucleotide/oligosaccharide binding domain 1
ADT	Androgen deprivation therapy
FOXA1	Forkhead box A1
FDA	Food and Drug Administration

Chapter 1

Introduction

In this current world cancer has become one of the most prevalent and life threatening diseases which is spreading as a result of our lifestyle we are leading (Mathur et al., 2015). Cancer is the uncontrollable cell growth which further activates oncogenes and/or deactivate tumor suppressor genes (Sarkar et al., 2013). After invading normal tissues and organs, due to the abnormality of tumor cells the cell itself can't respond properly to the signal of normal cell controlling behavior and further grows and divides in an uncontrolled manner and eventually spreads all over the body (Cooper, 2000). Cancer can be of various types and among them prostate cancer, breast cancer, bladder cancer, lung cancer, colon cancer, skin cancer are the most common in this current world. Currently in most developed countries Prostate cancer is the second leading cause of cancer-related death among men. According to a research conducted in 1997 it was found that around 2,09,900 American men were identified with prostate cancer where about 41,800 men died of it (Mazhar & Waxman, 2002). In the last 30 years in England and Wales the number of death rates tripled, where one in 13 people are being affected each year which clearly demonstrates the alarmingness of the disease. It is believed that survival of prostate cancer can be improved by early detection and treatment. In order to treat this disease currently therapies like radiation therapy, cryotherapy, hormone therapy, immunotherapy, targeted therapies and surgeries are available in the market (Mazhar & Waxman, 2002).

Parp inhibitor or Poly (ADP-Ribose) Polymerase which is one kind of drug and a type of targeted therapy is also used in terms of treating prostate cancer. In case of target therapy the drug is intended to be delivered to certain genes or proteins of cancer specific cells or tissues

that helps to promote cancer growth. Eventually, they identify and attack earmarked cancer cells by blocking the enzymes, proteins or other molecules while doing less harm to other cells (*Targeted Therapy* -2020). Parp inhibitors also work in the same way by blocking parp enzymes that help to repair DNA damage and blocking them will allow them to die as the cancer cells will be prevented from repairing (Chen, 2011). In recent times, PARP inhibitors have appeared to be playing a crucial role in combination with other cytotoxic agents in order to combat BRCA mutated tumors like prostate cancer, breast cancer, ovarian cancer, pancreatic cancer etc. Until now prostate cancer is the first disease which has an improved overall survival by using PARP inhibitors where somatic and/or germinal BRCA1 & 2 are the most predictive biomarkers of efficacy of PARP inhibitors (Teyssonneau et al., 2021).

1.1 Aim of the study

The aim of this study is to provide an overall idea about the role of PARP inhibitor specially focusing on it's mechanism of action, clinical significance, limitations and future prospect against the lethal prostate cancer.

1.2 Objective of the study

The objective of this study is to determine the efficacy, it's contribution towards advanced prostate cancer and all the relevant factors affecting the activity of PARP inhibitors. The study will also focus when and how PARP enzymes impact on the DNA damage and why they should be inhibited. The other objectives are to show the significance of improving them by overcoming the shortcomings so that in future they can help increase the survival of prostate cancer patients with their optimum efficacy.

Chapter 2

Methodology

This review which aims to discuss the potential of PARP Inhibitors in treating prostate cancer was accomplished on the basis of some current and prominent research publications and articles from high-impact journals. A detailed and in-depth study was conducted through the peer reviewed journals, articles and official reports. Search engines such as Research Gate, PubMed, Google Scholar, Science Direct, Elsevier, and others were used to gather impactful information from them. Moreover, google search was also used to gather basic information from credible and impactful websites as well. Finally, to generate the optimum quality review, a thorough screening of those articles were conducted to extract the most recent and relevant information.

Chapter 3

Prostate cancer

The prostate gland is the part of male reproductive organ that is found just below the bladder and in the area around the urethra**.** The prostate's primary job is to provide vital secretions to semen, which help to create ejaculate and maintain sperm viability. Tumors develop often in the cells of the prostate gland, most commonly in the mid-to-late stages of life (Rebello et al., 2021). An adult human prostate is split into three zones: central, transition, and peripheral, with fibromuscular and periurethral regions. The prostate glandular tissue residing in the peripheral zone forms more than 70% of the prostate glandular tissue in young adult males and contributes the most to normal prostate function. It is the most prevalent site of neoplasms in the elderly prostate, accounting for over 80% of all prostate tumors which are formed in this area (Rebello et al., 2021).

3.1 Pathogenesis

Dissociation and function of prostate including the growth and development of prostate cancer mostly dependent on androgen receptors (AR) signaling. Initially all prostate cancer gets dependent on the androgen receptor to interfere with the activity of androgens. A single copy of gene found in the X-chromosome encodes this AR and the protein is formed by 919 amino acids where the length may vary due to repeated unstable poly-glutamine, poly-glycine and poly-proline (Velcheti et al., 2008).Due to the highly dependency of prostate cancer growth on androgens, androgen-deprivation treatments are commonly being used for decades which are performed either by surgical or chemical castration resulting in suppressed androgen production. Though these kinds of treatment cease the tumor progression for almost 18 to 24 months, after that period a lethal drug resistant stage is formed and this phenomenon is termed

as hormone-refractory prostate cancer(HRPC) (Velcheti et al., 2008). Besides, when all the cancer cells of prostate gland become tumor independent then they will also be called hormone HRPC. Alteration in the DNA of AR gene, crosstalk between growth factor-AR be the probable mechanism of HRPC (Girling et al., 2007).

Prostate cancer develops and progresses in a complicated manner. Androgen receptor amplification or mutation can cause alterations of DNA in the AR gene. Besides, due to the crosstalk of AR signaling pathway with other pathways such as MAPK, Akt, PIP2, PIP3 etc effects on cellular processes like cell cycle, cell growth, cell differentiation and even on apoptosis and causes alteration of cells resulting in formation of tumors by following this adaptation in absence or decreased level of androgen. The rate of cell proliferation, apoptosis are balanced in normal prostate epithelium where in prostate cancer the balance is disrupted, resulting in tumor growth (Girling et al., 2007).

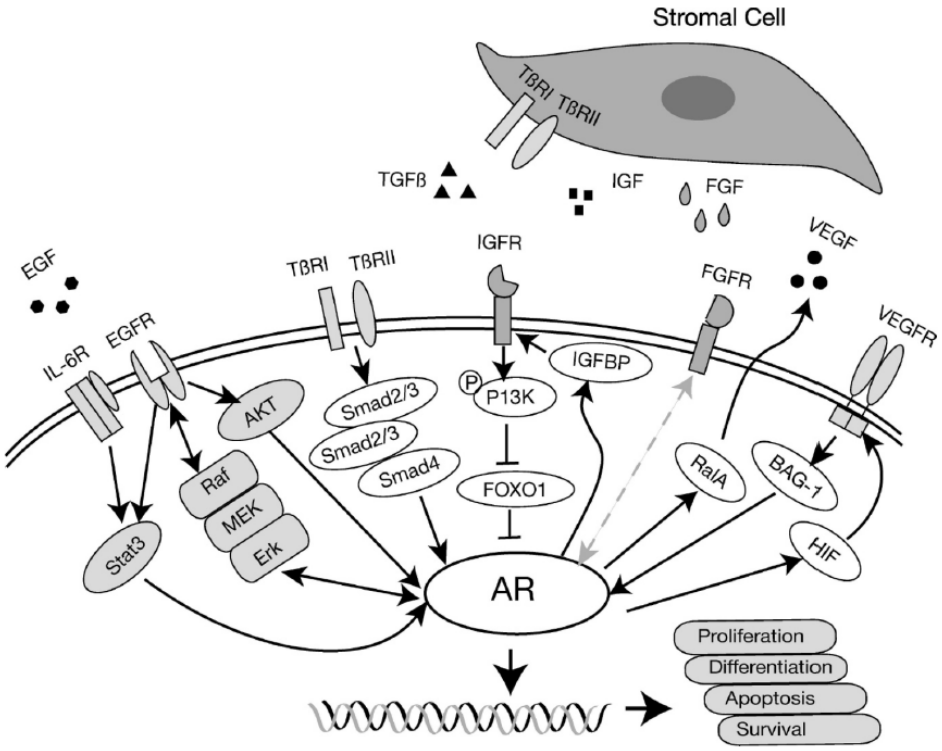

Figure 1: Crosstalk between AR receptor with other signaling pathway (Velcheti et al., 2008)

Apart from that, modifications in DNA damage recovery pathways (DDR) have recently been discovered to cause advanced prostate cancer. In general, homologous recombination and mismatch repair are the two pathways that DDR follows. Base excision repair (BER), nucleotide excision repair (NER) also helps in DNA Damage repair along with them. Non-homologous end joining (NHEJ) Homologous recombination mainly depends on BRCA1, BRCA2, ATM where mismatch repair relies on MLH1, MSH2, MSH6 and PMS2 (Vietri et al., 2021). In order to repair DNA double strand breaks, participation of proteins encoded by BRCA1, BRCA2, ATM, RAD51 genes are required which also act as tumor suppressor. In the case of DSBs the poly (ADP-ribose) polymerase 1 (PARP1) complex keeps a great role by detecting those disruption site of DSB lesions and marking those sites by attaching ADP ribose to chromatin bound proteins in order to repair them. But the problem occurs when those PARP can't recognize cancer cells and repair them and eventually cause proliferation of tumor cells (Vietri et al., 2021).

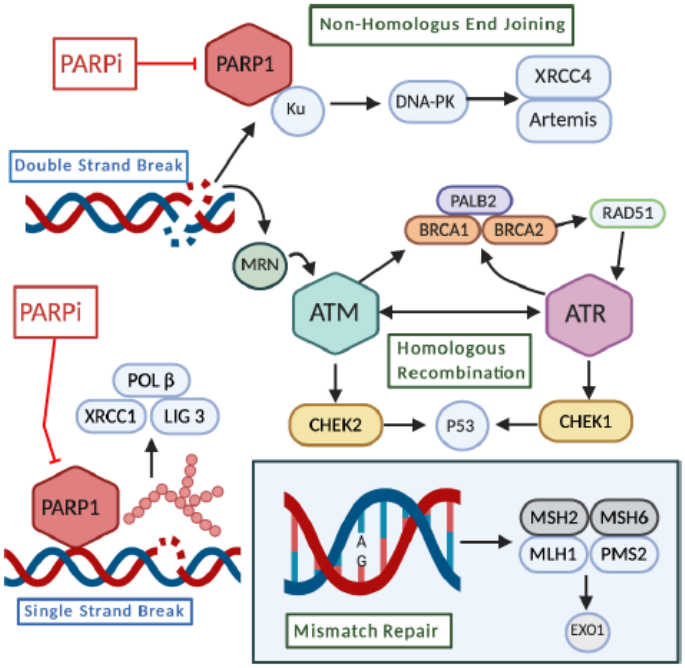

Figure 2: Mechanism of DNA Damage Repair pathways (Risdon et al., 2021)

3.2 Risk factors

The only two risk factors firmly linked to the development of Prostate cancer are age and heredity, specifically grandparents, parents or other close relatives having an experience of breast, cervical or ovarian cancers. According to research, around 36.3% cases of prostate cancer were found in the seventh decade where the rate was at 31.6% between the ages of 70 to 79. In 10% of patients, PC is hereditary carrying 2- to 3-fold increased risk, which may incline to a 5-fold greater risk in terms of having more than one affected relative (Heindenreich et al., 2014). Furthermore, multiple genes have been found to be linked with the progression of PC, creating it a polygenic disease. It is also well known that androgens and estrogens have a potent role in the development of PC. PC or prostatic hyperplasia is uncommon in patients having congenital androgen insufficiency (PH). However, patients may experience PC or PH if androgen ablation is conducted after puberty. An increased risk of PC, relapse and/or development is found to be linked with the presence of two or more components of metabolic syndrome (Castillejos-molina & Gabilondo-navarro, 2016). Apart from that, incidents like Asians who have migrated to the United States have a higher rate of PC than those who have stayed in their own country. These cases could be related to the adoption of new dietary habits that vary from those in their own country and this tendency backs up the theory that PC rates can also be influenced by some nutritional factors found in our regular diet. Besides, smoking has already been found to be linked with increased risk of PC as it enhances the level of circulating cadmium (Castillejos-molina & Gabilondo-navarro, 2016).

3.3 Stages

Depending on the expansion of the tumor cell, prostate cancer is usually divided into four stages which are stage I,II,III & IV. Stages I and II are the early stages where the cancer cells do not

expand outside the prostate. In stage III the tumor expands beyond the prostate but does not spread far away from the tissue. But in terms of stage IV which is also called advanced prostate cancer, the tumor expands beyond the prostate and even attacks lymph nodes, liver, lungs or bones (*Urology Care Foundation*, 2021). There are some advanced prostate cancer like Castration-Resistant Prostate Cancer (CRPC), Non-Metastatic Castration-Resistant Prostate Cancer (nmCRPC), Metastatic Prostate Cancer, Metastatic Hormone-Sensitive Prostate Cancer (mHSPC), Metastatic Castration-Resistant Prostate Cancer (mCRPC). When a PC is discovered in its early stages, it can be treated or monitored. Although there are several options for treatment of advanced PCs it is not "Curable" at all. Treatment can only help in slowing down the growth of advanced prostate cancer (*Urology Care Foundation*, 2021).

3.4 Diagnosis

For the diagnosis purpose of prostate cancer various diagnosing tools like PSA blood test, Digital rectal exam, Imaging & scans, Biopsy etc are currently available in the market. PSA or prostate specific antigen is a serine protease that is generated from the prostatic epithelium and periurethral glands which are abundant in prostatic secretions. PSA is produced only from the prostate and prostate cancer and the level of PSA are often expressed in Nano grams per milliliter of blood (ng/mL). Less than 4 ng mL is adopted as the normal reference range of serum PSA (Borley & Feneley, 2009). Then comes the Digital rectal examination or DRE which was the first screening test and offers the advantage of recognizing tumors that do not secrete PSA. During this test, alterations in the gland's form, nodularity, thickness or consistency. However, even in the competent examiner's hands, the DRE 'misses' a significant fraction of tumors. That is why it is still ordinarily used in combination with PSA testing (Borley & Feneley, 2009). Moreover, a prostate biopsy may be performed on men who have been detected with advanced prostate cancer. A biopsy is a procedure that involves taking a

specimen from the prostate or other organs and examining it for cancer cells. Prostate biopsies can be done in a variety of ways. These could be performed by placing a probe in rectum, through the perineum skin or by a specialized imaging instrument like an MRI. Biopsy requires small samples of tissue for observing under a microscope which takes 10 to 20 minutes to be completed. The pathologist examines the samples and do the "staging" of the tumor (*Urology Care Foundation*, 2021). Staging of prostate cancer depends on three factors which are TNM score, Gleason score and PSA score. TNM stands for the tumor, nodes and Metastasis, used for the classification of clinical and pathological stages of tumor. Gleason score is based on the degree of differentiation of the cells of the prostate and determined by histology. It is calculated by adding the grade of the most dominant cells in the samples and the highest grade of the remaining cells (Castillejos-molina & Gabilondo-navarro, 2016).

Table 1: Staging of prostate cancer depending on risk level (Castillejos-molina & Gabilondo-navarro, 2016)

Risk	PSA score	Gleason score	TNM score
Low	<10	≤6	T1-T2a
Intermediate	10-20	7	T2b
High	>20	8-10	≥T2c

Chapter 4

An overview on PARP Inhibitor

PARPs or poly-ADP-ribose polymerases are enzymes which mainly catalyze the transfer of ADP-ribose to certain target proteins and they are involved in a number of biological functions such as recombination, transcription, replication, cell proliferation and most importantly DNA damage repair. PARP family has almost 18 members and each of them are encoded from different genes sharing homology of a conserved domain (Morales et al., 2014). PARP1 and PARP2 isoforms are well recognized for their participation in DNA damage repair either by base excision repair against SSBs (Single Stranded DNA breaks) or by Nucleotide excision repair where the rest of PARPs are involved in the role of other cellular processes. But the problem is in terms of tumor cells they demonstrate a poor repair system and that's where the PARP inhibitors come causing the PARPs to block so that the cells can't repair themselves and lead them to death (Morales et al., 2014).

4.1 Design and optimization

PARP1, a member of PARP family, was initially the main target of PARPi which uses Nicotinamide adenine dinucleotide (NAD^+) as a substrate in order to construct mono or poly ADP adducts on the acceptor proteins. PARP-1 is made up of three primary domains: a catalytic domain, an auto modification domain and a DNA binding domain, all of which are involved in the DNA repair system. The DNA binding domain's zinc fingers play a great role for detecting DNA damage and attaching to the damaged spot. A structural change occurs and the auto modification domain firmly links with the catalytic domain as a result of that binding process, and eventually the auto modification domain gets ADP-ribosylated using NAD^+ as a substrate (Yelamos et al., 2018). This action activates PARP-1/2's catalytic machinery, causing branched

chain polymers of ADP-ribose to form on adjacent histone DNA binding proteins. The bulky, negatively charged polymers loosen the chromatin's tertiary structure and offer a platform for DNA repair enzymes like XRCC1 and DNA ligase to recruit. Poly (ADP-ribose) glycohydrolase (PARG) breaks down the ADP (ribose) polymers, allowing the repair enzymes to gain access to the damaged DNA. If this single strand repair is not performed, the single strand breaks might become double strand breaks, resulting in additional genomic instability and apoptotic cell death. Many cancer cell types use this PARP-mediated DNA repair pathway, which leads to drug resistance to DNA-damaging chemotherapeutics and tumor development. As a result, when a PARP-1/2 inhibitor is used in conjunction with DNA-damaging chemotherapeutics or radiation, causes cancer cell's DNA repair processes to be compromised, resulting in genomic malfunction and cell death. PARP-1/2 inhibitors can also be used as a single treatment for tumors that lack particular types of DNA repair systems (e.g. homologous recombination) and the phenomenon is termed as synthetic lethality (Thangue, 2011).

Because of the scope of PARP-1 oncological research, as well as various other considerations, many medicinal chemistry projects used a successful optimization strategy to find clinical candidate PARP-1 inhibitors (Ferraris, 2015). The optimization of several of the following parameters led to the discovery of many of the first generation PARP-1 inhibitors which are (1) Enzymatic inhibition of PARP-1; (2) ability to kill cells lacking DNA repair mechanisms; (3) in vitro characterization in cancer cell lines and the ability to potentiate chemotherapeutic agent's cytotoxicity and (4) physicochemical properties. Many medicinal chemistry groups have discovered 2nd generation inhibitors, which have some of the following properties like (1) In vitro profiling of PARP inhibitors against other members of the PARP(mostly PARP 2) family (2) In vitro and in vivo comparisons with current benchmark PARP-1 inhibitors; (3) ability to trap the PARP enzyme in a tight complex along with DNA, known as "PARP

trapping"; (4) ability to kill cancer cells those were resistant to other PARP-1 inhibitors (Ferraris, 2015).

4.2 The launch of PARP Inhibitor clinical development

Two seminal studies published in 2005 showed that tumor cells those lack BRCA1 or BRCA2, which are key tumor suppressor proteins engaged in double-strand DNA break (DSB) repair, are partially sensitive to those inhibitors of the PARP family based on the particular concept of synthetic lethality model. Synthetic lethality is basically a situation where cell death is caused by mutations (changes) in two genes, but not by a mutation in either gene alone (Mateo et al., 2019). A research found that PARP1 which is the main target of PARP Inhibitor, inhibiting it alone is not as lethal as the DNA lesions (occurs due to the PARPi) and the DNA can be recovered by DNA recovery pathway as well. To the contrary, in the absence of BRCA1/2 it was also found that PARPi-induced DNA lesions aren't repaired rather they seem to cause cytotoxicity. The mentioned preclinical discoveries led to the development of PARP inhibitor as a single agent in terms of treating BRCA1/2 defective tumors though they were originally created as radio and chemo-sensitizing medicines for the treatment of cancer. Following, in 2009 PARPi Olaparib clinically verified the synthetic lethal interaction between PARP1 inhibitor and BRCA1/2 deficient cell as a first man clinical trial (Mateo et al., 2019).

4.3 Mechanism of action

Pharmacological PARP inhibitors have two main effects: (I) catalytic inhibition of PARP1 (i.e. inhibiting PARylation) and (ii) locking or 'trapping' PARP1 on damaged DNA. Although the exact mechanisms underlying PARP1 entrapment is still unknown, two hypotheses have been suggested: (I) PARPi inhibits auto PARylation and hence prevents PARP1 from being released from DNA or (ii) PARP inhibitor binds to the catalytic site causing allosteric alterations in the

PARP1 structure by increasing DNA avidity. In both cases, trapped PARP1 prevents replication forks from progressing (Hopkins et al.,2015). HR has the ability to restore these halted replication forks in terms of normal, non-tumour cells. In cancer cells lacking one of the main HR proteins, such as BRCA1, BRCA2, PALB2, or RAD51, they use alternate DNA repair pathways primarily through non-homologous or micro homology mediated end-joining in order to repair DNA lesions occurred by PARPi. Instead of repairing the damaged DNA sequence to its original state, error-prone DNA repair activities result in genome fragmentation, which eventually kills the cell (Shen et al.,2013). PARPi activity in HRR-deficient cells is mediated by a variety of mechanisms. In the following diagram PARP inhibitor seems to inhibit SSB repair via altering the base excision repair (BER) pathway, as well as inducing PARP1 entrapment by blocking auto-PARylation and/or PARP removal from DNA. Unresolved DNA double-strand breaks (DSBs) result in cell death in HR repair (HRR)-deficient cells (Mateo et al., 2019).

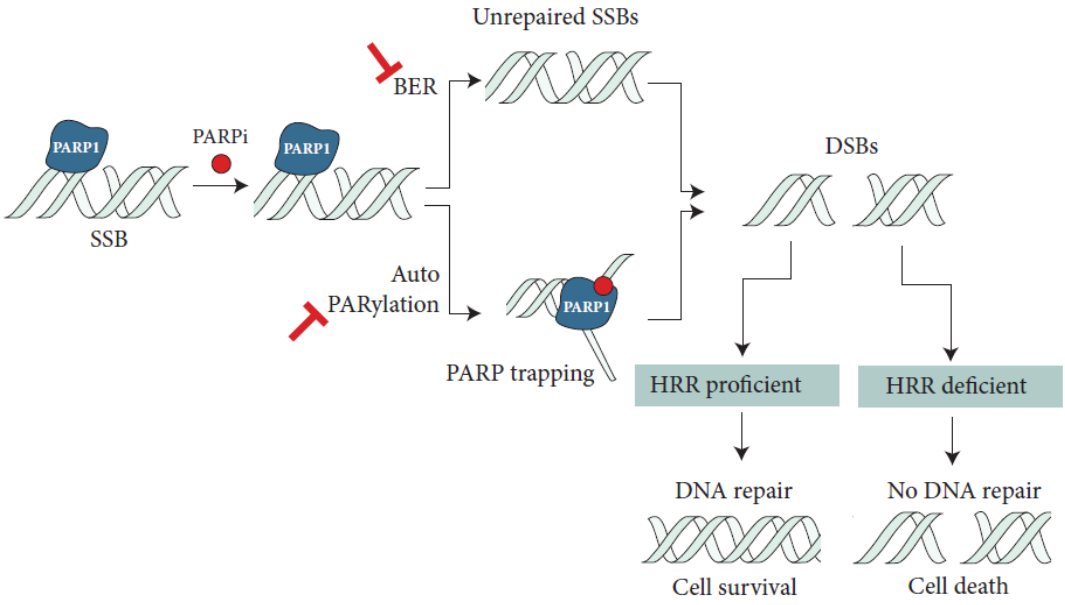

Figure 3- Mechanism of action of PARP inhibitor in terms of HRR-deficient cell (Mateo et al., 2019)

Chapter 5

Clinical significance of PARPi against Prostate cancer

Poly (adenosine diphosphate-ribose) polymerase inhibitors are the targeted medication intended to treat tumors with faulty homologous recombination repair (HRR) process. According to some preclinical data, PARP inhibition is particularly effective against prostate cancer (PC) in individuals with HRR-deficient tumors which can improve the death rate of patients having BRCA1/2 mutations through a synthetic lethality. PARPIs are also a fairly unique clinical therapy option for (mCRPC) (Xia et al., 2021). Apart from that, they are also being used as monotherapies as well as in combinations based on purported therapy synergy. While the first single-agent development focused on individuals with known impairments in DNA-repair pathways, combined approaches are being studied for a broader patient population (Pezaro, 2020).

5.1 PARPi against advanced prostate cancer

We know that DNA damage is linked to cancer and DNA damage response (DDR) pathways are developed to protect genomic stability or to protect from deletions, amplifications or any kinds of mutations. Prostate cancer can be caused by faulty DDR pathways where germline or somatic mutations in DDR genes are identified in both primary and metastatic prostate cancer. There are multiple DDR pathways such as BER, NER, MMR, homologous recombination and non-homologous end joining which play a crucial role in maintaining the integrity of DNA. Impaired DDR pathways can be dangerous because they can cause the survival and proliferation of damaged DNA leading to tumorigenesis. Advanced prostate cancer in association with malfunctioned HRR (Homologous recombination repair) including BRCA,

ATM, PALB2 mutations have also been reported to be treated with PARP inhibitors (Shah et al., 2021).

5.1.1 PARPi response to BRCA mutations

In case of germline or somatic mutations in PC, DDR damage mostly represents 25% of the whole cases where BRCA remains the most common scenario to occur in terms of advanced metastatic disease. BRCA1/2 genes located at 17q21 and 13q12 chromosomes are inherited in an autosomal dominant form with partial penetrance (Chatterjee et al., 2017). In general, The BRCA1 and BRCA2 genes are important DNA repair and transcription regulators which are linked to ovarian, prostate, and pancreatic cancer. To be specific, for controlling cellular systems like chromatin modeling, DNA Damage response, DNA transcription are responsible for a specific protein encoded by BRCA1 gene. The BRCA1 gene also helps in regulating the Androgen receptor which is responsible for mediating the development of prostate cancer through a signaling pathway. To the contrary, if we consider BRCA2, it's role is confined to DNA recombination and repair. BRCA 2 gene which also convey prostate cancer cluster region (PCCR) where the oligonucleotide/oligosaccharide binding domain 1 (OB1) and Tower domain 2 (OB2) are linked to the higher risk of developing prostate cancer (Patel et al., 2020). Two areas in BRCA2 (c.756-c 1000 and c.7914) were detected as susceptible to developing Gleason 8b prostate cancer which was observed through a global analysis of 6500 male patients having BRCA1 and BRCA2 mutagenic sequence variants. It was previously mentioned, both germline and somatic mutations in DDR genes have been identified with particular emphasis on the BRCA1/2 genes contributing to the progression of prostate cancer driving towards advanced stages. Due to the functional loss of BRCA1 and BRCA2 genes HR can't repair DSBs properly. Due to their absence or malfunctions, nonconservative and potentially mutagenic

methods are used to repair DNA. The tendency of cancer caused by deleterious mutations is thought to be caused by genomic instability of BRCA genes (Prakash et al., 2015).

As PARP is involved in DNA Damage response by repairing single strand breaks that's why their inhibitors are fairly effective in treatment of this pathology. The present usage of PARP inhibitors in cancer treatment is based on their mode of action, which specifically targets BRCA-mutant cancer cells. Synthetic lethality is the main method adopted by PARP inhibitors to treat BRCA mutated prostate cancer. Synthetic lethality is a process in which inactivation of one gene allele causes the cell to survive where disruption of multiple gene alleles leads the cell to death (Bednarz-Knoll et al., 2019). In general, oxidative stress is elevated in cancer cells and causes DNA damage. Normally, DDR pathways would repair the DNA damage, however due to the malfunctions, DDR inhibitors such as PARP inhibitors are utilized to generate synthetic lethality, which results in tumor cell apoptosis. Moreover, BRCA1 and BRCA2 mutant cells are vulnerable to PARP inhibitors and according to in vivo and ex vivo investigations of PARP inhibitors they have indicated to have potency to diminish AR function as well, which can be effective to decrease the growth of castration resistant prostate cancer. Alongside, PARP inhibitors may also be helpful in prostate cancer with genes that indirectly help in the HR pathway behaving like BRCA mutations (Shah et al., 2021)

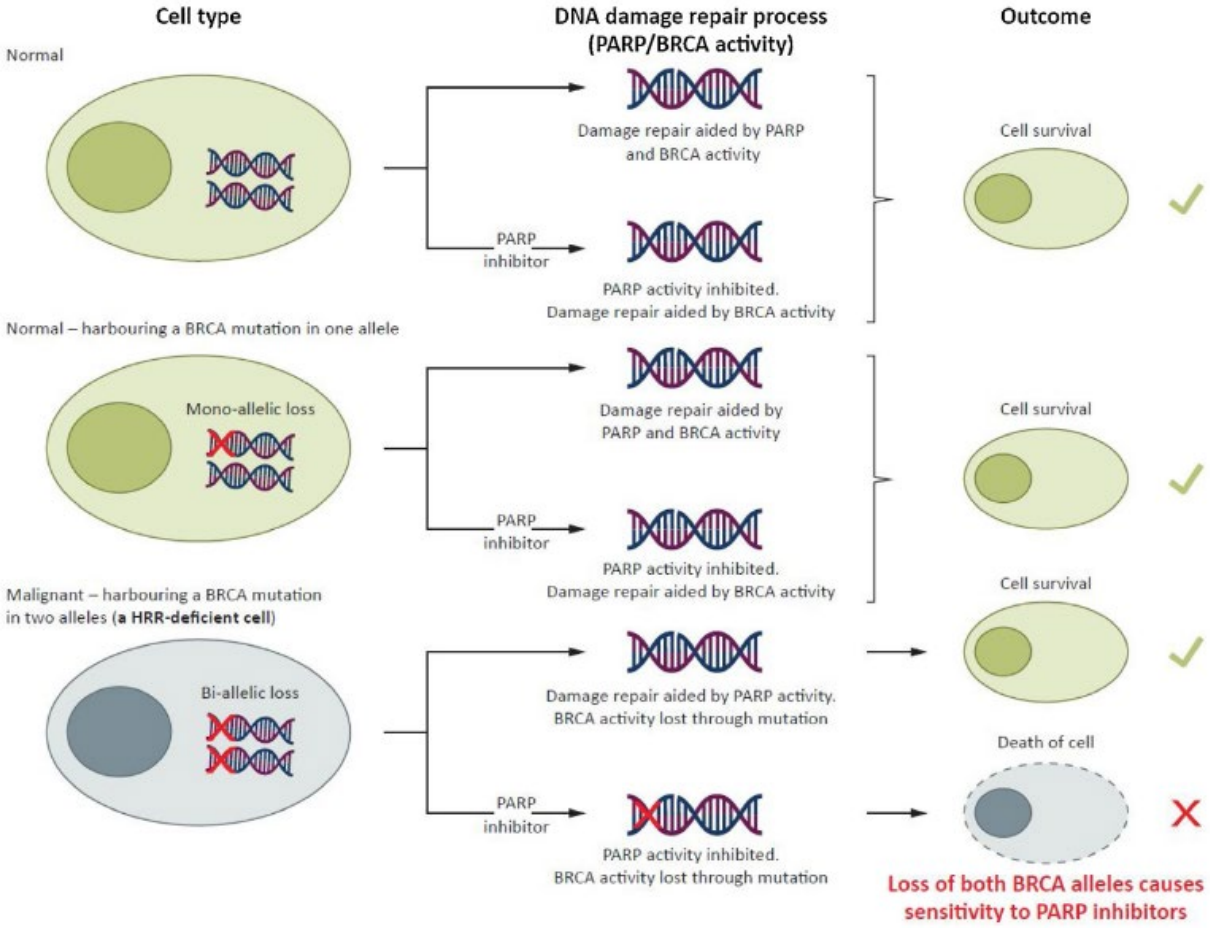

Figure 4: Role of PARPi in BRCA mutated cancer cell repair and apoptosis (Nizialek & Antonarakis, 2020)

5.1.2 PARPi response to Non-BRCA mutations

Apart from BRCA, mutations in other genes can be linked to a deficiency of DNA damage repair (DDR) and their tumor cells can also be vulnerable to PARP inhibitors. DNA damage repair genes other than BRCA for instance, ATM and CHEK2 as DNA damage sensors, CDK12 as a BRCA gene regulator, PALB2 and FANCA which deal with BRCA1 and/or BRCA2 genes during repair of DNA are were assumed to be sensitive against PARPi (Abida et al., 2020). In metastatic castration-resistant prostate cancer, genomic changes in these genes may induce synthetic lethality when PARP inhibition is used. In order to check this hypothesis,

Patients with mCRPC and deleterious non-BRCA 15 altered DDR genes were enrolled in the phase 2 TRITON2 research of Rucaparib to explore this possibility. In the TRITON2 test patients with mCRPC who had deteriorated from 1 to 2 lines of next-generation androgen receptor (AR)–directed therapy were basically enrolled. The test included patients having non-BRCA DDR gene mutations (ATM [n=49], CDK12 [n=15], CHEK2 [n=12], and additional DDR genes [n=14]) (Abida et al., 2020). The patients were given rucaparib and were screened to observe the balance of radiographic and PSA responses. From the test it was found that after providing a particular PARP inhibitor 2 people had responded for radiographic response among 19 evaluable patients and 1 person for PSA test among 49 individuals having ATM alteration. But in case of patients having CDK12 no individuals responded for the radiographic response and only 1 person responded in PSA test among overall 15 patients and the effect lasted for about 1.8 months (Abida et al., 2020). Moreover, among the patients with altered CHEK2 only 1 individual for radiographic test and 2 for PSA test responded accordingly among the evaluable 12 overall patients. However, in case of alteration PALB2 gene showed a slight positive response by responding 4 and 5 individuals respectively in radiographic and PSA test among 14 evaluable patients. Though the PARPi shows radiographic and PSA responses against BRCA alterations, in the case of non-BRCA it seems to be less effective in men with mCRPC having ATM,CDK12,CHEK2 alterations. However, the findings mentioned above suggest that the PARPi against prostate cancer patients with PALB2 mutations may have an optimistic future (Abida et al., 2020).

5.1.3 PARPi response to androgen receptor signaling

Prostate cancer (PC) growth and progression can be facilitated by AR-mediated gene expression. Advanced PCa can be treated with androgen deprivation therapy (ADT) but the problem is the patients who reacted to the treatment initially, however, will eventually develop

castration-resistant (CRPC) prostate cancer and that will be incurable. Moving on, According to studies of genome sequencing, FOXA1 is one of the most commonly altered genes in primary prostate cancer, and even more so in metastatic CRPC (Wedge et al., 2018) . FOXA1 is a gene that attaches to the enhancer sites in the genome, increasing local chromatin accessibility and making it easier for AR to recruit. FOXA1 is linked to PC formation and progression, most likely through its influence on the AR cistrome. As a result, inhibiting AR by targeting FOXA1 is a promising treatment option for CRPC. Cancer cells that lack BRCA1 or BRCA2 rely on PARP-regulated DNA repair systems and are highly susceptible to PARP inhibition (Gui et al., 2019). Based on the function of PARP-1 most of the PARP inhibitors mechanisms of action are designed against the cancer cells. As the action of AR has been related to DNA damage and responses, PARP-1, as an abundant protein, will interact with AR or act as a coactivator. In terms of transcription initiating and genomic reprogramming, the relationship between FOXA1 and the DNA-repair complex is crucial. As a result, PARP1 inhibition is likely to have some effect on AR-mediated transfection. Moving on, PARP-2 is also an integral part of the AR transcriptional machinery, interacting with the pioneer factor FOXA1 and enabling AR binding to prostate-specific enhancer sites across the genome. Instead of attacking AR directly, selective targeting of PARP-2 can provide an alternate pharmacological method for AR suppression through altering FOXA1 binding and these findings can enhance the clinical application in the area of prostate cancer through PARP targeted therapy(Gui et al., 2019).

5.2 PARPi in combination therapy

PARP inhibitors work in conjunction with DNA-damaging chemotherapy to prevent repair of the DNA, resulting in greater (lethal) damage. Several preclinical investigations, as well as certain clinical research, have shown that inhibiting DNA repair using PARP1 inhibitors can

enhance the potential of traditional chemotherapy or radiation therapy. DNA methylating drugs, and radiotherapy are all hypersensitive in PARP1-deficient or PARP-1 inhibitor-treated cells. Concerning the patient's safety, the chemotherapy as well as the periodic PARP inhibitor must be lowered in dosage. Furthermore, the combination of PARP inhibitors with PD1/PDL1 inhibitors are still under observation since they can be vulnerable towards immune checkpoint inhibitors due to the presence of immune related hallmarks in HRD deficient cancer (Greve et al., 2016).

Moreover, According to some preclinical investigations it was found that inhibition of both PARP and AR pathways provide a synergistic effect in prostate cancer (Nientiedt et al., 2021). Generally, in the treatment of prostate cancer Androgen receptor modulators (eg-enzalutamide) and cytochrome 17 (CYP17) inhibitors (eg-abiraterone) are also approved method of therapy and In terms of treating patients with mCRPC, both abiraterone and enzalutamide offer a minor but considerable impact. But then PARPi and those anti-androgen pairs in the hopes of inhibiting AR, they cause genomic instability and trigger PARPi synthetic lethality all at the same time (Dréan et al., 2016). Aside from second-generation antiandrogens, chemotherapy and immune checkpoint inhibitors a number of phase I/II trials are now undergoing to observe PARP inhibitors in combination with other treatments (Nientiedt et al., 2021).

Chapter 6

Examined PARPi to treat prostate cancer

Over the last decade, the treatment of metastatic prostate cancer has progressed dramatically. More recently, Poly-ADP-ribose polymerase (PARP) inhibitors have brought a breakthrough which have improved the prognosis of patients suffering from metastatic prostate cancer particularly having genetic alterations. Rucaparib (Rubraca) and Olaparib (Lynparza) are the first two PARP inhibitors authorized by the Food and Drug Administration (FDA) in May 2020 in the treatment of prostate cancer (Grewal et al., 2021). These two recent addition by the Food and Drug Administration (FDA) have created a whole new therapy option for some men having prostate cancer. These approved PARP inhibitors cover most of the requirements of a drug for treating prostate cancer, especially in terms of those patients whose tumor has spread (metastasized) and no longer responds to traditional hormone therapy, a condition known as castration-resistant disease (Virtanen et al., 2019). In general the metastatic prostate cancer treatment focuses on the medication that inhibits hormones so that it can't fuel the growth and spread of tumor cells. On the other hand, the drugs olaparib and rucaparib function in a different way. They inhibit the function of a protein called PARP, which aids cells in repairing certain DNA damage. According to studies, 20–30% of men having metastatic prostate cancer have genetic mutations which hamper DNA repair systems of the cells. In order to receive those 2 drugs, patients must have specific genetic mutations that stop it to repair DNA damage and that's why this is definitely a good news for prostate cancer patients as most of them have that mentioned specific genomic mutations in their body. Moreover, Niraparib is another PARP inhibitor which has a higher chance of approval in the near future (Virtanen et al., 2019).

Table 2- Examined PARP inhibitor in the treatment of Prostate Cancer (Grewal et al., 2021)

Clinical trial name	Primary objective	Takeaways
Rucaparib (FDA approved)		
Triton2 -(2016-present) - Clovis Oncology	To determine the response from patients with mCRPPC and HRR gene deficiency after treating with Rucaparib	-52% of patients having BRCA alterations showed decreased PSA level -Less response of patients having other alterations
Triton3 -(2017-present) -Clovis Oncology	To determine the efficacy of Rucaparib in patients with BRCA and ATM gene mutation who haven't undergone chemotherapy yet	- Based on Triton2 -Results pending
Olaparib (FDA approved)		
PROfound -Completed(2016-2020) -AstraZeneca	To evaluate the effectiveness of the drug as a single therapy for patients having mCRPC after receiving hormonal therapy	Increased patient survival and reduced cancer progression of patients having BRCA and ATM alterations
TOPARP -Completed(2012-2019) -Institute of Cancer Research,UK	To test the anti-tumor activity of the drug and to determine predictive biomarkers	Showed effective activity towards mCRPC patients with BRCA, ATM & PALB2 gene mutations
PROpel -(2018-present) -AstraZeneca	To test safety and efficacy of the Olaparib along with abiraterone in patients having mCRPC	Results pending
KEYLYNK -(2019-present) -Merck Sharp & Dohme Corp.	To test the efficacy of Olaparib in combination with pembrolizumab	Results pending

Niraparib (Pending approval)		
GALAHAD -(2016-present) -Janssen Research & Development	To evaluate the safety, efficacy and pharmacokinetics in men having mCRPC with DNA repair deficiency	Effective among mCRPC patients having BRCA mutations

6.1 Rucaparib

Rucaparib (RUBRACA) received accelerated approval from the FDA due to the trial on May 15, 2020, for mCRPC affected BRCA mutated patients who have already received androgen receptor-directed therapy and taxane-based chemotherapy. TRITON2 and TRITON3 studies are two recent clinical trials that cleared the path for Rucaparib's FDA approval. TRITON2 trial is mainly responsible for achieving the accelerated approval from FDA which is a phase II experiment investigating Rucaparib 600 mg dosages in patients with mCRPC associating BRCA1/BRCA2, ATM or any other DDR gene mutations. According to preliminary findings, 43.9% of patients with a BRCA mutation had a valid objective response rate (ORR) where a significant drop in PSA levels was also observed at 52% among those patients. But patients having mutations other than BRCA had a poor ORR and PSA response towards the treatment. Moving on, TRITON3 as a phase III clinical trial is currently ongoing to examine the effectiveness of Rucaparib compared with second line androgen receptor directed therapy in patients having mCRPC. In this trial all of the patients previously improved in the first line androgen receptor targeted therapy and had BRCA1/2 or ATM mutations but didn't receive any chemotherapy. The goal of this research was to confirm the benefits previously seen in the TRITON2 trial (Grewal et al., 2021). Following the trial TRITON2, FDA approved the use of

this medicine only for men with BRCA1/2 mutations who have progressing tumor cells even after taking hormone blocking treatment and chemotherapy (*National Cancer Institute*, 2020).

$C_{19}H_{18}FN_3O•C_{10}H_{16}O_4S$ is the chemical formula of Rucaparib having a molecular weight of 555.67 Dalton. It is structured to inhibit PARP1, PARP2 and PARP3 which are part of mammalian PARP enzymes and shows a versatile pharmacokinetic profile characterized by cancer patients. After assessing the pharmacokinetic profile it was found that Rucaparib shows time-independence and dose-proportionality along with a linear pharmacokinetic profile over a dose ranging from 240 to 840 mg twice daily. In terms of absorption, following the FDA approved recommended dose, the median T_{max} was found at 1.9 hours where the bioavailability of immediate-release rucaparib tablets was found between the range of 30% to 45% (Anscher et al., 2021). Accordingly injecting a single intravenous dose of 12–40 mg rucaparib, the volume of distribution was seen in a steady-state at the range between 113–262 L. Regarding elimination, following the same medication the clearance rate was found between the range of 15.3 to 79.2 L/hour. Finally, in terms of metabolism, after going through an in vitro test rucaparib showed a low metabolic turnover rate where CYP2D6 helped by metabolizing to a larger extent with a minor role played by CYP1A2 and CYP3A4. Apart from pharmacokinetic profile the FDA also found a favorable risk-benefit profile of Rucaparib which also helped it's accelerated approval (Anscher et al., 2021).

6.2Olaparib

On may 19, 2020, Olaparib (LYNPARZA) was approved by the FDA for the treatment of mCRPC affected cancer patients having germline or somatic HRR gene mutations. Olaparib also inhibits PARP1, PARP2 and PARP3 and eventually decrease the growth of tumors by inhibiting selective tumor cell lines. The PROfound clinical trial had a significant role behind achieving the approval from FDA. PROfound is a phase III trial which has recently concluded

and demonstrated the efficacy of Olaparib in the treatment of prostate cancer as a single therapy. All the participants who took part in this trial were suffering from mCRPC and progressed after receiving enzalutamide or abiraterone medication (Grewal et al., 2021). In the trial the patients were separated into two groups A & B. Group A had 245 members who had at least one mutation from BRCA1, BRCA2 or ATM. On the other hand group B consisted of 142 people who had other mutations than the previous ones. After that, both of groups of patients were given Olaparib or hormonal treatment (enzalutamide or abiraterone) in a random manner and it was found that in patients of group A who took olaparib had an overall greater survival rate than those who received hormonal therapy. Imaging based screening tests also confirmed that cancer progression was considerably low in those patients who took olaparib in group A. Apart from that currently two trials are still ongoing aiming to approach further with Olaparib. Phase III trials of both of them are ongoing in order to examine the safety and efficacy of them in combination with hormonal medicines to treat mCRPC. The Names of those two trials are PROpel and KEYLYNK which are being studied in the treatment of mCRPC in combination with abiraterone and pembrolizumab respectively focusing on the safety and effectiveness of the drug. Moreover, TOPARP is a phase II trial that is still ongoing in search of the anti-tumor activity of Olaparib in mCRPC patients along with determining the predictive biomarkers that responded positively towards Olaparib (Grewal et al., 2021).

$C_{24}H_{23}FN_4O_3$ is the chemical formula of Olaparib which basically induces cytotoxicity by inhibiting activity of PARP enzyme and increasing PARP DNA complexes that causes cellular disruption of homeostasis and apoptosis (Frampton, 2015). After analyzing the pharmacokinetic property it can be seen that Olaparib is rapidly absorbed following oral administration and can achieve a peak concentration of 4.7 to 9.1 mcg/ml within 1-3 hours. After a dose of 200mg the AUC of olaparib is reported to be 25.8 mcg.h/L, which can be extended upto 26% with continuous administration. The reported volume of distribution after

administration of a dosage of 100 mg/kg was 40.3 L having a plasma protein binding of 82 %. In terms of elimination, after 7 days, roughly 86% of the supplied dose is retrieved, with 44% detected in urine and 42% in feces. The elimination half-life has been found to be between 5 and 11 hours with a total clearance of 4.6 L/h. Moreover, Olaparib is metabolized in the liver by the CYP3A4 isoenzymes to a larger extent. Currently In the UK, 400 mg of Olaparib capsules with dosing of twice daily is approved for maintenance monotherapy (Frampton, 2015).

6.3 Niraparib

Niraparib is another important PARP inhibitor that has recently shown remarkable promise in the treatment of PC though it is not yet approved by the FDA. The GALAHAD trial, which has been ongoing since 2016, intends to evaluate Niraparib's effectiveness, safety, and pharmacokinetics in men who were suffering from mCRPC and DNA repair abnormalities (Grewal et al., 2021). On that test, a total of 289 patients participated where 182 (63%) received more than two systemic treatments to treat prostate cancer. Furthermore, from those 289 patients 223 patients participated in the overall efficacy analysis trial dividing into BRCA (n=142) and non-BRCA (n=81) groups. The preliminary findings of this trial revealed that Niraparib had an overall 38% response rate with 65% response rate in patients having BRCA mutation. The interpretation of the result confirmed that Niraparib is well tolerated and has potential antitumor function incase of pretreated mCRPC patients with BRCA mutations and DSBs. These initial reports imply that Niraparib may also have a crucial role as a PARP inhibitor in the treatment of mCRPC in near future (Smith et al., 2022).

The drug Niraparib was produced by Merck Research Laboratories that also works by preventing cancer cells from repairing DNA damage. To get access to the pharmacokinetic profile a study was performed in 60 individuals with advanced solid tumors at ten dose levels

between 30 and 400 mg/day. From the study it was found that Niraparib has a bioavailability of 73% along with 83% plasma proteins binding capacity between those dose range. Peak plasma concentration was attained in 3 hours after rapid absorption where the volume of distribution was found at 1220 liters on average. Moreover, the drug Niraparib is predominantly metabolized by carboxylesterases and on that previously mentioned dose it was observed 47.5 % of it was excreted through urine and 38.8% via feces within 21 days. At all dosages of 40 mg/day or more, a minimum concentration 288 nM or above were maintained. This concentration level has been proven to achieve continuous PARP1 inhibition through xenograft tests, which is crucial for monotherapy regimens (Longoria & Tewari, 2018).

Chapter 7

Challenges

Though over the past two decades survival rate has progressed, prostate cancer at the stage of metastatic castration-resistant (mCRPC) still remains a fatal disease which necessitates development in the therapeutic approaches. In the treatment of prostate cancer, PARP inhibitors are now expanding their path for precision therapeutic approaches. Though the discovery of PARP inhibitors remains a significant achievement, many questions remain unanswered, including the efficacy of alternative PARP inhibitors, the possible toxicity in combinations, resistance mechanisms, the biomarker panel to be used and some promising side effects. As a result, in order to increase patient safety, treatment efficacy, and maintain an adequate dose intensity, a thorough understanding of possible short and long-term adverse effects and how to manage them is required (Teyssonneau et al., 2021).

7.1 Acquisition of PARPi Resistance

The progression of acquired resistance in tumors is a key problem linked with anti-cancer therapy. According to human and rodent models, the degree of initial response to PARPi therapy and the extent of resistance are correlated. As a result, people who have achieved a significant effect after their first PARPi treatment are more likely to have a lower long-term response. PARPi acquired resistance is caused by a variety of mechanisms that have been studied in preclinical and clinical trials. Restoration of HRR activity is one of the most common mechanisms where the Secondary mutations replace the HRR function. DSBs can be efficiently repaired by restoring HR capability and the cancerous cell can end up living (Rose et al., 2020). d)Loss of DNA end production or e) the reduction of NHEJ activity are the most common causes behind this HR restoration (Dias et al., 2021).

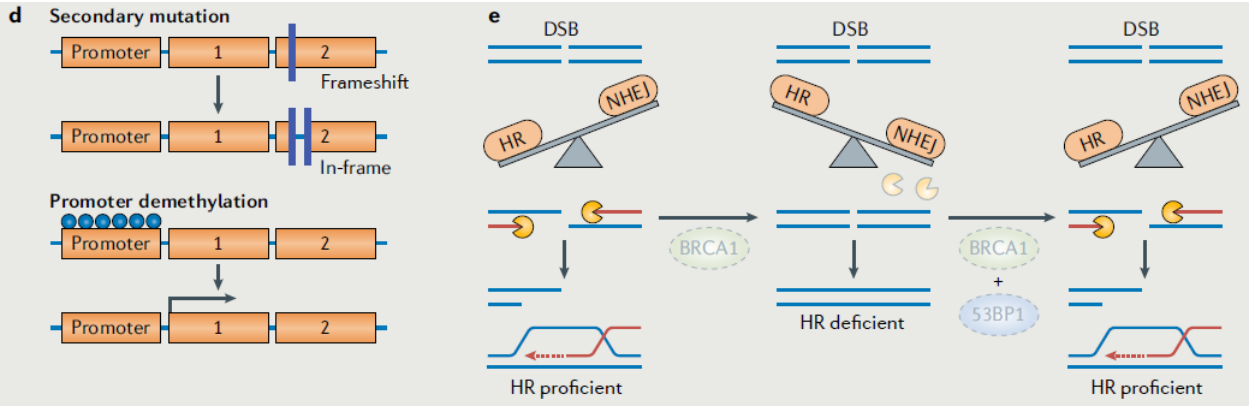

Figure 5- Mechanism of HR restoration (Dias et al., 2021)

Apart from HR restoration, increased drug efflux is also responsible for the resistance which is caused due to the overexpression of drug efflux transporter genes that end up increasing the amount of drug effluxion pump and inhibiting PARPi to reach the cell nucleus. Moreover, stabilization of stalled fork is also responsible for drug resistance which is caused by reduced

or delayed function of nucleus upon DNA due to the inhibition of proteins that recruit fork (Teyssonneau et al., 2021).

In order to overcome PARP inhibitor resistance many combination techniques have been proposed to improve the efficacy of poly(ADP-ribose) polymerase (PARP) inhibitors in the treatment of resistant tumors. To be more specific, reactivation of the HRR pathway along with PARPi resistance can be countered by treating patients with various tyrosine kinase inhibitors, agents that target epigenetic regulators of HR genes or by targeting mediators that promote genes of HR (Dias et al., 2021).

7.2 Adverse events

The PARP inhibitors can have some adverse effects which are linked to on- and off-target effects. Adverse effects of PARP inhibitors can be divided into class effects and drug specific. Adverse effects related to class effect is that event when some specific adverse events are associated with all the classes of PARPi such as Hematologic toxicity, fatigue, nausea, and vomiting which are examples of class effects of PARP inhibitors. There are also adverse effects which are more drug specific such as hypertension due to niraparib, AST/ due to rucaparib (Madariaga et al., 2020).

Fatigue is still one of the most common class effects of PARPi found in almost 50%-70% of cases grading 1-2 severity level. Generally, some massage treatment and psychological activities are also suggested for fatigue relief. Hematologic toxicity is another common class of adverse events that occur mostly due to the drug trapping of PARP1. It is observed more frequently in the first few months of treatment and gradually improves over time, needing dose suspensions or decreases on occasion to get relief. Anemia, thrombocytopenia, neutropenia, dyspepsia, diarrhea/constipation are the side effects that may occur with different frequencies

as a part of hematologic toxicity due to PARP inhibitors. Besides, nausea and vomiting as gastrointestinal disorders are also common side effects of PARPi's class effect (Madariaga et al., 2020).

7.3 Limitations of data

Though the area of PARP inhibitors is constantly developing, most of their studies are presented at international gatherings as interim results rather than publishing it in peer reviewed journals. Another drawback of the research is the presence of a wide range of inclusion criteria used to define HRD based on tumor genetics. Due to the coexistence of a vast range of HRD gene definitions in different studies, it becomes complicated to evaluate the significance of gene mutations and ATM is an example of such case. In group A of PROfound study ATM was added with BRCA1 and BRCA2 with undefined biologic reasoning. Moreover, no phase III study regarding the combination therapy of PARP inhibitors is reported yet though it is the optimum standard for the evaluation of a therapy (Nizialek & Antonarakis, 2020).

Chapter 8

Conclusion

The review demonstrates the significant efficacy of PARP inhibitors both as monotherapy and in combination for the treatment of prostate cancer. They have been shown to be so effective against mCRPC patients having HRR that led them to achieve FDA approval and those two approved drugs are olaparib and rucaparib. In order to personalize and strengthen the standard of the PARP inhibitors both as monotherapy or in combination, phase three trials are still eagerly anticipated which will also confirm whether they will continue as a potent addition to the currently available therapy for prostate cancer or not. Furthermore, though the potential of parp inhibitors against BRCA1 and BRCA2 mutations in germline or somatic cells are well documented, treatment options for other DDR gene mutations are yet to be perceived. Further studies regarding the possibility for synthetically lethal interactions between those DDR mutated genes may have potential to expand the number of individuals who can be benefitted from the PARP inhibitor or PARP inhibitor combo treatment. It is also necessary to make efforts to better interpret sequencing data along with streamlining both national and institutional screening guidelines and suggestions. To conclude, though PARPis includes some limitations, it has great potential for both present and future if expert management can be ensured.

8.1 Future Direction

The Diagnosis and therapy of prostate cancer are progressing significantly as a result of new developments in prostate cancer biology specially with the crucial role played by personalized medicine. Basic research, newer imaging processes and new clinical trials are expanding and creating opportunities of treatment options for this complex disease, including patient-specific

therapies. Though the early detection of this disease has become more advanced due to the upgraded diagnostic imaging, management of advanced stages of prostate cancer are still in the initial phase but development in this area is anticipated in near future due to the immense efforts in understanding cell migration, genetic metastasis, cell and molecular level (Schatten, 2018).

In the case of PARP inhibitors, the development in medicinal chemistry may boost the selectivity and efficacy of future generations of PARP inhibitors. A better and advanced understanding of pathogenesis of different diseases will definitely spot out new PARP1 interacting pathways which will lead to synergistic treatment strategies and can be used in such therapies that target both PARP1 and relevant pathways at the same time. For instance, overlapping of PARP1 and AKT pathways and simultaneous manipulation of these systems could be useful in oncological studies (Curtin & Szabo, 2020). Moreover, study and findings of new PARP targets will help to find newer therapeutic targets. According to some recent research it was found that Serine responds to the DNA damage as a target of ADP- ribosylation which partially depends on histone Parylation factor 1. Further investigation revealed that in the modification of adjoining serine and lysine residing on histone, PARP1 plays a great role by competing with histone acetyltransferases and these findings can also impact on the further study of both oncology and non-oncology studies. Apart from that, focusing on all the basic research and the development in the field of PARP family are expected to make these inhibitors hand-in-hand by producing them more selective and potential (Curtin & Szabo, 2020).

Reference

Abida, W., Campbell, D., Patnaik, A., Shapiro, J. D., Sautois, B., Vogelzang, N. J., Voog, E. G., Bryce, A. H., McDermott, R., Ricci, F., Rowe, J., Zhang, J., Piulats, J. M., Fizazi, K., Merseburger, A. S., Higano, C. S., Krieger, L. E., Ryan, C. J., Feng, F. Y., … Chowdhury, S. (2020). Non-BRCA DNA Damage Repair Gene Alterations and Response to the PARP Inhibitor Rucaparib in Metastatic Castration-Resistant Prostate Cancer: Analysis From the Phase II TRITON2 Study. *Clinical Cancer Research : An Official Journal of the American Association for Cancer Research*, *26*(11), 2487–2496. https://doi.org/10.1158/1078-0432.CCR-20-0394

Advanced Prostate Cancer: Symptoms, Diagnosis & Treatment - Urology Care Foundation. (2021). Retrieved March 19, 2022, from https://www.urologyhealth.org/urology-a-z/a_/advanced-prostate-cancer

Anscher, M. S., Chang, E., Gao, X., Gong, Y., Weinstock, C., Bloomquist, E., Adeniyi, O., Charlab, R., Zimmerman, S., Serlemitsos-Day, M., Ning, Y. M., Mayrosh, R., Fuller, B., Trentacosti, A. M., Gallagher, P., Bijwaard, K., Philip, R., Ghosh, S., Fahnbulleh, F., … Beaver, J. A. (2021). FDA Approval Summary: Rucaparib for the Treatment of Patients with Deleterious BRCA-Mutated Metastatic Castrate-Resistant Prostate Cancer. *Oncologist*, *26*(2), 139–146. https://doi.org/10.1002/onco.13585

Bednarz-Knoll, N.; Eltze, E.; Semjonow, A.; Brandt, B. BRCAness in prostate cancer. *Oncotarget* 2019, 10, 2421–2422

Borley, N., & Feneley, M. R. (2009). Prostate cancer: diagnosis and staging. *Asian Journal of Andrology*, *11*(1), 74. https://doi.org/10.1038/AJA.2008.19

Castillejos-molina, R. A., & Gabilondo-navarro, F. B. (2016). Castillejos-Molina. Prostate cancer. *Salud Pública de México*, *58*(2), 279–284

Chatterjee, N.; Walker, G.C. Mechanisms of DNA damage, repair, and mutagenesis. *Environ. Mol. Mutagen*. 2017, 58, 235–263

Chen, A. (2011). PARP inhibitors: its role in treatment of cancer. *Chinese Journal of Cancer*, *30*(7), 463–471. https://doi.org/10.5732/cjc.011.10111

Cooper, G. (2000). The Cell: A Molecular Approach. 2nd edition. Sunderland (MA): Sinauer Associates; 2000. *The Development and Causes of Cancer*. Retrived from: https://www.ncbi.nlm.nih.gov/books/NBK9963/

Curtin, N. J., & Szabo, C. (2020). Poly(ADP-ribose) polymerase inhibition: past, present and future. *Nature Reviews Drug Discovery*, *19*(10), 711–736. https://doi.org/10.1038/s41573-020-0076-6

Definition of targeted therapy - NCI Dictionary of Cancer Terms - National Cancer Institute. (n.d.). Retrieved March 19, 2022, from https://www.cancer.gov/publications/dictionaries/cancer-terms/def/targeted-therapy

Dias, M. P., Moser, S. C., Ganesan, S., & Jonkers, J. (2021). Understanding and overcoming resistance to PARP inhibitors in cancer therapy. *Nature Reviews Clinical Oncology*, *18*(12), 773–791. https://doi.org/10.1038/s41571-021-00532-x

Dréan, A., Lord, C. J., & Ashworth, A. (2016). PARP inhibitor combination therapy. *Critical Reviews in Oncology/Hematology*, *108*, 73–85. https://doi.org/10.1016/j.critrevonc.2016.10.010

D. C. Wedge et al.; CAMCAP Study Group; TCGA Consortium, Sequencing of prostate cancers identifies new cancer genes, routes of progression and drug targets. *Nat. Genet*. 50, 682–692 (2018)

FDA Approves Olaparib, Rucaparib to Treat Prostate Cancer - National Cancer Institute. (2020). Retrieved March 19, 2022, from https://www.cancer.gov/news-events/cancer-currents-blog/2020/fda-olaparib-rucaparib-prostate-cancer

Ferraris, D. (2015). Overview of PARP inhibitor design and optimization. *Cancer Drug Discovery and Development*, *83*, 183–203. https://doi.org/10.1007/978-3-319-14151-0_7

Frampton, J. E. (2015). Olaparib: A review of its use as maintenance therapy in patients with ovarian cancer. *BioDrugs*, *29*(2), 143–150. https://doi.org/10.1007/s40259-015-0125-6

Girling, J. S., Whitaker, H. C., Mills, I. G., & Neal, D. E. (2007). Pathogenesis of prostate cancer and hormone refractory prostate cancer. *Indian Journal of Urology : IJU : Journal of the Urological Society of India*, *23*(1), 35. https://doi.org/10.4103/0970-1591.30265

Greve, J. De, Decoster, L., Shahi, R. B., Brussel, V. U., & Fontaine, C. (2016). *Pharmacotherapy Parp inhibitors*

Grewal, K., Grewal, K., & Tabbara, I. A. (2021). PARP inhibitors in prostate cancer. *Anticancer Research*, *41*(2), 551–556. https://doi.org/10.21873/ANTICANRES.14807

Gui, B., Gui, F., Takai, T., Feng, C., Bai, X., Fazli, L., Dong, X., Liu, S., Zhang, X., Zhang, W., Kibel, A. S., & Jia, L. (2019). Selective targeting of PARP-2 inhibits androgen receptor signaling and prostate cancer growth through disruption of FOXA1 function. *Proceedings of the National Academy of Sciences of the United States of America*, *116*(29), 14573–14582. https://doi.org/10.1073/pnas.1908547116

Heindenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, van der Kwast T, et al. EAU guidelines on prostate cáncer. Part 1: screening, diagnosis, and local treatment with curative intent-update 2013. *Eur Urol* 2014;65(1):124-137

Hopkins TA, Shi Y, Rodriguez LE et al. Mechanistic dissection of PARP1 trapping and the impact on in vivo tolerability and efficacy of PARP inhibitors. *Mol Cancer Res* 2015; 13(11): 1465–1477

La Thangue NB, Kerr DJ (2011) Predictive biomarkers: a paradigm shift towards personalized cancer medicine. *Nat Rev Clin Onco*l 8:587

Longoria, T. C., & Tewari, K. S. (2018). Pharmacokinetic drug evaluation of niraparib for the treatment of ovarian cancer. *Expert Opinion on Drug Metabolism and Toxicology*, *14*(5), 543–550. https://doi.org/10.1080/17425255.2018.1461838

Madariaga, A., Bowering, V., Ahrari, S., Oza, A. M., & Lheureux, S. (2020). Manage wisely: poly (ADP-ribose) polymerase inhibitor (PARPi) treatment and adverse events. *International Journal of Gynecological Cancer*, *30*(7), 903. https://doi.org/10.1136/IJGC-2020-001288

Mateo, J., Lord, C. J., Serra, V., Tutt, A., Balmaña, J., Castroviejo-Bermejo, M., Cruz, C., Oaknin, A., Kaye, S. B., & De Bono, J. S. (2019). A decade of clinical development of PARP inhibitors in perspective. *Annals of Oncology*, *30*(9), 1437–1447. https://doi.org/10.1093/annonc/mdz192

Mathur, G., Nain, S., & Sharma, P. (2015). Cancer : an overview Cancer : An Overview. *Academic J. Cancer Res*, *8*(1), 1–9. https://doi.org/10.5829/idosi.ajcr.2015.8.1.9336

Mazhar, D., & Waxman, J. (2002). Prostate cancer. *Postgraduate Medical Journal*, *78*(924), 590–595. https://doi.org/10.1136/PMJ.78.924.590

Morales, J. C., Li, L., Fattah, F. J., Dong, Y., Bey, E. A., Patel, M., Gao, J., & Boothman, D.

A. (2014). Review of poly (ADP-ribose) polymerase (PARP) mechanisms of action and rationale for targeting in cancer and other diseases. *Critical Reviews in Eukaryotic Gene Expression*, *24*(1), 15–28. https://doi.org/10.1615/CRITREVEUKARYOTGENEEXPR.2013006875

Nientiedt, C., Duensing, A., Zschäbitz, S., Jäger, D., Hohenfellner, M., Stenzinger, A., & Duensing, S. (2021). PARP inhibition in prostate cancer. *Genes Chromosomes and Cancer*, *60*(5), 344–351. https://doi.org/10.1002/gcc.22903

Nizialek, E., & Antonarakis, E. S. (2020). PARP Inhibitors in Metastatic Prostate Cancer: Evidence to Date. *Cancer Management and Research*, *12*, 8105. https://doi.org/10.2147/CMAR.S227033

Patel, V.L.; Busch, E.L.; Friebel, T.M.; Cronin, A.; Leslie, G.; McGuffog, L.; Adlard, J.; Agata, S.; Agnarsson, B.A.; Ahmed, M.; et al. Association of Genomic Domains in BRCA1 and BRCA2 with Prostate Cancer Risk and Aggressiveness. *Cancer Res*. 2020, 80, 624–638

Pezaro, C. (2020). PARP inhibitor combinations in prostate cancer. *Therapeutic Advances in Medical Oncology*, *12*, 1–10. https://doi.org/10.1177/1758835919897537

Prakash, R.; Zhang, Y.; Feng, W.; Jasin, M. Homologous recombination and human health: The roles of BRCA1, BRCA2, and associated proteins. *Cold Spring Harb Perspect Biology*. 2015, 7, a016600

Rebello, R. J., Oing, C., Knudsen, K. E., Loeb, S., Johnson, D. C., Reiter, R. E., Gillessen, S., Van der Kwast, T., & Bristow, R. G. (2021). Prostate cancer. *Nature Reviews Disease Primers*, *7*(1). https://doi.org/10.1038/s41572-020-00243-0

Risdon, E. N., Chau, C. H., Price, D. K., Sartor, O., & Figg, W. D. (2021). PARP Inhibitors and Prostate Cancer: To Infinity and Beyond BRCA . *The Oncologist*, *26*(1), e115–e129. https://doi.org/10.1634/theoncologist.2020-0697

Rose, M., Burgess, J. T., O'Byrne, K., Richard, D. J., & Bolderson, E. (2020). PARP Inhibitors: Clinical Relevance, Mechanisms of Action and Tumor Resistance. *Frontiers in Cell and Developmental Biology*, *8*(September), 1–22. https://doi.org/10.3389/fcell.2020.564601

Sarkar, S., Horn, G., Moulton, K., Oza, A., Byler, S., Kokolus, S., & Longacre, M. (2013). Cancer Development, Progression, and Therapy: An Epigenetic Overview. *International Journal of Molecular Sciences 2013, Vol. 14, Pages 21087-21113*, *14*(10), 21087–21113. https://doi.org/10.3390/IJMS141021087

Schatten, H. (2018). Brief overview of prostate cancer statistics, grading, diagnosis and treatment strategies. *Advances in Experimental Medicine and Biology*, *1095*, 1–14. https://doi.org/10.1007/978-3-319-95693-0_1

Shah, S., Rachmat, R., Enyioma, S., Ghose, A., Revythis, A., & Boussios, S. (2021). BRCA Mutations in Prostate Cancer: Assessment, Implications and Treatment Considerations. *International Journal of Molecular Sciences 2021, Vol. 22, Page 12628*, *22*(23), 12628. https://doi.org/10.3390/IJMS222312628

Shen Y, Rehman FL, Feng Y et al. BMN 673, a novel and highly potent PARP1/2 inhibitor for the treatment of human cancers with DNA repair deficiency. *Clin Cancer Res* 2013; 19(18): 5003–5015

Smith, M. R., Scher, H. I., Sandhu, S., Efstathiou, E., Lara, P. N., Yu, E. Y., George, D. J., Chi, K. N., Saad, F., Ståhl, O., Olmos, D., Danila, D. C., Mason, G. E., Espina, B. M., Zhao, X., Urtishak, K. A., Francis, P., Lopez-Gitlitz, A., Fizazi, K., … Moon, H. (2022). Niraparib in patients with metastatic castration-resistant prostate cancer and DNA repair gene defects (GALAHAD): a multicentre, open-label, phase 2 trial. *The Lancet Oncology*, *23*(3), 362–373. https://doi.org/10.1016/S1470-2045(21)00757-9

Teyssonneau, D., Margot, H., Cabart, M., Anonnay, M., Sargos, P., Vuong, N. S., Soubeyran,

I., Sevenet, N., & Roubaud, G. (2021). Prostate cancer and PARP inhibitors: progress and challenges. *Journal of Hematology and Oncology*, *14*(1), 1–19. https://doi.org/10.1186/s13045-021-01061-x

Velcheti, V., Karnik, S., Bardot, S. F., & Prakash, O. (2008). Pathogenesis of Prostate Cancer: Lessons from Basic Research. *The Ochsner Journal*, *8*(4), 213.

Vietri, M. T., D'elia, G., Caliendo, G., Resse, M., Casamassimi, A., Passariello, L., Albanese, L., Cioffi, M., & Molinari, A. M. (2021). Hereditary Prostate Cancer: Genes Related, Target Therapy and Prevention. *International Journal of Molecular Sciences*, *22*(7). https://doi.org/10.3390/IJMS22073753

Virtanen, V., Paunu, K., Ahlskog, J. K., Varnai, R., Sipeky, C., & Sundvall, M. (2019). PARP inhibitors in prostate cancer—The preclinical rationale and current clinical development. *Genes*, *10*(8). https://doi.org/10.3390/GENES10080565

Xia, M., Guo, Z., & Hu, Z. (2021). The Role of PARP Inhibitors in the Treatment of Prostate Cancer: Recent Advances in Clinical Trials. *Biomolecules*, *11*(5). https://doi.org/10.3390/BIOM11050722

Yelamos J, Schreiber V, Dantzer F (2008) Toward specific functions of poly(ADP-ribose) polymerase-2. *Trends in Molecular Medicine* 14:169