Recent advances in clinical practice

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DNA damage repair as a target in pancreatic cancer: state-of-the-art and future perspectives

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Journal club presentation

Session 2

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https://www.mdanderson.org/documents/Labs/Wood-Laboratory/human-dna-repair-genes.html#Human%20DNA%20Repair%20Genes

Human DNA Repair Genes

(MD Anderson)

Human DNA Repair Genes

This is an update of the table cited in Wood RD, Mitchell M, & Lindahl T Mutation Research, 2005, in Science, 2001, in the reference book DNA Repair and Mutagenesis, 2nd edition, 2006, and in Nature Reviews Cancer, 2011

This table was last modified by R. Wood and M. Lowery on *Wednesday 10th June 2020*

Gene Name (synonyms) linked to GeneCards *Some gene products act in more than one pathway, but each is listed only once below*	Activity linked to OMIM	Chromosome location linked to Genome Data Viewer	Accession number linked to NCBI Entrez
Base excision repair (BER)	**DNA glycosylases: major altered base released**		Top of Page

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Base excision repair (BER)	**DNA glycosylases: major altered base released**		Top of Page
UNG	U	12q24.11	NM_080911
SMUG1	U	12q13.13	NM_014311
MBD4	U or T opposite G at CpG sequences	3q21.3	NM_003925
TDG	U, T or ethenoC opposite G	12q23.3	NM_003211
OGG1	8-oxoG opposite C	3p25.3	NM_016821
MUTYH (MYH)	A opposite 8-oxoG	1p34.1	NM_012222
NTHL1 (NTH1)	Ring-saturated or fragmented pyrimidines	16p13.3	NM_002528
MPG	3-meA, ethenoA, hypoxanthine	16p13.3	NM_002434
NEIL1	Removes thymine glycol	15q24.2	NM_024608
NEIL2	Removes oxidative products of pyrimidines	8p23.1	NM_145043
NEIL3	Removes oxidative products of pyrimidines	4q34	NM_018248
Other BER and strand break joining factors			Top of Page
APEX1 (APE1)	AP endonuclease	14q11.2	NM_001641
APEX2	AP endonuclease	Xp11.21	NM_014481
LIG3	DNA Ligase III	17q12	NM_013975
XRCC1	LIG3 accessory factor	19q13.31	NM_006297
PNKP	Converts some DNA breaks to ligatable ends	19q13.33	NM_007254
APLF	Accessory factor for DNA end-joining	2p13.3	NM_173545
HMCES	Reacts with AP sites	3q21.3	NM_020187
Poly(ADP-ribose) polymerase (PARP) enzymes that bind to DNA			Top of Page
PARP1 (ADPRT)	Protects strand interruptions	1q42.12	NM_001618
PARP2 (ADPRTL2)	PARP-like enzyme	14q11.2	NM_005484
PARP3 (ADPRTL3)	PARP-like enzyme	3p21.1	NM_001003931
PARG	Poly(ADP-ribose) glycohydrolase	10q11.23	NM_003631
PARPBP	Binds PARP and modulates recombination	12q23.2	NM_001319988
Direct reversal of damage			Top of Page

DNA DAMAGE REPAIR DEFECTS AND PANCREATIC CANCER

- PDAC incidence varies in different countries (highest incidence in **high-income countries**)

- Although the cause of PDAC is complex and multifactorial, a variety of inherited and non-inherited **risk factors** have been described, some of which may explain these variations.

Non-inherited risk factors:

- Chronic pancreatitis
- Diabetes mellitus
- Smoking
- Alcohol consumption
- Obesity
- Possibly *Helicobacter pylori* infection

Sporadic pancreatic cancer with somatic DDR gene mutations

- Large-scale genomic analysis revealed **63 genetic alterations per single PDAC**, with '*DNA damage control*' being one of the most prominent term.

- ***ATM*** *serine/threonine kinase* appears to be the most frequently mutated DDR gene in somatically mutated sporadic PDAC, with an overall mutational frequency of approximately 4%, followed by ***BRCA2***, ***STK11*** and ***BRCA1***.

- Loss of *ATM* occurs in precancerous lesions such as PanINs or IPMNs and in primary tumors, underpinning its crucial role in genomic integrity.

- The **ultimate therapeutic strategy** for PDAC is the delineation of patient subgroups who might be **susceptible to an interference with the DDR** due to the **intrinsically high DNA damage load**, leading to a further increase **beyond a tolerable threshold**.

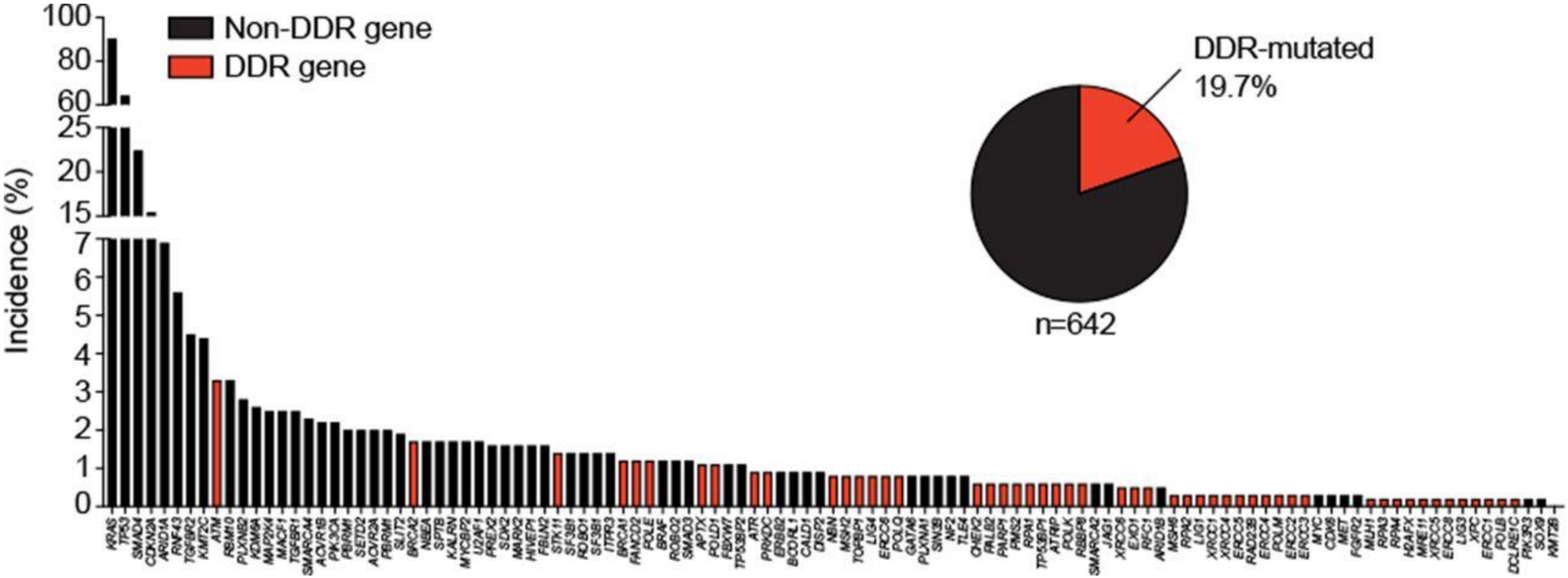


Figure 2 Frequency of gene alterations in primary pancreatic ductal adenocarcinomas. **Three available pancreatic cancer sequencing data** sets123 124 125 (n=751) were assessed for somatic gene mutations (panel of 118 genes from 16 123 and additionally extended in more detail for DNA damage repair genes from **cBioPortal**). DDR, DNA damage repair.

DDR gene mutations in the germline of patients with pancreatic cancer

Familial pancreatic cancers (FPC):

- Only 10%–20% have a clearly identifiable germline mutation.

- Inheritance can be frequently attributed to germline DDR gene mutations (*ATM*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *PALB2*, *PMS2* and *STK11*) and to mutations in classical cancer susceptibility genes such as *CDKN2A* or *TP53*.

Table 1 Frequency of the most common deleteriously mutated genes in familial pancreatic cancer

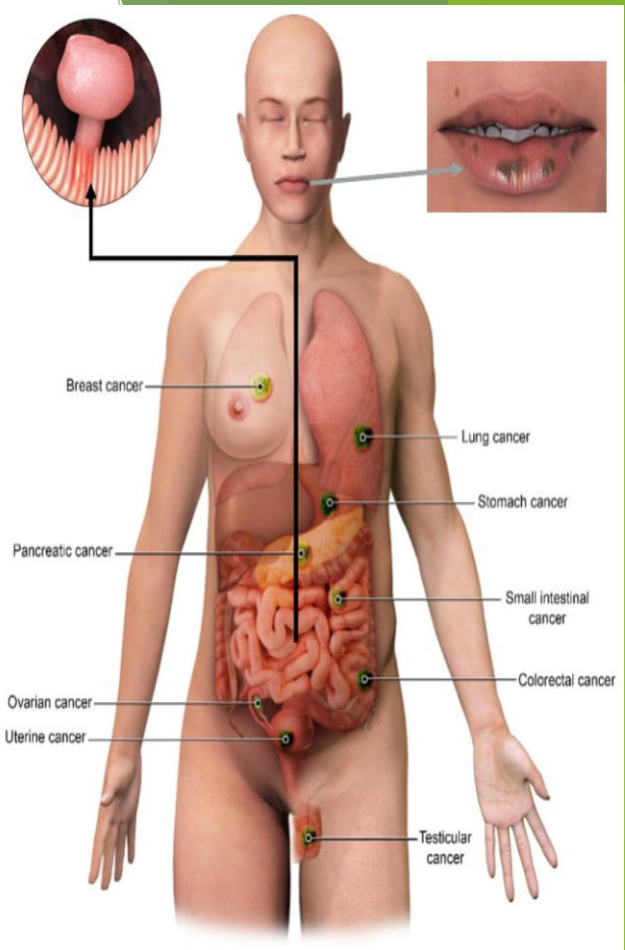
Gene	Zhen *et al*[44] (n=515)	Roberts *et al*[22] (n=166)	Takai *et al*[45] (n=54)	Mutation prevalence (%)
BRCA2	19	n.a.	3	3.9
ATM	n.a.	4	2	2.7
CDKN2A	13	n.a.	n.a.	2.5
BRCA1	6	n.a.	n.a.	1.2
PALB2	3	n.a.	2	0.9

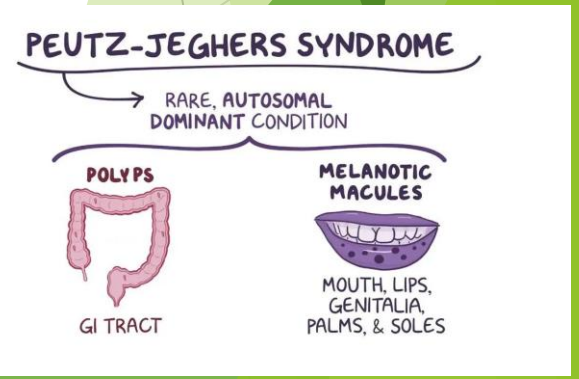
Mutations data were analysed from three familial pancreatic cancer cohorts (735 samples).
n.a., not applicable.

Hereditary pancreatic cancer syndromes

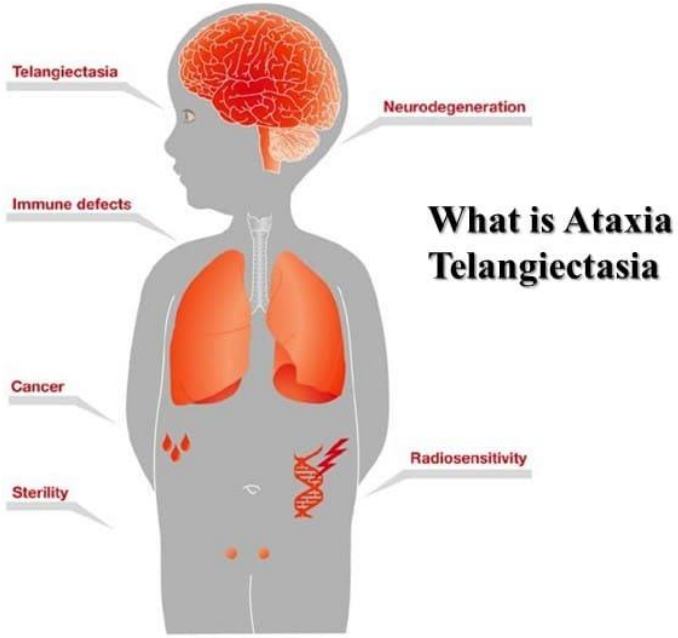
Inherited cancer predisposition syndromes are characterised by usually monoallelic, dominantly inherited autosomal mutations that predispose to PDAC and other cancers such as prostate, breast and ovarian cancer.

- Peutz-Jeghers caused by ***STK11* mutations.**
- Lynch syndrome caused by ***MLH1* and *MSH2* mutations.**
- Familial adenomatous polyposis caused by *APC* mutations.
- Familial atypical multiple-mole melanoma syndrome (FAMMM) caused by *CDK2NA* mutations.
- Hereditary pancreatitis caused by *PRSS1* and *SPINK1* mutations.
- Li-Fraumeni syndrome caused by *TP53* mutations.





Sporadic pancreatic cancer with germline mutations



- Interestingly, in about **3.9%–13.5% of patients** with apparently sporadic PDAC, **DDR gene mutations** can be detected in the germline, although negative family history of cancer (This mirrors an incomplete penetration, rather than a de novo mutation in the germline)

- *ATM serine/threonine kinase* is the most frequently mutated DDR gene in this group.

- Biallelic mutations in *ATM* cause a syndrome known as ataxia telangiectasia that predisposes to various cancers, including PDAC.

- *BRCA1/2* mutations are also frequent in this subgroup and have the highest prevalence (12.1%) in Ashkenazi Jews.

Table 2 Frequency of germline mutations in DNA damage repair and cell cycle control genes in sporadic pancreatic ductal adenocarcinoma and frequency of loss-of-function variants in gnomAD controls

Gene	Grant *et al*[53] (n=290)	Shindo *et al*[54] (n=854)	Hu *et al*[55] (n=2999)	Brand *et al*[56] (n=298)	Yurgelun *et al*[57] (n=289)	Mutation prevalence (%)	pLoF variants in gnomAD controls (%)
BRCA2	2	12	57	4	4	1.67	0.335
BRCA1	1	3	18	4	3	0.61	0.207
PALB2	n.a.	2	12	1	1	0.34	0.167
MSH6	1	n.a.	6	1	2	0.21	0.376
MLH1	1	2	4	n.a.	n.a.	0.15	0.066
MSH2	2	n.a.	1	n.a.	1	0.08	0.022
ATM	3	10	69	10	4	2.03	0.312
CDKN2A	–	1	9	1	2	0.27	0.006
TP53	1	1	6	1	1	0.21	0.006

Germline mutations data were analysed from five sporadic PDAC cohorts (4730 samples).
gnomAD, Genome Aggregation Database; LoF, loss-of-function; n.a., not applicable.

BRCAness revisited

- Over the past 20 years, there has been considerable progress in our understanding of the biological functions of the *BRCA1* and *BRCA2* cancer susceptibility genes.

- This has led to the development of new therapeutic approaches that target tumours with **loss-of-function mutations in either *BRCA1* or *BRCA2*** (PARP inhibitors, etc.)

- Tumors with 'BRCAness': **share molecular features of BRCA-mutant** tumors

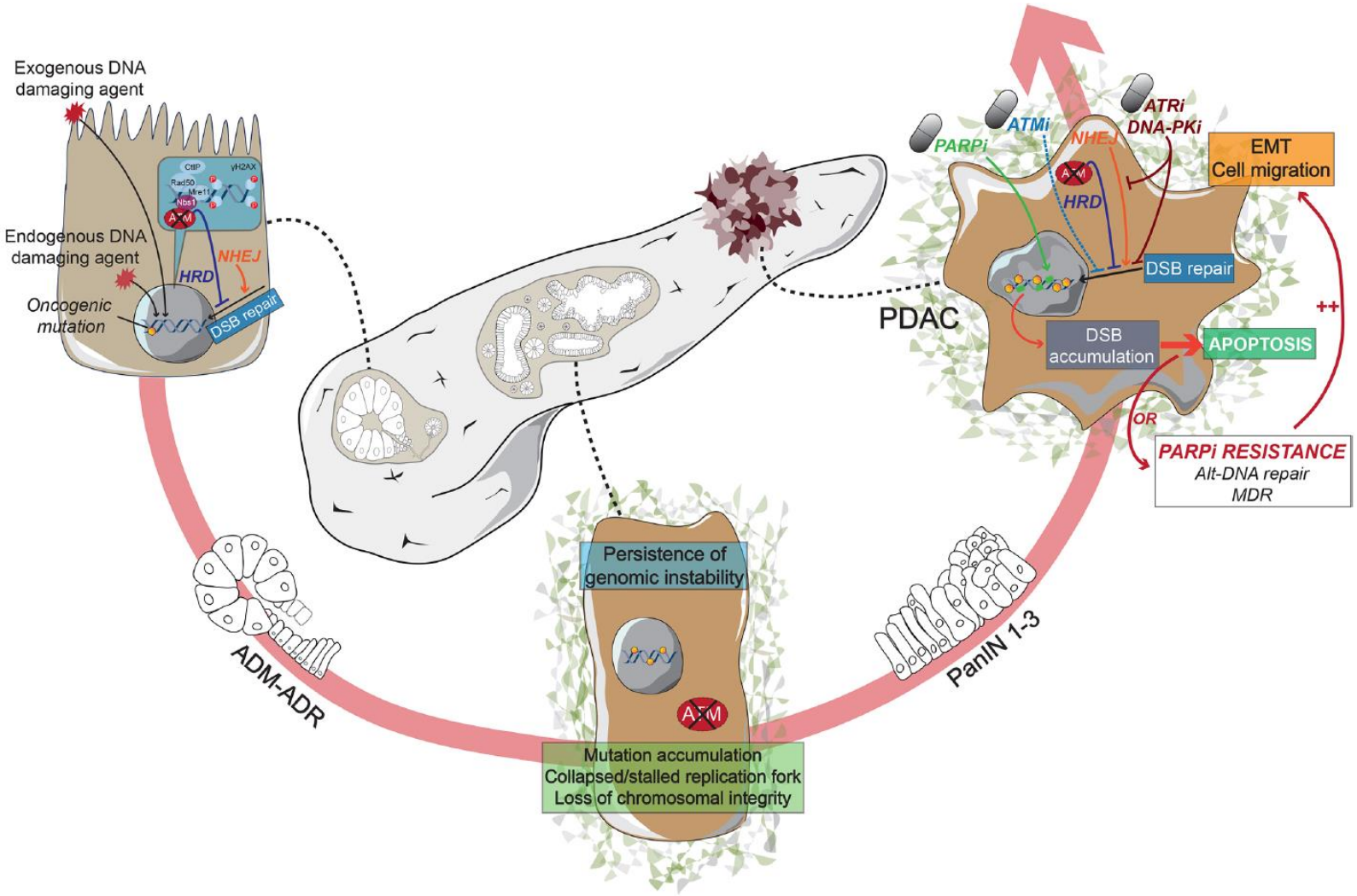
- BRCAness tumors may also respond to similar therapeutic approaches.

(Christopher J. Lord and Alan Ashworth . Nature Review Cancer, 2016)

Table 1 | **Cancer-associated alterations in BRCAness genes**

Gene	Tumour types with somatic alterations (mutations, gene deletions and promoter hypermethylation)	Tumour types and syndromes with germline mutations
ATM	T-PLL, breast cancer, GBM, ccRCC, lung adenocarcinoma, sarcoma, and prostate, gastric, bladder, colorectal, uterine and pancreatic cancer	Leukaemia, lymphoma, medulloblastoma, glioma and ataxia telangiectasia
ATR	Breast, colorectal, head and neck, gastric and uterine cancer	Oropharyngeal cancer and familial cutaneous telangiectasia and cancer syndrome
BAP1	ccRCC, cholangiosarcoma, liver cancer and uveal melanoma	Mesothelioma and uveal melanoma
BRCA1	TNBC, HGS-OvCa, lung cancer, prostate cancer, mCRPC and PDAC	TNBC, HGS-OvCa and PDAC
BRCA2	Breast cancer, HGS-OvCa, PDAC, prostate cancer, mCRPC, gastric, bladder and lung cancer, DLBCL and sarcoma	Breast cancer, HGS-OvCa, PDAC and leukaemia
CDK12	HGS-OvCa?, mCRPC and gastric cancer	
CHEK2 (*CHK2*)	Uterine cancer and HGS-OvCa	Breast cancer
FANCA	HGS-OvCa and lung adenocarcinoma	AML, leukaemia and Fanconi anaemia
FANCC		AML, leukaemia and Fanconi anaemia
FANCD2	ccRCC	AML, leukaemia and Fanconi anaemia
FANCE		AML, leukaemia and Fanconi anaemia
FANCF		AML, leukaemia and Fanconi anaemia
PALB2	Gastric cancer and HGS-OvCa	Wilms tumour, medulloblastoma, AML, Fanconi anaemia, breast cancer, PDAC and HGS-OvCa
NBS1 (*NBN*)	Gastric and uterine cancer	
WRN	HGS-OvCa, mCRPC, lung adenocarcinoma and uterine cancer	Werner syndrome
RAD51C	HGS-OvCa	Breast cancer and HGS-OvCa
RAD51D		Breast cancer and HGS-OvCa
MRE11A	Colorectal cancer	
CHEK1 (*CHK1*)	PDAC and sarcoma	
BLM		Bloom syndrome
RAD51B	HGS-OvCa	
BRIP1	HGS-OvCa	

Data are based on an analysis of data included in the cBIO database[101,102] and references described in the main text. AML, acute myeloid leukaemia; *ATM*, ataxia telangiectasia mutated; *ATR*, ataxia telangiectasia and Rad3-related; *BAP1*, BRCA1-associated protein 1; *BLM*, Bloom syndrome, RecQ helicase-like; *BRIP1*, BRCA1 interacting protein C-terminal helicase 1; ccRCC, clear cell renal cell carcinoma; *CDK12*, cyclin-dependent kinase 12; DLBCL, diffuse large B cell lymphoma; *FANC*, Fanconi anaemia complementation group; GBM, glioblastoma; HGS-OvCa, high-grade serous ovarian cancer; mCRPC, metastatic castration-resistant prostate cancer; *MRE11A*, meiotic recombination 11 homologue A; *NBS1*, Nijmegen breakage syndrome 1; PDAC, pancreatic ductal adenocarcinoma; *PALB2*, partner and localizer of BRCA2; TNBC, triple-negative breast cancer; T-PLL, T cell prolymphocytic leukaemia; *WRN*, Werner syndrome, RecQ helicase-like.



- Smart tailored use of synergistically druggable vulnerabilities within the DNA damage repair machinery could be exploited to hit HRD tumors **“hard and early”** and prevent further MDR acquisition, as eg, recently shown upon inhibition of PARP, ATR and DNA-PKcs.

Therapeutic interference with the DDR in pancreatic cancer: Platinum analogues

- Platinum agents **can crosslink purine bases on the DNA**, thereby interrupting DNA transcription and stall replication which can consecutively lead to **DSBs**.

- The repair of interstrand crosslinks and consequent DSB uses the **FA pathway, translesion synthesis and HR**, making these agents interesting for patients with an ***HRDness (BRCAness)*** **phenotype**.

- Structural differences in platinum agents cause differences in DDR recognition as has been observed for cisplatin and oxaliplatin. These differences in recognition, excision and processing affect the cytotoxicity and activity of the individual platinum adducts.

- The response of **820 patients with PDAC** to a **platinum-based** regimen was recently evaluated in a large registry with a comprehensive genomic profiling program.
- ***HRDness*-causing germline or somatic mutations** were grouped into three categories:

(i) *BRCA1*/*BRCA2*/*PALB2*

(ii) *ATM*/*ATR*

(iii) FA core/MRN complex effectors.

- Overall, HR mutations were prevalent in 16.5% of patients.
- Patients with advanced **HR-defective (HRD)** PDAC had a **worse outcome** than patients with **HR-proficient (HRP)** PDAC if they were not treated with platinum, underpinning their overall **more aggressive tumour biology** and particular platinum susceptibility (mOS: HRD 0.76 years vs HRP 1.13 years, p=0.1535).

- In line **platinum treatment substantially prolonged mOS** in the HRD patients (n=53) compared with the HRP patients (n=258) (mOS: HRD 2.37 years vs HRP 1.45 years; p=0.000072; HR, 0.44, 95% CI 0.29 to 0.66).

- Golan *et al* collected data from 43 patients with advanced *BRCA1/2*-mutated PDAC, showing a significant **survival benefit for platinum treatment** compared with platinum-naïve patients (22 vs 9 months; $p<0.039$).84

- Platinum agents are assoiciated with longer survival in HRD (Homologous recombination deficient) compared with HRP (homologous recombination proficient) patients

Table 3 Retrospective studies on platinum-based chemotherapy in patients with advanced homologous recombination-deficient PDAC

Mutations	Design	Therapy line	Therapy	Number of pts.	mPFS	mOS	Efficacy	Reference
Group 1: *BRCA1/2*, *PALB2* (n=38) **Group 2**: *ATM/ATR/ATRX* (n=22) **Group 3**: *BAP1*, *BARD1*, *BRIP1*, *CHEK1/2*, *RAD50/51/51B*, *FANCA/C/D2/E/F/G/L* (n=12)	Retrospective	Various	Platinum-containing any therapy line Platinum-naïve	Total: 443 HRD: 72 HRP: 371	First-line: HRD+platinum (n=53): 13.7 m HRP+platinum (n=268): 8.2 m Second-line: HRD+platinum (n=28): 8.6 m HRP+platinum (n=103): 4.1 m	HRD+platinum (n=53): 2.37 y HRD-platinum (n=19): 0.76 y HRP+platinum (n=258): 1.45 y HRP-platinum (n=113): 1.13 y	HRD+platinum: p=0.001	83
BRCA1 *BRCA2*	Retrospective	First-line	Platinum-containing any therapy line Platinum-naïve	Total: 43	n.a.	HRD+platinum (n=22): 22 m HRD-platinum (n=21): 9 m	p=0.0389	84
BRCA1 (n=7) *BRCA2* (n=5) *PALB2* (n=3) *MSH2* (n=1) *FANCF* (n=1)	Retrospective	First-line	FOLFIRINOX	Total: 36 HRD: 12	n.a.	HRD: 14 m HRP: 5 m	HRD vs HRP: p=0.08	126
BRCA2 (n=10) *ATM* (n=8) *BRCA1* (n=2) *CHEK2* (n=2) *ATR* (n=1) *PALB2* (n=1)	Retrospective	Various	Platinum-containing any therapy line	Total: 28 HRD: 13	HRD+platinum: 20.8 m HRP+platinum : 1.7 m	n.a.	p=0.049	127
gBRCA2 (n=3) *BRCA2* (n=2) *BRCA1* (n=1) *POLE* (n *gRAD51C* (n=1) *gMUTYH* (n=1)	Retrospective	First-line	FOLFIRINOX	Total: 40	HRD+platinum: 18.5 m HRP+platinum: 6.9 m	11.5 m	mPFS: p=0.003	128
BRCA1 (n=5) *BRCA2* (n=17) *PALB2* (n=4)	Retrospective	Various	Platinum-containing any therapy line	Total: 78 HRD: 26 HRP: 52	HRD+platinum: 10.1 m HRP+platinum: 6.9 m	HRD+platinum: 24.6 m HRP+platinum: 18.8 m	mPFS: p=0.0068 mOS: p=0.0467	129

FOLFIRINOX, folinic acid, fluouracil, irinotecan, oxaliplatin; HRD, homologous recombination-deficient; HRP, homologous recombination-proficient; m, month; mOS, median overall survival; mPFS, median progression-free survival; n.a., not applicable; pts., patients; y, year.

- FOLFIRINOX is the only platinum-containing treatment for patients with advanced PDAC established in a positive phase III trial.
- However, only about 25% of patients are eligible for FOLFIRINOX, due to its high level of adverse effects.

Table 4 Retrospective studies on platinum-based chemotherapy in patients with resected homologous recombination-deficient PDAC

Disease setting	Mutations	Design	Therapy line	Therapy	Number of pts.	mDFS	mOS	Reference
Resected	**Group 1**: *BRCA1/2* or *PALB2* **Group 2**: *ATM/ATR/ATRX* **Group 3**: *BAP1*, *BARD1*, *BRIP1*, *CHEK1/2*, *RAD50/51/51B* or *FANCA/CID2/E/F/G/L*	Retrospective	Adjuvant	Platinum-containing Platinum-naïve	Total: 377 HRD: 63 HRP: 314	n.a.	HRD+platinum (n=49): 4.53 y HRD-platinum (n=14): 1.8 y HRP+platinum (n=220): 2.96 y HRP-platinum (n=94): 3.09 y	83
Resected	*BRCA1* *BRCA2*	Retrospective	n.a.	n.a.	Total: 20	13 m	n.a.	84
Resected	*BRCA1* *BRCA2* *PALB2*	Retrospective	Various	Platinum-containing Platinum-naïve	Total: 96 HRD: 32 HRP: 64	HRD+perioperative platinum: 19.9 m HRP+perioperative platinum: 11.7 m	HRD+perioperative platinum: not reached HRP+perioperative platinum: 23.1 m	89
Resected	*BRCA1 (n=4)* *gBRCA2 (n=18)*	Retrospective	Adjuvant	Platinum-containing Platinum-naïve	Total: 127 HRD: 22 HRP: 105		HRD+platinum (n=10): 31 m HRD-platinum (n=8): 17.8 m HRP+platinum: 33 m HRP-platinum: 28 m	130

HRD, homologous recombination-deficient; HRP, homologous recombination-proficient; m, month; n.a., not applicable; pts., patients; y, year.

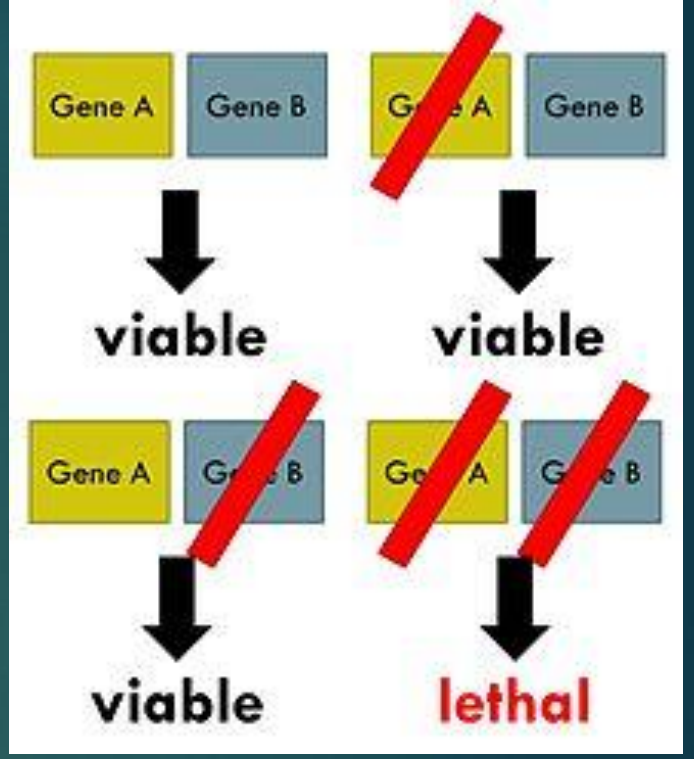
PARP inhibitors

PARP1 was originally described in SSB repair through base excision but is now well-accepted as also participating in:

- DSB repair (HR)
- Stalled replication fork sensing
- Recruitment of DNA repair proteins at DNA damage sites

- As PARP1/2 are crucial enzymes during HR-mediated DSB repair in most cancer cells, targeting these enzymes in HRD tumors seems to be an elegant method (the principle of **synthetic lethality**).

Synthetic lethality



- Two genes or proteins are synthetic lethal when inactivation of either one is compatible with cell viability but inactivation of both genes or proteins results in cell death.

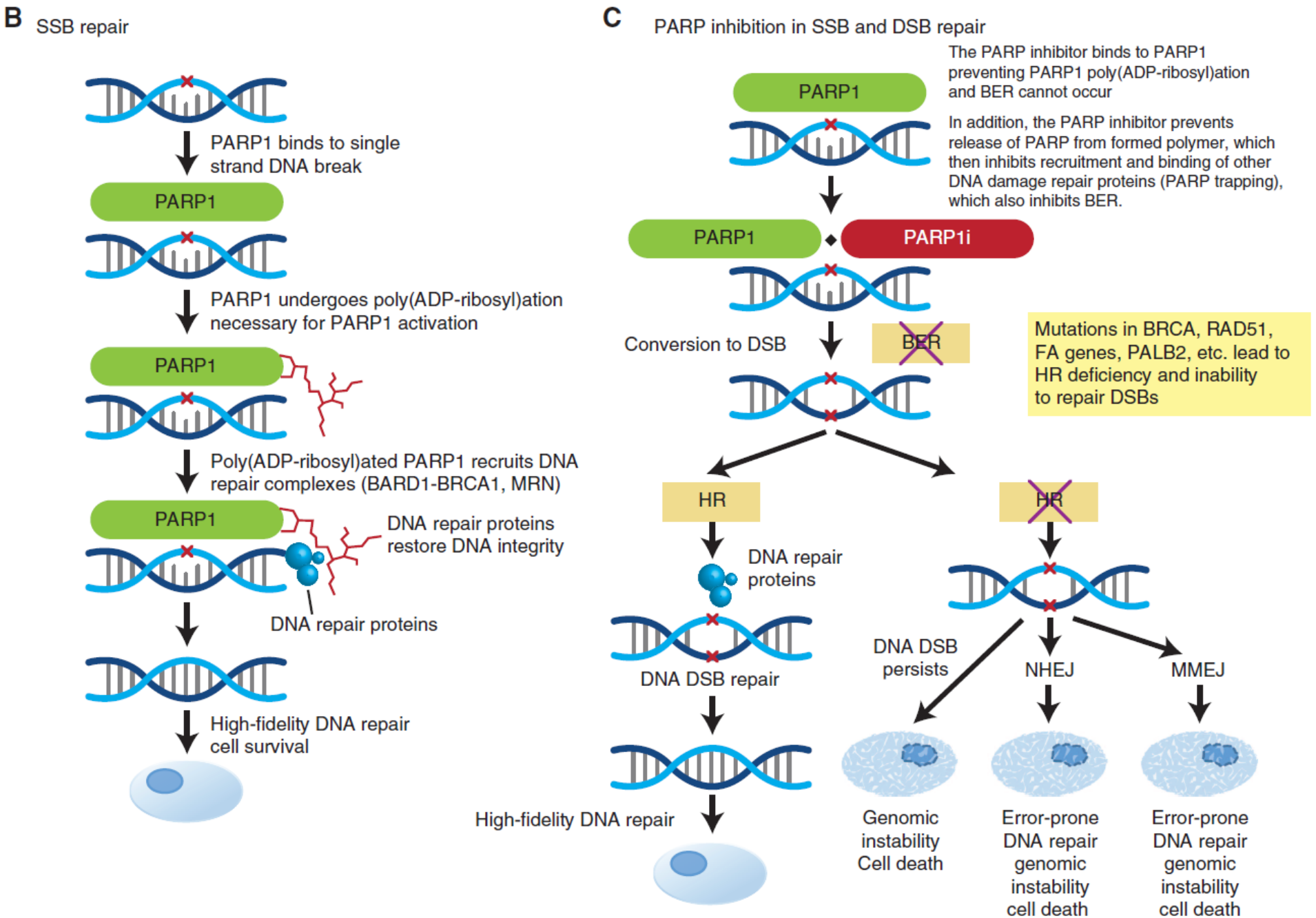

B
SSB repair
PARP1 binds to single strand DNA break
PARP1
PARP1 undergoes poly(ADP-ribosyl)ation necessary for PARP1 activation
PARP1
Poly(ADP-ribosyl)ated PARP1 recruits DNA repair complexes (BARD1-BRCA1, MRN)
PARP1
DNA repair proteins restore DNA integrity
DNA repair proteins
High-fidelity DNA repair cell survival
C
PARP inhibition in SSB and DSB repair
The PARP inhibitor binds to PARP1 preventing PARP1 poly(ADP-ribosyl)ation and BER cannot occur
In addition, the PARP inhibitor prevents release of PARP from formed polymer, which then inhibits recruitment and binding of other DNA damage repair proteins (PARP trapping), which also inhibits BER.
PARP1
PARP1
PARP1i
Conversion to DSB
BER
Mutations in BRCA, RAD51, FA genes, PALB2, etc. lead to HR deficiency and inability to repair DSBs
HR
HR
DNA repair proteins
DNA DSB repair
High-fidelity DNA repair
DNA DSB persists
NHEJ
MMEJ
Genomic instability Cell death
Error-prone DNA repair genomic instability cell death
Error-prone DNA repair genomic instability cell death

Table 5 Clinical trials with PARP inhibitors on patients with advanced PDAC

Mutations	Design	Therapy line	Therapy	Number of pts.	mPFS	mOS	Efficacy	Reference	Abstract-based publication
gBRCA1/2	Phase I	First-line	Cisplatin Gemcitabine Veliparib	Total: 17 HRD: 9 HRP: 7 Unknown: 1	n.a.	HRD: 23.3 m HRP: 11 m	n.a.	[102]	No
gBRCA1 (n=12) *gBRCA2* (n=35) *gPALB2* (n=3)	Phase II	First-line	Cisplatin Gemcitabine A. +Veliparib B. – Veliparib	Total: 50 A. 27 B. 23	A. 10.1 m B. 9.7 m	A. 15.5 m B. 16.4 m	mPFS: p=0.73 mOS: p=0.6	[86]	Yes
gBRCA1/2 (n=16) *sBRCA1/2* (n=3)	Phase II	≥Second-line	Rucaparib	Total: 19	n.a.*	n.a.*	n.a.*	[95]	No
gBRCA1 (n=5) *gBRCA2* (n=11)	Phase II	≥Second-line	Veliparib	Total: 16 HRD: 9 HRP: 7	1.7 m	3.1 m	n.a.	[97]	No
gBRCA1 (n=5) *gBRCA2* (n=17) *gBRCA1*/2 (n=1)	Phase II	≥Second-line	Olaparib	Total: 23	4.6 m	9.8 m	n.a.	[96]	No
DDR mutation (eg, *BRCA1/2, PALB2, ATM*)	Phase I/II	Various	mFOLFOX Veliparib	Total: 57 HRD: 16 HRP 41	HRD: 7.2 m HRP: 3.5 m	HRD: 11.1 m HRP: 6.8 m	n.a.	[99]	Yes
gBRCA1 (n=3) *gBRCA2* (n=13) *gPALB2* (n=2) *sBRCA2* (n=1)	Phase II	First-line maintenance after platinum induction	Rucaparib	Total: 19	9.1 m	n.a.	n.a.	[101]	Yes
gBRCA1 (n=45) *gBRCA2* (n=108) *gBRCA1/2* (n=1)	Phase III	First-line maintenance after platinum induction	A. Olaparib B. Placebo	Total: 154 A. 92 B. 62	A. 7.4 m B. 3.8 m	A. 18.9 m B. 18.1 m	mPFS: p=0.004 mOS: p=0.91	[100]	No

*As prespecified in the protocol, enrolment was stopped because of an insufficient response rate among the first 15 patients.
FOLFOX, folinic acid, fluouracil, oxaliplatin
; HRD, homologous recombination-deficient; HRP, homologous recombination-proficient; m, month; mOS, median overall survival; mPFS, median progression-free survival; n.a., not applicable; pts., patients.

- While the efficacy of PARP1 inhibitors is established in BRCA-associated cancer types (**Ovary and Breast**), their specific role in PDAC has only recently been demonstrated.

- Studies without **genetic stratification** did not show a meaningful benefit.

PARP inhibitors represent the first targeted therapy to show efficacy in a subpopulation of patients with advanced PDAC in a phase III clinical trial.

- The most promising evidence of PARP inhibition in advanced PDAC was published recently from the **phase III POLO trial**:

Patients with germline ***BRCA1/BRCA2*-mutated advanced PDAC** without progress to platinum-based first-line chemotherapy (≥16 weeks) received either **olaparib** as **maintenance treatment** or placebo. Olaparib nearly **doubled the median PFS** compared with placebo (7.4 vs 3.8 months; p=0.004), while OS remained similar in both arms (18.9 vs 18.1 months).

- The interim analysis of a single-arm **phase II trial with rucaparib** as maintenance therapy after platinum-based induction in the case of any pathogenic ***BRCA1*, *BRCA2* or *PALB2* mutation** also **demonstrated an ORR of 37%** with minimal toxicity in 19 patients.

Table 6 Ongoing clinical trials of therapies affecting DNA damage repair pathways that include patients with pancreatic cancer

Trial	Design	Patients	Treatment	Status
NCT02950064	Phase I trial, open-label	*BRCA*-mutated pancreatic, ovarian, triple-negative breast or prostate cancers or solid tumours with other DDR mutations	BTP-114, a novel platinum product	Active, not recruiting
NCT01489865	Phase I/II trial, single arm	PDAC with *BRCA* mutation or personal or family history of hereditary breast or ovarian cancer	ABT-888 (a new PARP inhibitor) with mFOLFOX6	Active, not recruiting
NCT01585805	Phase II, open-label, randomised	Metastatic or locally advanced *BRCA*-mutated PDAC	Veliparib alone vs gemcitabine/cisplatin vs veliparib and gemcitabine/cisplatin	Active, not recruiting
NCT02498613	Phase II trial, single arm	Advanced solid tumours with failure to at least one line of standard systemic treatment	Olaparib+cediranib (anti-VEGF)	Recruiting
NCT03162627	Phase I/II	Refractory advanced cancer	Olaparib+selumetinib (anti-MEK)	Recruiting
NCT03404960	Phase Ib/II, open-label, randomised	Metastatic or locally advanced PDAC, with 16 weeks of platinum-based treatment without progression	Niraparib+nivolumab or ipilimumab	Recruiting
NCT02630199	Phase I, open-label	Advanced, refractory cancer	Paclitaxel and AZD6738 (ATR inhibitor)	Recruiting
NCT02223923	Phase I, single group	Solid tumour refractory to conventional treatment	AZD6738 (ATR inhibitor) with radiotherapy	Recruiting
NCT03669601	Phase I, non-randomised	Locally advanced or metastatic solid tumour that has progressed on standard therapy	AZD6738 and gemcitabine	Recruiting
NCT02264678	Phase I, two-part, open-label	Solid malignant tumour that is not considered appropriate for further standard treatment	AZD6738 with different drugs, including carboplatin and olaparib	Recruiting
NCT03682289	Phase II	Locally advanced or metastatic solid tumour malignancy, including any pancreatic cancers	AZD6738 alone or in combination with olaparib	Recruiting
NCT02576444	Phase II	Metastatic progressive cancer	Patients with HRD will be treated with olaparib and AZD6738	Active, not recruiting
NCT02723864	Phase I, single group	Metastatic cancer with previous fail to survival prolonging therapies	Veliparib+cisplatin+VX-970 (ATR inhibitor)	Recruiting
NCT02595931	Phase I, single group	Metastatic or unresectable malignancy that is refractory to standard therapy or for which no standard therapy exists and where irinotecan is deemed a reasonable treatment option	VX-970 and irinotecan	Recruiting
NCT02588105	Phase I	Locally advanced/metastatic cancer that is refractory or resistant to standard therapy, or have no effective standard	AZD0156+olaparib, AZD0156+irinotecan/ FOLFIRI	Active, not recruiting
NCT02194829	Phase I	A phase I and randomised phase II study of nab-paclitaxel/gemcitabine with or without AZD1775 for treatment of metastatic adenocarcinoma of the pancreas	Nab-paclitaxel/gemcitabine Nab-paclitaxel/gemcitabine+AZD1775	Active, not recruiting

FOLFIRI, folinic acid, fluouracil, irinotecan
; FOLFOX, folinic acid, fluouracil, oxaliplatin
; nab, nanosized albumin-bound; PDAC, pancreatic ductal adenocarcinoma

Which DDR gene assigns sensitivity to PARP inhibitors (*HRDness*-causing mutations)

- Most of the data collected are on *BRCA1/2* mutations and data on non-*BRCA* mutations are purely preclinical.

Inducing homologous recombination deficiency and future directions

- New treatment modalities aim at **inducing or maintaining an HRD state independent of the mutational make-up** of a given tumor. This could increase the efficacy of DDR-interfering agents and **increase the patient cohort**.

- **Hypoxia** might impair HR, for instance, by silencing the *BRCA1* promoter or downregulation of RAD51/52.

- Anti-angiogenic agents (AA) counteract hypoxia-induced angiogenesis and, in turn, lower blood perfusion and thereby oxygen tension.

- **The phosphoinositide 3-kinase (PI3K)-Akt-mTor** pathway seems relevant in maintaining HR, thereby blocking PI3K sensitizing to PARP inhibitors via BRCA1/2 downregulation in triple-negative breast cancer cells.112

- **MEK inhibition** causes repression of both HR and NHEJ repair activity in PDAC cells.

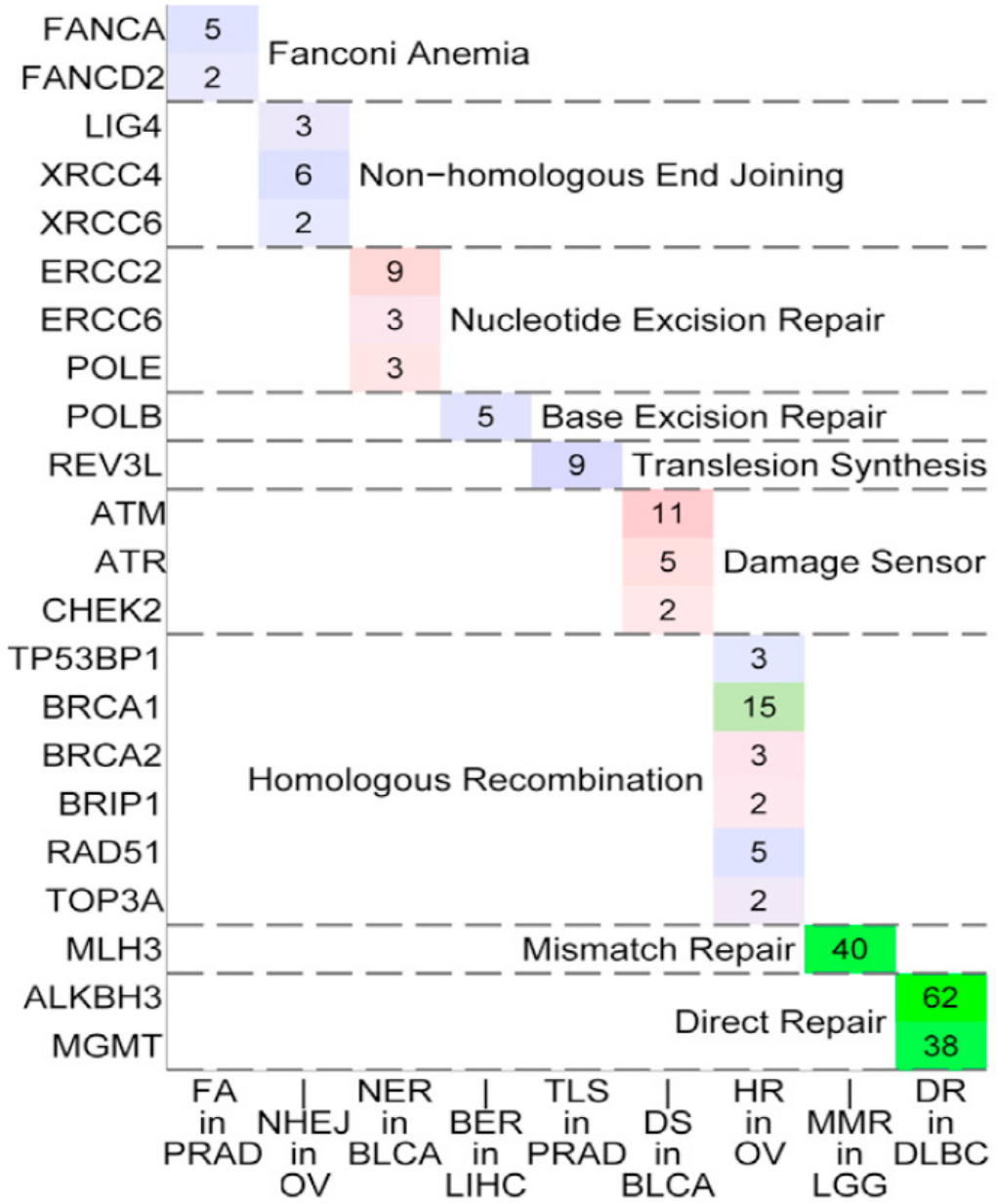
- Inhibition of the nuclear serine/threonine kinase **WEE1 can induce *HRDness* in PDAC**. The DNA damage checkpoint WEE1 impairs unscheduled replication origin firing and thus prevents nucleotide pool depletion and replication stress, ultimately resulting in DSBs.

- Molecules mimicking *BRCA2* mutations that **disrupt the RAD51-BRCA2 complex**.

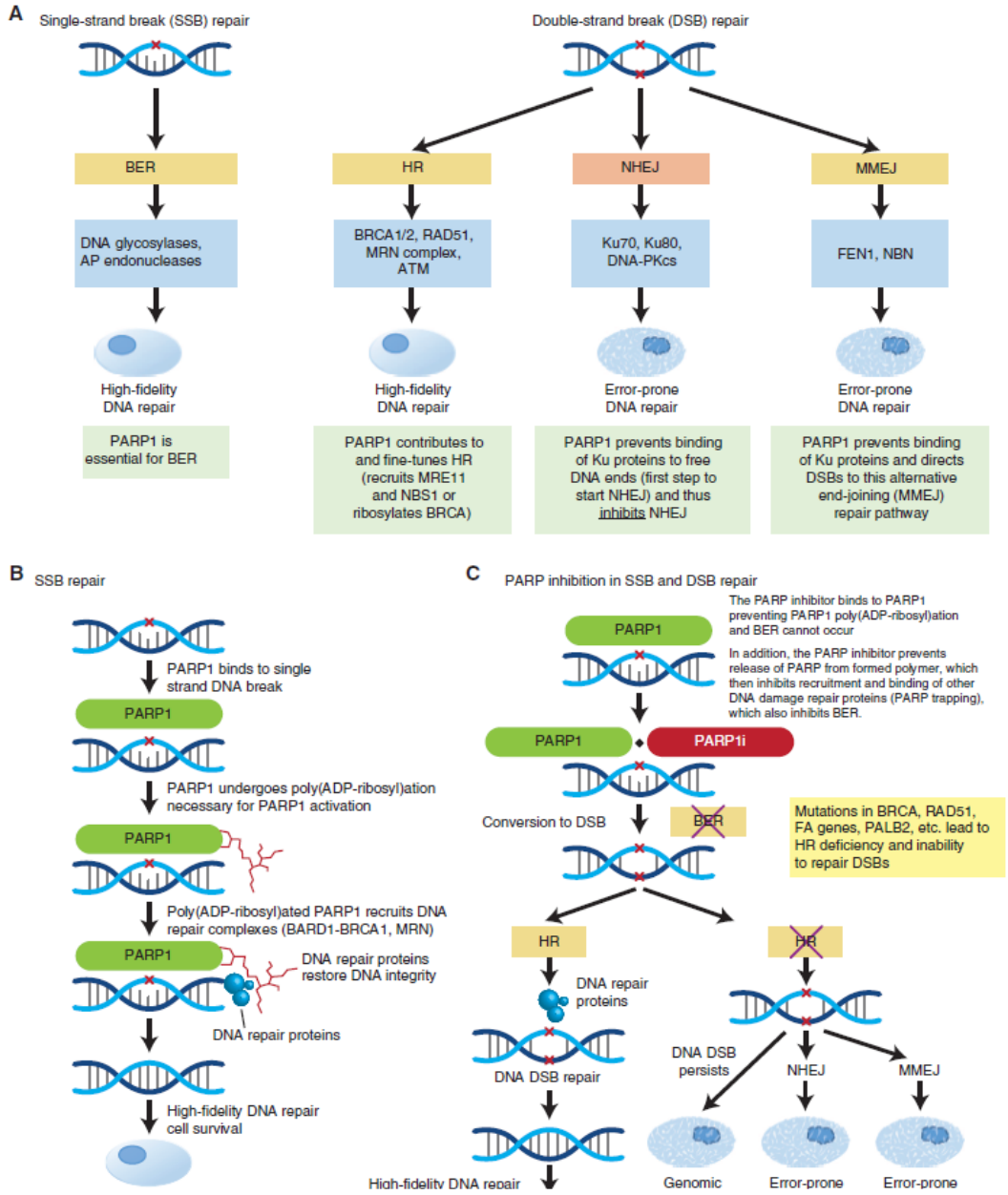
- **ATM inhibitors** (AZD0156, KU60019, AZD1390), which directly prevent downstream ATM phosphorylation, can sensitize tumour cells to DDR interfering strategies.

CONCLUSIONS

- Impaired DNA damage repair is an important characteristic of PDAC.
- **Loss-of- function mutations** in genes involved in DNA damage repair justify therapeutic targeting with a **platinum agent** in the polychemotherapy and/or **PARP inhibitors.**
- At least for BRCA-associated cancer types (pancreatic, prostate, breast or ovarian cancer), *BRCA1/2* mutations remain clinically relevant.
- **Maintenance with PARP inhibitors** after induction chemotherapy is a promising approach that is likely to be incorporated in clinical practice for patients with a *BRCA1/2* germline mutation.
- With the ultimate goal of hitting PDACs **'hard and early'** and avoiding the emergence of **resistant clones**, more studies are urgently needed to demonstrate the efficacy of **combinatorial approaches** to DDR inhibition and to identify the best combinations.
- Potential '***HRDness* inducers'** creating **artificial vulnerabilities**, in combination with DNA-damaging drugs such as PARP inhibitors and/or alternative DDR inhibitors, could provide a significant benefit for a **larger group of patients** with PDAC.


FANCA
FANCD2
5
2
Fanconi Anemia
LIG4
XRCC4
XRCC6
3
6
2
Non−homologous End Joining
ERCC2
ERCC6
POLE
9
3
3
Nucleotide Excision Repair
POLB
5
Base Excision Repair
REV3L
9
Translesion Synthesis
ATM
ATR
CHEK2
11
5
2
Damage Sensor
TP53BP1
BRCA1
BRCA2
BRIP1
RAD51
TOP3A
3
15
3
2
5
2
Homologous Recombination
MLH3
Mismatch Repair
40
ALKBH3
MGMT
62
38
Direct Repair
FA in PRAD
NHEJ in OV
NER in BLCA
BER in LIHC
TLS in PRAD
DS in BLCA
HR in OV
MMR in LGG
DR in DLBC

Konecny


A
Single-strand break (SSB) repair
Double-strand break (DSB) repair
BER
HR
NHEJ
MMEJ
DNA glycosylases, AP endonucleases
BRCA1/2, RAD51, MRN complex, ATM
Ku70, Ku80, DNA-PKcs
FEN1, NBN
High-fidelity DNA repair
High-fidelity DNA repair
Error-prone DNA repair
Error-prone DNA repair
PARP1 is essential for BER
PARP1 contributes to and fine-tunes HR (recruits MRE11 and NBS1 or ribosylates BRCA)
PARP1 prevents binding of Ku proteins to free DNA ends (first step to start NHEJ) and thus inhibits NHEJ
PARP1 prevents binding of Ku proteins and directs DSBs to this alternative end-joining (MMEJ) repair pathway
B
SSB repair
PARP1 binds to single strand DNA break
PARP1
PARP1 undergoes poly(ADP-ribosyl)ation necessary for PARP1 activation
PARP1
Poly(ADP-ribosyl)ated PARP1 recruits DNA repair complexes (BARD1-BRCA1, MRN)
PARP1
DNA repair proteins restore DNA integrity
DNA repair proteins
High-fidelity DNA repair cell survival
C
PARP inhibition in SSB and DSB repair
The PARP inhibitor binds to PARP1 preventing PARP1 poly(ADP-ribosyl)ation and BER cannot occur
In addition, the PARP inhibitor prevents release of PARP from formed polymer, which then inhibits recruitment and binding of other DNA damage repair proteins (PARP trapping), which also inhibits BER.
PARP1
PARP1
PARP1i
Conversion to DSB
BER
Mutations in BRCA, RAD51, FA genes, PALB2, etc. lead to HR deficiency and inability to repair DSBs
HR
HR
DNA repair proteins
DNA DSB repair
DNA DSB persists
NHEJ
MMEJ
High-fidelity DNA repair
Genomic
Error-prone
Error-prone