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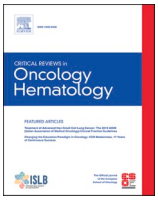

Potential agnostic role of *BRCA* alterations in patients with several solid tumors: One for all, all for one?

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ABSTRACT

Germline *BRCA1/2* alterations in the Homologous Recombination (HR) pathway are considered as main susceptibility biomarkers to Hereditary Breast and Ovarian Cancers (HBOC). The modern molecular biology technologies allowed to characterize germline and somatic *BRCA1/2* alterations in several malignancies, broadening the landscape of *BRCA1/2*-altered tumors. In the last years, *BRCA* genetic testing, beyond the preventive value, also assumed a predictive and prognostic significance for patient management. The approval of molecules with agnostic indication is leading to a new clinical model, defined "mutational". Among these drugs, the Poly (ADP)-Ribose Polymerase inhibitors (PARPi) for *BRCA1/2*-deficient tumors were widely studied leading to increasing therapeutic implications. In this Review we provided an overview of the main clinical studies describing the association between *BRCA*-mutated tumors and PARPi response, focusing on the controversial evidence about the potential agnostic indication based on *BRCA1/2* alterations in several solid tumors.

1. Introduction

BRCA1 and *BRCA2* genes are the main effectors of the Homologous Recombination (HR) DNA repair pathway (Vergote et al., 2022). Germline Pathogenic/Likely Pathogenic Variants (PVs/LPVs) in these tumor-suppressor genes have been associated to a high lifetime risk of developing the Hereditary Breast and Ovarian Cancer (HBOC) syndrome (Fanale et al., 2021), which, in its phenotypic spectrum, includes, beyond hereditary breast cancer (BC) and ovarian cancer (OC), also pancreatic cancer (PC), prostate cancer (PrC), and melanoma (Boyd, 2000; Incorvaia et al., 2020a; Bono et al., 2021; von Werdt et al., 2021). Germline and somatic *BRCA1/2* alterations have been shown to confer sensitivity to platinum-based drugs and Poly (ADP-Ribose) Polymerase inhibitors (PARPi), demonstrating their effectiveness in a variety of neoplasms with HR deficiency (HRD) (Sokol et al., 2020; Heeke et al., 2018). The recent approval of drugs defined as agnostics led to a "genomics-driven" clinical model, called "mutational" (Garraway, 2013), through which the precision oncology provided targeted molecular therapies, allowing to obtain excellent results and improving patient's outcome and in disease control (Le Tourneau et al., 2019; Seebacher et al., 2019; Lee et al., 2018; Pucci et al., 2019). In this scenario, the PARPi treatment has been emerging as monotherapy based on "synthetic lethality" mechanism, by selectively inducing tumor cell death and demonstrating a great effectiveness in *BRCA1/2*-related HRD tumors (Fong et al., 2009, 2010; Coleman et al., 2019; Tuli et al., 2019). In a HRD status, where a *BRCA1/2* PV/LPV is considered the main predictive factor for treatment choice, the inhibition of PARP enzymes determines a block of Base Excision Repair (BER) pathway, making cells more prone to error and causing the selective tumor cell death (Pujol et al., 2021; Lord and Ashworth, 2017). The synthetic lethality mechanism was explained in 2005 and, in subsequent years, were published the first evidences about the efficacy of PARPi in *BRCA1/2*-deficient BC,

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OC and PrC (Faraoni and Graziani, 2018; Bryant et al., 2005; Farmer et al., 2005). Since the first approval by FDA and EMA to date, three PARPi have been approved for the treatment of OC and two for the management of BC harbouring germline *BRCA1/2* PVs/LPVs, if HER2-negative (Curtin et al., 2019). Moreover, two PARPi became "breakthrough therapy" for the treatment of metastatic castration-resistant PrC (mCRPC) (von Werdt et al., 2021; Nuhn et al., 2019; Helleday, 2016), and one PARPi has been approved as maintenance therapy in patients with *BRCA1/2*-mutated pancreatic ductal adenocarcinoma (PDAC) (Singh et al., 2021; Golan et al., 2019). Until 2022, slightly less than 400 clinical trials regarding PARPi administration in different metastatic tumors, such as trials investigating PARPi-based treatment in HRD-positive tumors with controversial evidence in neoadjuvant and adjuvant settings, are underway (Luo and Keyomarsi, 2022; Wolford et al., 2022). Anyway, many alternative strategies are under investigation, including the combination of PARPi with radiation therapies or other drugs, such as chemotherapeutic, targeted, or immunotherapic drugs (Lord and Ashworth, 2017; Peyraud and Italiano, 2020). However, some findings are showing less confidence in PARPi administration and in *BRCA1/2* genes alterations predictive and/or prognostic role (Jonsson et al., 2019). PARPi mechanism of action seems to be varying among *BRCA1/2*-alterated tumors, and new findings about the synthetic lethality and the HRD molecular scenario could give more detailed explanations (Curtin et al., 2019; Kim et al., 2021a). In this review, we want to look inside the controversial "pan-cancer" landscape (Nguyen et al., 2020), in which *BRCA1/2* PVs/LPVs could find a possible agnostic indication, by evaluating the PARPi treatment evidence among different *BRCA1/2*-deficient solid tumors.

2. DNA damage repair pathways related to *BRCA1/2*

2.1. Double-stranded DNA damage repair

The genome undergoes to changes by exogenous and/or endogenous agents and errors can also arise due to DNA polymerases activity (Rattray and Strathern, 2003). However, very accurate DNA repair systems may alter tolerance and cell death mechanisms (Chatterjee and Walker, 2017; Reed, 2010). DNA damages can be single-stranded or double-stranded triggering the intervention of different repair systems. Double-strand breaks (DSBs) generally arise from stalled or broken DNA replication fork, or derive from ionizing radiation, reactive oxygen species (ROS) or mechanical stress. These alterations can be mainly repaired by Non-Homologous End Joining (NHEJ) and HR pathways (Lieber, 2010).

The cell uses NHEJ to repair DBSs with the broken DNA strands stitched by DNA ligation (Chang et al., 2017). NHEJ mechanism is particularly error-prone due to the loss of nucleotides, causing rearrangements which increase chromosomal instability (Wang et al., 2006). Cell recurs to the HR system as repairing pathway during, or immediately after, the replication in the S-/G2-phase of the cell cycle (Venkitaraman, 2002; Zimmer et al., 2021).

The HR pathway involves several proteins, including BRCA1 and BRCA2, RAD50, RAD51, ATM, PALB2 (Frey and Pothuri, 2017; Fanale et al., 2020) (Fig. 1). This system is slower than NHEJ but more efficient, because faithfully respects the original DNA sequence. The NHEJ system, in fact, plays its role mainly in case of HRD and it is faster than the HR system (Wang et al., 2006; Khanna and Jackson, 2001). HR repairs DSBs by exchanging DNA strands between a pair of homologous sister chromatids, with a template-dependent mechanism (Li and Heyer, 2008).

BRCA1 and BRCA2 play an important role in preventing cancer through avoiding the cell cycle's delay, the apoptosis trigger, or the ignition of damaged DNA (Yoshida and Miki, 2004; Yang and Lippman, 1999; Her and Bunting, 2018). BRCA1 protein interacts with DNA damage sensors, DNA Damage Response (DDR) effectors and cell cycle

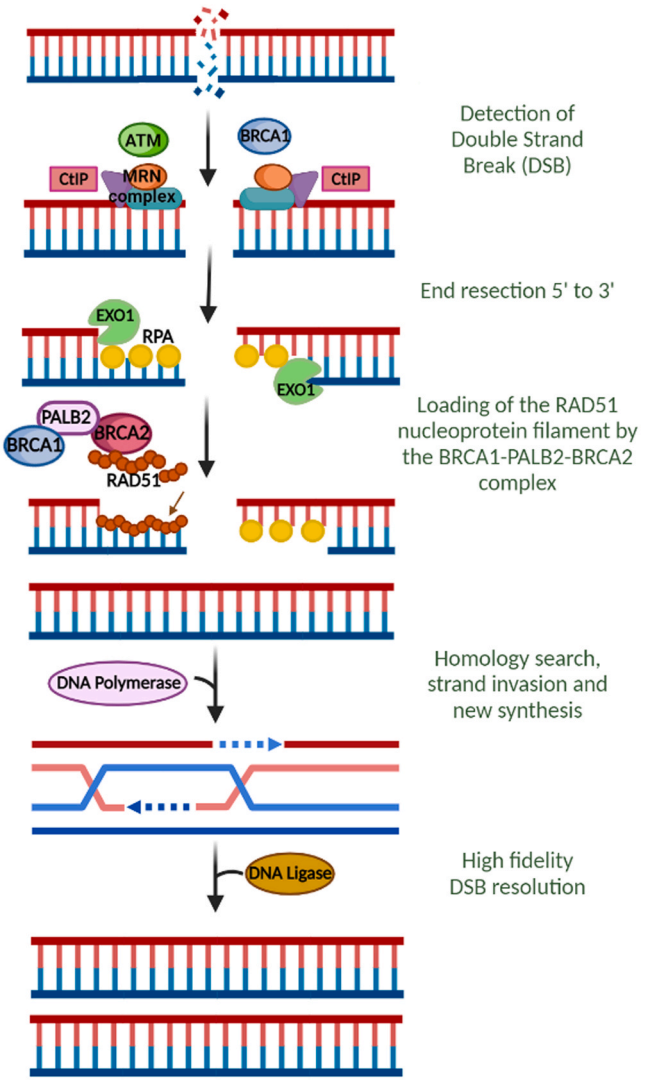

Fig. 1. Double Strand Break (DSB) repair by Homologous Recombination (HR). The image was created with BioRender Software (https://biorender.com/).

regulators, working ahead of BRCA2 and with several roles due to its different structural domains (Roy et al., 2011).

In subjects carrying germline and/or somatic *BRCA1/2* alterations, the loss of both functional alleles results in a HRD, leading a disease-causing genomic instability (Hanahan and Weinberg, 2011; Andor et al., 2017; Fanale et al., 2013). In fact, the crucial step in carcinogenesis is the loss of heterozygosity (LOH) occurring for both alleles encoding even for one of the tumor-suppressor genes, leading to an unfunctional HR system in cancer cells (Bono et al., 2021; Westphalen et al., 2022).

BRCA1-deficient cells have been observed to carry more often chromosomal aberrations or rearrangements (Lord and Ashworth, 2016), whereas *BRCA2*-deficient cells are more subject to aneuploidy (Karaayvaz-Yildirim et al., 2020). Controversial opinions suggest that the LOH could not represent the condition request for HRD status (Roy et al., 2011) and underline that the promotor methylation of *BRCA1/2* genes could determine the loss of function (LOF), more frequently in sporadic cancers (Moschetta et al., 2016; Vos et al., 2017).

Moreover, the *BRCA1/2* LOH is not always leading to HRD, since the 60% of OCs is in a HRD condition, but only the 20% is *BRCA1/2*-related (Mukhopadhyay et al., 2010). In addition, secondary alterations restoring the *BRCA1/2* function, or competing genes which replace it,

can recover the HR function (Dhillon et al., 2011; Bunting et al., 2010).

Deeper researches about the potential agnostic role of aberrant *BRCA1/2* variants have been performed, highlighting that a more accurate estimation of HRD rate, through the finding of new biomarkers, is needed (Jonsson et al., 2019; Fanale et al., 2020).

2.2. Single-stranded DNA damage repair: PARP enzymes and synthetic lethality

There are three main pathways involved in single-strand breaks (SSBs): i) the Mismatch Repair (MMR) system, able to recognize and repair insertions, deletions, and mis-incorporations of nucleotides in DNA, during replication and recombination (Fishel, 2015; Fanale et al., 2022a, 2022a); ii) the Nucleotide Excision Repair (NER), mainly used to remove large DNA damages caused by UV light, environmental factors and adducts from chemotherapeutic agents (Scharer, 2013), and iii) BER, a pathway involving PARP enzymes and repairing damages due to alkylation, oxidation, and deamination (Chatterjee and Walker, 2017; Cetin et al., 2020) (Fig. 2).

PARP enzymes consist in a protein family involved in several cellular mechanisms, including stress response, DNA repair and apoptosis (Krishnakumar and Kraus, 2010; Pines et al., 2012; Vyas et al., 2013), but firstly PARP acts against endogenous DNA damages, especially in HRD status (Lindahl, 1993). Among the 17 members of PARP family, PARP1 is associated with the detection and repair of DNA SSBs through BER system (Heeke et al., 2018; Fisher et al., 2007). In the BER pathway, PARP1 is recruited to the SSB, by binding the broken DNA through its own zinc finger domains (Ali et al., 2012). Usually, PARP1 has a weak catalytic activity, due to its helical domain interacting with the catalytic one causing an inhibition, but its binding to the SSB induces a conformational change, which allows to the catalytic site to act freely (Rose et al., 2020). PARP1 starts to produce poly ADP-ribose at the damaged strand through auto-PARylation. After the polymerization, nucleotides are transferred to the targeted proteins in the SSB, bringing to the chromatin change and repairing the DNA lesion (Ali et al., 2012; Rose et al., 2020; Alemasova and Lavrik, 2019) (Fig. 2).

Experimental evidence showed that PARPi can bind the catalytic site of the enzyme, preventing its conformational change, but also entrap PARP1 at the SSB, inducing an allosteric change making it unable to dislodge, causing collapses the replication fork and leading to a DSB (Mateo et al., 2019; Rimar et al., 2017).

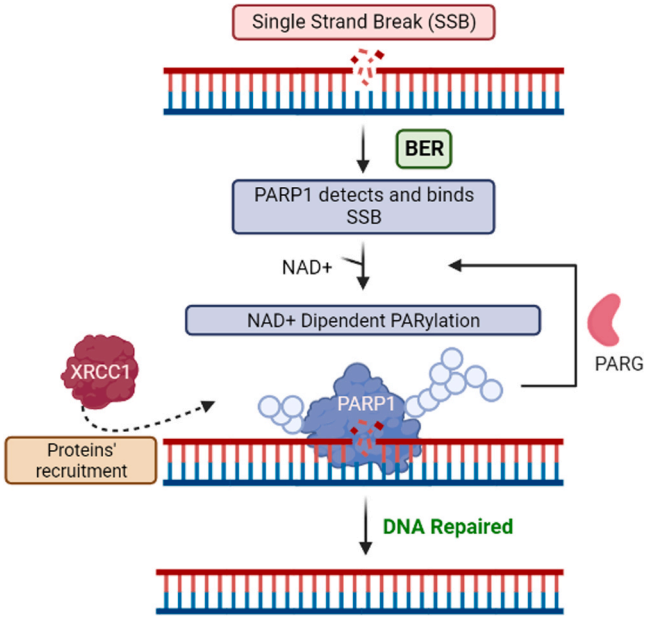

Fig. 2. Single Strand Break (SSB) repair by PARP-dependent Base Excision Repair (BER) pathway. The image was created with BioRender Software (https://biorender.com/).

In 2005, two studies demonstrated that PARPi have no effect on cells with a heterozygous *BRCA1/2* PV/LPV. Conversely, if the alteration is present in a homozygous condition with LOH in one of the two genes, the simultaneous presence of a PARPi and the absence of BRCA1/2 function, or alterations in other HR genes, such as *PALB2* and *RAD51*, determines a blockage of the HR system (Bryant et al., 2005; Farmer et al., 2005). Thus, the DSB is not repaired and the system collapses, leading to a cytotoxicity-induced cell death. This mechanism, called "synthetic lethality", represents the basis of PARPi-based therapy (Fig. 3).

3. Exploring the potential "agnostic" role of *BRCA1/2* alterations in HBOC-associated tumors

Germline and somatic *BRCA1/2* PVs/LPVs represent the main predictive biomarkers for therapeutic indications to PARPi (Ganguly et al., 2016). Understanding if a "pan-cancer" role of these variants exists or not represents an important goal for scientific community to improve patients' healthcare. Since the first PARPi approval in 2014, many researchers tried to identify novel biomarkers for predicting PARPi sensitivity. To date, a lot of promising results have been obtained, and the use of PARPi has been introduced as a treatment in BC, OC, PC and PrC. Further studies have been launched about its effectiveness in different solid tumors (Jonsson et al., 2019; Hu et al., 2019).

3.1. Breast Cancer

BC is one of the most common cancers among women worldwide, with 5–10% due to inherited genomic alterations in *BRCA1/2* genes (Incorvaia et al., 2020b). The *BRCA1/2* genetic testing, beyond primarily preventive purposes (Domchek, 2010), has assumed, in the last years, also therapeutic implications, suggesting that *BRCA1/2*-related BC are sensitive to PARPi (Ganguly et al., 2016). Moreover, in the neo-adjuvant setting, the addition of platinum salts to standard chemotherapy may be considered in TNBC patients (Dieci et al., 2019).

In 2017, the phase III, multicentric, open label, randomized controlled (2:1) trial OlympiAD (NCT02000622) showed that the olaparib-based maintenance therapy significantly increased Progression-Free Survival (PFS) in metastatic HER2-negative BC patients harbouring a germline *BRCA1/2* alteration, compared to standard chemotherapy (Robson et al., 2017, 2019). Among the 302 patients, the median PFS was longer in patients treated with olaparib than in patients treated with standard chemotherapy (7.0 *vs* 4.2 months), as well as the Overall Survival (OS) (19.3 *vs* 17.1 months). The risk of progression of disease or death was 42% lower compared to patients receiving ordinary chemotherapy (Robson et al., 2017). Olaparib obtained the FDA's approval in 2018 and EMA's approval in 2019, as a monotherapy for the treatment of metastatic HER2-negative BC with a germline *BRCA1/2* PV/LPV, after conventional chemotherapy treatments (Le and Gelmon, 2018) (Table 1).

In 2018, the TALA study (NCT03499353) highlighted, for the first time, the efficacy of talazoparib monotherapy in the treatment of *BRCA1/2*-altered locally advanced BC (Litton et al., 2021, 2018). In the same year, the EMBRACA study (NCT01945775) was published, as an open label, randomized (2:1), phase III trial including 431 patients receiving talazoparib or standard chemotherapy. Talazoparib monotherapy has been shown to significantly increase PFS of 46% in advanced HER2-negative BC patients with a germline *BRCA1/2* PV/LPV compared to conventional treatments (8.6 months *vs* 5.6 months) (Litton et al., 2018; Ettl et al., 2018), as well as the OS (22.3 *vs* 19.5 months). In 2018, FDA and EMA approved talazoparib as monotherapy in advanced or metastatic BC, in presence of a germline *BRCA1/2* PV/LPV (Litton et al., 2018; Ettl et al., 2018; Hurvitz et al., 2018) (Table 1). Recently, in 2021, the OlympiA study (NCT02032823), a phase III, international,

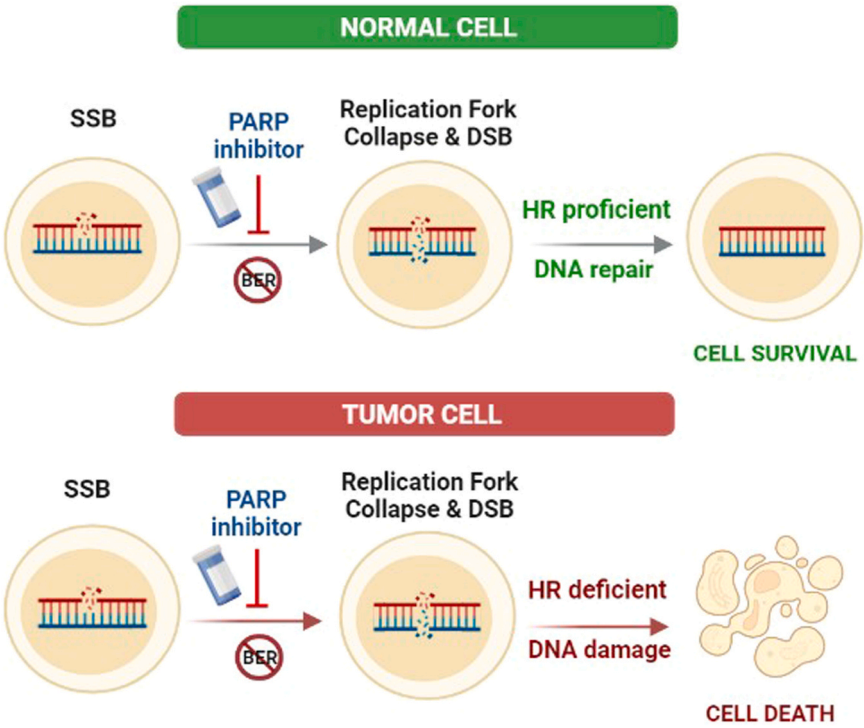

Fig. 3. Mechanism of action of PARP inhibitors by synthetic lethality. The image was created with BioRender Software (https://biorender.com/).

double-blind, placebo-controlled, randomized (1:1) trial, has enrolled 1836 patients with localized HER2-negative BC and germline *BRCA1/2* alterations. The aim was to evaluate the benefits of olaparib as adjuvant therapy in early-stage BC patients with germline *BRCA1/2* alterations. This study demonstrated that olaparib increases the Invasive Disease-Free Survival (IDFS) compared to the placebo (85,9% *vs* 77,1%), with an important effect of risk reduction of Distant Disease-Free Survival (DDFS) by 42%. The 3 years-OS was higher with olaparib than with placebo (92% *vs* 88.3%). PARPi, used as adjuvant therapy, showed that germline *BRCA1/2* PVs/LPVs are important biomarkers in the choice of systemic therapy in patients with early BC (Tutt et al., 2021).

3.2. Ovarian cancer

OC is the 7th most diagnosed cancer and the 8th most common cause of cancer death worldwide (Fanale et al., 2023). The risk of OC is higher in women with *BRCA1/2* PVs/LPVs, which were detected in 10–15% of all OCs, regardless of age at diagnosis and family history of cancer. The prevalence of *BRCA1/2* PVs/LPVs rises to 20% in patients with serous OC and 25% in those with high-grade OC (Bryant et al., 2005; Soegaard et al., 2008; Turashvili et al., 2020; Schrader et al., 2012). Findings showed that patients with *BRCA1/2*-deficient OC have an increased sensitivity to treatments by platinum derivatives (Atsushi et al., 1994), and germinal or somatic *BRCA1/2* PVs/LPVs have been shown to be predictive markers of increased sensitivity to PARPi treatment (Damia and Broggini, 2019; Valabrega et al., 2021). Somatic genetic testing allows to identify *BRCA1/2* PVs/LPVs in order to plan an appropriate therapeutic strategy, but also to confirm or exclude the presence of these alterations in germline, where they could have a preventive role (Incorvaia et al., 2020a; Bono et al., 2021). To date, the *BRCA1/2* testing is recommended for patients with non-mucinous and non-borderline ovarian, fallopian tube or primary peritoneal carcinoma (Fanale et al., 2022b). The effectiveness of olaparib-based maintenance treatment has been demonstrated in the NCT0107662 study. The olaparib therapy was approved in 2014 by the FDA and EMA in advanced OC patients harbouring a germline *BRCA1/2* PV/LPV (Franzese et al., 2019; Kaufman et al., 2015) (Table 1). In 2017, the SOLO-2 study (NCT01874353), an international, randomized (2:1), double-blind, placebo-controlled, phase III trial, tested the olaparib maintenance monotherapy compared to placebo, in platinum-sensitive recurrent OC patients carrying germline *BRCA1/2* alterations (Pujade-Lauraine et al., 2017). For 295 randomized patients, the median PFS was higher in olaparib arm (19.1 *vs* 5.5 month). Moreover, the PFS measured by Blinded Independent Central Review (BICR) showed a median PFS of 30.2 months in olaparib group compared to 5.5 months in placebo group (Pujade-Lauraine et al., 2017). These data support the findings of Study 19 confirming the efficacy of olaparib in women with high-serous OC and *BRCA1/2* alterations (Ledermann et al., 2012). In 2017, Olaparib was approved by FDA and EMA as maintenance therapy in patients with recurrent ovarian, fallopian, and primary peritoneal carcinoma, regardless of *BRCA1/2* mutational status (Table 1). In the 2018, the SOLO-1 study (NCT01844986), an international, randomized (2:1), double-blind, phase III trial, evaluated the olaparib maintenance monotherapy in patients affected by newly diagnosed advanced high-grade serous or endometrioid OC, primary peritoneal cancer, or fallopian-tube cancer, in presence of a *BRCA1/2* PV/LPV, with complete or partial response after platinum-based chemotherapy. Overall, for 391 randomized women, olaparib showed a risk reduction of 69% in disease progression or death (Miller et al., 2019). In 2019, FDA and EMA approved olaparib as first-line maintenance therapy for women with advanced ovarian, fallopian, and primary peritoneal carcinoma, in presence of a *BRCA1/2* PV/LPV, with complete or partial response after chemotherapy (Moore et al., 2018) (Table 1). In 2019, some researchers tested the combination of olaparib with bevacizumab in patients affected by newly diagnosed locally advanced OC, with complete or partial response to first-line platinum-based chemotherapy. This was the goal of the PAOLA-1 study (NCT02477644), an international, double-blind, phase III, randomized (2:1) study, testing 806 patients, about 30% of which had *BRCA1/2* PVs/LPVs. The combo reduced the risk of disease progression or death and improved the median PFS (37.2 *vs* 21.7 months in *BRCA1/2*-positive; 18.9 *vs* 16 months in *BRCA1/2*-negative). In the HRD-positive subgroup with deleterious *BRCA1/2* alterations, the median PFS was 37.2 months (combo group) *vs* 17.7 months (Bevacizumab alone) (Ray-Coquard et al., 2019). In 2020, FDA approved the combo

Table 1
Overview of the pathway of PARPi approval in A) Breast Cancer, B) Ovarian Cancer, C) Pancreatic Cancer and D) Prostate Cancer, looking at the *BRCA1/2* mutational status.

Type of cancer	PARP inhibitor	Approval (Year)	Indication	References
A) Breast Cancer	Olaparib	FDA and EMA 2018 2019	*HER2-negative metastatic breast cancer harbouring germline pathogenic variants in BRCA1/2 genes*	OlympiAD (Robson et al., 2017)
	Talazoparib	FDA and EMA 2018	*HER2-negative advanced or metastatic breast cancer harbouring germline pathogenic variants in BRCA1/2 genes*	EMBRACA Study (Ettl et al., 2018)
B) Ovarian Cancer	Olaparib	FDA and EMA 2014	*Advanced ovarian cancer harbouring germline pathogenic variants in BRCA1/2 genes*	NCT0107662 (Kaufman et al., 2015)
		FDA and EMA 2017	*Maintenance therapy in recurrent ovarian, fallopian tubes, and primary peritoneal carcinoma regardless of mutational status of BRCA1/2 genes*	SOLO-2 (Pujade-Lauraine et al., 2017)
		FDA and EMA 2018 2019	*First-line maintenance therapy of advanced ovarian, fallopian tubes, and primary peritoneal carcinoma in presence of pathogenic variants in the BRCA1/2 genes, which had complete or partial clinical response after chemotherapy.*	SOLO-1 (Moore et al., 2018)
		FDA 2020	*First-line maintenance therapy of HRD-positive, advanced ovarian, fallopian tubes, and primary peritoneal carcinoma in combination with bevacizumab, that had complete or partial clinical response after chemotherapy.*	PAOLA-1 (Ray-Coquard et al., 2019)
	Rucaparib	FDA and EMA 2016 2018	*Advanced ovarian carcinoma in presence of germline/somatic pathogenic variants in BRCA1/2 genes, after multiple chemotherapy treatments*	ARIEL2 and Study 10 (Oza et al., 2017)
		FDA and EMA 2019 2020	*Maintenance therapy in recurrent ovarian, fallopian tubes, and primary peritoneal carcinoma, regardless of BRCA1/2 mutational status, after response to platinum-based chemotherapy*	ARIEL3 (Coleman et al., 2019)
	Niraparib	FDA and EMA 2017	*Reoccurring ovarian, fallopian tubes and primary peritoneal carcinoma, regardless of BRCA1/2 mutational status, after complete or partial chemotherapy response.*	ENGOT-OV16/NOVA Study (Mirza et al., 2016)
		FDA 2019	*Reoccurring ovarian, fallopian tubes and primary peritoneal carcinoma (HRD-positive), regardless of chemotherapy response*	QUADRA Study (Moore et al., 2019)
		FDA and EMA 2020	*Reoccurring ovarian, fallopian tubes and primary peritoneal carcinoma, regardless of biomarker status, after complete or partial chemotherapy response.*	PRIMA Study (González-Martín et al., 2019)
C) Pancreatic cancer	Olaparib	FDA 2019	*Maintenance therapy in metastatic pancreatic carcinoma in presence of germline pathogenic variants in BRCA1/2 genes*	POLO (Golan et al., 2019)
D) Prostate cancer	Rucaparib	FDA 2020	*Metastatic castration-resistant prostate cancer harbouring germline or somatic pathogenic variants in BRCA1/2 genes*	TRITON2 (Abida et al., 2020)
	Olaparib	FDA 2020	*Metastatic castration-resistant prostate cancer, HRD positive*	PROfound (de Bono et al., 2020)

Abbreviations: FDA, Food and Drug Administration; EMA, European Medicines Agency; HER2, Human Epidermal Growth Factor Receptor 2.

Olaparib-Bevacizumab as first-line maintenance therapy of HRD-positive patients with advanced ovarian, fallopian, and primary peritoneal carcinoma having a complete or partial response after chemotherapy (Ray-Coquard et al., 2019) (Table 1). The phase II, open-label, single-arm ARIEL2 trial (NCT01891344) and Study 10 (NCT01482715), published in 2017, demonstrated the usefulness of maintenance therapy by rucaparib, another PARPi, in platinum-sensitive OC patients (Swisher et al., 2017). Specifically, 192 patients with recurrent, platinum-sensitive, high-grade OC, distinguished into three HRD subgroups (germline or somatic *BRCA1/2* mutant, *BRCA1/2* wild-type and LOH high, or *BRCA1/2* wild-type and LOH low) were included in the Part 1 of ARIEL2 study (Swisher et al., 2017). A median PFS of 12.8 months was observed in the *BRCA1/2* mutant subgroup, 5.7 months in the LOH high subgroup, and 5.2 months in the LOH low subgroup. FDA, in 2016, and EMA, in 2018, approved treatment with rucaparib for patients with advanced high-grade OC carrying a germinal or somatic *BRCA1/2* PV/LPV, who previously received platinum (Table 1). The international, phase III, double-blind, placebo-controlled ARIEL3 study (NCT01968213) demonstrated the efficacy of rucaparib maintenance therapy in women with high-grade platinum-sensitive OC, in partial or complete response to platinum-based therapy, showing advantages not only in *BRCA1/2*-alterated cancers. In 2019, the FDA and, in 2020, the EMA approved the use of rucaparib as maintenance therapy in recurrent ovarian, fallopian, and primary peritoneal carcinoma, regardless of *BRCA1/2* mutational status, after complete or partial chemotherapy response (Table 1). In 2016, the double-blind, randomized study ENGOT-OV16/NOVA (NCT01847274) including 553 platinum-sensitive OC patients evaluated the efficacy of another PARPi called niraparib compared to placebo. Niraparib maintenance therapy showed an improvement of PFS both in *BRCA1/2*-mutated OC patients and wild-type-*BRCA1/2* OC patients (Mirza et al., 2014). In 2017, FDA and EMA approved niriparib for the treatment of recurring ovarian, fallopian, and primary peritoneal carcinoma, regardless of *BRCA1/2* mutational status, after complete or partial chemotherapy response (Table 1). In 2019, QUADRA trial (NCT02354586), an open-label, single-arm, phase II study, evaluated Niraparib in women with recurrent, high-grade serous epithelial ovarian, fallopian tube, or primary peritoneal carcinoma, previously treated with three or more chemotherapy lines. Among the 463 enrolled patients, pretreated OC women had a greater response, especially in HRD platinum-sensitive diseases (Moore et al., 2019). In 2019, the FDA approved Niriparib for the treatment of HRD-positive recurring ovarian, fallopian, and primary peritoneal carcinoma, regardless of chemotherapy response (Table 1). In 2019, PRIMA study (NCT02655016), a randomized (2:1), double-blind, phase III trial, enrolled patients with newly diagnosed advanced OC and tested Niraparib *vs* placebo after

response to platinum-based drugs. Among the 733 patients, 373 HRD-positive receiving Niriparib had a longer PFS compared to placebo (21.9 *vs* 10.4 months), with a total PFS of 13.8 *vs* 8.2 months among all patients. The OS was about 84% in Niriparib arm and 77% in placebo arm (González-Martín et al., 2019). In 2020, FDA and EMA approved Niriparib in the treatment of recurring ovarian, fallopian, and primary peritoneal carcinoma, regardless of HRD status, after complete or partial chemotherapy response (Table 1). To date, VELIA trial (NCT02470585) tested PARPi, called veliparib, as first-line therapy in 1000 patients with a new diagnosed OC, in combination with chemotherapy *vs* chemotherapy plus placebo, followed by a maintenance with veliparib or placebo. A longer median PFS was observed in veliparib group (24 *vs* 17 months), with further benefits in *BRCA1/2*-mutated patients. These findings encourage the use of PARPis as first-line drugs in OC patients (Coleman et al., 2019).

3.3. Pancreatic cancer

PC is the fourth most frequent cancer worldwide with a 5-year survival rate of 5% (Malvezzi et al., 2014). The PC progression is asymptomatic until advanced-stage disease. The surgical and adjuvant interventions are advancing, but underline the need to improve patient outcome (Brunner et al., 2019). Although most of PC is sporadic, $<$ 10% of cases are associated with germinal *BRCA1/2* PVs/LPVs. Alterations in *BRCA2* and *CDKN2A* genes are the alterations most frequently associated to PC onset. Overall, up to 4–7% of all PC patients harbours a germinal *BRCA1/2* alteration, regardless of family history (Iqbal et al., 2012). Among sporadic cases, *BRCA1* and *BRCA2* alterations were also found in 2% and 7%, respectively (Yeo, 2015). In 2019, the results of the phase III, randomized, double-blind, placebo-controlled trial called POLO (NCT02184195) showed that a germinal *BRCA1/2* PV/LPV in PC patients represents a predictive marker of PARPi sensitivity for the maintenance treatment of metastatic PDAC, previously treated with platinum-based therapy (Golan et al., 2019). The study evaluated 3315 patients, detecting *BRCA1/2* alterations in 7.5% of cases (274 patients). Interestingly, 22.1% of patients receiving Olaparib treatment has been shown to have not disease progression after two years, while 9.6% of patients receiving placebo showed no tumor progression. The median PFS was significantly longer in patients treated with Olaparib compared to placebo (7.4 *vs* 3.8 months). No significant differences in OS or quality of life were found, but it was offered as an alternative treatment with lower toxicity (Golan et al., 2019). However, today, there are conflicting opinions about olaparib-related adverse events in *BRCA1/2*-mutated PC patients. POLO study results allowed the olaparib approval by FDA in 2019, as maintenance therapy in metastatic PC carrying germline deleterious *BRCA1/2* alterations (Table 1).

3.4. Prostate cancer

PrC is the most frequent cancer in Western countries, particularly in males older than 50 years. This malignancy is mainly due to genetic and environmental factors, and a small percentage of cases is related to HBOC and Lynch syndromes (Mersch et al., 2015). In 12% of patients with metastatic PrC (mPrC) have been detected germinal deleterious alterations in at least one of the tumor-suppressor genes involved in DNA repair pathway, most frequently in *BRCA2* gene (Eeles et al., 2013). Germline *BRCA1/2* alterations confer an increased lifetime risk of developing PrC, with early onset and increased aggressiveness (Na et al., 2017). PrC is often associated with somatic aberrant variants in *BRCA1/2* genes, which account for 19% of cases of localized tumor and 23% of mCRPC, more often involving *BRCA2* gene (Robinson et al., 2015; Abeshouse et al., 2015). In 2020 was published the TRITON2 trial (NCT02952534), a multicentric, open-label, phase II study evaluating the efficacy of rucaparib in patients progressing after one to two lines of Androgen-Receptor Signaling Inhibitors (ARSi) and taxane chemotherapy for mCRPC, in presence of DDR deficiency, through genetic testing from plasma or tumor samples. In 2020, the FDA approved rucaparib for the treatment of mCRPC, in presence of germline or somatic PV/LPV *BRCA1/2* (Abida et al., 2020) (Table 1). The TRITON3 phase III trial, which is a study confirming the clinical benefit of rucaparib in patients with mCRPC, is also currently underway (Abida et al., 2020). In 2020, the phase II TOPARP study (NCT01682772) results demonstrated that 54.3% of mCRPC patients, carriers of a PV/LPV in DDR genes, had a composite response at a two-year of follow up after olaparib treatment (Mateo et al., 2020). In 2020, the PROfound study (NCT02987543), a prospective, biomarker-selected, randomized, phase III trial evaluated the efficacy of olaparib *vs* ARSi in mCRPC patients. The subjects were stratified into two cohorts: the first included individuals with alterations in *BRCA1/2* and *ATM* genes, the second including patients with alterations in other genes. In this study, 2792 biopsies were analyzed for 15 genes involved in DDR pathway. Alterations were found in 28% of patients, mainly in *BRCA2* gene (8.7%), followed by alterations in *CDK12* and *ATM* (6.3% and 5.9%, respectively) (de Bono et al., 2020). Patients with *BRCA1/2* and/or *ATM* alterations showed a median PFS of 7.39 months in the arm receiving olaparib *versus* 3.55 months in the arm under ARSi. The median OS was also higher in patients treated with olaparib (18.5 *vs* 15.11 months, respectively) (de Bono et al., 2020). In 2020, the FDA approved olaparib in HRD-positive mCRPC patients (de Bono et al., 2020), already treated with an anti-androgenic and a taxane-based therapy (Table 1). The more recent phase II trial, the GALAHAD study, highlighted the effect of niraparib therapy in mCRPC individuals. The results of this research showed how the 65% of mCRPC patients with a *BRCA1/2* PV/LPV and 31% of subjects with other altered DDR genes had a great response (Smith et al., 2022, 2020).

3.5. Melanoma

Melanoma accounts for only about 1% of skin cancers, but it is the cause of a large majority of skin cancer deaths each year. Up to 10% of all cases of cutaneous malignant melanoma occurs in a familial setting. Familial genetic linkage studies allowed to identify 2 high-penetrance susceptibility genes, such as *CDKN2A* and *CDK4*, involved in senescence and cell cycle arrest (Di Lorenzo et al., 2015).

Melanomas having a HRD status constitutes a subset of this disease which could benefit from PARPi-based treatment and immunotherapy. Overall, alterations in DDR genes have been detected in 20–40% of cutaneous melanoma (Chan et al., 2021). For several decades, the role of germline *BRCA1/2* alterations in melanoma susceptibility has been controversial, but there is strong evidence suggesting tumors harbouring HR/DDR alterations, which could benefit from PARPi administration (Adams et al., 2019). *In vitro* studies testing the efficacy of niraparib on melanoma cell lines showed a decreased survival and induction of apoptosis in HR/DDR-altered cells (Kim et al., 2021b). A RNA sequencing analysis on *BRCA1*-mutated patient-derived xenograft (PDX) models treated with niraparib showed alterations in cell cycle, integrin signaling, collagen and matrix remodeling, and triglyceride and fatty acid metabolism (Kim et al., 2021b). Moreover, mice previously receiving PARPi administration showed a reduction of metastatic lesions and lower levels of endothelial markers (Clurman et al., 2013). The effectiveness of PARPi-based therapy in melanoma patients was studied in combination with conventional chemotherapy, such as TMZ, to overcome resistance to alkylating agents. However, in the phase II, double-blind NCT00804908 trial, statistically significant improvements in PFS were not observed in advanced stage III or IV metastatic melanoma patients receiving TMZ plus veliparib or placebo (Middleton et al., 2015), as reported also by other researchers (Plummer et al., 2013). A recent case report showed the use of olaparib as single agent in an advanced melanoma patient carrying a somatic *PALB2* alteration. After a previous progression of disease, when treated with ipilimumab plus nivolumab, the patient showed partial response to olaparib at six months (Lau et al., 2021). The main studies related to PARPi administration, on

the basis of the *BRCA1/2* and/or HR mutational status, in different settings of melanoma patients are reported in Table 2.

4. Exploring the potential agnostic role of *BRCA1/2* deleterious alterations in other solid tumors

Recent evidence showed that germline/somatic *BRCA1/2* LPVs/PVs could be present also in other tumors, including CRC, LC, and cancers of uterus, non-melanoma skin, thyroid, kidney, brain, bladder, and gastroesophageal and/or hepatobiliary tract, allowing to expand the number of tumors generally associated with HBOC syndrome (Weiss et al., 2023).

4.1. Lung cancer

Molecular profiling analysis define lung cancer (LC) as a transcriptionally active tumor, with a 90% of LOF genomic variants in tumor-suppressor genes, such as *TP53* and *RB1* (Knelson et al., 2021; Sherr and McCormick, 2002; Passiglia et al., 2015). Germline *BRCA1/2* PVs/LPVs have been shown to be associated with 5% of all LC cases (Mamdani et al., 2019; Liu et al., 2018). Findings showed that deleterious *BRCA1/2* alterations were detected in LC patients with strong family history of cancer and early tumor onset. The *BRCA2* gene showed the strongest association, suggesting a potential preventive meaning and treatment implications (Hu et al., 2019; Reckamp et al., 2021). The simultaneous presence of germline *BRCA1/2* PVs/LPVs and LC-associated driver somatic alterations seems to be associated with an early onset of disease (Li et al., 2019). In 2012, Byers et al (Byers et al., 2012). originally identified PARP as a potential target for therapy against Small-Cell LC (SCLC) through a Reverse-Phase Protein Arrays (RPPA) on cancer cell lines. The obtained data showed that PARP1 transcript and other DDR genes resulted overexpressed in SCLC compared to Non Small Cell Lung Carcinoma (NSCLC) (Byers et al., 2012). To date, multiple trials investigated the involvement of *BRCA1/2* PVs/LPVs in LC as predictive factors of PARPi treatment response in addition to conventional therapies (Table 3). In 2018, Laird et al (Laird et al., 2018). carried out a study on cell lines and *in vivo* xenografts to explore if PARP trapping could lead to an ionizing radiation sensitization in SCLC patients. This study demonstrated that the use of Talazoparib confers a radio-sensitization, as well as Veliparib, even if in a reduced manner (Laird et al., 2018). In 2019, the NCT02446704 study, a phase I/II trial, tested the combination of Olaparib plus Temozolomide (TMZ) treatment in recurrent SCLC, showing an Overall Response Rate (ORR) of 41.7% (Farago et al., 2019). In the same year, the phase I/II trial (NCT02484404) tested the efficacy of Durvalumab in combination with Olaparib and Cediranib in SCLC patients treated firstly with Durvalumab alone, evaluating the PARPi activity looking at the conferred susceptibility to immune-checkpoint blockade (Zimmer et al., 2019). In 2020, the PIN study (NCT01788332), a multicentric, double-blind, placebo controlled, randomized phase II trial, tested Olaparib in metastatic NSCLC patients responding to platinum-based chemotherapy. From this study did not emerge any benefits in PFS and OS in Olaparib-treated patients comparing to placebo arm. On the other hand, Fluzoparib was considered as conferring radiosensitivity in NSCLC in absence of *BRCA1/2* alterations. Fluzoparib has been used in the initial stages of preliminary phase I/II trials and in combination with inhibitors of PD-L1, such as SHR-1316 (Wang et al., 2019; Luo et al., 2019). In 2019, a study demonstrated that *SLFN11* gene is a potential predictive biomarker of PARPi sensitivity for the treatment of SCLC identifying the therapeutic combination with TMZ as a particularly promising therapeutic choice (Liang, 2019). Other studies, including the NCT04209595, are evaluating the combination PARPi plus DNA damaging agents, such as pegylated SN-38. The simultaneous evaluation of PARPi administration in presence alterations in *BRCA1/2* and/or DDR genes has been more rarely evaluated in LC patients (Table 3). The PARPi-based therapy in SCLC has been defined as advantaging in genomic instability and LOF of *TP53* and *RB1* genes genomic variants. In clinical trial, the single agent has demonstrated poor results, while the combination TMZ plus Olaparib and other has improved patient outcomes or are in progress. Studies are searching for novel potential biomarkers or specific setting of disease to identify patient subsets likely to respond to PARPi (Knelson et al., 2021). Recently, in multicenter cohort study including 138 NSCLC patients, Jove et al (Jove et al., 2023). showed that 14% of subjects with early tumor onset harbored some clinically “actionable” germline alterations in other cancer susceptibility genes, including *ATM*, *NBN*, *PMS2*, *SDHA*, *POLH*.

4.2. Gastro-Intestinal cancers

Recent findings support a PARP family’s role in the development and progression of gastrointestinal (GI) tumors, highlighting the potential function of HRD as predictive factor of PARPi-based treatment response (Table 4). However, a low percentage of *BRCA1/2*-altered GI cancers was observed and only a few trials investigated the presence of a germline or somatic *BRCA1/2* alteration in these malignancies (Hanna et al., 2022).

4.2.1. Hepatobiliary cancer

The most common form of liver cancer is the hepatocellular carcinoma (HCC), followed by intrahepatic cholangiocarcinoma. Hepatobiliary cancers have a low prevalence of *BRCA1/2* sequence variants (Hanna et al., 2022). Preclinical results underline the potential role of PARPi-based therapy in HCC (Guillot et al., 2014), since a higher level of PARP1/2 expression has been observed in cancer tissues compared to healthy (Alhusaini et al., 2021; Lin et al., 2016). Studies on molecular profiling showed a frequency of 20–25% in alteration of HR genes. The most frequently involved gene, related to the HCC type, was *ATM* (5%), while *BRCA1/2* (4.8%), particularly *BRCA2*, were altered in cholangiocarcinoma (Zimmer et al., 2021; Lin et al., 2019). A small group of biliary cancers demonstrated sensitivity to platinum-based chemotherapy in presence of an alteration in a DDR gene (Golan et al., 2017). In 2017, through a retrospective analysis, Golan et al (Golan et al., 2017). observed that cholangiocarcinoma patients harbouring *BRCA1/2* PVs/LPVs, treated with PARPi and platinum-based chemotherapy, respectively, showed a 50% of benefits in survival. In a pre-clinical study, PARPi sensitivity has been associated to isocitrate dehydrogenase (IDH) alterations. Indeed, *IDH1/2* alterations are commonly detected in cholangiocarcinoma characterized by a HRD conditions (Salati et al., 2020). In multiple studies, such as the NCT02715089, carried out by Lin et al (Lin et al., 2019). in 2019, *BRCA1/2* PV/LPV carrier patients have been treated with olaparib, after previous treatment, showing a partial response to therapy. Lin et al. identified liver cancer patients (4.8%) with aberrant germline/somatic *BRCA1/2* alterations, some of which (8 individuals) received olaparib treatment. Interestingly, 3 out of 8 patients showed a partial response to therapy and a germline *BRCA1/2* alteration, while 3 had progression disease and a somatic alteration (Lin et al., 2019). Moreover, the combination of TMZ plus Veliparib showed good results in *in vitro* studies (Muñoz-Gámez et al., 2015), showing a good level of safety and tolerance in NCT00526617 trial, which involved different solid tumors patients, among which HCC (Nuthalapati et al., 2017; Gabrielson et al., 2015; Le Grazie et al., 2017). In preclinical studies, the combination of PARPi plus arsenic trioxide, histone deacetylase inhibitors and NFκB inhibitors was investigated in HCC (Lampiasi et al., 2014; Liang et al., 2015; Luo et al., 2015). To date, the use of PARPi in HCC has been discouraged, due to lack of biomarkers able to predict resistance mechanisms or strategies to overcome this. The inhibition of EGFR and MET, which are overexpressed in HCC cells, has been shown to sensitize HCC cells to PARPi treatment. This finding suggests the use of possible drug combinations in order to obtain a response to PARPi therapy (Dong et al., 2019).

Table 2
Overview of the most recent ongoing and/or completed studies related to PARPi administration and *BRCA1/2* and/or HR mutational status in different settings of melanoma patients.

*NCT number**	*Status*	*PARPi*	*Start-last update*	*Title*
1) **NCT00516802**	Completed	KU-0059436 (AZD2281)	January 2007-May 15, 2009	*A Study to Assess the Safety and Pharmacokinetics of an Inhibitor of PARP in Combination With Dacarbazine*
2) **NCT03207347**	Active, not recruiting	Niraparib	August 13, 2018-December 27, 2021	*A Trial of Niraparib in BAP1 and Other DNA Damage Response (DDR) Deficient Neoplasms (UFSTO-ETI-001)*
3) **NCT03925350**	Recruiting	Niraparib	March 20, 2019-October 22, 2021	*Efficacy and Safety Study of Niraparib in Melanoma With Genetic Homologous Recombination (HR) Mutation*
4) **NCT04633902**	Recruiting	Olaparib	March 3, 2021-May 3, 2021	*Phase II Study of Olaparib and Pembrolizumab in Advanced Melanoma With Homologous Recombination (HR) Mutation*
5) **NCT01618136**	Completed	E7449	January 2012-November 16, 2016	*An Open-Label, Multicenter, Phase 1/2 Study of Poly(ADPRibose) Polymerase (PARP) Inhibitor E7449 as Single Agent in Subjects With Advanced Solid Tumors or With B-cell Malignancies and in Combination With Temozolomide (TMZ) or With Carboplatin and Paclitaxel in Subjects With Advanced Solid Tumors*
6) **NCT00526617**	Completed	ABT-888	August 2007-November 21, 2017	*A Phase I Study of ABT-888 in Combination With Temozolomide in Cancer Patients*
7) **NCT02419495**	Recruiting	Olaparib	June 26, 2015-November 19, 2021	*Selinexor With Multiple Standard Chemotherapy or Immunotherapy Regimens in Treating Patients With Advanced Malignancies*
8) **NCT04187833**	Recruiting	Talazoparib	June 5, 2020-March 23, 2022	*Nivolumab in Combination With Talazoparib in Melanoma and Mutations in BRCA or BRCAness Genes*
9) **NCT05482074**	Not yet recruiting	Olaparib	February 2023-August 1, 2022	*Olaparib in Unresectable/ Metastatic Melanoma With BRCA1/2*

* The studies are registered on ClinicalTrials.gov.

Table 3
Overview of the most recent ongoing and/or completed studies related to PARPi administration and *BRCA1/2* and/or HR genes mutational status in different settings of lung cancer patients.

*NCT number**	*Status*	*PARPi*	*Start/last update*	*Title*
1) **NCT03009682**	Completed	Olaparib	August 2016-February 18, 2021	*Olaparib Monotherapy in Relapsed Small Cell Lung Cancer Patients With HR Pathway Gene Mutations Not Limited to BRCA 1/2 Mutations, ATM Deficiency or MRE11A Mutations*
2) **NCT03845296**	Active, not recruiting	Rucaparib	January 28, 2019-February 22, 2022	*Rucaparib in Treating Patients With Genomic LOH High and/or Deleterious BRCA1/2 Mutation Stage IV or Recurrent Non-small Cell Lung Cancer (A Lung-MAP Treatment Trial)*
3) **NCT00883480**	Completed	Erlotinib	June 2005-June 13, 2022	*Individualized Treatment Based on Epidermal Growth Factor Receptor Mutations and Level of BRCA1 Expression in Advanced Adenocarcinoma*
4) **NCT03377556**	Completed	Talazoparib	March 3, 2017-June 23, 2021	*Lung-MAP: Talazoparib in Treating Patients With HRRD Positive Recurrent Stage IV Squamous Cell Lung Cancer*
5) **NCT01562028**	Completed	Erlotinib	June 2012-April 13, 2021	*BELIEF (Bevacizumab and ErLotinib In EGFR Mut+ NSCLC)*
6) **NCT01638546**	Completed	Veliparib	June 2012-November 19, 2019	*Temozolomide With or Without Veliparib in Treating Patients With Relapsed or Refractory Small Cell Lung Cancer*
7) **NCT03531840**	Completed	Olaparib	July 11, 2018-April 9, 2021	*Olaparib in People With Malignant Mesothelioma*
8) **NCT04171700**	Active, not recruiting	Rucaparib	November 21, 2019-March 28, 2022	*A Study to Evaluate Rucaparib in Patients With Solid Tumors and With Deleterious Mutations in HRR Genes*
9) **NCT03654833**	Recruiting	Rucaparib	January 28, 2019-April 7, 2022	*Mesothelioma Stratified Therapy (MiST): A Multi-drug Phase II Trial in Malignant Mesothelioma*
10) **NCT02734004**	Completed	Olaparib	March 17, 2016-October 18, 2021	*A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors*

* The studies are registered on ClinicalTrials.gov.

4.2.2. Colorectal Cancer

Colorectal cancer (CRC) is the third most common cancer worldwide accounting for more than 3 million of novel cases each year (Rawla et al., 2019). The correlation between *BRCA1/2* alterations and CRC has been often observed in women under the age of 50 and, usually, in tumors with mucinous histotype (Inra and Syngal, 2014). However, these features have been associated also with somatic and germline alterations in other DDR genes, identified in 15–20% of all CRC (Catalano et al., 2022). To date, the *BRCA1/2* mutational status has been rarely considered in clinical trials aiming at investigating the effectiveness of PARPi therapy in CRC. Multiple studies tested PARPi-based treatment, especially in combination with other molecules and in pretreated metastatic CRC, without exploring the mutational status of DDR genes (Berlin et al., 2018; Samol et al., 2011; Kummar et al., 2011; Czito et al., 2017; Leijen et al., 2016). In 2016, the NCT00912743 phase II trial tested olaparib in CRC patients after standard chemotherapy and with confirmed tumor MSI instability. This study did not report any effectiveness associated with the olaparib administration (Leichman et al., 2016). In 2019, the LODESTAR phase II, open label, single-arm trial (NCT04171700) enrolled patients with several solid tumors, including CRC, selected according to the mutational status of *BRCA1*, *BRCA2*, *PALB2* and other DDR genes, in order to test the efficacy of rucaparib (Zimmer et al., 2021). NCT03842228 and NCT04276376 are other ongoing trials, which are recruiting advanced solid tumor patients. The aim of first study is to test olaparib plus durvalumab plus copanlisib hydrochloride, while the second is aimed to assess the efficacy of rucaparib plus atezolizumab, both exploring the mutational status of DDR genes through germline and somatic analysis.

4.2.3. Gastroesophageal cancer

Gastroesophageal tumors show a *BRCA1/2* alteration in 3–12% of cases, mainly involving *BRCA2* gene, while HR genes are involved in 12% of cases (Zimmer et al., 2021; Hanna et al., 2022; Thompson and Easton, 2001; Nakagawa and Fujita, 2018). In 2016, Secrier et al (Secrier et al., 2016). carried out a whole-genome sequencing analysis starting from 129 esophageal cancer specimens aiming at characterizing

Table 4
Overview of the most recent ongoing and/or completed studies related to PARPi administration and *BRCA1/2* and/or HR genes mutational status in different settings of gastrointestinal patients.

NCT number[*]	*Status*	*PARPi*	*Start/last update*	*Title*
1) **NCT03337087**	Recruiting	Rucaparib	November 2, 2018-June 3, 2022	*Liposomal Irinotecan, Fluorouracil, Leucovorin Calcium, and Rucaparib in Treating Patients With Metastatic Pancreatic, Colorectal, Gastroesophageal, or Biliary Cancer*
2) **NCT01339650**	Completed	ABT-767	May 6, 2011-January 2, 2018	*Study of ABT-767 in Subjects With Breast Cancer 1 and Breast Cancer 2 (BRCA 1 and BRCA 2) Mutations and Solid Tumors or High Grade Serous Ovarian, Fallopian Tube, or Primary Peritoneal Cancer*
3) **NCT05222971**	Recruiting	Olaparib	April 1, 2022-April 12, 2022	*Olaparib With or Without Durvalumab for DDR Gene Mutated Biliary Tract Cancer Following Platinum-based Chemotherapy*
4) **NCT05379972**	Not yet recruiting	Olaparib	November 2022-May 26, 2022	*Study of SBRT/Olaparib Followed by Pembrolizumab/ Olaparib in Gastric Cancers*
5) **NCT01233505**	Terminated	Veliparib	October 2010-April 2, 2014	*Veliparib, Oxaliplatin, and Capecitabine in Treating Patients With Advanced Solid Tumors*
6) **NCT05201612**	Not yet recruiting	Olaparib	June 2022-February 17, 2022	*Pembrolizumab and Olaparib in Homologous-recombination Deficient (HRD) Advanced Colorectal Cancer (CRC)*
7) **NCT02734004**	Completed	Olaparib	March 17, 2016-October 18, 2021	*A Phase I/II Study of MEDI4736 in Combination With Olaparib in Patients With Advanced Solid Tumors*
8) **NCT04171700**	Terminated	Rucaparib	November 21, 2019-July 15, 2022	*A Study to Evaluate Rucaparib in Patients With Solid Tumors and With Deleterious Mutations in HRR Genes*
9) **NCT03842228**	Recruiting	Olaparib	August 12, 2019- June 1, 2023	*Testing the Combination of the Anti-cancer Drugs Copanlisib, Olaparib, and MEDI4736 (Durvalumab) in Patients With Advanced Solid Tumors With Selected Mutations*
10) **NCT04276376**	Recruiting	Rucaparib	April 12, 2019- April 2025	*Efficacy and Safety of the Combination of Rucaparib (PARP Inhibitor) and Atezolizumab (Anti-PD-L1 Antibody) in Patients With DNA Repair-deficient or Platinum-sensitive Solid Tumors*

[*] The studies are registered on ClinicalTrials.gov.

different molecular profile to develop targeted therapeutic strategies. The results of this study reported unique profile among the sampling (Secrier et al., 2016). No large-scale clinical trials have been conducted about gastroesophageal tumors and PARPi administration according to DDR mutational status. In 2013, Chen et al (Chen et al., 2013). investigated the prognostic role of *BRCA1* expression in gastric cancer patients undergoing surgery and platinum-based chemotherapy, observing a better response to therapy in 34% of patients. Esophageal cancer patients harbouring alterations in HR genes have been enrolled in the LODESTAR trial (NCT04171700), with the aim to evaluate the rucaparib-based therapy. To date, the ongoing NCT03840967 trial is testing the efficacy of niriparib treatment in previously treated metastatic gastroesophageal tumors. Other trials are investigating the effectiveness of the olaparib-based therapy, with or without VEGF inhibitor (NCT03008278, NCT038829345). Moreover, the combination of rucaparib plus ramucirumab with or without nivolumab administration is under testing in the NCT03995017 study, and olaparib plus paclitaxel in combination with pembrolizumab is under testing in the NCT04592211 trial. To date, the NCT03427814 phase III trial is active, aimed at evaluating the pamiparib-based maintenance therapy *vs* placebo administration in metastatic GI cancer responding to platinum-based classical chemotherapy (Ciardiello et al., 2019). In 2020, Koustas et al (Koustas et al., 2020). investigated the co-inhibition of c-MET and PARP enzymes, starting from cell lines derived from GI cancers, showing an upregulation in apoptosis mechanisms, mainly in case of *BRCA1/2* deficiency. Other studies focused on other strategies, such as the simultaneous targeting of WEE1 and PLK1 by AZD1775 to investigate the efficacy of olaparib administration, reporting interesting evidences in GI cancer cell lines (Wright et al., 2017). Recently, the role of the *ATM* gene, altered in 13–22% of cases, is increasingly emerging, as it seems to be a potential molecular biomarker of response to PARPi even in GI cancers, with controversial data in literature (Zimmer et al., 2021; Alhusaini et al., 2021).

5. Conclusions

BRCA1/2 are tumor suppressor genes playing a key role in HR pathway. The presence of PVs/LPVs in *BRCA1/2* genes significantly increase the risk of developing the HBOC syndrome, which mainly includes BC and OC (Fanale et al., 2021; Incorvaia et al., 2020a; Russo et al., 2008). To date, also the onset of pancreatic and prostate cancers was associated with this syndrome (Iqbal et al., 2012; Robinson et al., 2015). However, since recent evidence suggested that other cancers may also be associated with germline *BRCA1/2* LPVs/PVs and NGS-based pan-cancer analysis showed a significant rate of somatic HRD alterations in common non-HBOC associated cancers, therefore HBOC could be misnomer to describe a wide spectrum inherited syndrome which occurs by several tumor phenotypes (Weiss et al., 2023).

The recent approval of novel therapeutic options led to a new way of conceiving cancer treatment which implicates the concept of precision oncology, allowing to obtain excellent results in disease control with reduced off-target side effects. Over the last few years, the genetic *BRCA* testing assumed not only a preventive meaning, but also a predictive value for PARPi administration as monotherapy or in combinations with other drugs, showing promising, but controversial results in a broad spectrum of solid tumors harbouring germline/somatic *BRCA1/2* alterations (Lau et al., 2021; Farago et al., 2019; Gorbunova et al., 2018). Recently, has been demonstrate the involvement of the PARP family enzimes in the development and progression of GI cancers, highlighting the potential efficacy of PARPi administration also in treatment of some GI tumors. Moreover, the role of PARP family in repairing the cytotoxic therapy-induced DNA damage suggests the potential use of PARPi as therapy againsts GI cancer. This hypothesis is supported by preclinical studies, which reported a better treatment response due to the therapy combination of cytotoxic agents and PARPi. Additionally, clinical trials showed promising results, in terms of benefits on the survival, using PARPi in GI cancers (Alhusaini et al., 2021). Encouraging results have been reported also for SCLC. Also, the combination with immunotherapy seems to improve therapy response in melanoma patients with and without HR-DDR defects (Chan et al., 2021; Knelson et al., 2021). In large prospective studies carried out in Canada, United States and Europe, an association between *BRCA1/2* alterations and risk of other types of cancer, including CRC, bladder and anal cancers and intrahepatic bile duct carcinoma, has been investigated. No cases of gastric cancer have emerged, although previous studies had suggested an association (Bermejo et al., 2004; Sopik et al., 2015; Phelan et al., 2013).

These observations suggested that *BRCA1/2*-related tumorigenesis depends on the tumor lineage and, therefore, *BRCA1/2* alterations are not the ideal markers for selecting patients for treatment with PARPi for other types of carcinomas. The analysis of the clinical data confirmed this hypothesis, since the patients who obtained clinical benefit following treatment with PARPi were those with cancers already

associated with alterations in *BRCA1/2* genes in the HBOC syndrome and not those with other forms of cancer, except for uterine sarcoma, where the alteration in *BRCA2* gene is common (6.5%) (Jonsson et al., 2019). Surely, understanding more deeply which are the signatures that could be considered predictive of HRD, such as biomarkers, molecular alterations, HRD score based on loss of heterozygosity (LOH) and other structural genomic aberrations, will be the key to improve patient clinical outcome and management, including a more accurate patient stratification and a tailored PARPi administration (Jonsson et al., 2019; Fanale et al., 2020). Over time, there have been significant improves in our understanding of the mechanisms underlying tumor sensibility and resistance to PARPi and in the extension of the use of PARPi to treat several cancer types. Such as, deeply understanding the predictive role of *BRCA1/2* PVs/LPVs could be also fundamental to enable the building of new therapeutic strategies for patients carrying these alterations. In the next future, the tissue-agnostic evaluation of *BRCA1/2* mutational status could become the common denominator for the PARPi treatment of individuals with different solid tumors, in order to select patient subgroups which may benefit from this therapy.

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CRediT authorship contribution statement

D.F., L.R.C., E.P., U.R., A.R. and V.B. conceived, wrote, and critically revised the manuscript with the contribution of A.F., M.D.P., C.B., L.R.C., L.M., S.C., P.P., T.D.B.R., and C.C.; Literature data were acquired and analyzed by D.F., A.F., E.P., U.R., M.D.P., L.R.C., C.B., L.M., S.C., P.P., T.D.B.R., and C.C; The figures of the manuscript were conceived and designed by D.F., A.F., E.P., U.R., L.R.C., C.B., P.P., and T.D.B.R.; The tables were conceived and designed by D.F., A.F., E.P., U.R., L.R.C., S.C., and T.D.B.R; D.F., L.R.C. and C.C. participated to the critical revision of the manuscript. All authors have read and approved the final version of the manuscript. Daniele Fanale, Antonio Russo and Viviana Bazan are the authors who verified the data reported in the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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