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Targeting DNA damage repair precision medicine strategies in cancer

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Abstract

DNA repair targeted therapeutics is a promising precision medicine strategy in cancer. The development and clinical use of PARP inhibitors has transformed lives for many patients with *BRCA* germline deficient breast and ovarian cancer as well as platinum sensitive epithelial ovarian cancers. However, lessons learnt from the clinical use of PARP inhibitors also confirm that not all patients respond either due to intrinsic or acquired resistance. Therefore, the search for additional synthetic lethality approaches is an active area of translational and clinical research. Here, we review the current clinical state of PARP inhibitors and other evolving DNA repair targets including ATM, ATR, WEE1 inhibitors and others in cancer.

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Introduction

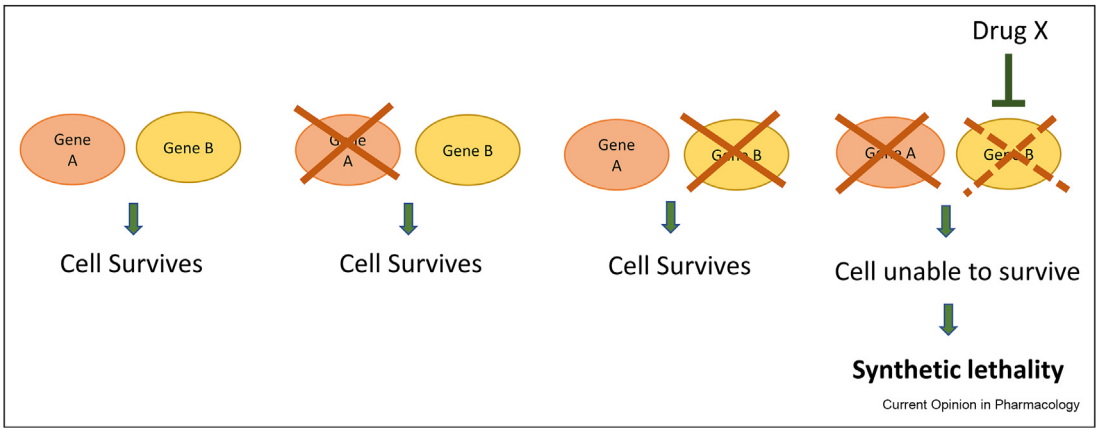
Endogenous and exogenous DNA damage can threaten genomic integrity. Cells have evolved highly conserved DNA repair pathways to scan and rectify such damaging lesions. Here, we will focus on the role of *BRCA* genes and their critical role during double strand break (DSB) repair. *BRCA1* and *BRCA2* tumour suppressor genes are intimately involved in the process of homologous recombination (HR) in which an exact replica of the damaged region of DNA is created using the sister chromatid as a template [1].

Loss of *BRCA1/2* function forces the use of the more error-prone non-homologous end joining (NHEJ) pathway which results in chromosomal instability and makes carriers more vulnerable to a range of cancers including breast, ovarian, pancreatic and prostate [2,3]. *BRCA1/2* mutations have been identified in around 3.4% of breast cancers [4]. Female carriers of a pathogenic variant of *BRCA1* have a 65% chance of developing breast cancer and 39% chance of developing ovarian cancer by the age of 70 years [1,5]. However, resultant loss of function of the HR pathway can be used as a specific target for treatment. Indeed, it is in the context of *BRCA* germline mutation and the associated HR deficiency (HRD) that the first clinical application of a novel precision medicine treatment strategy – synthetic lethality – has been applied. In the current review, we will focus on the concept of synthetic lethality and the current clinical state of poly-ADP-ribose polymerase inhibitors (PARPi) in *BRCA* germline deficient cancers. We will also provide an overview of emerging DNA repair targets such as ATM, ATR, WEE1 inhibitors for precision oncology.

Synthetic lethality with PARP inhibition in the context of BRCA mutation

Synthetically lethal pairs can be identified in cells with a genetic mutation; in the context of which impairment or inhibition of a second pathway becomes fatal to the cell [6,7] (Figure 1). Such a synthetic lethality interaction has been well described with poly-ADP-ribose polymerase (PARP1) inhibition in the context of *BRCA* germline mutations and HRD. DNA repair intermediates such as single-strand breaks (SSB) activate PARP1 which in turn leads to the synthesis of PAR (poly-ADP-ribose) polymers. Auto-PARylation of PARP1 leads to the recruitment of additional repair factors at sites of DNA damage resulting in efficient DNA repair. Inhibition of PARP1 catalytic activity by inhibitors such

Figure 1



Synthetic lethality approach in cancer. Knockout or inhibition of Gene B in the context of loss of function of Gene A leads to cell death. However, cells with loss of function of one gene only can survive (adapted from Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. Science. 2017;355(6330):1152–8.).

as olaparib, talazoparib, niraparib and rucaparib (Figure 2) prevents auto-PARylation; this impairs coordination of DNA repair and stabilises binding of PARP1 to the DNA intermediate. DNA-bound immobilised PARP-1 disrupts replication fork progression (phenomenon called 'PARP trapping') and leads to DSB accumulation. In the context of *BRCA* deficiency where DSBs are not repaired, the accumulated DSBs eventually lead to cancer cell specific apoptosis. The ability for PARP trapping varies between PARPi. talazoparib is about 100 more potent than niraparib for PARP trapping. niraparib, in turn, traps PARP more potently than olaparib and rucaparib [6,7].

Following several pre-clinical studies deciphering the mechanisms of action [8,9], PARPi rapidly entered clinical trials. A summary of completed and ongoing clinical trials of PARPi in the context of BRCA mutation is presented in Table 1. Results from studies so far have led to FDA (Food and Drug Administration) approval for both olaparib and talazoparib for use in metastatic HER2 negative breast cancer with *BRCA1/2* germline mutations [10,11] and for PARP inhibition with olaparib, rucaparib or niraparib in the treatment of ovarian cancers with *BRCA* germline mutation [12,13]. In platinum sensitive sporadic epithelial ovarian cancer, PARPi (niraparib, olaparib, rucaparib) maintenance therapy was also shown to significantly increase progression free survival (PFS) [12,14,15]. Following success in clinical trials, olaparib has also been FDA approved for metastatic castration resistant prostate cancer (mCRPC) with HRD (including *BRCA* mutation) and similarly, rucaparib is approved for mCRPC with *BRCA* mutation [3]. Recently, olaparib has been approved for maintenance therapy in pancreatic cancer with *BRCA* mutation.

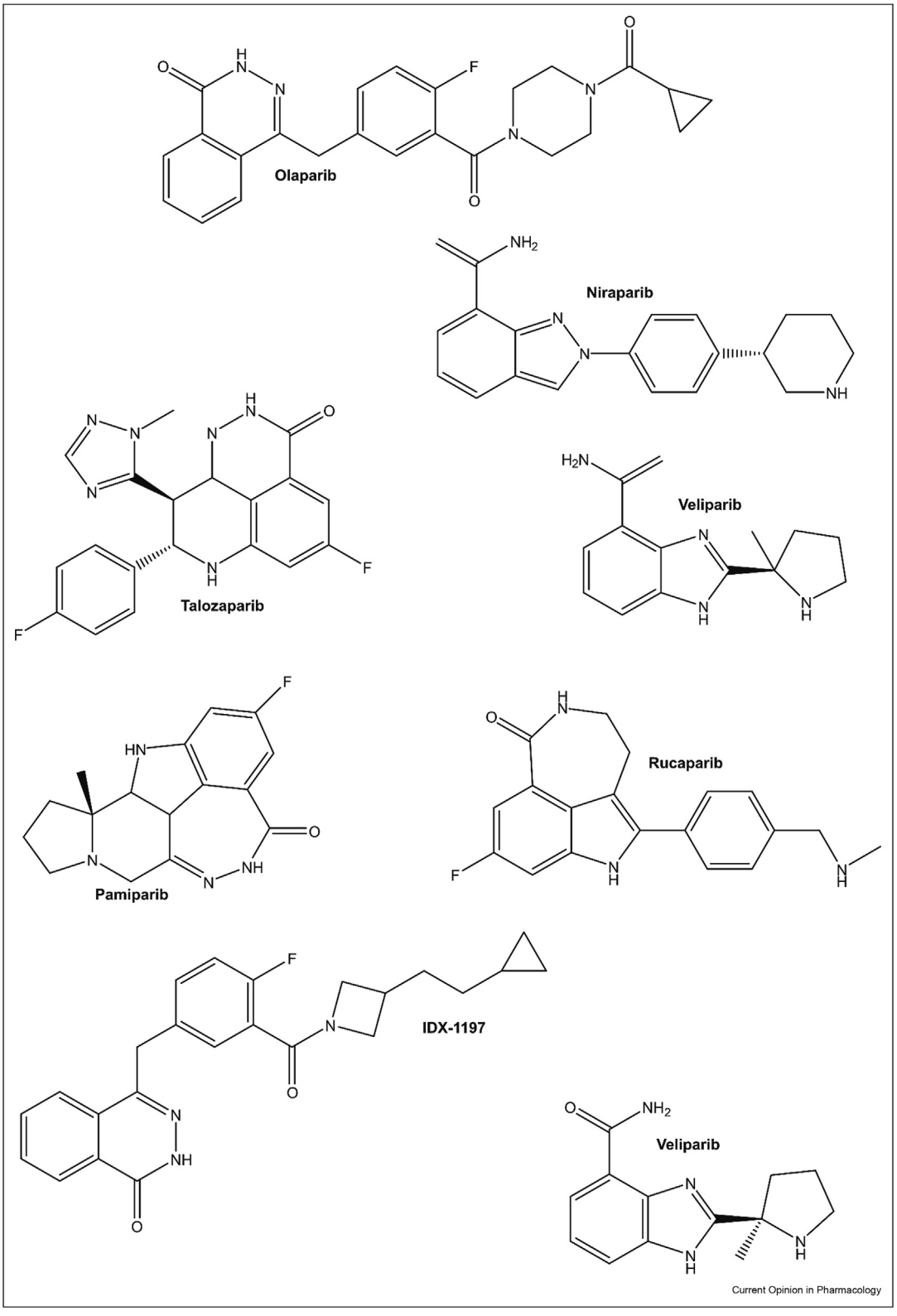
Although PARPi therapy has positively impacted patient outcomes, 40%–70% of patients develop intrinsic or acquired resistance creating an ongoing challenge in the clinic [7]. Several mechanisms of resistance have been described pre-clinically including restoration of HR [reactivation of *BRCA* function, inactivation of 53BP1 and others] and restoration of stalled replication fork protection [7]. Therefore, the search for alternative synthetic lethality approaches using PARPi in other DNA damage repair (DDR) backgrounds and the development of inhibitors beyond PARPi is an area of intense investigation. Ongoing clinical studies of PARPi in cancers with aberrant mutations in DDR in solid tumours are shown in Table 2 with many candidate mutations being involved in the repair of DSBs.

PARP inhibition in the context of other mechanisms of HRD

Initiation of DSB repair begins with formation of the MRN complex, consisting of MRE11, RAD50 and NBS1. Preclinically, MRE11 deficiency has been associated with decreased cell viability following treatment with PARPi [30]. Human fibroblasts lacking NBS1 were found to be sensitive to PARPi; an effect reversed by the addition of NBS1cDNA [31]. ATM (ataxia-telangiectasia mutated protein) interacts with NBS1 [19] and is involved in regulation of the cell cycle via the checkpoint kinase *CHK2* [20]. CHK2 can be pharmacologically inhibited using PHI-101, a compound currently undergoing phase I trials for use in platinum resistant peritoneal/ovarian/fallopian tube cancers following success in pre-clinical investigations (NCT04678102) [23].

Synthetic lethality has been shown preclinically in ATM deficient cells treated with PARPi and tumour burden

Figure 2



Chemical structures of clinically relevant PARP inhibitors.

Table 1

Published clinical trials of PARP Inhibitors in BRCA germline mutated cancers.

Study Title	Author	Year	Cancer/s	PARP inhibitor	Comparator	Sample size	Medial progression-free survival	Median overall survival	Objective response rate (ORR)	Other relevant results	Reference
Rucaparib vs. standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial	Kristeleit et al.	2022	Ovarian	Rucaparib (600 mg BD)	Chemotherapy	349	Rucaparib 7.4 months vs. chemotherapy 5.7 months (p = 0.001)	NA	NA	NA	[16]
Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial	Banerjee et al.	2021	Ovarian	Olaparib (300 mg BD)	Placebo	391	Olaparib 56.0 months vs. placebo 13.8 months	NA	NA	NA	[17]
Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial	Diéras et al.	2020	Breast	Veliparib (120 mg BD) plus chemotherapy	Placebo plus chemotherapy	513	Veliparib plus chemotherapy 14.5 months vs. placebo plus chemotherapy 12.6 months (p = 0.0016)	NA	NA	NA	[18]
Olaparib vs. nonplatinum chemotherapy in patients with platinum-sensitive-relapsed ovarian cancer and a germline BRCA1/2 Mutation (SOLO3): A randomized phase III trial	Penson et al.	2020	Ovarian	Olaparib (300 mg BD)	Physician's choice single-agent non-platinum chemotherapy	266	Olaparib 13.4 months vs. physician choice chemotherapy 9.2 months (p = 0.013)	NA	ORR significantly higher for olaparib (72.2% vs. 51.4%)	NA	[19]
GeparOLA: A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin	Fasching et al.	2019	Breast	Olaparib (100 mg BD) plus chemotherapy	Chemotherapy	107	NA	NA	NA	Pathological complete response rate: olaparib plus chemotherapy 55.1% vs chemotherapy 48.6%	[20]

followed by epirubicin/ cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD)											
Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer	Coleman et al.	2019	Ovarian	Veliparib (150 mg OD) plus chemotherapy followed by veliparib maintenance	Chemotherapy plus placebo, chemotherapy plus veliparib followed by placebo maintenance	1140	Veliparib maintenance 23.5 months vs. chemotherapy plus placebo 17.3 months ($p < 0.001$)	NA	NA	In BRCA positive group mPFS: 34.7 months for veliparib maintenance vs. 22.0 months for placebo. In HR defect group mPFS: 31.9 months for veliparib maintenance vs. 20.5 months for placebo ($p < 0.001$ for both)	[21]
Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer	Golan et al.	2019	Pancreatic	Olaparib (300 mg BD)	Placebo	154	Olaparib 7.4 months vs. placebo 3.8 months ($p = 0.004$)	Olaparib 18.9 months vs placebo 18.1 months ($p = 0.68$)	NA	NA	[7]
Talazoparib in patients with advanced breast cancer and a germline BRCA Mutation	Litton et al.	2018	Breast	Talozaparib (1 mg OD)	Chemotherapy	431	Talozaparib 8.6 months vs. chemotherapy 5.6 months ($p < 0.001$)	NA	Talozaparib 62.6% vs. chemotherapy 27.2%	NA	[22]
Veliparib with temozolomide or carboplatin/paclitaxel vs. placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: randomized phase II study	Han et al.	2018	Breast	Veliparib (120 mg BD) plus chemotherapy or veliparib (40 mg BD) plus temozolomide (150–200 mg/m^2)	Placebo plus chemotherapy	290	Veliparib plus chemotherapy 14.1 months ($p = 0.0227$) vs. veliparib plus temozolomide 7.4 months ($p = 0.001$) vs. placebo plus chemotherapy 12.3 months	Veliparib plus chemotherapy 28.3 months ($p = 0.156$) vs veliparib plus temozolomide 19.1 months ($p = 0.032$) vs. placebo plus chemotherapy 25.9 months	Veliparib plus chemotherapy 77.8% ($p = 0.027$) vs veliparib plus temozolomide 28.6% ($p < 0.001$) vs. placebo plus chemotherapy 61.3%	NA	[23]
Olaparib for metastatic breast cancer in patients with a germline BRCA mutation	Robson et al.	2017	Breast	Olaparib (300 mg BD)	Chemotherapy	302	Olaparib 7.0 months vs. chemotherapy 4.2 months ($p < 0.001$)	NA	Olaparib 59.9% vs. chemotherapy 28.8%	NA	[15]
Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised,	Pujade-Lauraine et al.	2017	Ovarian	Olaparib (300 mg BD)	Placebo	295	Olaparib plus bevacizumab 19.1 months vs. placebo 5.5 months ($p < 0.0001$)	NA	NA	NA	[24]

(*continued on next page*)

Table 1. (*continued*)

Study Title	Author	Year	Cancer/s	PARP inhibitor	Comparator	Sample size	Medial progression-free survival	Median overall survival	Objective response rate (ORR)	Other relevant results	Reference
placebo-controlled, phase 3 trial											
Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer	Mirza et al.	2016	Ovarian	Niraparib (300 mg OD)	Placebo	553	In gBRCA cohort: 21.0 months for niraparib vs. 5.5 months placebo. In non-BRCA group: 9.3 months for niraparib vs. 3.9 months placebo ($p < 0.001$ for both)	NA	NA	For non-BRCA group with HR deficiency – mPFS: 12.9 months with niraparib vs. 3.8 months with placebo ($p < 0.001$).	[25]
Cisplatin with or without rucaparib after preoperative chemotherapy in patients with triple negative breast cancer: Final efficacy results of Hoosier Oncology Group BRE09-146.	Miller et al.	2015	Breast	Rucaparib (30 mg IV then 100 mg OD PO or 30 mg IV) plus cisplatin (75 mg/m^2 3 weekly)	Cisplatin alone	128	NA	NA	NA	2 year DFS for rucaparib plus cisplatin 63.1% vs. cisplatin alone 58.3%	[26]
Randomized trial of oral cyclophosphamide and veliparib in high-grade serous ovarian, primary peritoneal, or fallopian tube cancers, or BRCA-mutant ovarian cancer	Kummar et al.	2015	Ovarian	Veliparib (60 mg OD) plus cyclophosphamide (50 mg OD)	Cyclophosphamide (50 mg OD) alone	75	NA	NA	NA	1 complete response in each arm, 3 partial responses in the veliparib group and 6 partial responses in the cyclophosphamide group	[27]
Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer	Ledermann et al.	2012 and 2016	Ovarian	Olaparib (400 mg BD)	Placebo	265	mPFS olaparib 8.4 months vs. placebo 4.8 months ($p < 0.001$)	Olaparib 29.8 months vs. placebo 27.8 months ($p = 0.025$)	NA	NA	[28] [29]

Table 2

Ongoing phase 2/3 clinical trials of PARP inhibitors in DNA repair deficient cancers.

NCT	Ph	Progress	PARPi	Type of cancer	DNA repair deficiency	N	Previous chemotherapy
NCT04276376	2	Recruiting	Rucaparib with atezolizumab (anti-PD-L1 antibody)	NSCLC, urothelial bladder cancer, mCRPC, breast cancer, ovarian, gastric, renal cell	loss of function of pre-defined DDR genes[a]	1000	
NCT04550494	2	Recruiting	Talazoparib	Advanced solid tumours	Functional mutation in pre-defined DDR gene[b]	36	No prior PARPi, disease progression despite standard therapy
NCT03442556	2	Recruiting	Rucaparib with docetaxel and carboplatin	mCRPC	mutation in HR gene 'at investigator's discression'	20	Ongoing antiandrogen therapy
NCT03375307	2	Recruiting	Olaparib	metastatic bladder/ genitourinary tumours	(likely)pathogenic variant in DDR genes in the FoundationOneCDx (F1CDx) panel[c]	60	
NCT03601923	2	Recruiting	Niraparib	Pancreatic	Germline or somatic mutation in: BRCA1, BRCA2, PALB2, CHEK2 or ATM	32	Must have received 1+ lines of standard therapy
NCT03233204	2	Active, not recruiting	Olaparib	Paediatric advanced solid tumour/lymphoma/ histiocytic disorder	Actionable mutation as per NCT03155620	49	
NCT04740190	2	Recruiting	Talazoparib and carboplatin	Recurrent high-grade glioma	IDH mutation, PTEN mutation and 'BRCAness' signature[d]	33	
NCT03787680	2	Active, not recruiting	Olaparib and AZD6738	Prostate	Biopsy to determine DNA repair status	49	Disease progression on prior therapy, no prior PARPi
NCT04483544	2	Recruiting	Olaparib and pembrolizumab	Advanced cervical	Competent vs deficient in Fanconi anaemia repair pathway	48	
NCT04985721	2	Recruiting	Pamiparib with tiselizumab	Advanced tumours	(suspected) deleterious mutation in HR related genes[e]	60	No prior PARPi
NCT04030559	2	Recruiting	Niraparib before surgery	High risk localized prostate cancer	alterations in key DNA repair genes identified on Foundation One assay[f]	30	No prior PARPi
NCT03207347	2	Active, not recruiting	Niraparib	Solid tumour	Pre-defined list of known mutations[g]	35	Must have had/declined all known effective life prolonging therapy
NCT05174455	2	Not yet recruiting	Niraparib	Leiomyosarcoma	Loss of function of: BARD1, BRCA1, BRCA2, BRIP1, PALB2, RAD51, RAD51B, RAD51C, or RAD51D	22	No prior PARPi
NCT03127215	2	Recruiting	Olaparib and trabectedin	Solid tumour	'Identification of defective DNA repair via HR'	102	No prior PARPi
NCT04779151	2	Recruiting	Niraparib and dostarlimab		Loss of function of pre-defined DDR genes[h]	112	No prior PARPi

(*continued on next page*)

Table 2. (*continued*)

NCT	Ph	Progress	PARPi	Type of cancer	DNA repair deficiency	N	Previous chemotherapy
				DNA Repair-deficient or Platinum-sensitive solid tumour			
NCT05327010	2	Active, not recruiting	Talazoparib and ZEN-3694 (BET bromodomain inhibitor)	Advanced solid tumours	Cohort 2 must have mutation in:BARD1; FANCA; BRIP1; PALB2; RAD51; RAD51C; RAD51D	88	must have received PARPi
NCT03025035	2	Recruiting	Olaparib and pembrolizumab	BRCA mutated or HDR-deficient breast cancer		20	must have had prior therapy
NCT03344965	2	Recruiting	Olaparib	Metastatic breast	Loss of function of pre-defined DDR genes or at discression of named investigator[j]	114	No prior PARPi
NCT03786796	2	Recruiting	Olaparib	Metastatic renal cell carcinoma	Loss of function of pre-defined DDR genes or at discression of named investigator[j]	20	Prior treatment with at least 1 immune checkpoint inhibitor/anti-VEGF
NCT05412706	2	Active, not recruiting	Niraparib maintenance	metastatic colorectal cancer with complete or partial response after Oxaliplatin-based induction therapy	Other outcome measure to compare 'HRDetect' mutational signature with progression-free survival	46	Oxaliplatin based induction therapy
NCT03581292	2	Active, not recruiting	Veliparib with temozolomide and radiation	Malignant Glioma	Explore the burden of … alterations in HRD genes	115	Newly diagnosed without specific, treatable mutation
NCT04858334	2	Recruiting	Olaparib	Surgically removed pancreatic cancer	BRCA or PALB2 mutation	152	
NCT04042831	2	Recruiting	Olaparib	Metastatic biliary tract cancer	Known mutation in: ATM, ATR, CHEK2, BRCA 1/2, RAD51, BRIP1, PALB2, PTEN, FANC, NBN, EMSY, MRE11, ARID1A	36	No prior PARPi
NCT04716686	2	Recruiting	Niraparib maintenance	Endometrial Serous Carcinoma	'Blood samples for testing … HRR mutations'	83	No prior PARPi
NCT03810105	2	Active, not recruiting	Olaparib and durvalumab	Castration sensitive recurrent non-metastatic prostate cancer	Known mutation in: BRCA1, BRCA2, ATM, CHEK2, FANCA, RAD51C, RAD51D, PALB2, BRIP1, BARD1, or CDK12	5	No prior PARPi
NCT05461690	2	Active, not recruiting	Niraparib	Metastatic TNBC	HRR mutation or/and HRD score$\geq$42	50	No prior PARPi + no more than 2 prev chemo lines, did have anthracycline/taxane
NCT03012321	2	Recruiting	Olaparib and/or abiraterone/ prenisolone	mCRPC	Pre-defined list of known DDR mutations[k]	70	No prior PARPi
NCT04508803	2	Recruiting	Niraparib and HX008 (PD-1 inhibitor)	Germline mutated breast cancer	pathogenic/suspected pathogenic germline mutations in BRCA1/2, or PALB2, or CHEK2.	37	No prior PARPi, no more than 2 prev chemo lines

NCT03047135	2	Recruiting	Olaparib	Biochemically recurrent prostate cancer after radical prostatectomy	(suspected) deleterious mutation in DDR related genes[l]	50	No prior IV chemo
NCT03337087	2	Recruiting	Rucaparib with liposomal irinotecan, fluorouracil, leucovorin	Includes group with metastatic pancreatic adenocarcinoma	BRCA1, BRCA2, and PALB2	18 total pts	No prior treatment for metastatic disease
NCT05167175	2	Active, not recruiting	Olaparib and/or abiraterone/ prenisolone	metastatic hormone sensitive prostate cancer	Pre-defined list of known HRD mutations[m]	30	No prior PARPi or DNA damaging cytotoxic
NCT05201612	2	Active, not recruiting	Olaparib and pembrolizumab	Advanced colorectal cancer	BRCA mutation or RAD 51 score < 10%	40	Two to four prior lines of treatment, No prior PARPi
NCT04978012	2	Recruiting	Fluzoparib and camrelizumab	Nasopharyngeal	Homologous recombination repair status	48	Prior chemo, No prior PARPi
NCT05406999	2	Recruiting	PARP inhibitor + Androgen deprivation therapy	Advanced prostate cancer	HRR mutation verified by molecular testing	50	
NCT05327621	2	Recruiting	Pamiparib	mCRPC	HRD score at least 9	50	No prior PARPi
NCT03522246 (ATHENA)	3	Active, not recruiting.	Rucaparib + Nivolumab	Ovarian/peritoneal/ fallopian	Analysis based on homologous recombination status	1000	Prior chemo and surgery
NCT02975934 (TRITON3)	3	Active, not recruiting.	Rucaparib	mCRPC	BRCA1/2 or ATM	405	
NCT04821622	3	Recruiting	Talzoparib with enzalutamide	mCSPC	DDR gene mutation	550	Ongoing hormone therapy
NCT04455750 (CASPAR)	3	Recruiting	Rucaparib with enzalutamide	mCRPC	HRR status	1002	No prior PARPi
NCT04592211	1/2	Active, not recruiting.	Olaparib, paclitaxel and pembrolizumab	Recurrent/Advanced Gastric cancer	known/suspected loss of function of pre-defined DDR genes[n]	71	Failed first line therapy
NCT03317392	1/2	Recruiting	Olaparib and radium-233	Advanced prostate cancer with bone metastasis	Oncopanel testing or DDR	133	
NCT04174716	1/2	Recruiting	IDX-1197	Solid tumour	'Homologous repair mutation'	310	No prev PARPi, 1+ lines of standard therapy
NCT05432791	2/3	Active, not recruiting	Olaparib and temozolomide	Uterine leiomyosarcoma	Loss of function of pre-defined HR genes	70	At least 2 prior lines of chemotherapy, No prior PARPi/TMZ

Pre-defined genes involved in DDR included in studies.

[a] ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, PALB2, RAD51C, RAD51D, FANCA, NBN, RAD51, RAD54L.

[b] ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, CDK12, CHK1, CHK2, IDH1, IDH2, MRE11A, NBN, PALB2, RAD50, RAD51, RAD51B, RAD51C, RAD51D, RAD54L or genes involves in fanconi anaemia pathway.

[c] Panel = ABL1, ATR, ATRX, BARD1, BRD4, CCND1, CHEK1, CHEK2, DOT1L, FANCC, FANCE, FANCG, FANCL, IKBKE, MEN1, MLH1, MSH2, MSH6, MUTYH, NPM1, PMS2, POLD1, POLE, RAD51, SMARCB1, STK11, TP53.

[d] BRCAness signature ATM, ATR, BAP1, BRCA1, BRCA2, CDK12, CHEK1, CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, PALB2, NGS1, WRN, RAD50, RAD51B, RAD51C, RAD51D, MRE11A, BLM, BRIP1.

[e] ATM, CDK12, PALB2, ARID1A, ATRX, BLM, BARD1, BRIP1, CHEK1, CHEK2, FANCA, FANCF, FANCG, FANCI, FANCL, FANCM, MSH2, NBN, RAD50, RAD51C, RAD51D, WRN.

[f] Including BRCA1/2, ATM, CDK12, CHEK1/2 FANCA, FANCD2, FANCL, GEN1, NBN, PALB2, RAD51, RAD51c, and BRIP1.

[g] ARID1A, ATM, ATR, BACH1 (BRIP1), BAP1, BARD1, BLM, CHEK1, CHEK2, CDK2, CDK4, ERCC, FAM175A, FEN1, IDH1, IDH2, MRE11A, NBN (NBS1), PALB2, POLD1, PRKDC (DNA-PK) PTEN, RAD50, RAD51, RAD52, RAD54, RPA1, SLX4, WRN, or XRCC.

[h] ARID1A, ARID2, ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, IDH1, IDH2, NBN, PALB2, PBRM1, RAD51C, RAD51D, FANCA, NBN, RAD51, RAD54L, SMARCA4.
[i] ATM, ATR, BARD1, BRIP1 (FANCJ), CHEK2, FANCA, FANCC, FANCD2, FANCE, FANCF, FANCM, MRE11A, NBN, PALB2, RAD50, RAD51C, RAD51D.
[j] BAP-1, ATM, BRCA1, BRCA2, PALB2, CHEK2, BRIP1, RAD51C, BARD1, CDK12, CHEK1, FANCL, PP2R2A, RAD51B, RAD51D, or RAD54L.
[k] BARD1, BRCA1, BRCA2, BRIP1, FANCA, NBN, PALB2, RAD51, RAD51B, RAD51C, RAD51D; or actionable mutations in the PTEN gene, or hotspot mutations in the PIK3CA gene.
[l] ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, or other DNA repair genes.
[m] BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD 51C, RAD51D and RAD54L.
[n] BRCA1, BRCA2, ATM, or other HRR-genes: BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, PPP2R2A, RAD51B, RAD51C, RAD51D, and RAD54.

was reduced following olaparib treatment in a murine xenograft of ATM mutant mantle cell leukaemia [24,26]. Pharmacological inhibitors of ATM have been developed and are currently being evaluated for safety and efficacy in advanced solid tumours, both as a monotherapy (NCT04882917, NCT05002140, NCT03423628) and in combination with antitumour agents including olaparib (NCT02588105).

ATR (Ataxia telangiectasia and Rad3 related protein) is involved in cellular signalling of DNA damage and in cell cycle checkpoint inhibition (via CHK1) to facilitate DNA repair [20]. Pharmacological inhibitors of ATR (ATRi) continue to undergo phase I/II trials in advanced solid tumours (NCT05338346, NCT03188965, NCT04616534, NCT02595892) and the ATRi berzosertib has been shown to be tolerated in patients with solid tumours [27,29]. In a multicentre trial, conducted with patients with high grade serous ovarian cancer, median progression free survival was 22.9 weeks in 24 patients receiving Gemcitabine plus berzosertib vs 14.7 weeks in the 36 patients receiving gemcitabine alone [32]. ATRi are also being investigated in combination with PARPi and preliminary results from a phase I trial of Berzosertib alongside veliparib and cisplatin identified a partial response in three patients, of whom two had ATM mutation (one in non-small cell lung cancer and the other in oesophageal cancer) [33] (NCT02723864). olaparib is being investigated alongside ATRi in multiple phase II trials in advanced cancers (NCT04065269, NCT03682289, NCT03462342).

CHK1 inhibitors are also being tested in phase I/II trials alongside other antitumour agents (NCT03495323, NCT01870596) and in the context of HRD (including BRCA mutation) (NCT02873975). Olaparib treatment alongside CHK1 inhibition (using prexasertib) resulted in a partial response in four of 18 patients with *BRCA1* mutated PARPi resistant high grade serous ovarian cancer and prexasertib treatment was associated with increased DNA damage [34].

Wee1 is another protein kinase involved in arresting the cell cycle in order for the DDR to take place [19]. Preclinically, AZD1775 (an inhibitor of Wee1) acted synergistically with olaparib to reduce viability in cellular models of small-cell lung cancer [35]. Initial safety and efficacy of AZD1175 was shown in a phase I trial of its use as a monotherapy and also alongside gemcitabine ± cisplatin [36]. Several phase II trials of Wee1 inhibitor monotherapy and in addition to chemotherapy are ongoing (NCT04590248, NCT01164995). However, haematological toxicities have been noted in trials with the Wee1 inhibitor adavosertib, particularly with the addition of further chemotherapy [37,38] and PARP inhibition may therefore represent a more successful combinatorial approach. Indeed, treatment with either adavosertib or

ATRi alongside olaparib in patients with triple negative breast cancer (TNBC) is currently the focus of a phase II trial (NCT03330847).

Following recognition of a DSB by the MRN complex, BRCA1 becomes activated and forms a complex with PALB2 and BARDI with resultant recruitment of BRCA2 and RAD51 [1]. Mutations in PALB2 therefore lead to HRD, making it another possible context for synthetic lethality with PARPi. Analysis of data from the TRITON2 study of rucaparib in mCRPC showed a decrease in prostate specific antigen (PSA) levels following PARPi treatment in both patients with PALB2 mutation [39]. Phase II trials are currently ongoing to investigate PARPi treatment in cancers with mutations in DDR, including PALB2 (see Table 2).

RAD51 is important in the exchange of DNA strands for HR. RAD51 knockout using siRNA in HeLa cells was associated with a 1000-fold decrease in cell viability following addition of PARPi [31] and the increased killing effect has also been noted in RAD51 deficient ovarian cancer cells [40]. The ARIEL2 trial of rucaparib in ovarian cancer included four patients with RAD51C mutation, all of whom responded to rucaparib treatment [41]. Chandran and Kennedy reported a case study of a patient with germline RAD51 mutated ovarian carcinosarcoma who responded to treatment with olaparib [42]. RAD51 is another gene of interest in continuing trials included in Table 2 (NCT03786796, NCT04030559).

Other emerging targets in the context of *BRCA* deficiency

DNA Polymerase θ (Polθ) is involved in NHEJ and loss of function of Polθ has been shown to increase the activity of DNA repair via HR in cells [43]. Preclinically, addition of ShRNA against Polθ reduced clonogenic survival in *BRCA1/2* deficient cells with an observed four-fold increase in chromatid and chromosome breaks [44]. Impairment of Polθ activity in the context of *BRCA1/2* deficiencies resulted in increased sensitivity to existing anticancer agents including PARPi both *in vitro* and in xeonograft models [43,45]. An open label multicentre phase I/II trial is currently ongoing to investigate the safety and preliminary efficacy of a Polθ inhibitor (ART4215) both as a monotherapy and alongside PARPi in the treatment of advanced solid tumours including *BRCA* mutated breast cancers (NCT04991480).

Ovarian cancer cells with *BRCA1* mutation were shown to be more sensitive to ATRi (with VE-821) than wild type cells [46] and BRCA depletion alongside ATR inhibition has been shown to sensitise cells to other antitumour agents [47]. A preliminary trial of Wee1 inhibition (using AZD1775) in refractory solid tumours included six patients with *BRCA* mutation, of whom two showed a partial response to treatment [48]. A further phase II trial of the Wee1 inhibitor adavosertib in *BRCA* mutated solid and haematological malignancies is ongoing (NCT04439227).

ATR inhibition in the context of ATM mutation

As discussed above, ATM is important in the recognition of DSBs and initiation of repair. ATM mutation was noted in 11% of 631 patients with advanced prostate cancer [49]. *In vitro*, ATM deficient cells are more susceptible to ATRi than their wild-type counterparts and this has also been shown in xenograft models [49]. Preliminary results from an ongoing trial of ATRi (using BAY1895344) in advanced solid tumours show ATM aberration in all four patients with partial response [50] (NCT03188965). Several phase II trials of ATRi in solid tumours are ongoing and include an intended group of patients with aberrant ATM mutation for analysis (NCT04564027, NCT02264678).

Targeting base excision repair (BER)

PARP1 is essential during SSB repair. In addition, PARP has been shown to interact with several components of the BER pathways (such as X-ray repair cross complementing 1 (XRCC1), polymerase β (Pol β) and flap endonuclease 1 (FEN1)) to facilitate efficient repair. This provides potential opportunities for novel synthetic lethality interactions, an area we have recently investigated in several pre-clinical studies.

During BER, aberrant base(s) are removed by a glycosylase and then apurinic/apyrimidinic endonuclease (APE1) makes a nick in the DNA backbone before Pol β adds the preliminary complementary base. APE1 inhibitors have been shown to be selectively toxic to cells deficient in either BRCA or ATM [51]. In addition, small molecule inhibitors of Pol β have been shown to selectively kill ovarian and HeLa cells lacking *BRCA2* [52]. FEN1 is involved in the addition of complementary bases in the long patch repair pathway of BER. Like Pol β, inhibition of FEN1 has also been shown to be synthetically lethal in cells with *BRCA* deficiency [53,54]. Interestingly, FEN1 inhibition can also preferentially reduce cell viability in ovarian cancer cells with Pol β knockout [53].

XRCC1 is a scaffolding protein involved in BER. Loss of XRCC1 expression, identified in 16% of breast cancers, is associated with an aggressive tumour phenotype [55]. In vitro, ATRi reduced survival of ovarian cells with XRCC1 mutation more so than in wild type cells [55]. ATM/ATR/Wee1 inhibition was found to reduce cell viability in TNBC or HeLa cells with XRCC1 knockout and PARPi acted synergistically with all three compounds [56]. MCF cells depleted of XRCC1 were shown to be 100 times more sensitive to olaparib than wild type cells [57]. This preclinical data identifies

XRCC1 mutation as a context for specific synthetic lethality strategies targeting either HR or PARP. Thus APE1, Pol β, FEN1 and XRCC1 have been identified as possible targets as part of a synthetic lethality strategy for ongoing research. Taken together, these BER targeting approaches appear to be promising but further *in vivo* investigations will have to be completed to accelerate the pharmaceutical development of BER inhibitors.

Conclusions

Efficient DNA repair is fundamental to the maintenance of cellular genomic integrity. Whilst impaired DNA repair capacity will predispose to cancer development, the last decade has seen the development of precision oncology strategies that can exploit these DNA repair deficiency states in cancer through synthetic lethality. The recent success of PARPi in *BRCA* germline deficient breast, ovarian, pancreatic and prostate cancers prove that this approach is clinically meaningful. However, the clinical benefit is not long lasting and the eventual development of resistance to PARPi is an ongoing clinical challenge. Whether combinatorial approaches targeting PARP and other DNA repair factor(s) can mitigate this problem is an area of ongoing clinical investigation. We and others have also shown that PARPi may also have applications beyond BRCA deficiency. Ongoing and future clinical studies will hopefully clarify additional clinical applications for PARPi. Moreover, the search for additional synthetic interactions within the DNA repair machinery, beyond PARP, is an exciting area of precision oncology.

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.

References

Papers of particular interest, published within the period of review, have been highlighted as:

* of special interest
** of outstanding interest

1. Neiger HE, Siegler EL, Shi Y: **Breast cancer predisposition genes and synthetic lethality**. *Int J Mol Sci* 2021, **22**.

2. Golan T, Hammel P, Reni M, Van Cutsem E, Macarulla T, Hall MJ, *et al.*: **Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer**. *N Engl J Med* 2019, **381**: 317–327.

3. * de Bono J, Kang J, Hussain M: **Olaparib for metastatic castration-resistant prostate cancer**. Reply *N Engl J Med.* 2020, **383**:891.
Randomized phase III trial of Olaparib in mCRPC showing longer progression free survival in patients with mutations in genes involved in homologous repair

4. Baretta Z, Mocellin S, Goldin E, Olopade OI, Huo D: **Effect of BRCA germline mutations on breast cancer prognosis: a systematic review and meta-analysis**. *Medicine* 2016, **95**: e4975.

5. Antoniou A, Pharoah PD, Narod S, Risch HA, Eyfjord JE, Hopper JL, *et al.*: **Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case Series unselected for family history: a combined analysis of 22 studies**. *Am J Hum Genet* 2003, **72**:1117–1130.

6. Huang A, Garraway LA, Ashworth A, Weber B: **Synthetic lethality as an engine for cancer drug target discovery**. *Nat Rev Drug Discov* 2020, **19**:23–38.

7. Lord CJ, Ashworth A: **PARP inhibitors: synthetic lethality in the clinic**. *Science* 2017, **355**:1152–1158.

8. Bryant HE, Schultz N, Thomas HD, Parker KM, Flower D, Lopez E, *et al.*: **Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase**. *Nature* 2005, **434**:913–917.

9. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, *et al.*: **Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy**. *Nature* 2005, **434**: 917–921.

10. Robson M, Im SA, Senkus E, Xu B, Domchek SM, Masuda N, *et al.*: **Olaparib for metastatic breast cancer in patients with a germline BRCA mutation**. *N Engl J Med* 2017, **377**:523–533.

11. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, *et al.*: **Talazoparib in patients with advanced breast cancer and a germline BRCA mutation**. *N Engl J Med* 2018, **379**: 753–763.

12. Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, *et al.*: **Niraparib maintenance therapy in platinum-sensitive, recurrent ovarian cancer**. *N Engl J Med* 2016, **375**:2154–2164.

13. * Kristeleit R, Lisyanskaya A, Fedenko A, Dvorkin M, de Melo AC, Shparyk Y, *et al.*: **Rucaparib versus standard-of-care chemotherapy in patients with relapsed ovarian cancer and a deleterious BRCA1 or BRCA2 mutation (ARIEL4): an international, open-label, randomised, phase 3 trial**. *Lancet Oncol* 2022, **23**:465–478.
Recent trial showing significantly improved PFS with addition of Rucaparib to chemotherapy in patients with ovarian cancer

14. * Banerjee S, Moore KN, Colombo N, Scambia G, Kim BG, Oaknin A, *et al.*: **Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation (SOLO1/GOG 3004): 5-year follow-up of a randomised, double-blind, placebo-controlled, phase 3 trial**. *Lancet Oncol* 2021, **22**:1721–1731.
This study included the longest follow-up of PARPi in BRCA mutated ovarian cancer thus far and showed improvement in progression free survival with Olaparib maintenance therapy

15. Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, *et al.*: **Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer**. *N Engl J Med* 2012, **366**: 1382–1392.

16. Pujade-Lauraine E, Ledermann JA, Selle F, Gebski V, Penson RT, Oza AM, *et al.*: **Olaparib tablets as maintenance therapy in patients with platinum-sensitive, relapsed ovarian cancer and a BRCA1/2 mutation (SOLO2/ENGOT-Ov21): a double-blind, randomised, placebo-controlled, phase 3 trial**. *Lancet Oncol* 2017, **18**:1274–1284.

17. Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, *et al.*: **Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer**. *N Engl J Med* 2019, **381**:2403–2415.

18. Penson RT, Valencia RV, Cibula D, Colombo N, Leath CA, Bidziński M, *et al.*: **Olaparib versus nonplatinum chemotherapy in patients with platinum-sensitive relapsed ovarian cancer and a germline BRCA1/2 mutation (SOLO3): a randomized phase III trial**. *J Clin Oncol* 2020, **38**:1164–1174.

19. Topatana W, Juengpanich S, Li S, Cao J, Hu J, Lee J, *et al.*: **Advances in synthetic lethality for cancer therapy: cellular mechanism and clinical translation**. *J Hematol Oncol* 2020, **13**: 118.

20. Klinakis A, Karagiannis D, Rampias T: **Targeting DNA repair in cancer: current state and novel approaches**. *Cell Mol Life Sci* 2020, **77**:677–703.

21. Han HS, Diéras V, Robson M, Palácová M, Marcom PK, Jager A, *et al.*: **Veliparib with temozolomide or carboplatin/paclitaxel versus placebo with carboplatin/paclitaxel in patients with BRCA1/2 locally recurrent/metastatic breast cancer: randomized phase II study**. *Ann Oncol* 2018, **29**:154–161.

22. Diéras V, Han HS, Kaufman B, Wildiers H, Friedlander M, Ayoub JP, *et al.*: **Veliparib with carboplatin and paclitaxel in BRCA-mutated advanced breast cancer (BROCADE3): a randomised, double-blind, placebo-controlled, phase 3 trial**. *Lancet Oncol* 2020, **21**:1269–1282.

23. Park SJ, Chang SJ, Suh DH, Kong TW, Song H, Kim TH, *et al.*: **A phase IA dose-escalation study of PHI-101, a new checkpoint kinase 2 inhibitor, for platinum-resistant recurrent ovarian cancer**. *BMC Cancer* 2022, **22**:28.

24. Aguilar-Quesada R, Muñoz-Gámez JA, Martín-Oliva D, Peralta A, Valenzuela MT, Matínez-Romero R, *et al.*: **Interaction between ATM and PARP-1 in response to DNA damage and sensitization of ATM deficient cells through PARP inhibition**. *BMC Mol Biol* 2007, **8**:29.

25. Fasching PA, Link T, Hauke J, Seither F, Jackisch C, Klare P, *et al.*: **Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study)**. *Ann Oncol* 2021, **32**:49–57.

26. Weston VJ, Oldreive CE, Skowronska A, Oscier DG, Pratt G, Dyer MJ, *et al.*: **The PARP inhibitor olaparib induces significant killing of ATM-deficient lymphoid tumor cells in vitro and in vivo**. *Blood* 2010, **116**:4578–4587.

27. Yap TA, O'Carrigan B, Penney MS, Lim JS, Brown JS, de Miguel Luken MJ, *et al.*: **Phase I trial of first-in-class ATR inhibitor M6620 (VX-970) as monotherapy or in combination with carboplatin in patients with advanced solid tumors**. *J Clin Oncol* 2020, **38**:3195–3204.

28. Ledermann JA, Pujade-Lauraine E: **Olaparib as maintenance treatment for patients with platinum-sensitive relapsed ovarian cancer**. *Ther Adv Med Oncol* 2019, **11**, 1758835919849753.

29. Middleton MR, Dean E, Evans TRJ, Shapiro GI, Pollard J, Hendriks BS, *et al.*: **Phase 1 study of the ATR inhibitor berzosertib (formerly M6620, VX-970) combined with gemcitabine ± cisplatin in patients with advanced solid tumours**. *Br J Cancer* 2021, **125**:510–519.

30. McPherson LA, Shen Y, Ford JM: **Poly (ADP-ribose) polymerase inhibitor LT-626: sensitivity correlates with MRE11 mutations and synergizes with platinums and irinotecan in colorectal cancer cells**. *Cancer Lett* 2014, **343**:217–223.

31. McCabe N, Turner NC, Lord CJ, Kluzek K, Bialkowska A, Swift S, *et al.*: **Deficiency in the repair of DNA damage by homologous recombination and sensitivity to poly(ADP-ribose) polymerase inhibition**. *Cancer Res* 2006, **66**:8109–8115.

32. Konstantinopoulos PA, Cheng SC, Wahner Hendrickson AE, Penson RT, Schumer ST, Doyle LA, *et al.*: **Berzosertib plus gemcitabine versus gemcitabine alone in platinum-resistant high-grade serous ovarian cancer: a multicentre, open-label, randomised, phase 2 trial**. *Lancet Oncol* 2020, **21**:957–968.

33. Mittra A, Coyne GH, Do KT, Piha-Paul SA, Kummar S, *et al.*: **Safety and tolerability of veliparib, an oral PARP inhibitor, and M6620 (VX-970), an ATR inhibitor, in combination with cisplatin in patients with refractory solid tumors**. *J Clin Oncol* 2019, **37**:3067.

34. * Do KT, Kochupurakkal B, Kelland S, de Jonge A, Hedglin J, Powers A, *et al.*: **Phase 1 combination study of the CHK1 inhibitor Prexasertib and the PARP inhibitor olaparib in high-grade serous ovarian cancer and other solid tumors**. *Clin Cancer Res* 2021, **27**:4710–4716.

First clinical trial of CHK1 inhibition alongside PARPi showing that the combination lead to increased DNA damage and a partial clinical response in four of the 18 patients

35. Lallo A, Frese KK, Morrow CJ, Sloane R, Gulati S, Schenk MW, *et al.*: **The combination of the PARP inhibitor olaparib and the WEE1 inhibitor AZD1775 as a new therapeutic option for small cell lung cancer**. *Clin Cancer Res* 2018, **24**:5153–5164.

36. Leijen S, van Geel RM, Pavlick AC, Tibes R, Rosen L, Razak AR, *et al.*: **Phase I study evaluating WEE1 inhibitor AZD1775 as monotherapy and in combination with gemcitabine, cisplatin, or carboplatin in patients with advanced solid tumors**. *J Clin Oncol* 2016, **34**:4371–4380.

37. Moore KN, Chambers SK, Hamilton EP, Chen LM, Oza AM, Ghamande SA, *et al.*: **Adavosertib with chemotherapy in patients with primary platinum-resistant ovarian, fallopian tube, or peritoneal cancer: an open-label, four-arm, phase II study**. *Clin Cancer Res* 2022, **28**:36–44.

38. Lheureux S, Cristea MC, Bruce JP, Garg S, Cabanero M, Mantia-Smaldone G, *et al.*: **Adavosertib plus gemcitabine for platinum-resistant or platinum-refractory recurrent ovarian cancer: a double-blind, randomised, placebo-controlled, phase 2 trial**. *Lancet* 2021, **397**:281–292.

39. ** Abida W, Campbell D, Patnaik A, Shapiro JD, Sautois B, Vogelzang NJ, *et al.*: **Non-BRCA DNA damage repair gene alterations and response to the PARP inhibitor rucaparib in metastatic castration-resistant prostate cancer: analysis from the phase II TRITON2 study**. *Clin Cancer Res* 2020, **26**:2487–2496.

First analysis of PARPi efficacy in cancer patients with pathological genetic mutations in one of many different DDR genes including results by specific gene mutated. Results from 78 patients with non-BRCA DDR mutation are analysed

40. Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, *et al.*: **Germline mutations in RAD51D confer susceptibility to ovarian cancer**. *Nat Genet* 2011, **43**:879–882.

41. Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun J, *et al.*: **Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial**. *Lancet Oncol* 2017, **18**:75–87.

42. Chandran EA, Kennedy I: **Significant tumor response to the poly (ADP-ribose) polymerase inhibitor olaparib in heavily pretreated patient with ovarian carcinosarcoma harboring a germline RAD51D mutation**. *JCO Precis Oncol* 2018, **2**:1–4.

43. Ceccaldi R, Liu JC, Amunugama R, Hajdu I, Primack B, Petalcorin MI, *et al.*: **Homologous-recombination-deficient tumours are dependent on Polθ-mediated repair**. *Nature* 2015, **518**:258–262.

44. Mateos-Gomez PA, Gong F, Nair N, Miller KM, Lazzerini-Denchi E, Sfeir A: **Mammalian polymerase θ promotes alternative NHEJ and suppresses recombination**. *Nature* 2015, **518**:254–257.

45. * Zhou J, Gelot C, Pantelidou C, Li A, Yücel H, Davis RE, *et al.*: **A first-in-class polymerase theta inhibitor selectively targets homologous-recombination-deficient tumors**. *Nat Can* 2021, **2**:598–610.

a study of a novel target for synthetic lethality

46. Burgess BT, Anderson AM, McCorkle JR, Wu J, Ueland FR, Kolesar JM: **Olaparib combined with an ATR or Chk1 inhibitor as a treatment strategy for acquired olaparib-resistant**. *Diagnostics* 2020, **10**.

47. Huntoon CJ, Flatten KS, Wahner Hendrickson AE, Huehls AM, Sutor SL, Kaufmann SH, *et al.*: **ATR inhibition broadly sensitizes ovarian cancer cells to chemotherapy independent of BRCA status**. *Cancer Res* 2013, **73**:3683–3691.

48. Do K, Wilsker D, Ji J, Zlott J, Freshwater T, Kinders RJ, *et al.*: **Phase I study of single-agent AZD1775 (MK-1775), a Wee1 kinase inhibitor, in patients with refractory solid tumors**. *J Clin Oncol* 2015, **33**:3409–3415.

49. Neeb A, Herranz N, Arce-Gallego S, Miranda S, Buroni L, Yuan W, *et al.*: **Advanced prostate cancer with ATM loss: PARP and ATR inhibitors**. *Eur Urol* 2021, **79**:200–211.

50. * Yap TA, Tolcher AW, Plummer ER, Becker A, Fleuranceau-Morel P, Goddemeier T, *et al.*: **A first-in-human phase I study of ATR inhibitor M1774 in patients with solid tumors**. *J Clin Oncol* 2021, **39**(suppl):TPS3153.

Preliminary results have shown all four patients with partial response to ATRi treatment have mutation in ATM; an interesting result for further validation in current trials

51. Sultana R, McNeill DR, Abbotts R, Mohammed MZ, Zdzienicka MZ, Qutob H, *et al.*: **Synthetic lethal targeting of DNA double-strand break repair deficient cells by human apurinic/apyrimidinic endonuclease inhibitors**. *Int J Cancer* 2012, **131**:2433–2444.

52. Ali R, Alblihy A, Miligy IM, Alabdullah ML, Alsaleem M, Toss MS, *et al.*: **Molecular disruption of DNA polymerase β for platinum sensitisation and synthetic lethality in epithelial ovarian cancers**. *Oncogene* 2021, **40**:2496–2508.

53. Mesquita KA, Ali R, Doherty R, Toss MS, Miligy I, Alblihy A, *et al.*: **FEN1 blockade for platinum chemo-sensitization and synthetic lethality in epithelial ovarian cancers**. *Cancers* 2021, **13**.

54. Guo E, Ishii Y, Mueller J, Srivatsan A, Gahman T, Putnam CD, *et al.*: **FEN1 endonuclease as a therapeutic target for human cancers with defects in homologous recombination**. *Proc Natl Acad Sci U S A* 2020, **117**:19415–19424.

55. Sultana R, Abdel-Fatah T, Perry C, Moseley P, Albarakti N, Mohan V, *et al.*: **Ataxia telangiectasia mutated and Rad3 related (ATR) protein kinase inhibition is synthetically lethal in XRCC1 deficient ovarian cancer cells**. *PLoS One* 2013, **8**, e57098.

56. * Ali R, Alblihy A, Toss MS, Algethami M, Al Sunni R, Green AR, *et al.*: **XRCC1 deficient triple negative breast cancers are sensitive to ATR, ATM and Wee1 inhibitor either alone or in combination with Olaparib**. *Ther Adv Med Oncol* 2020, **12**, 1758835920974201.

Pre-clinical data identifies a novel synthetic lethality target for ATR/ATM/Wee1 inhibitors

57. Hirota K, Ooka M, Shimizu N, Yamada K, Tsuda M, Ibrahim MA, *et al.*: **XRCC1 counteracts poly(ADP ribose)polymerase (PARP) poisons, olaparib and talazoparib, and a clinical alkylating agent, temozolomide, by promoting the removal of trapped PARP1 from broken DNA**. *Gene Cell* 2022, **27**:331–344.