DNA Repair Enzymes Promising in Cancer Therapy; Poly (ADP-Ribose) Polymerase Inhibitors

Kanser Tedavisinde Önemli olan DNA Onarım Enzimleri; Poli (ADP-Ribose) Polimeraz İnhibitörleri

Zehra Demir[1], Bensu Karahalil[2]

[1]Altay District. 2668th Str. Fıratlife, B block. No:251, 06794, Ankara, Turkey
[2]Gazi University, Faculty of Pharmacy, Toxicology Department, 06330, Ankara, Turkey

ABSTRACT

DNA repair pathways maintain genomic integrity and stability when DNA damages take place in cells by endogenous or exogenous sources. Any functional problem or deficiency in DNA repair pathways is associated with the initiation and development of cancer. Cancer is important health concerns and characterized by growing uncontrollably and spread to other tissues. It is the second leading cause of death and every year more than 150 000 people are died and more than 250 000 new cases occur in Turkey. It is required improving treatment strategies. Currently, traditional cancer therapy is performed with chemo- and/or radiotherapy as well as operation, the removal of cancer cells. The major challenge in traditional cancer treatment is that treatment cannot differentiate cancerous cells from healthy cells and kill both of cells including hair cells that are normal cells. Furthermore, many side effects that are difficult to tolerate occur during or after administration of cancer treatment. The problem is that traditional cancer treatment is not targeted therapy, so, it does not target tissue which is located cancer lesions. Last more than 30 years, studies have conducted on DNA repair pathways for cancer treatment. There are many DNA repair proteins, which have major functions, especially on major DNA repair pathways such as Base Excision Repair, Nucleotide Excision Repair. Among them, the first study was performed on Poly (ADP-ribose) polymerase inhibitors (PARPi) and Lynparza was approved as cancer drug and increase the survival rate and provide low side effects. Studies associated with the effects of PARP inhibitors and with the other DNA repair pathways on cancer keep continuing. Targeted therapy with low side effects and high efficacy provides huge advantageous when resistance occurs against the traditional cancer treatments. However, similar resistance problem also is valid for DNA repair inhibitors. All these improvements and experience will lead to discover new cancer treatments. In our review, we have given brief information on DNA repair pathways and their use in cancer treatment.

Key Words: DNA repair, chemotherapy, cancer, PARP inhibitors, PARP1 proteins

Received: 03.25.2022 **Accepted:** 04.13.2022

ÖZET

DNA onarım yolları, hücrelerde endojen veya eksojen kaynaklar tarafından DNA hasarları meydana geldiğinde genomik bütünlüğü ve kararlılığı korur. DNA onarım yollarındaki herhangi bir işlevsel sorun veya eksiklik, kanserin başlaması ve gelişmesiyle ilişkilidir. Kanser önemli bir sağlık sorunudur ve kontrolsüz bir şekilde büyümesi ve diğer dokulara yayılması ile karakterizedir. İkinci önde gelen ölüm nedenidir ve Türkiye'de her yıl 150.000'den fazla insan ölmekte ve 250.000'den fazla yeni vaka meydana gelmektedir. Tedavi stratejilerinin iyileştirilmesi gereklidir. Günümüzde geleneksel kanser tedavisi, kemo- ve/veya radyoterapinin yanı sıra operasyon, kanser hücrelerinin çıkarılması ile uygulanmaktadır. Geleneksel kanser tedavisindeki en büyük zorluk, tedavinin kanserli hücreleri sağlıklı hücrelerden ayırt edememesi ve normal hücreler olan saç hücreleri de dahil olmak üzere her iki hücreyi de öldürmesidir. Ayrıca, kanser tedavisinin uygulanması sırasında veya sonrasında tolere edilmesi zor olan birçok yan etki meydana gelir. Sorun, geleneksel kanser tedavisinin hedefe yönelik tedavi olmamasıdır, bu nedenle kanser lezyonlarının bulunduğu dokuyu hedef almaz. Son 30 yıldan fazla bir süredir, kanser tedavisi için DNA onarım yolları üzerinde çalışmalar yapılmıştır. Baz Eksizyon Onarımı, Nükleotid Eksizyon Onarımı gibi özellikle majör DNA onarım yollarında majör işlevleri olan birçok DNA onarım proteini vardır. Bunlar arasında ilk çalışma Poly (ADP-riboz) polimeraz inhibitörleri (PARPi) üzerinde yapılmış ve Lynparza'nın kanser ilacı olduğu onaylanarak hayatta kalma oranını artırmış ve düşük yan etkiler sağlamıştır. PARP inhibitörlerinin ve diğer DNA onarım yollarının kanser üzerindeki etkileri ile ilgili çalışmalar devam etmektedir. Düşük yan etkileri ve yüksek etkinliği ile hedefe yönelik tedavi, geleneksel kanser tedavilerine karşı direnç oluştuğunda büyük avantaj sağlar. Ancak benzer direnç sorunu DNA onarım inhibitörleri için de geçerlidir. Tüm bu gelişmeler ve deneyimler, yeni kanser tedavilerinin keşfedilmesine yol açacaktır. Derlememizde DNA onarım yolları ve kanser tedavisinde kullanımları hakkında kısa bilgiler verdik.

Anahtar Sözcükler: DNA onarımı, kemoterapi, kanser, PARP inhibitörleri, PARP1 proteinleri

Geliş Tarihi: 25.03.2022 **Kabul Tarihi:** 13.04.2022

ORCID IDs: Z.D. 0000-0001-6411-9113,B.K. 0000-0003-1625-6337

Address for Correspondence / Yazışma Adresi:Bensu Karahalil, PhD Gazi University Faculty of Pharmacy Toxicology Department, 06330, Ankara, Turkey E-mail: bensuka@gmail.com

doi:http://dx.doi.org/10.12996/gmj.2022.72

INTRODUCTION

Cancer is a disease characterized by the development of abnormal cells. Cancer causes cell to divide uncontrollably and has the ability to infiltrate and destroy normal body tissue. Cells largely transform to cancer cells because of mutations that are errors during cell division. These mutations cause rapid cell growth, fail to stop uncontrolled cell growth, and make mistakes when repairing DNA errors. Gene mutations are either congenital or occur after birth. Numerous genes are packaged in the cell's DNA, each gene contains a set of instructions, and These are instructions that tell cells what functions to do, how to grow and divide. Errors in the instructions can cause to stop the normal functions of cell and the cell turns into a cancer cell (1). DNA damages are caused by endogenous factors during normal metabolism or exogenous factors such as cigarette smoking, X-rays, sunlight (uv), certain foods, disease, and drugs (2). Cells have DNA repair pathways that repair errors and prevent cancer by preventing mutations (1).

Cancer Statistics in Turkey

Cancer is the second leading cause of death globally. An estimated 9.6 million deaths, or 1 in 6 deaths, occur in 2018. Gastric cancer, liver, lung colorectal, and prostate cancer in men are frequently observed cancer types; breast, colorectal, lung, cervical and thyroid cancers are also common in women. The burden of cancer globally keep grows by a huge physical, emotional, and financial pressure on person, families, communities, and health systems. Health system is not ready to manage this cancer burden in both low and middle-income countries. Therefore, many cancer patients do not have access to the qualified diagnosis and treatment. The survival rate of many cancer patients increases in these countries since countries have powerful health systems, the accessible early diagnosis service and the qualified treatment and care for survival. The survival rates are being improved for many types of cancer, through to advances in cancer screening, cancer treatment, and prevention from cancer (3).

According to World Health Organization (WHO), the incidence of cancer in the world and in Turkey was evaluated. The incidence rates of cancer cases per 100 000 people worldwide in 2020 were graded by estimated age-standardize. The human population in the world in 2019 was 7 676 965 500 people. The total number of cancer cases was 18 078 957 in 2018. The total number of cancer deaths was 9 555 027 in 2018 (3).

According to WHO, the total population in Turkey in 2019 was 83 429 607 people. The total number of cancer cases was 210 537 in 2018. The rate of mortality in 2018 was 116 710. According to Global Cancer Observatory statistics 2020, the total population in Turkey was 84 339 067 people. The number of new cancer cases was 132 816 in males and 101 018 in females. The number of deaths was 78 949 in males and 47 386 in (4). Data based on all above statistics approve that cancer is important health concern and new drugs need to be discovered and novel treatment strategies need to be improved.

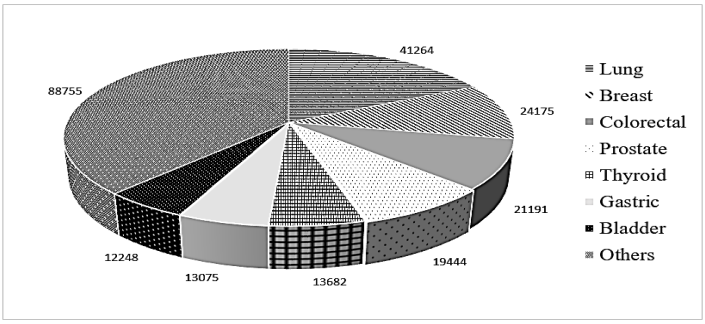


Figure 1. Estimated the number of new cases in Turkey by 2020 (people of both genders and all ages)

New Treatment Strategy Against To "One Size Fits All" Approach

Traditionally, so far, cancer has treated using a "one size fits all" to approach, such as chemotherapy and radiation. Currently, new treatment model which is a more effective model which is based on Personalized Medicine is developed and started to adopt substitute of "One size fit all" traditional approach has many advantages. For this reason, pharmaceutical research has gained momentum in this direction (5).

In traditional cancer treatment, chemotherapy and radiation treatments kill all cells, both health and cancerous, without distinguishing between a cancerous cell and a healthy cell (hair follicle, bone, and digestive system cell etc.) (6). Furthermore, individual differences are huge therefore, traditional treatments vary widely among individuals in efficacy and side effects. While some patients suffer from severe side effects, some people do not benefit from treatment (5). Often, treatment strategy with just one drug is not enough for patients, it has understood the combination therapy will be a cornerstone of cancer therapy (7). On the other hand, in traditional cancer treatment, unfortunately, it often takes trial- error to determine which treatments are effective for a patient. Patients have to endure treatment and side effects before physicians can determine the effectiveness of treatment, and this sometimes take weeks and, furthermore, economic burden to patient and government. Even though administered treatment is successful at the beginning of treatment, later, many cancers may be show resistance to the administered therapy and treatment selection process have to restart again and this is a destructive process. In new approach which based on person, "personalized Medicine", target in cancer therapy is DNA repair enzymes and pathways and therefore, understanding mechanisms of these pathways will help to know how to use them in cancer therapy, and cause new drug discoveries with different DNA repair enzymes.

DNA Repair Pathways

DNA repair is essential to ensures the survival of a species by passing genetic material (DNA) to next generations and preserves also the health of people. Genetic code made of 3 DNA bases carries information and the occurrence of mutations in this genetic code can lead to cancers and other genetic diseases. s mentioned above, endogenous, and exogenous factors attack to DNA and lead to the occurrence of more than 20 important DNA damages. These are oxidation of DNA bases (like 8-okso-7,8-dihydroguanine which is biomarker of oxidative stress), alkylation of DNA bases (methylation of DNA such as 7-methyl guanosine, 1-methyl adenine, 6-o-methylguanine), hydrolysis of DNA bases (deamination and depurination), DNA bulky adducts (benzo (a) pyrene diol epoxide-dG adducts) and mono- and di-adducts (8).

DNA Repair Pathways in Cancer Therapy and Resistance

It is known very well that chemotherapy and radiotherapy are used in cancer treatment to remove tumor cells and tried to cure disease. The way to reach that target is that DNA damage is induced in tumor cells. There are many types of DNA damages and as usual, DNA repair pathways repair damages, unfortunately, they also repair the damage we intentionally cause in tumors for therapeutic purposes. Effective repair in tumor cells can act in reverse way. It removes drug-induces DNA damages and thus by growing, surviving, and proliferating of tumor cells. In this case, chemoresistance occurs, especially, when it takes place intensive repair in tumor cells. Nowadays, resistance improves in many chemotherapeutic agents widely used in cancer treatment such as cisplatin, carboplatin, 5-fluorouracil (5-FU), methotrexate, bleomycin, and docetaxel (9).

Carcinogenesis has been initiated by a lack of DNA repair; this can be detected throughout the development of cancer. A decreased DNA repair function can be hereditary or may be induced by exposure to DNA damaging agents. In addition, Cancer patients with low repair capacity have a poor prognosis. On the other hand, it is showed that low capacity of DNA repair enzymes in tumor tissue may be the better prognostic factor for longer survival (10).

All this evidence-based information has become milestones in the creation of a new treatment model in cancer. DNA repair mechanisms affect the response to cytotoxic treatments in a high extent, for this reason understanding those systems and finding ways to turn dysregulated repair processes against themselves to induce tumor death is the aim of all DNA repair inhibition efforts (11). For this reason, studies are concentrated on inhibition of DNA repair enzymes. DNA repair inhibitors can use the combination with an anticancer agent that damage to DNA. This approach increases the efficacy of cancer treatment by preventing DNA repair. In the present review article, basic inhibitors of DNA repair enzymes have summarized.

Main DNA Repair Pathways and Their Inhibitors

Base Excision Repair (BER) and Its Inhibitors

BER is used for basically correcting small base lesions and initiated by the removal of the damaged DNA bases. It is repaired mostly single base damage caused by oxidation, alkylation, deamination, and ionizing radiation (IR). Many DNA lesions from these types of damages can cause abnormal base pairing, this can eventually result in even a wrong base removed by a DNA polymerase, resulting in a mutation. To maintain genomic integrity, the cell must repair these the damaged bases. BER is divided 2 sub-pathways. Short-patch BER (SP-BER) and Long-Patch BER (LP-BER) (12). Alkylating agents, platinated agents, cytotoxic antibiotics and taxans are DNA lesions by normally repairing BER pathway (11).

This pathway is used in cancer treatment by creating inhibition of some enzymes/factors. The inhibition of BER holds promise to potentiate the effects of these treatments since BER is repaired the DNA lesions which is caused by some antineoplastic agents. Inhibitors of 4 BER proteins are being developed namely, APE1, Pol β, FEN1, PARP and they are attractive candidates for inhibition. The apurinic/apyrimidinic endonuclease 1 (APE1) is an only DNA repair protein that regulates reduction-oxidation (redox). Redox functions affect indirectly DNA repair and many transcription factors that have in cancer promotion and progression. It is aimed to be used in cancer treatment by taking advantage of these properties of BER. Aberrant expression and localization of APE1 in tumors are specific reasons resistance to therapy. The resistance is associated with a shorter time and worse prognosis (13). APE1 is up regulated and irregular in many solid cancers including pancreas, prostate, cervical cancer, over, hepatocellular, germ cell tumor, rhabdomyosarcoma, and colon cancers. (11,14,15).

Second candidate is (DNA polymerase β) DNA pol β which involves in many repair pathways such as BER, Nucleotide Excision Repair (NER), Double Strand Break repair (DSBR), Mismatch Repair (MMR). It is very attractive target for inhibition for 3 reasons. BER inhibition takes place DNA resynthesis and the removal of blocking 5'-deoxyribose-5-phosphate (5'-dRP) residue in both SPR and LPR. Lyase activity associated with it is generally rate- limiting in BER. Lyase activity is upregulated in many cancers that contribute to resistance to IR, bleomycin monofunctional alkylating agents and cisplatin (16). Pol β inhibitors (PARPis) PARPis studied in clinical trials are presented in Table 2.

Nucleotide Excision Repair (NER) and Its Inhibitors

Nucleotide Excision Repair (NER) is one of the main pathways to protect against different structural and chemical DNA lesions**.** The most common lesions are bulky covalent adducts of chemically active endogenous metabolites including nitrogenous bases affected by UV light, IR, electrophilic chemical mutagens, certain drugs, and reactive oxygen and nitrogen species (17). NER in higher eukaryotic cells removes correctly 24-32 -nt DNA fragments containing the damaged lesion. NER also involves protein-protein interactions. Reparative synthesis using an undamaged strand as a template, followed by ligation of the damaged single-stranded break, is the final step in DNA repair. Available information on key genes inactivated in NER-defective cells and the protein factors and enzymes encoded by these genes suggest that the process involves the coordinated action of about 30 proteins that form cascade complexes with variable compositions on DNA. NER has major role to remove cisplatin-induced DNA damage. NER has resistance to platinum-based therapy. Over expression of ERCC1 is responsible for resistance to therapy. To prevent the resistance ERCC1 activity is inhibited and can be used a drug for therapeutic aims without resistance (18). NER inhibition is still in early stages and NER inhibitors are non-specific, needs more studies on them. 7-hydroxystaurosporine [UCN-01] is NER inhibitor which is checkpoint inhibitor. It is tried the efficacy in both blood and solid tumors in 18 phase I and 7 phase II as monotherapy and combined therapies. Another, NER inhibitor for cancer treatment, Topoisomerase I and II (F11782) active on inhibition NER's helicase or incision step (19). Deficiencies in NER pathway sensitizes cells to platinating agents that attempt to arrest the cell cycle at G2 (11). The success of this class of drugs has been demonstrated most strikingly in the 95% cure rate of testicular cancer treated with cisplatin (20).

However, since intact NER activity can repair damage caused by cisplatin, carboplatin, and oxaliplatin causes chemoresistance [MCI13E, a new isoborneol haloacetate (SMI, MCI13E), shows promise in cell studies as an inhibitor and a sensitizer to platinating agents. SMI irreversibly inhibits RPA binding to ssDNA in vitro. Another RPA inhibitor is TDRL-505 which a reversible inhibitor. It by disrupting RPA and blocks p70 central OB-fold-DNA interactions (21).

Mismatch Repair (MR) and Its Inhibitors

Mismatch Repair (MR) plays a role in the elimination of DNA base mismatches during DNA replication. MMR is the main pathway responsible for repairing base-base mismatches and insertion and/or deletion cycles during DNA replication (22). The lack of MMR increases spontaneous mutation rates. Paradoxically, impaired MMR functionality promotes damage tolerance, which contributes to increased mutagenicity, tumor heterogeneity, and chemoresistance (23). One way to exploit the deficiency of one or more of the MMR genes is to create a synthetic lethality to make sure the damage is truly irreparable. Studies show that the high accumulation of oxidative stress induced in MMR-deficient cells can produce such a synthetic death. Cisplatin and carboplatin are more resistance in defective MMR cells via this mechanism (24). Deficiencies in MSH2 is associated with colon cancer. A Phase II clinical trial is ongoing to test the efficacy of methotrexate on MSH2-deficient cells (25). Cell studies indicate that a Pol β inhibitor can produce a synthetic lethal effect in MSH2-deficient cells. Similarly, a Pol γ inhibitor can induce synthetic lethality in cells lacking MSH2 (26). Both polymerase inhibitors (Pol β and Pol γ) produce abundant 8-oxoG lesions (27). The BER pathway normally repairs such oxidative lesions; however, since these polymerase inhibitors will also affect BER pathway, a synthetic lethality is created. MMR competence increases sensitivity to alkylating agents, antimetabolites, and fluoropyrimidines by 2 to 100-fold, enabling to arrest the cell cycle in the G2 stage and then trigger cell death pathways (28). Studies on MMR inhibitors are still ongoing.

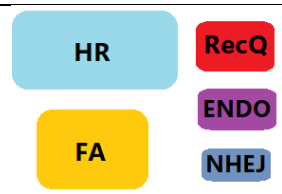
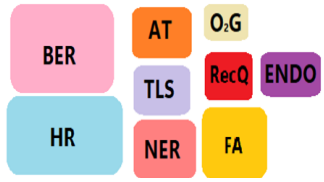
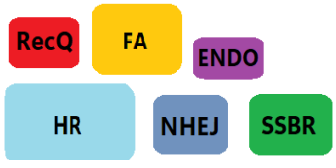
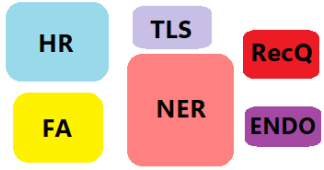
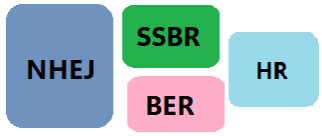
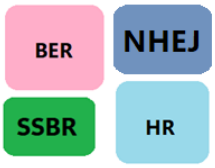
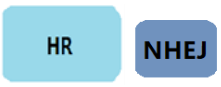
DNA Repair Inhibitors by Homologous Recombination (HR) And Non-Homologous End Junction (NHEJ)

DNA damage bases can inhibit replication and give damage to DNA synthesis. Among DNA damages, DNA DSBs are the most devastating type of DNA damage, and they are repaired by Homologous Recombination (HR) and Non-Homologous End Junction (NHEJ). Even a single unrepaired DSB is highly toxic and can lead to aneuploidy, genetic abnormality, or cell death (29). Such damages can occur naturally when topoisomerases dissolve DNA or are induced by IR or chemotherapeutic agents. The most common situation is where replication forks stop and break where unrepaired DNA lesions form without elimination (30). These repair pathways repair DSBs. NHEJ inhibition take place the repair in less than 30 min however, it takes long times in HR repair. Many investigated compounds are the lack of HR specificity (31). Small molecules that directly inhibit specific HR proteins are not in development (11). Three HR-related proteins show promise for indirectly inhibiting HR for anticancer activity: PARP, cAbl and HSP90 (32). NHEJ is active during all cell cycle however, especially, it is more active in G0/G1 stages. It directly rejoins two broken DNA ends with minimal post-processing, regardless of sequence homology. Such activity at the G0/G1 stages is preferred because the majority of the genome is non-coding. The involvement of HR in G0/G1 stages can cause deletions, duplications, misalignments, and crossovers (33).

Like MMR, decreased or defective NHEJ function leads to an increased risk of cancer, particularly lymphoid malignancies. Dysfunctional NHEJ also results in damage tolerance and chemoresistance Thus, intact NHEJ function is thought to be associated with better prognosis or good response to the treatment (34). However, inhibiting NHEJ and thereby forcing cells to perform DSB repair via the more time-intensive HR can induce a synthetic lethality in HR-deficient tumors. These and other technical issues are still obstacles to the inhibition of NHEJ today. Regarding the direct inhibition of NHEJ proteins, the most promising candidate is the catalytic subunit of DNA- DNA-dependent protein kinase (PKcs) and DNA-Protein kinase (PK) which has role in broken DNA ends and function on other repair molecules. Overexpression of DNA-PKcs is associated with radioresistance in oral squamous cell carcinoma, lung carcinoma, and esophageal cancer (35,36).

Thus, chemical inhibition of DNA- PK can increase HR.

Table 1. Overview of DNA repair pathways which play role in DNA lesion repairs caused by cancer treatments.

Cancer Treatment	Toxic Lesions	Main Repair Pathways*
Replication Inhibitors Aphidicolin Hydroxyurea	DSBs Replication Lesions	
Monofunctional Alkylators Alkylsulphonates Nitrosourea Compounds, Temozolomide	DNA Base Damage Replication Lesions Bulky Adducts	
Topoisomeriase Inhibitors Camptothecins, Etposide (Vp16)	SSBs DSBs Replication Lesions	
Bifunctional Alkylators (Nitrogen Mustard, Mitomycin C, Cisplatin	DSBs Crosslinking of DNA Replication Lesions Bulky Adducts	
Antimetabolites (5-Fluoroucil, Thiopurines, Folate Analogues	Undefined DNA Base Damage Replication Lesions	
Radiotherapy and Radiomimetics IR, Bleomycin	SSBs DSBs DNA Base Damage	
MGMT Inhibitor Lomeguatrib PaTrin-2	MGMT inactivation	
APE-1 Inhibitors Lucanthone CRT0044876 Methoxyamine	Undefined DNA Base Damage	
RAD51 Inhibitors B02 RI-1	DSBs Replication Lesions	
PARP Inhibitors AG-14361 A-966492 Olaparib (AZD2281) Veliparib (ABT-888)	DSBs Replication Lesions	
ATM Inhibitors KU-55933 ETP-46464 VE-821 AZ20 CGK733	SSBs DSBs Replication Lesions	
DNA-PK Inhibitors NU7026 NU7441	DSBs Replication Lesions	

*The relative contributions of major repair pathways to the respective types of DNA damage outlined are indicated by the sizes of the boxes

Double Strand Break s, DSBs, SSBs, Single Strand Breaks; SSBR, Single Strand Break Repair, O2G DNA dioxygenases; RecQ RecQ-mediated repair; AT; Alkyltransferase, Fanconi Anemia (FA) Repair, Translesion Synthesis (TS) which is a DNA damage tolerance process; Ionizing Radiation IR. Modified by (34).

Table 1 Summarizes main DNA repair pathways which play role in DNA lesion repairs caused by cancer treatments. The relative contributions of major repair pathways to the respective types of DNA damage outlined are indicated by the sizes of the boxes. This is based on the degree of sensitivity of repair-deficient cells to each category of anticancer drugs. DNA-damaging agents used in cancer treatment cause various toxic DNA lesions. Replication inhibitors cause the replication fork to stall and collapse, resulting in indirect DSBs. Monofunctional and bifunctional alkylators induce DNA base modifications that interfere with DNA synthesis. Lesions produced by some alkylators are processed into toxic lesions due to MMR. BER and NER pathways are major repair pathways with alkyltransferases (ATs), while other repair pathways repair toxic replication lesions such as those produced by inter-strand crosslinks. topoisomerase poisons trap topoisomerase I or II in temporary cleavage complexes with DNA, thereby creating DNA breaks and inhibiting replication. Antimetabolites interfere with nucleotide metabolism and DNA synthesis, causing as yet uncharacterized replication lesions. MR mediates the toxicity of some antimetabolites (eg, thiopurines). The repair pathways involved in repairing antimetabolite-induced lesions have been poorly characterized apart from BER. IR and radiomimetic drugs are cause DSBs that are mainly repaired with NHEJ.

Poly (ADP-Ribose) Polymerase (PARP) Enzyme

Poly (ADP-ribose) polymerase **(**PARP) is a family of proteins involved in a number of cellular processes such as DNA repair, genomic stability, and programmed cell death. PARP is responsible for post-translational modification of proteins in response to numerous endogenous and exogenous agents. PARP and poly (ADP-ribosyl) ation (PARylation) are important for the regulation of many cellular processes, such as DNA repair, cell death, chromatin functions, and genomic stability. Activation of PARP is one of the early DNA damage responses among other DNA sensor molecules such as DNA-PK, ATM and p53 (37). When PARP detects an SSBs, it binds to DNA, undergoes a structural change, and initiates the synthesis of a polymeric adenosine diphosphate ribose (poly (ADP-ribose) or PAR) strand that serves as a signal for other DNA repair enzymes (38). Of all the known roles of PAR, the best-studied role is that of a stress signal. Specifically, PAR acts as a critical survival factor by locating DNA damage (39). Initially, PARP-1 was the only known enzyme with poly (ADP-ribosylation) activity, but studies have proven that family members PARP-2 and PARP-3 (DDR-PARPs) are catalytically activated in the presence of damaged DNA and function as damage sensors. Although PARPs share a conserved catalytic domain, the unique regulatory domains of individual family members confer unique properties and cellular functions to PARPs (40,41). The most important of these isoforms is the PARP-1 isoform. The important roles and functions of PARP1 and PAR in DNA repair pathways have been demonstrated by various studies. Studies showed that PARP1 binds AP site in BER and has ADP-ribosylates XPA and ADP-ribosylates MSH6 functions in NER and MMR, respectively. Furthermore, auto-modified PARP1 recruits the BER complex in SSBR. In DSBs repaired by NHEJ, Ku enhances PARP1 ADP-ribosylation activity and ADP-ribosylates and activates DNA-PKcs. In SSBs repaired by HR, Auto-modified PARP1 recruits Mre1. PAR activates ATM signaling (42).

Poly (ADP-Ribose) Polymerase Inhibitors (PARPi)

Current efforts to improve PARP inhibitors as anticancer drugs have become the culmination of more than 40 years of research. PARP1 facilitates the repair, by binding to DNA breaks and attracting DNA repair proteins to the site of damage. Two DNA damage-activated PARPs in the nucleus of mammalian cells are PARP1 and PARP2 and both of them are inhibited by PARP inhibitors (PARPis). Furthermore, PARP inhibitors not only bind the catalytic domains of PARP1 and PARP2, they also have other effects. Enzymatic activity can be blocked without interfering with the essential functions of the catalytic site itself and other PARP family members since PARP1 has multiple domains that bind DNA damage. This effect is extremely important as it can increase specificity and reduce possible side effects of treatment (43). PARPis are the first clinically approved drugs which benefit from synthetic lethality. Synthetic lethality was introduced in 2005 and PARPis could be used as single agent to treat BRCA-deficient cell lines (44). They are sensitive to tumors since tumors occurred patients having BRCA1 and BRCA2 proteins, which are crucial for the error-free repair of HR, mutations have specific DNA repair defect. PARPis have treatment activity in cancers carrying this repair defect. This approach exploits a putative differential reliance on the BER pathway for repair of therapeutic damage between malignant and normal tissues, such that inhibition of PARP can selectively increase cytotoxicity from DNA-damaging radiotherapy or chemotherapy. This approach is based on that inhibition of PARP can selectively increase cytotoxicity from DNA-damaging radiotherapy or chemotherapy (45). Two different approaches are followed in the clinical use of PARP inhibitors (46). I. targeting cells that are genetically predisposed to die when PARP activity is lost; and II. Combining PARP inhibition with DNA-damaging therapeutic agents to provide additional therapeutic benefit from DNA damage. PARP-1 uses multiple domains to detect DNA damage and damage detection is coupled to a massive increase PAR production. PARPi binds to the catalytic domain to inhibit PARP-1 activity. PARPi affects PARP-1 allostericy and holds PARP-1 on DNA (47). Of course, like in other repair inhibitors, resistance can improve to PARPis in some advanced cancers. Especially, prolonged oral usage of PARPi causes PARPi resistance (48). For example, the first Phase I study of AZD2461 was recently completed, showing clinical effect on Lynparza-resistant tumors with PARPi (49). This is due in part to structural differences of AZD2461, but what these differences are is not yet known. The success of PARP against BRCA1 and BRCA2 breast cancer has accelerated studies in PARP inhibition. Since then, numerous clinical studies have examined PARP inhibitors as both monotherapy and combination therapy. Like many other DNA repair proteins, PARP proteins are multifunctional. While inhibiting a multifunctional protein can affect multiple pathways and theoretically increase tumor-killing ability. In the other hand, unexpected results take place such as the increase toxicities (50). A number of different PARPi targeting PARP have been approved for the treatment of breast or ovarian cancers. PARPis have many functions to bind and trap PARPs on DNA, preventing the release of PARPs from DNA break sites and removing PARPs from their normal catalytic cycle. Thus, drugs that are PARPis cause less adverse effects and their benefits are high. Niraparib (ZEJULA), Olaparib (Lynparza), and rucaparib (RUBRACA) are used for treatment of recurrent ovarian cancer patients (51).

Substituted benzamines, benzamides or nicotinamide analogues whose are First and second generation PARPi's. Their specificities and potencies vary widely. Many third generation PARPi are derived from the 3-aminobenzamide structure, others are polycyclic lactams, and most are competitive inhibitors (52,53). Ongoing research into the structural and mechanical aspects of PARPi is being done to elucidate the reasons for these differences. Many clinical studies are examined PARPis and keep examining them. PARPis are started to defined as "they are double edged knife" since different results are obtained from different studies with them. As a result of the studies carried out so far, the following information on PARP is accepted. PARP proteins are not involved in DNA repair. At the same time, they play role transcription, telomere replication, cellular transport, NF-KB regulation and HSP90 expression. Regarding PARP functions yet to be discovered, it appears outside the catalytic domain of PARP. Although the catalytic domain is conserved among the 18 members of the PARP family, differences in PARP's auto-modification domain and DNA binding domain distinguish each PARP from each other (54). The 'toxicity' of a PARP inhibitor depends on the compound's ability to stabilize PARP-DNA complexes independent of catalytic inhibition of compound. Therefore, the extent to which PARP trapping occurs has a greater clinical effect on cell killing than enzymatic inhibition of PARP activity (55). This is a reasonable explanation for why various PARP inhibitors perform differently even in the same patient cohort (52). The synthetic lethality provided by PARP inhibition (due to weakness in the HR repair pathway) is not limited to BRCA1 and BRCA2 deficient cancers.Genetic deficiencies conferring high sensitivity to PARP inhibitors include deficiencies in XRCC2, XRCC3, RAD54 and H2AX (55). Cancers including PTEN1 and ATM deficiencies and microsatellite instability (as seen in colorectal cancers) also respond well to PARP inhibitors. These new approaches and discoveries not only enable broader therapeutic applications; it also provides clues on how to approach the development and use of other DNA repair inhibitors.

PARP Inhibitors in The Market and Clinical Studies

Lynparza (Olaparib)

Lynparza is the first targeted treatment. It blocks DNA damage response in cells/tumours in deficiency in HR such as BRCA1 and/or BRCA2 mutated cells. There were 301 ongoing and completed studies with Lynparza. Currently, on May 20, 2020, FDA HRR gene mutated metastatic castration-resistant prostate has approved Lynparza for cancer. Lynparza is currently approved in several countries, including EU countries, for the maintenance treatment of platinum-sensitive recurrent ovarian cancer. It was approved in a number of countries (the US, China, the EU, Japan, and several other countries) for the maintenance treatment of platinum-sensitive relapsed ovarian cancer. Regulatory reviews are ongoing in various countries for ovarian, breast, pancreatic and prostate cancers (56).

Rucaparib (Rubraca)

Rucaparib is used in the ongoing treatment of patients with ovarian cancer, fallopian tube cancer or recurrent primary peritoneal cancer. It is used in patients who have received full or partial treatment with platinum-based cancer drugs. The most recent study, the ARIEL4 trial by Clovis Oncology and Foundation Medicine, was designed as a confirmatory phase 3 trial to further demonstrate the benefit of rucaparib. It is a study created in consultation with the Food and Drug Administration (FDA) and European Medicine Agency (EMA). As a result of clinical trials with 349 patients, according to the discontinuous range in the study, 51% of patients were resistant to platinum-based drugs, 28% were partially sensitive to platinum-based drugs, and 21% were completely sensitive to platinum-based drugs. The number of patients with reversion mutations in BRCA genes was 23 (6.6%). During the treatment period, patients were randomized to receive rucaparib (40.3%) and chemotherapy (32.3%). Patients randomized to the rucaparib arm received 600 mg of oral rucaparib twice daily in continuous 28-day cycles. Patients randomized to the chemotherapy (control group) arm received weekly intravenous paclitaxel or platinum-based chemotherapy according to investigator choice and standard of care.

Considering the data obtained as a result of the treatment; progression-free survival in the efficacy population was 7.4 months with rucaparib and 5.7 months with chemotherapy. Improvements in both progression-free survival (PFS) and response time were noted in patients with BRCA mutated advanced, relapsing ovarian cancer treated with rucaparib. There was no significant difference between the 2 treatment arms over time in either population group over 7 cycles of treatment (57).

Niraparib (Zejula)

Niraparib is indicated as monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high-grade serous epithelial ovary, fallopian tube, or primary peritoneal cancer responding (complete or partial) to platinum-based chemotherapy. On April 29, 2020, the FDA approved niraparib (ZEJULA, GlaxoSmithKline) for the maintenance treatment of adult patients with advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had a complete or partial response to first-line platinum-based chemotherapy (58). The Phase 3 PRIMA trial of Zejula® (niraparib) is the first to demonstrate that a PARP inhibitor significantly improves PFS when given as monotherapy in women with first-line platinum-sensitive advanced ovarian cancer, regardless of biomarker status (59).

Talazoparib (Talzenna)

Talzenna is indicated as monotherapy for the treatment of adult patients with HER2-negative locally advanced or metastatic breast cancer with the germline BRCA1/2-mutation. Patients must have been previously treated with an anthracycline and/or taxane in the (neo)adjuvant, locally advanced, or metastatic setting. Patients with hormone receptor (HR) positive breast cancer should have been previously treated with an endocrine-based therapy or should not be considered eligible for endocrine-based therapy. On October 16, 2018, the FDA approved talazoparib as a PARPi for patients with harmful and suspected germline BRCA mutation (gBRCAm), HER2-negative locally advanced or metastatic breast cancer (TALZENNA, Pfizer Inc.). The results of the study showed statistically significant overall improvements and delays in time to clinically significant deterioration in both general health status, quality of life, and breast symptom scales, supporting the physician's choice of treatment versus talazoparib. Talazoparib remains an option for patients with advanced breast cancer and germline BRCA mutations thanks to its PFS results. Considering its other advantages, taking it orally once a day increases patient compliance considerably. At the same time, studies have shown that there are improvements in the quality of life of patients with metastatic breast cancer (60).

Table 2. Clinical studies of PARP inhibitors

Compound	NCT IDs	Ongoing Clinical Trials	Targeted Cancers	References
Olaparib (AZD2281, KU-0069436)	NCT04586335, NCT01851265, NCT01929603, NCT01562210, NCT02093351	Phase 1	Ovarian Cancer Breast Cancer Solid Tumours Prostate Cancer Endometrial Cancer	(61) (62) (63) (64) (65)
	NCT03786796, NCT02681562, NCT05158062, NCT04669002, NCT04641728	Phase 2	Renal Cell Carcinoma Metastatic Renal Cell Carcinoma Kidney Cancer Renal Carcinoma Kidney Cancer Metastatic Breast Cancer Triple Negative Breast Cancer Ovarian Cancer Cervical Cancer	(66) (67) (68) (69) (70)
	NCT02184195, NCT01874353, NCT05262608	Phase 3	BRCA Mutated Relapsed Ovarian Cancer Prostate Cancer	(71) (72) (73)
AZD2461	NCT01247168	Phase 1	Solid Tumours C	(74)
Rucaparib (CO-338, AG-014699, PF-01367338)	NCT03542175, NCT03521037, NCT03318445	Phase 1	Breast Cancer Neoplasms Solid Tumor	(75) (76) (77)
	NCT01891344, NCT04171700, NCT03795272	Phase 2	Ovarian Cancer Epithelial Ovarian Cancer Fallopian Tube Cancer Peritoneal Cancer Solid Tumor	(78) (79) (80)
	NCT01968213, NCT02855944, NCT01968213	Phase 3	Ovarian Cancer Fallopian Tube Cancer Peritoneal Cancer Epithelial Ovarian Cancer	(81) (82) (83)
	NCT03209401, NCT04149145, NCT02500901	Phase 1	Solid Tumor, Adult HR Deficiency Ovarian Cancer Metastatic Prostate Cancer	(84) (85) (86)
Niraparib (MK-4827)	NCT04395612, NCT04068753, NCT05126342	Phase 2	Ovarian Cancer Fallopian Tube Cancer Primary Peritoneal Cancer Cervix Cancer Progressive Cervix Cancer Cervical Cancer	(87) (88) (89)
	NCT05009082, NCT04915755	Phase 3	Ovarian Cancer Fallopian Tube Cancer Peritoneal Cancer Neoplasms, Breast Cancer	(90) (91)
	NCT03343054, NCT03968406	Phase 1	Malignant Female Reproductive System Neoplasm Neoplasms Breast Neoplasms Cervical Cancer	(92) (93)
Talazoparib (BMN-673)	NCT03330405, NCT04068831, NCT05288127	Phase 2	Locally Advanced or Metastatic Solid Tumours Metastatic Renal Cell Carcinoma Fumarate Hydratase Deficient Renal Cell Carcinoma Succinate Dehydrogenase Deficient Renal Cell Carcinoma Triple Negative Breast Cancer	(94) (95) (96)
	NCT03642132, NCT01945775, NCT04821622	Phase 3	Ovarian Cancer Breast Neoplasms BRCA 1 Gene Mutation BRCA 2 Gene Mutation Prostate Cancer	(97) (98) (99)
2X-121	NCT03562832	Phase 2	Metastatic Breast Cancer	(100)

CONCLUSION

Adverse effect and low efficacy are important issues in cancer therapy. Chemo- and radiotherapy cannot differentiate cancerous cells than healthy cells, so investigations have accelerated on the targeted cancer therapy to reduce, especially, adverse effect. The potential of DNA repair inhibitors is high in cancer therapy. Although selective inhibition of DNA repair pathways can be used to improve traditional cancer therapy, the most attractive use of DNA repair inhibitors may be the benefit from repair defects for selective cell killing. Benefits from tumor mutations in DNA repair pathways to transform spontaneous DNA lesions into lethal replication lesions. This type of therapy is highly advantageous compared to traditional cancer therapy as it is likely to produce minimal side effects while resulting in highly toxic lesions that should actively induce cell death in cancer cells. A potential limitation of this approach is that it is suitable for tumors with defects in DNA repair, and resistance mechanisms may develop like in other therapies. Studies on DNA repair enzymes and concomitant studies for the simultaneous development of DNA repair enzyme inhibitors as well as their targeted-specific usage are growing day by day. In future, basic research to better understand the nature of toxic replication lesions, as well as to learn more about all DNA repair pathways and their interactions, to administer DNA repair inhibitors as single agent in cancer therapy is extremely important. Therefore, studies in this direction should be supported and accelerated.

In summary, cancer cells are potentially exposed to unusually high levels of replication stress and endogenous or exogenous DNA damage during cancer development. A future challenge will be to identify and characterize the forms of replication lesions that occur during carcinogenesis and neoplastic progression that could benefit for selective therapy. Thanks to these definitions and future studies, personalized treatment and survival will increase.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Mayo Clinic. (2021, April 27). Cancer - Symptoms and causes. Retrieved December 9, 2021, from https://www.mayoclinic.org/diseases-conditions/cancer/symptoms-causes/syc-20370588. Accessed Date: March 1, 2022

2. Bhattacharyya, A., Chattopadhyay, R., Mitra, S., & Crowe, S. E. (2014). Oxidative stress: an essential factor in the pathogenesis of gastrointestinal mucosal diseases. Physiological reviews, 94(2), 329–354.

3. World Health Organization. (2019, July 12). Cancer. WHO. Retrieved March 2, 2022, from https://www.who.int/health-topics/cancer#tab=tab_1

4. World Health Organization. (2021, March). Turkey fact sheets. WHO. Retrieved March 2, 2022, from https://gco.iarc.fr/today/data/factsheets/populations/792-turkey-fact-sheets.pdf

5. Krzyszczyk, P., Acevedo, A., Davidoff, E. J., Timmins, L. M., Marrero-Berrios, I., Patel, M., White, C., Lowe, C., Sherba, J. J., Hartmanshenn, C., O'Neill, K. M., Balter, M. L., Fritz, Z. R., Androulakis, I. P., Schloss, R. S., & Yarmush, M. L. (2018). The growing role of precision and personalized medicine for cancer treatment. Technology, 6(3-4), 79–100.

6. Georgetown University Medical Center. (n.d.). The Power of Cancer Systems Biology. Predicting the best treatment- Georgetown | Lombardi Center for Cancer Systems Biology. Retrieved December 8, 2021, from http://cancersystemsbiology.net/predicting.html

7. Bayat Mokhtari, R., Homayouni, T. S., Baluch, N., Morgatskaya, E., Kumar, S., Das, B., & Yeger, H. (2017). Combination therapy in combating cancer. Oncotarget, 8(23), 38022–38043.

8. Kavaklı, H., Gül, Ş., Berkel, Ç., Bulut, S., Tardu, M., & Barış, İ. (2018, Ocak) Kanserde DNA tamiri ve tedavide DNA tamir yolakları. Kanser Moleküler Biyolojisi (ss.173-184)

9. Sakthivel, K. M., & Hariharan, S. (2017). Regulatory players of DNA damage repair mechanisms: Role in Cancer Chemoresistance. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie, 93, 1238–1245.

10. Kiwerska, K., & Szyfter, K. (2019). DNA repair in cancer initiation, progression, and therapy-a double-edged sword. Journal of applied genetics, 60(3-4), 329–334.

11. Kelley, M. R., Logsdon, D., & Fishel, M. L. (2014). Targeting DNA repair pathways for cancer treatment: what's new?. Future oncology (London, England), 10(7), 1215–1237.

12. Robertson, A. B., Klungland, A., Rognes, T., & Leiros, I. (2009). DNA repair in mammalian cells: Base excision repair: the long and short of it. Cellular and molecular life sciences : CMLS, 66(6), 981–993.

13. Kelley, M. R., Georgiadis, M. M., & Fishel, M. L. (2012). APE1/Ref-1 role in redox signaling: translational applications of targeting the redox function of the DNA repair/redox protein APE1/Ref-1. Current molecular pharmacology, 5(1), 36–53.

14. Luo, M., He, H., Kelley, M. R., & Georgiadis, M. M. (2010). Redox regulation of DNA repair: implications for human health and cancer therapeutic development. Antioxidants & redox signaling, 12(11), 1247–1269.

15. Abbotts, R., & Madhusudan, S. (2010). Human AP endonuclease 1 (APE1): from mechanistic insights to druggable target in cancer. Cancer treatment reviews, 36(5), 425–435.

16. Goellner, E. M., Svilar, D., Almeida, K. H., & Sobol, R. W. (2012). Targeting DNA polymerase ß for therapeutic intervention. Current molecular pharmacology, 5(1), 68–87.

17. Gillet, L. C., & Schärer, O. D. (2006). Molecular mechanisms of mammalian global genome nucleotide excision repair. Chemical reviews, 106 (2), 253–276.

18. Barakat, K., & Tuszynski, J. (2013). Nucleotide Excision Repair Inhibitors: Still a Long Way to Go. In (Ed.), New Research Directions in DNA Repair. IntechOpen.

19. Barret, J. M., Cadou, M., & Hill, B. T. (2002). Inhibition of nucleotide excision repair and sensitisation of cells to DNA cross-linking anticancer drugs by F 11782, a novel fluorinated epipodophylloid. Biochemical pharmacology, 63(2), 251–258.

20. Shuck, S. C., Short, E. A., & Turchi, J. J. (2008). Eukaryotic nucleotide excision repair: from understanding mechanisms to influencing biology. Cell research, 18(1), 64–72.

21. Neher, T. M., Bodenmiller, D., Fitch, R. W., Jalal, S. I., & Turchi, J. J. (2011). Novel irreversible small molecule inhibitors of replication protein A display single-agent activity and synergize with cisplatin. Molecular cancer therapeutics, 10(10), 1796–1806.

22. Martin, S. A., Lord, C. J., & Ashworth, A. (2010). Therapeutic targeting of the DNA mismatch repair pathway. Clinical cancer research : an official journal of the American Association for Cancer Research, 16(21), 5107–5113.

23. Li G. M. (2008). Mechanisms and functions of DNA mismatch repair. Cell research, 18(1), 85–98.

24. Heinen C. D. (2016). Mismatch repair defects and Lynch syndrome: The role of the basic scientist in the battle against cancer. DNA repair, 38, 127–134. **25.** Royal Marsden NHS Foundation Trust. (2016, October 14). Methotrexate in metastatic colorectal cancer with MSH2 deficiency. Clinical Trials. Retrieved March 13, 2022, from https://clinicaltrials.gov/ct2/show/NCT00952016

26.Martin, S. A., Hewish, M., Sims, D., Lord, C. J., & Ashworth, A. (2011). Parallel high-throughput RNA interference screens identify PINK1 as a potential therapeutic target for the treatment of DNA mismatch repair-deficient cancers. Cancer research, 71(5), 1836–1848.

27. Dianov, G., Bischoff, C., Piotrowski, J., & Bohr, V. A. (1998). Repair pathways for processing of 8-oxoguanine in DNA by mammalian cell extracts. The Journal of biological chemistry, 273(50), 33811–33816.

28. Kinsella T. J. (2009). Coordination of DNA mismatch repair and base excision repair processing of chemotherapy and radiation damage for targeting resistant cancers. Clinical cancer research : an official journal of the American Association for Cancer Research, 15(6), 1853–1859. **29.** Krejci, L., Altmannova, V., Spirek, M., & Zhao, X. (2012). Homologous recombination and its regulation. Nucleic acids research, 40(13), 5795–5818.

30. Kramara, J., Osia, B., & Malkova, A. (2018). Break-Induced Replication: The Where, The Why, and The How. Trends in genetics : TIG, 34(7), 518–531. **31.** Budke, B., Logan, H. L., Kalin, J. H., Zelivianskaia, A. S., Cameron McGuire, W., Miller, L. L., Stark, J. M., Kozikowski, A. P., Bishop, D. K., & Connell, P. P. (2012). RI-1: a chemical inhibitor of RAD51 that disrupts homologous recombination in human cells. Nucleic acids research, 40(15), 7347–7357.

32. Chen, G., Yuan, S. S., Liu, W., Xu, Y., Trujillo, K., Song, B., Cong, F., Goff, S. P., Wu, Y., Arlinghaus, R., Baltimore, D., Gasser, P. J., Park, M. S., Sung, P., & Lee, E. Y. (1999). Radiation-induced assembly of Rad51 and Rad52 recombination complex requires ATM and c-Abl. The Journal of biological chemistry, 274(18), 12748–12752.

33. Meek, K., Dang, V., & Lees-Miller, S. P. (2008). DNA-PK: the means to justify the ends?. Advances in immunology, 99, 33–58.

34. Helleday, T., Petermann, E., Lundin, C., Hodgson, B., & Sharma, R. A. (2008). DNA repair pathways as targets for cancer therapy. Nature reviews. Cancer, 8(3), 193–204.

35. Hsu, F. M., Zhang, S., & Chen, B. P. (2012). Role of DNA-dependent protein kinase catalytic subunit in cancer development and treatment. Translational cancer research, 1(1), 22–34.

36. Davidson, D., Amrein, L., Panasci, L., & Aloyz, R. (2013). Small Molecules, Inhibitors of DNA-PK, Targeting DNA Repair, and Beyond. Frontiers in pharmacology, 4, 5.

37. Herceg, Z., & Wang, Z. Q. (2001). Functions of poly(ADP-ribose) polymerase (PARP) in DNA repair, genomic integrity and cell death. Mutation research, 477(1-2), 97–110. **38.** Isabelle, M., Moreel, X., Gagné, J. P., Rouleau, M., Ethier, C., Gagné, P., Hendzel, M. J., & Poirier, G. G. (2010). Investigation of PARP-1, PARP-2, and PARG interactomes by affinity-purification mass spectrometry. Proteome science, 8, 22.

39. Ménissier de Murcia, J., Ricoul, M., Tartier, L., Niedergang, C., Huber, A., Dantzer, F., Schreiber, V., Amé, J. C., Dierich, A., LeMeur, M., Sabatier, L., Chambon, P., & de Murcia, G. (2003). Functional interaction between PARP-1 and PARP-2 in chromosome stability and embryonic development in mouse. The EMBO journal, 22(9), 2255–2263.

40. Eisemann, T., & Pascal, J. M. (2020). Poly(ADP-ribose) polymerase enzymes and the maintenance of genome integrity. Cellular and molecular life sciences : CMLS, 77(1), 19–33.

41. Steffen, J. D., Brody, J. R., Armen, R. S., & Pascal, J. M. (2013). Structural Implications for Selective Targeting of PARPs. Frontiers in oncology, 3, 301.

42. Ko, H. L., & Ren, E. C. (2012). Functional Aspects of PARP1 in DNA Repair and Transcription. Biomolecules, 2(4), 524–548.

43. Alemasova, E. E., & Lavrik, O. I. (2019). Poly(ADP-ribosyl)ation by PARP1: reaction mechanism and regulatory proteins. Nucleic acids research, 47(8), 3811–3827.

44. Bryant, H. E., Schultz, N., Thomas, H. D., Parker, K. M., Flower, D., Lopez, E., Kyle, S., Meuth, M., Curtin, N. J., & Helleday, T. (2005). Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature, 434(7035), 913–917.

45. Glendenning, J., & Tutt, A. (2011). PARP inhibitors--current status and the walk towards early breast cancer. Breast (Edinburgh, Scotland), 20 Suppl 3, S12–S19.

46. Rouleau, M., Patel, A., Hendzel, M. J., Kaufmann, S. H., & Poirier, G. G. (2010). PARP inhibition: PARP1 and beyond. Nature reviews. Cancer, 10(4), 293–301.
47. Steffen, J. D., McCauley, M. M., & Pascal, J. M. (2016). Fluorescent sensors of PARP-1 structural dynamics and allosteric regulation in response to DNA damage. Nucleic acids research, 44(20), 9771–9783.
48. Lord, C. J., & Ashworth, A. (2017). PARP inhibitors: Synthetic lethality in the clinic. Science (New York, N.Y.), 355(6330), 1152–1158.
49. Camero, S., Ceccarelli, S., De Felice, F., Marampon, F., Mannarino, O., Camicia, L., Vescarelli, E., Pontecorvi, P., Pizer, B., Shukla, R., Schiavetti, A., Mollace, M. G., Pizzuti, A., Tombolini, V., Marchese, C., Megiorni, F., & Dominici, C. (2019). PARP inhibitors affect growth, survival and radiation susceptibility of human alveolar and embryonal rhabdomyosarcoma cell lines. Journal of cancer research and clinical oncology, 145(1), 137–152.
50. Matta, E., Kiribayeva, A., Khassenov, B., Matkarimov, B. T., & Ishchenko, A. A. (2020). Insight into DNA substrate specificity of PARP1-catalysed DNA poly(ADP-ribosyl)ation. Scientific reports, 10(1), 3699.
51 Li, H., Liu, Z. Y., Wu, N., Chen, Y. C., Cheng, Q., & Wang, J. (2020). PARP inhibitor resistance: the underlying mechanisms and clinical implications. Molecular cancer, 19(1), 107.
52. Papeo, G., Casale, E., Montagnoli, A., & Cirla, A. (2013). PARP inhibitors in cancer therapy: an update. Expert opinion on therapeutic patents, 23(4), 503–514.
53. Leung, M., Rosen, D., Fields, S., Cesano, A., & Budman, D. R. (2011). Poly(ADP-ribose) polymerase-1 inhibition: preclinical and clinical development of synthetic lethality. Molecular medicine (Cambridge, Mass.), 17(7-8), 854–862. **54.** Plummer, R., Jones, C., Middleton, M., Wilson, R., Evans, J., Olsen, A., Curtin, N., Boddy, A., McHugh, P., Newell, D., Harris, A., Johnson, P., Steinfeldt, H., Dewji, R., Wang, D., Robson, L., & Calvert, H. (2008). Phase I study of the poly(ADP-ribose) polymerase inhibitor, AG014699, in combination with temozolomide in patients with advanced solid tumors. Clinical cancer research : an official journal of the American Association for Cancer Research, 14(23), 7917–7923.
55. Murai, J., Huang, S. Y., Das, B. B., Renaud, A., Zhang, Y., Doroshow, J. H., Ji, J., Takeda, S., & Pommier, Y. (2012). Trapping of PARP1 and PARP2 by Clinical PARP Inhibitors. Cancer research, 72(21), 5588–5599.
56. Adrian Kemp, A. D. & AstraZeneca. (2021, September 24). Lynparza in combination with abiraterone significantly delayed disease progression in all-comers in PROpel phase III trial in 1st-line metastatic castration-resistant prostate cancer. AstraZeneca. Retrieved March 2, 2022, from https://www.astrazeneca.com/media-centre/press-releases/2021/lynparza-propel-trial-meets-primary-endpoint.html
57. Astor, L. (2021, March 20). ARIEL4 trial confirms PFS benefit of rucaparib in BRCA+ relapsed ovarian cancer. Cancer Network. Retrieved March 14, 2022, from https://www.cancernetwork.com/view/ariel4-trial-confirms-pfs-benefit-of-rucaparib-in-brca-relapsed-ovarian-cancer
58. Center for Drug Evaluation and Research. (2020, April 29). FDA approves niraparib for first-line maintenance of advanced ovarian cancer. U.S. Food and Drug Administration. Retrieved March 11, 2022, from https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approvesniraparib-first-line-maintenance-advanced-ovarian-cancer
59. GlaxoSmithKline. (n.d.). Phase 3 PRIMA trial of zejula® (niraparib) is the first study to show a PARP inhibitor significantly improves PFS, regardless of biomarker status, when given as monotherapy in women with first-line platinum responsive advanced ovarian cancer | GSK. Retrieved March 24, 2022, from https://www.gsk.com/en-gb/media/press-releases/phase-3-prima-trial-of-zejula-niraparib-is-the-first-study-to-show-a-parp-inhibitor-significantly-improves-pfs-regardless-of-biomarker-status/
60. European Medicines Agency. (2021, December 7). Talzenna. Retrieved March 14, 2022, from https://www.ema.europa.eu/en/medicines/human/EPAR/talzenna
61. Haihe Biopharma Co., Ltd. (2021, February 8). Study of CYH33 in combination with olaparib an oral PARP inhibitor in patients with advanced solid tumors. Clinical Trials. Retrieved March 24, 2022, from https://clinicaltrials.gov/ct2/show/NCT04586335?cond=olaparib&phase=0&draw=2&rank=1
62. AstraZeneca. (2017, August 27). Food interaction with olaparib capsule in patients with solid tumours. Clinical Trials. Retrieved March 24, 2022, from https://clinicaltrials.gov/ct2/show/NCT01851265
63. Merck Sharp & Dohme Corp. (2022, March 14). A study of pembrolizumab (MK-3475) with or without maintenance olaparib in first-line metastatic squamous non-small cell lung cancer (NSCLC, MK-7339-008/KEYLYNK-008). Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT03976362
64. AstraZeneca. (2020, March 17). Olaparib dose escalating trial + concurrent RT with or without cisplatin in locally advanced NSCLC. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT01562210
65. National Cancer Institute. (2021, July 16). Phase I/IIa study of concomitant radiotherapy with olaparib and temozolomide in unresectable high grade gliomas patients. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT03212742
66. AstraZeneca. (2022, March 16). Study of olaparib in metastatic renal cell carcinoma patients with DNA repair gene mutations - full text view. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT03786796
67. Istituti Ospitalieri di Cremona. (2016, February 15). Olaparib in locally advanced ER, PgR and HER2 negative (triple negative) and in locally advanced germline BRCA mutation-positive breast cancer patients. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT02681562
68. Kosei Hasegawa. (2021, December 15). Pembrolizumab and bevacizumab with chemotherapy followed by pembrolizumab, bevacizumab and olaparib in recurrent ovarian cancer. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT05158062?cond=olaparib&phase=1&draw=2&rank=3
69. Ellipses Pharma. (2021, November 9). EP0057 in combination with olaparib in advanced ovarian cancer. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT04669002
70. Saitama Medical University International Medical Center. (2021, December 3). Pembrolizumab plus olaparib in patients with recurrent cervical cancer. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT04641728?cond=olaparib&phase=1&draw=2&rank=5
71. AstraZeneca. (2022, March 2). Olaparib in gBRCA mutated pancreatic cancer whose disease has not progressed on first line Platinum-Based chemotherapy (POLO). Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT02184195?cond=olaparib&phase=2&draw=2&rank=1
72. AstraZeneca. (2022, March 22). Olaparib treatment in BRCA mutated ovarian cancer patients after complete or partial response to platinum chemotherapy. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT01874353
73. AstraZeneca. (2022, March 2). The study of olaparib in newly diagnosed mCRPC patients with HRR gene mutation (PROspect). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT05262608?cond=olaparib&draw=2&rank=13
74. AstraZeneca. (2012, July 6). An Open-Label, Dose-Escalation study of AZD2461. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT01247168?cond=AZD2461&draw=2&rank=1
75. Memorial Sloan Kettering Cancer Center. (2022, March 22). A study of rucaparib administered with radiation in patients with triple negative breast cancer with an incomplete response following chemotherapy. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03542175?cond=rucaparib&phase=0&draw=2&rank=1
76. Clovis Oncology, Inc. (2021, October 27). Rucaparib hepatic impairment study in patients with a solid tumor. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03521037?cond=rucaparib&phase=0&draw=2&rank=2
77. Pamela Munster, P. M. & Clovis Oncology, Inc. (2021, March 4). Rucaparib and irinotecan in cancers with mutations in DNA repair. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03318445?cond=rucaparib&phase=0&draw=2&rank=5
78. Clovis Oncology, Inc. (2022, February 4). A study of rucaparib in patients with Platinum-Sensitive, relapsed, High-Grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (ARIEL2) (ARIEL2). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT01891344?cond=rucaparib&phase=1&draw=2&rank=12
79. Clovis Oncology, Inc. (2022, January 12). A study to evaluate rucaparib in patients with solid tumors and with deleterious mutations in HRR genes (LODESTAR). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT04171700?cond=rucaparib&phase=1&draw=2&rank=10
80. Nordic Society of Gynaecological Oncology - Clinical Trials Unit. (2019, November 1). Rucaparib maintenance therapy in advanced cervical cancer (MaRuC). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03795272?cond=rucaparib&phase=1&draw=2&rank=2
81. Clovis Oncology, Inc. (2021, May 26). A study of rucaparib as switch maintenance following Platinum-Based chemotherapy in patients with Platinum-Sensitive, High-Grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3). Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT01968213
82. Clovis Oncology, Inc. (2022c, March 3). ARIEL4: A study of rucaparib versus chemotherapy BRCA mutant ovarian, fallopian tube, or primary peritoneal cancer patients. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT02855944
83. Clovis Oncology, Inc. (2021, May 26). A study of rucaparib as switch maintenance following Platinum-Based chemotherapy in patients with Platinum-Sensitive, High-Grade serous or endometrioid epithelial ovarian, primary peritoneal or fallopian tube cancer (ARIEL3). Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT01968213
84. Georgetown University. (2021, September 1). Niraparib plus carboplatin in patients with homologous recombination deficient advanced solid tumor malignancies. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT03209401
85. Rebecca Arend & University of Alabama at Birmingham. (2022, January 24). Rial of m4344 and niraparib in patients with poly (ADP-ribose) polymerase (PARP) resistant recurrent ovarian cancer (PARP). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT04149145?cond=Niraparib&phase=0&draw=2&rank=4

86. Paul Mathew, MD, P. M. & Hoosier Cancer Research Network. (2019, October 21). Enzalutamide and niraparib in the treatment of metastatic Castrate-Resistant prostate cancer (CRPC). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT02500901?cond=Niraparib&phase=0&draw=2&rank=5

87. Qi Zhou, Q. Z. & Chongqing University Cancer Hospital. (2021, May 21). Niraparib combined with brivanib or toripalimab in patients with cervical cancer (CQGOG0101). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT04395612?cond=Niraparib&phase=1&draw=2&rank=1

88. University of Oklahoma. (2022, February 22). Niraparib in combination with dostarlimab in patients with recurrent or progressive cervix cancer (STAR). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT04068753?cond=Niraparib&phase=1&draw=2&rank=2

89. GlaxoSmithKline & AGO Research GmbH. (2021, November 19). Study to estimate efficacy of combining dostarlimab and niraparib in relapsed EOC after treatment with PARPi. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT05126342?cond=Niraparib&phase=1&draw=2&rank=3

90. European Network of Gynaecological Oncological Trial Groups (ENGOT) & AGO Study Group. (2021, August 17). Niraparib vs niraparib plus bevacizumab in patients with platinum/taxane-based chemotherapy in advanced ovarian cancer. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT05009082?cond=Niraparib&phase=2&draw=2&rank=2

91. GlaxoSmithKline. (2022, March 2). Efficacy and safety comparison of niraparib to placebo in participants with human epidermal growth factor 2 negative (HER2-) breast cancer susceptibility gene mutation (BRCAmut) or Triple-Negative breast cancer (TNBC) with molecular disease (ZEST). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT04915755?cond=Niraparib&phase=2&draw=2&rank=6

92. Pfizer. (2022, March 10). A phase 1 study of talazoparib, PARP inhibitor, in japanese patients with advanced solid tumors. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03343054?cond=Talazoparib&phase=0&draw=2&rank=3

93. National Cancer Institute (NCI) & M.D. Anderson Cancer Center. (2022, March 15). Talazoparib and radiation therapy in treating patients with locally recurrent gynecologic cancers. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03968406?cond=Talazoparib&phase=0&draw=2&rank=5

94. Pfizer. (2022, March 10). Javelin parp medley: Avelumab plus talazoparib in locally advanced or metastatic solid tumors. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT03330405

95. Memorial Sloan Kettering Cancer Center. (2022, January 11). Talazoparib and avelumab in participants with metastatic renal cell carcinoma. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT04068831

96. Ho Gwo Fuang, H. G. F., University of Malaya, & Pfizer. (2022, March 21). Efficacy of talazoparib in asian metastatic breast cancer patients with a homologous recombinant deficiency (HRD) signature. Clinical Trials. Retrieved March 25, 2022, from https://clinicaltrials.gov/ct2/show/NCT05288127

97. Pfizer. (2022, February 24). Avelumab and Talazoparib in Untreated Advanced Ovarian Cancer (JAVELIN OVARIAN PARP 100). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03642132?cond=Talazoparib&phase=2&draw=2&rank=2

98. Pfizer. (2022, January 20). A study evaluating talazoparib (BMN 673), a PARP inhibitor, in advanced and/or metastatic breast cancer patients with BRCA mutation (EMBRACA study) (EMBRACA). Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT01945775?cond=Talazoparib&phase=2&draw=2&rank=

99. Pfizer. (2022, March 21). Study of talazoparib with enzalutamide in men with DDR gene mutated mCSPC. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT04821622?cond=Talazoparib&phase=2&draw=2&rank=3

100. Allarity Therapeutics. (2022, January 11). Investigation of anti-tumour effect and tolerability of the PARP inhibitor 2X-121 in patients with metastatic breast cancer selected by the 2X-121 DRP. Clinical Trials. Retrieved March 25, 2022, from https://www.clinicaltrials.gov/ct2/show/NCT03562832?cond=Parp+inhibitor&draw=2&rank=6