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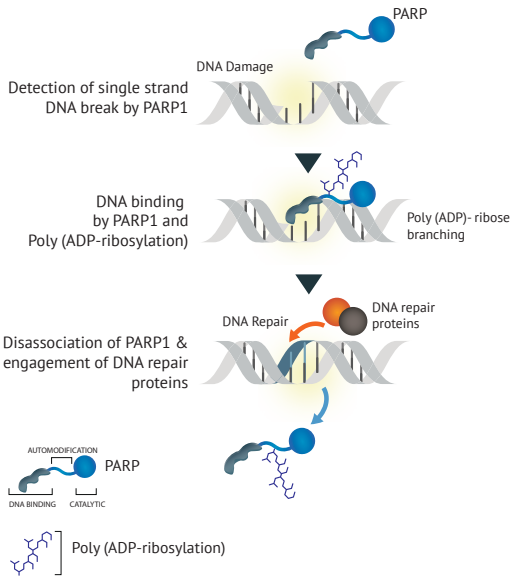
PARPi BLUEPRINT

Document purpose

To provide a brief introduction and a reference guide to key aspects of PARP inhibition (PARPi) and its role in cancer therapy. This BluePrint is intended for the broader professional oncology community, including oncologists, surgeons, radiation oncologists, research nurses etc. - involved in treating patients with cancer. It is recommended to use this BluePrint together with the accompanying BluePrint on DDR.

The PARP family are key mediators of DNA repair

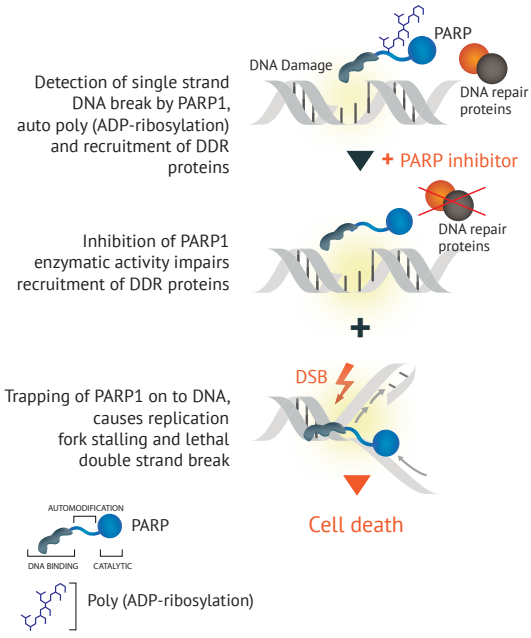
The PARP family consists of 17 different enzymes that play key roles in multiple biological functions including DNA repair and replication fork protection.



At the molecular level, DNA damage (break) is detected by **PARP1** through its DNA binding domain, triggering its activation (formation of homodimer) and cleavage of nicotinamide adenine dinucleotide (NAD+) generating nicotinamide and ADP-ribose. Successive addition of ADP-ribose units leads to the formation of long and branched chains of poly (ADP-ribose) (PAR), covalently attached to acceptor proteins, including histones and other DNA repair proteins, resulting in PAR polymers adjacent to the DNA breaks. These highly negatively charged polymers form a scaffold that recruits critical proteins for DNA repair.

PARP Inhibition in treatment of cancer

Inhibition of PARP and the concept of synthetic lethality (see accompanying DDR BluePrint) have been successfully exploited in anticancer drug development and at present, three PARP-1/2 inhibitors (olaparib, rucaparib and niraparib) have received marketing authorization.



PARP inhibitors act not only by inhibiting the enzymatic activity but also by trapping PARP on DNA, which is key as it presents a physical obstacle to the replication machinery. To resolve the PARP-DNA interaction Homologous Recombination Repair (HRR) is necessary. Therefore, in HRR-deficient cancer cells, trapped PARP results in replication fork collapse and finally cell death.

Three PARP Inhibitors are currently approved for clinical use in ovarian cancer

In ovarian cancer, PARPi are used in the maintenance or monotherapy setting for patients with germline or somatic BRCA mutations. In patients with wild type BRCA tumours, maintenance with PARPi is a treatment option for disease that is platinum sensitive.

PARPi	Approval Indication
Olaparib* (**Lynparza™**, AstraZeneca)	• EMA (Dec2014): As monotherapy for maintenance treatment of platinum-sensitive relapsed BRCA-mutated (germline and/or somatic) high-grade serous ovarian cancer patients who are in response (complete response or partial response) to platinum-based chemotherapy. • FDA (Dec2014): As monotherapy for the treatment of germline BRCA1/2 mutated (as detected by an FDA-approved test) advanced ovarian cancer patients that have been treated with three or more prior lines of chemotherapy (capsule formulation). • FDA (Aug2017): As maintenance treatment of adult patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer, who are in a complete or partial response to platinum-based chemotherapy (tablet formulation).
Rucaparib (**Rubraca™**, Clovis Oncology)	• FDA (Dec2016): As monotherapy for the treatment of patients with deleterious BRCA mutation (germline and/or somatic) associated with advanced ovarian cancer who have been treated with two or more chemotherapies (patient selection using an FDA-approved companion diagnostic (CDx) for Rubraca™).
Niraparib (**Zejula™**, Tesaro)	• FDA (Mar2017): As monotherapy for maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer, whose tumours have a complete or partial response to platinum-based chemotherapy. • EMA (Sept2017): As monotherapy for the maintenance treatment of adult patients with platinum-sensitive relapsed high grade serous epithelial ovarian, fallopian tube, or primary peritoneal cancer who are in response (complete or partial) to platinum-based chemotherapy.

** Following completion of this PARPi BluePrint document, on January 12th 2018, AstraZeneca and Merck announced that the US Food and Drug Administration (FDA) approved LYNPARZA® (olaparib), for use in patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm), human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who have been previously treated with chemotherapy in the neoadjuvant, adjuvant or metastatic setting. Patients with hormone receptor positive (HR+) breast cancer should have been treated with a prior endocrine therapy or be considered inappropriate for endocrine therapy. Patients are selected for therapy based on an FDA-approved companion diagnostic for LYNPARZA.*

Efficacy of PARP Inhibitors

In advanced ovarian cancer patients, all three approved products display similar efficacy which in the **maintenance setting** depends on the genetic background of the patient - germline (gBRCA1/BRCA2) mutation carrier and/or tumour, somatic (sBRCA1/BRCA2) mutation carrier whereas for **monotherapy** on the number of previous lines of treatment received.

Olaparib - maintenance (Study 19): Platinum-sensitive, relapsed, high-grade serous[1]	
OS vs placebo - all patients	29.8 (26.9-35.7) vs 27.8 (24.9-33.7); HR 0.73 (95%CI 0.55-0.96) p=0.025
OS vs placebo - BRCA mutation	34.9 (29.2-54.6) vs 30.2 (23.1-40.7); HR 0.62 (95%CI 0.41-0.94) p=0.025
OS vs placebo - BRCA WT	24.5 (19.8-35.0) vs 26.6 (23.1-32.5); HR 0.83 (95%CI 0.55-1.24) p=0.37

Olaparib - maintenance (SOLO2): Platinum sensitive, relapsed, g BRCA1/2 mutations[2]	
PFS vs placebo	19.1 (16.3-25.7) vs 5.5 (5.2-5.8); HR 0.30 (95%CI 0.22-0.41) p<0.0001
TTFST or Death	27.9 (22.6-NC) vs 7.1 (6.3-8.3); HR 0.28 (95%CI 0.21-0.38) p<0.0001
TTSP or Death	NR (24.1-NC) vs 18.4 (15.4-22.8); HR 0.50 (95%CI 0.34-0.72) p<0.0002
TSST or Death	Not reached (NC) vs 18.2 (15.0-20.5); HR 0.37 (95%CI 0.26-0.53) p<0.0001

Niraparib - maintenance (NOVA): Platinum-sensitive, recurrent[3]	
PFS vs placebo - gBRCA	21.0 vs 5.5; HR 0.27 (95% CI 0.17-0.41) p<0.001
PFS vs placebo - Non gBRCA	9.3 vs 3.9; HR 0.45 (95% CI 0.34-0.61) p<0.001
PFS vs placebo – HRD+ve/Non-gBRCA	12.9 vs 3.8; HR 0.38 (95% CI 0.24-0.59) p<0.001
TFST vs placebo - gBRCA	21.0 (17.5–NR) vs 8.4 (6.6–10.6); HR 0.31 (95% CI 0.21–0.48) p<0.001
TFST vs placebo - Non gBRCA	11.8 (9.7–13.1) vs 7.2 (5.7–8.5); HR 0.55 (95% CI 0.41–0.72) p<0.001
PFS2 vs placebo - gBRCA	25.8 (20.3–NR) vs 19.5 (13.3–NR); HR 0.48 (95% CI 0.28–0.82) p = 0.006
PFS2 vs placebo - Non gBRCA	18.6 (16.2–21.7) vs 15.6 (13.2–20.9); HR 0.69 (95% CI 0.49–0.96) p = 0.03

Olaparib – monotherapy (Study 42): gBRCA1/2 mutations, after ≥3 lines of previous therapy[4]	
PFS - all patients	6.7 (5.5-7.6)
PFS - platinum sensitive	9.4 (6.7-11.4)
PFS - platinum resistant	5.5 (4.2-6.7)

Rucaparib – monotherapy (ARIEL 2): Relapsed, platinum-sensitive high-grade, after ≥3 lines of previous therapy[5]	
PFS - g/s BRCA mutation	12.8 (9.0-14.7); HR vs BRCA WT & LOH Low = 0.27, 95% CI 0.16–0.44, p<0.0001)
PFS - BRCA WT & LOH High	5.7 (5.3-7.6); HR vs BRCA WT & LOH Low = 0.62, 95% CI 0.42–0.90, p=0.011
PFS - BRCA WT & LOH Low	5.2 (3.6-5.5)

Rucaparib – maintenance (ARIEL 3): Relapsed, platinum-sensitive high-grade, after ≥2 lines of previous therapy[6]	
PFS vs control – g/s BRCA mutation	16.6 (13.4-22.9) vs 5.4 (3.4-6.7); HR 0.23 (95%CI 0.16-0.34), p<0.0001
PFS vs control – HRD deficient	13.6 (10.9-16.2) vs 5.4 (5.1-5.6); HR 0.32, (95% CI 0.24–0.42), p<0.0001
PFS vs control – LOH High	9.7 (7.9-13.1) vs 5.4 (4.1-5.7); HR 0.44, (95% CI 0.29–0.66), p<0.0001
PFS vs control – LOH Low	6.7 (5.4-9.1) vs 5.4 (5.3-7.4); HR 0.58, (95% CI 0.40–0.85), p=0.0049

Unless otherwise indicated all data is in months (95% CI).
g/s: germline or somatic mutations, LOH: loss of heterozygosity, NC: Non calculable, NR: Not reached, OS: Overall Survival, PFS: Progression Free Survival, PFS2: Progression Free Survival 2, TFST: Time to First Subsequent Therapy, TTSP: Time to Second Progression, TSST: Time to Second Subsequent Therapy, WT: wild type (see also Glossary)
[1] Ledermann et al., Lancet Oncol 2016;17:1579-89.; [2] Pujade-Lauraine et al., Lancet Oncol 2017; 18: 1274–1284; [3] Mirza et al., New Engl J Med 2016; 375(22):2154-2164.; [4] Domchek et al., GynecolOncol 2016; 140(2):199-203.; [5] Swisher et al., Lancet Oncol 2016;18(1):75-87; [6] Coleman et al., Lancet 2017; 390(10106):1949-1961.

Safety of PARP Inhibitors

All approved PARPi carry a similar safety profile. However, drug-specific differences do exist. The main adverse events are shown in the table below. It is worth noting they were also invariably seen in the placebo arms. Discontinuation rates ranged from approx. 10-15%.

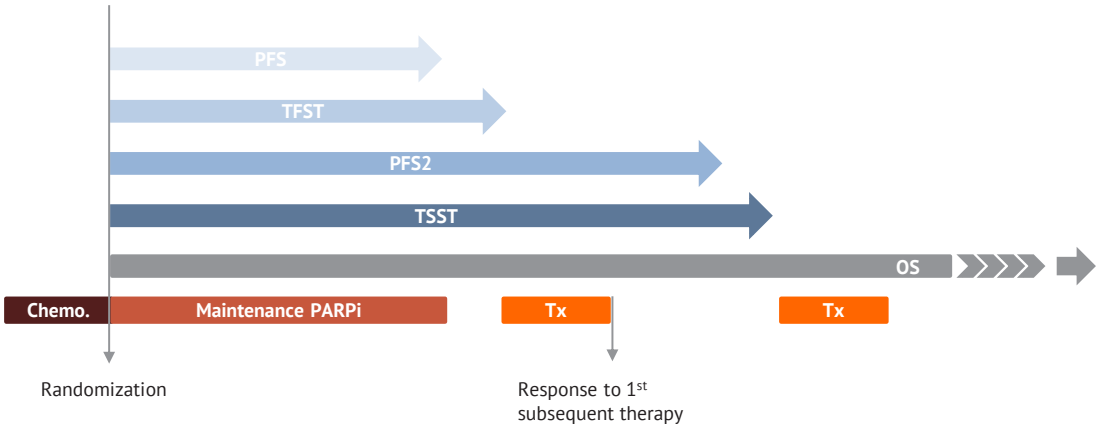
Safety overview of the approved PARPi

% AE Incidence - any grade (% AE Incidence – Grade 3/Grade 4)				
	Olaparib		Niraparib	Rucaparib
AE Preferred Term	**Study 19[1]** (400 mg bid capsule)	**SOLO2[2]** (300 mg bid tablet)	**NOVA[3]** (300 mg od)	**ARIEL2[4]** (600 mg bid)
Anaemia	21 (6)	44 (20)	50 (25)	37 (19)
Neutropenia	7 (4)	20 (5)	30 (20)	18 (7)
Thrombocytopenia	4 (1)	8 (0)	61 (34)	28 (5)
Nausea	71 (2)	76 (3)	74 (3)	75 (4)
Fatigue	63 (9)	66 (4)	60 (8)	69 (7)
Vomiting	35 (2)	37 (3)	34 (2)	37 (4)
Diarrhoea	27 (2)*[5]	33 (1)		32 (1)
Dysgeusia	-	27 (0)	10 (0)	39 (0)
Headache	-	25 (1)	26 (0)	18 (<1)
Decreased appetite	-	22 (11)	25 (0)	23 (1)
Constipation	-	21 (0)	40 (1)	37 (2)
Transaminase elevation	-	5	-	34 (10)
Hypertension	-	-	19 (8)	-
Hypotension	-	-	-	-
MDS/AML	2*[6]	2*[7]	1*[8]	-

*[1] Gourley et al, ASCO 2017; [2] Pujade-Lauraine et al., Lancet Oncol 2017; [3] Mirza et al., New Engl J Med 2016; 375(22):2154-2164; [4] Coleman et al., Lancet 2017; 390:1949–1961. *[5]similar incidence in control arm [24(2)]; *[6]incidence in control arm 1%; *[7]incidence higher in control arm (4%); *[8]similar incidence in control arm (1%).*

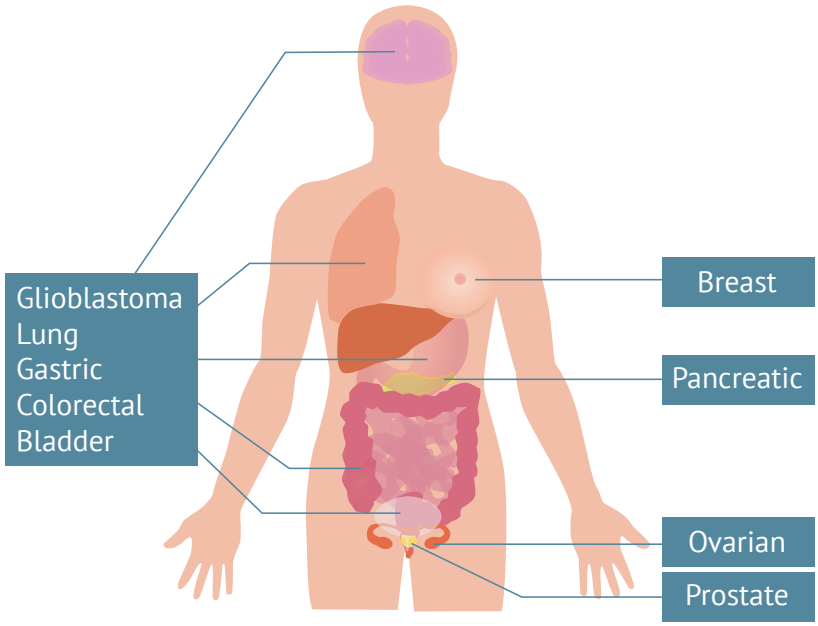
An overview of all key efficacy and safety data of the three approved products can be found in Appendix I.

The use of **intermediate clinical endpoints** is an evolving concept in evaluating the efficacy of anticancer agents in the maintenance setting. Such endpoints have been extensively employed in clinical trials with PARP inhibitors (see Figure and Glossary).



Intermediate Clinical Endpoints
Clinical trials with PARPi have implemented novel intermediate clinical endpoints including, Progression Free Survival 2 (PFS2) and Time to First or Second Subsequent Therapy or death (TFST/TSST). These endpoints complement PFS in determining the efficacy of therapies in disease settings where patients experience prolonged PFS or post-progression survival benefit in multiple subsequent lines of therapies *(diagram adapted from Matulonis et al., Cancer 2015)*.

PARPi have shown activity in cancer types other than ovarian cancer



The activity of PARPi extends beyond ovarian cancer and BRCA mutations. Germline and/or somatic mutations in *BRCA1* and *BRCA2*, as well as other DNA repair genes, have been described not only in **ovarian** but also in **breast**, **pancreatic** and **prostate cancer**. Such mutations have also been described in sizable proportions of patients with lung, bladder, colorectal or gastric cancer and glioblastoma (see also accompanying DDR BluePrint paper). Consequently, several trials are currently investigating the activity of PARPi in these tumor types (see Appendix II).

OlympiAD - Clinical activity of olaparib in metastatic breast cancer patients with gBRCA mutation

OlympiAD conducted in patients with metastatic breast cancer and gBRCA1/2 mutations, has been the first randomised phase III trial of a PARPi in a non-ovarian cancer type *(Robson et al., N Engl J Med 2017)*.

	ORR (%)	Median PFS (months)	PFS2 (months)	Grade ≥3 AEs (%)
Olaparib	59.9	7.0	13.2	36.6
Treatment of Physician's Choice	28.8	4.2	9.3	50.5
HR	-	0.58; P=0.0009	0.57; P=0.0033	-

AEs: Adverse Events; HR: Hazard Ratio; ORR: Objective Response Rate; PFS: Progression Free Survival; TPC: Treatment of Physician's Choice

Several other novel PARPi molecules are also in late stage development in solid tumours excluding ovarian (see Appendix II). In the 2017 San Antonio Breast Cancer Symposium, the phase III study (EMBRACA) of talazoparib versus chemotherapy in patients with locally advanced or metastatic HER2-negative breast cancer and germline BRCA1 or BRCA2 mutation, reported a median PFS of 8.6 months (95% CI, 7.2-9.3) with talazoparib compared to 5.6 months (95% CI, 4.2-6.7) with physician's choice of therapy (HR, 0.54; 95% CI, 0.41-0.71; P <.0001). The ORR was 62.6% (95% CI, 55.8-69.0) versus 27.2% (95% CI, 19.3-36.3), respectively (odds ratio, 4.99; 95% CI, 2.9-8.8; 2-sided P value <.0001). In Triple Negative Breast Cancer for example, in the neoadjuvant setting, addition of veliparib plus carboplatin to paclitaxel followed by standard chemotherapy showed a significant improvement in pathological complete response (pCR) compared to paclitaxel followed by standard chemotherapy (53.2% vs 31.0%, P<0.001) *(Geyer et al., ASCO 2017)*.

BRCA-based selection has driven the development of PARPi in ovarian cancer. However, the application of such agents is extending **beyond BRCA mutated and ovarian tumours**. Various biomarkers and technologies are being explored in the field of PARP and DDR targeting – see accompanying DDR BluePrint.

Several mechanisms of resistance to PARPi have been identified

Several mechanisms of resistance to PARPi treatment have been described in pre-clinical settings. However, to date, only **restoration of HRR** and **expression of hypomorphic forms of BRCA1** have been shown to be clinically relevant. This may be brought about via secondary mutations that restore the open reading frame and consequently the function of BRCA1, BRCA2 or RAD51C (also responsible for resistance to platinum).

It is likely that in different cancers different mechanisms of resistance may emerge, depending on the germline or other mutational profile.

Combination therapy is key to extending the success of PARPi therapy

Combination of PARPi with other therapies has posed a significant challenge, mainly due to overlapping toxicities and particularly with chemotherapies. At the same time, the multiple biological functions of PARPs underscore the rationale for combining PARPi with other therapies. These include:

1. Combination with Standard of Care:

As for example with DNA damaging chemotherapy e.g., platinum salts, temozolimide, gemcitabine or topoisomerase inhibitors and radiotherapy.

2. Combination with other DDR-targeting agents:

Several such trials are already underway including, Phase II of Olaparib + AZD-6738 (ATR) (NCT02264678) and Phase Ib of Olaparib + AZD-1775 (WEE1) (NCT02511795).

3. Combination with other therapies:

- **Angiogenesis inhibitors**: even though the mechanism of action of such combinations is still poorly understood several studies have shown promising results. Ongoing clinical trials in patients with relapsed platinum-sensitive ovarian cancer include: olaparib + cediranib in the maintenance setting (ICON9), olaparib + bevacizumab in first-line treatment (PAOLA-1), and olaparib monotherapy or in combination with cediranib (NRG-GY004/005).
- **Immunotherapies**: PARPi has been shown to upregulate PD-L1 expression and to enhance tumour-associated immunosuppression. Moreover, germline BRCA1 mutated tumours show increased levels of lymphocyte infiltrates and neoantigen expression. Ongoing clinical trials combining PARPi with various types of immunotherapies include: BGB-A317 (anti-PD-1) + BGB-290 (PARPi) Phase I in solid tumours (NCT02660034); durvalumab (anti-PD-L1) + olaparib and/or cediranib Phase I/II in advanced solid tumours and advanced or recurrent ovarian, triple negative breast, lung, prostate and colorectal cancers (NCT02484404) and niraparib in combination with pembrolizumab Phase I/II in triple-negative breast cancer or ovarian cancer (TOPACIO).

PARPi are firmly established as effective therapies for selected patients with ovarian cancer

The first PARP inhibitor is now also approved for the treatment of breast cancer. The therapeutic reach of PARPi is likely to expand to include other cancer types in the near future. Evolving biological insight within the overall context of DDR, replication stress, and immunological responses will allow us to use these agents in the most appropriate clinical setting to improve patient care.

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Glossary

Adenosine Diphosphate (ADP) Ribose
An ester molecule that is the basic building in the formation of poly(ADP-ribose) chains by the poly(ADP-ribose) polymerase (PARP) family of enzymes.

Chromatid Breaks
Breaks in the chromatid structure resulting from DNA double-strand breaks leading in turn to DNA damage. Have been shown to accumulate in BRCA-deficient cells

PARP Family
- Consists of 17 protein members with a structurally similar catalytic domain, albeit only PARP-1, PARP-2, PARP-3, Vault PARP and Tankyrases 1 and 2 have proven ADP-ribose polymerising activity.
- Members have multiple biological functions in: DNA repair, replication fork protection, transcription, metabolism, chromatin dynamics, apoptosis and protein degradation.
- PARPs are also involved in repairing single strand breaks through BER and double strand breaks through HR, NHEJ and MMEJ

PARPi Resistance Mechanism
demonstrated in pre-clinical models:
- Upregulation of P-glycoprotein (pgP) transporter
- Loss of DNA DSB end resection regulation
- Activation of translesional synthesis (TLS) polymerases
- Decrease in NHEJ capacity
- Expression of hypomorphic forms of BRCA1

Progression Free Survival 2 (PFS2)
Time from initial randomization to second objective disease progression (after first subsequent therapy) or death. Subsequent therapy can be any or pre-specified. Patients without second disease progression are censored at the time they were last known to be alive.

Time to First Subsequent Therapy (TFST)
Time from initial randomization to first subsequent therapy or death. In case of subsequent therapy this should be due to disease progression and not due to adverse reactions associated with previous therapy.

Time to Second Subsequent Therapy (TTST)
Time from initial randomization to second subsequent therapy or death – a proxy for PFS2. In case of subsequent therapy this should be due to disease progression and not due to adverse reactions associated with previous therapy.

Nicotinamide adenine dinucleotide (NAD)
A coenzyme form of the vitamin niacin involved in various metabolic pathways and, of relevance to PARPi, in post-translational modifications thus regulating cell survival and cell-death as well as other biological functions of the PARP family of proteins.

Abbreviations

AE	Adverse Event	**MMEJ**	Microhomology-mediated end joining
ADP	Adenosine diphosphate	**NAD+**	Nicotinamide adenine dinucleotide
ALT	Alanine aminotransferase	**NHEJ**	Non-homologous end joining
ASCO	American Society of Clinical Oncology	**ORR**	Objective Response Rate
AST	Aspartate aminotransferase	**OS**	Overall survival
ATM	Ataxia telangiectasia mutated kinase	**PALB2**	Partner and localizer of BRCA2
ATR	Ataxia-and Rad-related kinase	**PAR**	Poly(ADP-ribose)
BER	Base excision repair	**PARP**	Poly(ADP-ribose) polymerase
BRCA1/2	Breast cancer 1/2 susceptibility protein	**PARPi**	Poly(ADP-ribose) polymerase inhibitor
CDx	Companion diagnostic	**pCR**	Pathological complete response
Chk2	Checkpoint kinase 2	**PD-1**	PDCD1, programmed cell death protein 1
CI	Confidence intervals	**PD-L1**	Programmed cell death protein-ligand 1
DDR	DNA damage response	**PFS**	Progression free survival
DNA	Deoxyribonucleic acid	**pgP**	P-glycoprotein
DSB	Double strand break	**RAD51**	RAD51 recombinase
EMA	European Medicines Agency	**TFST**	Time to first subsequent therapy or death
FDA	Food and Drug Administration (US)	**TKI**	Tyrosine kinase inhibitor
gBRCA	Germline BRCA1 and/2 mutation	**TLS**	Translesional synthesis
g/sBRCA	Germline/somatic BRCA1 and/2 mutation	**TSST**	Time to second subsequent therapy or death
HRD	Homologous Recombination Deficiency	**Tx**	Therapies
HRR	Homologous Recombination Repair	**VEGF**	Vascular Endothelial Growth Factor
HR	Hazard ratio	**VEGFR**	Vascular Endothelial Growth Factor Receptor
LOH	Loss of heterozygosity		

Appendix I: (A) Clinical activity and (B) Ongoing clinical trials of approved PARPi in ovarian cancer

A - Efficacy & safety data in ovarian cancer (monotherapy)

Study 19 - Olaparib as **maintenance** therapy platinum-sensitive, relapsed, high-grade serous ovarian cancer, all comers (Ledermann et al., Lancet Oncol 2016;17:1579-89)

	Median PFS (months)		Median OS (months)		Median TFST (months)		Median TSST (months)	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
All patients (n = 265*)	8.4 (7.4-11.5)	4.8 (4.0-5.5)	29.8 (27.2-35.7)	27.8 (24.4-34.0)	13.4 (11.3-15.7)	6.7 (5.7-8.2)	19.1 (16.6-22.3)	14.8 (14.0-16.7)
Mut. BRCA (n = 136)	11.2 (8.3-NC)	4.3 (3.0-5.4)	34.9 (29.2-NC)	31.9 (23.1-40.7)	15.6 (12.3-28.2)	6.2 (5.3-9.2)	23.8 (17.7-NC)	15.2 (13.9- 18.7)
WT BRCA (n = 118)	7.4 (5.5-10.3)	5.5 (3.7-5.6)	24.5 (19.8-35.0)	26.2 (22.6-33.7)	12.9 (7.8- 15.3)	6.9 (5.7-9.3)	17.1 (15.2-20.0)	14.7 (12.8- 18.1)

**n=264 for the TFST & TSST calculation; CI: Confidence Intervals, HR: Hazard ratio, NC: Not Calculable; OS: Overall Survival, PFS: Progression Free Survival, TFST: Time to first subsequent therapy or death, TSST: Time to second subsequent therapy or death*

***Safety**: Seven patients in the olaparib group discontinued study treatment due to adverse events (AEs) and two patients in the placebo group. More patients in the olaparib group than in the placebo group had dose interruptions (49 [36%] of 136 vs 21 [16%] of 128) or dose reductions 57 [42%] vs 28 [22%]): vomiting, nausea, and fatigue were the most common causes for dose interruptions or reductions in the olaparib group. The most frequently reported AEs in the olaparib versus placebo group were: nausea (71% vs 36%), fatigue (52% vs 39%), vomiting (34% vs 14%), diarrhoea (27% vs 24%) and abdominal pain (25% vs 27%). Serious AEs were reported in 25 (18%) patients who received olaparib and 11 (9%) who received placebo. Tolerability was similar in patients with mutated BRCA and the overall population.*

SOLO2 - Olaparib as **maintenance** therapy in platinum sensitive, relapsed, germline or somatic BRCA1/2 mutated, ovarian cancer (*Pujade-Lauraine et al., Lancet Oncol 2017*)

	Median PFS (months) By investigator		Median PFS (months) By Sensitivity BICR		Median TFST (months)		Median TSST (months)	
	Olaparib (n= 196)	Placebo (n=99)	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
	19.1 (16.3-25.7)	5.5 (5.2-5.8)	30.2	5.5	27.9 (22.6-NC)	7.1 (6.3-8.3)	NC	18.2 (15.4-22.8)
HR (95% CI)	0.30 (0.22-0.41; p<0.0001)		0.25 (0.18-0.35; p<0.0001)		0.28 (0.21-0.38; p<0.0001)		0.37 (0.26-0.53; p<0.0001)	

CI: Confidence Intervals, HR: Hazard ratio, NC: Not Calculable; OS: Overall Survival, PFS: Progression Free Survival, TFST: Time to first subsequent therapy or death, TSST: Time to second subsequent therapy or death

***Safety:** In the olaparib group approx. 11% of patients discontinued treatment due to side effects (vs 2% in the control arm). The main adverse events (all grades) in the olaparib vs placebo group were: nausea (76% vs 33%), fatigue (66% vs 40%), vomiting (37% vs 19%) and diarrhoea (33% vs 20%). Serious adverse events occurred in 18% of the olaparib arm vs 8% of controls, and anaemia ≥ grade 3 was observed in 19% and 2%, respectively.*

NOVA - Niraparib **maintenance** therapy in platinum-sensitive, recurrent ovarian cancer *(Mirza et al., N Engl J Med 2016; 375(22):2154-2164)*

	gBRCA Median PFS (months)		Non-gBRCA Median PFS (months)		HRD but Non-gBRCA Median PFS (months)		gBRCA Chemotherapy-free Interval (months)		Non-gBRCA Chemotherapy-free Interval (months)	
	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo	Niraparib	Placebo
	21.0	5.5	9.3	3.9	12.9	3.8	22.8	9.4	12.7	8.6
HR (95% CI)	0.25 (0.17-0.41)		0.45 (0.34-0.61)		0.38 (0.24-0.59)		0.26 (0.17-0.41)		0.50 (0.37-0.67)	

HR: Hazard Ratio, PFS: Progression Free Survival; LOH: Loss of Heterozygosity (as assessed by the Myriad MyChoice assay)

***Safety**: The most common grade 3 or 4 adverse events that were reported in the niraparib group were thrombocytopenia (in 33.8%), anaemia (in 25.3%), and neutropenia (in 19.6%). Although grade 3 or 4 hematologic abnormalities were common they were effectively managed through dose modifications.*

Study 42 – Olaparib **(single agent therapy)** in germline BRCA1/2 mutation carriers with advanced ovarian cancer after three or more lines of previous therapy *(Kim et al., Clin Cancer Res 2015; 21(19); 4257–61 & Domchek et al., GynecolOncol 2016; 140(2):199-203)*

Platinum sensitivity status[a]	Confirmed Responders[b] (n)	ORR (%; 95% CI)	Median DoR (months; 95% CI)
Median Total (N=137)	46	34 (26-42)	7.9 (5.6-9.6)
Platinum sensitive (N=39)[c]	18	46 (30-63)	8.2 (5.6-13.5)
Platinum resistant (N=81)	24	30 (20-41)	8.0 (4.8-14.8)
Platinum refractory (N=14)	2	14 (2-43)	6.4 (5.4-7.4)
Platinum status unknown (N=3)	2	67 (9-99)	6.3 (4.7-7.9)

[a]Sensitive, time from completion of last platinum therapy to study start (TFP) >6 months; resistant, TFP <6 months; refractory, TFP <2 months and best response to last platinum was progressive disease [b]Confirmed CR or PR [c]Platinum sensitive but ineligible to receive further platinum-based chemotherapy.
CI: Confidence Intervals, DoR: Duration of Response, HR: Hazard ratio, ORR: Objective Response Rate, OS: Overall Survival, PFS: Progression Free Survival, TFST: Time to first subsequent therapy or death, TSST: Time to second subsequent therapy or death
***Safety**: With the exception of abdominal pain, the most commonly reported AEs were low-grade nausea, fatigue, vomiting, and anaemia.*

ARIEL 2 - Rucaparib **(single agent therapy)** in relapsed, platinum-sensitive high-grade ovarian carcinoma, after at least 3 prior chemotherapy regimens (*Swisher et al., Lancet Oncol 2016;18(1):75-87*)

	ORR (%; 95% CI)	PFS (months; 95% CI)
BRCA mutant (n=40)	80 (64-91)	12.8 (9.0-14.7)
BRCA WT & LOH High (n=82)	29 (20-40)	5.7 (5.3-7.6)
BRCA WT & LOH Low (n=70)	10 (4-10)	5.2 (3.6-5.5)

CI: Confidence Intervals, PFS: Progression Free Survival; LOH: Loss of Heterozygosity (as assessed by the Foundation Medicine assay)
***Safety**: Most common grade 3 or worse treatment emergent adverse events were anaemia or decreased haemoglobin (45 [22%] patients), elevations in ALT or AST (25 [12%]). Common serious adverse events included small intestinal obstruction (10 [5%] of 204 patients), and anaemia (nine [4%]).*
Note: FDA approval of Rucaparib was based on 106 patients from study 10 and ARIEL 2.

ARIEL 3 - Rucaparib **(maintenance)** in relapsed, platinum-sensitive high-grade, after ≥2 lines of previous therapy (Coleman et al., Lancet 2017; 390(10106):1949-1961)

	PFS vs Control (months; 95% CI)
BRCA mutant (130 vs 66)	16.6 (13.4-22.9) vs 5.4 (3.4-6.7); HR 0.23 (95%CI 0.16-0.34), p<0.0001
HRD deficient (236 vs 118)	13.6 (10.9-16.2) vs 5.4 (5.1-5.6); HR 0.32, (95% CI 0.24–0.42), p<0.0001
BRCA WT & LOH High (106 vs 52)	9.7 (7.9-13.1) vs 5.4 (4.1-5.7); HR 0.44, (95% CI 0.29–0.66), p<0.0001
BRCA WT & LOH Low (107 vs 54)	6.7 (5.4-9.1) vs 5.4 (5.3-7.4); HR 0.58, (95% CI 0.40–0.85), p=0.0049

CI: Confidence Intervals, PFS: Progression Free Survival; LOH: Loss of Heterozygosity
***Safety**: The most common TEAEs (reported in at least 35% of patients in either group) were nausea, asthenia or fatigue, dysgeusia, anaemia or decreased haemoglobin concentration, constipation, and vomiting. TEAEs grade ≥ 3 were reported in 209 (56%) patients in the rucaparib group and 28 (15%) in the placebo group, the most common of which were anaemia or decreased haemoglobin concentration and increase in alanine aminotransferase or aspartate aminotransferase concentration. The most common SAEs reported in the rucaparib vs placebo group were anaemia (16 [4%] vs one [1%]), pyrexia (six [2%] vs none), vomiting (six [2%] vs two [1%]), and small intestinal obstruction (three [1%] vs three [2%]). Myelodysplastic syndrome and acute myeloid leukaemia were reported in three (1%) patients in the rucaparib and none in the placebo group. Treatment interruption and dose reduction due to a TEAE were 237 (64%) vs 19 (10%) and 203 (55%) and vs eight (4%) in the rucaparib vs placebo group, respectively. Of patients who received rucaparib, 50 (13%) discontinued because of a TEAE adverse event (excluding disease progression) compared with three (2%) patients in the placebo group.*

B - Ongoing clinical trials in ovarian cancer (monotherapy)

Compound	Trial ID	Trial title	Phase
Niraparib	NCT01847274	A Maintenance Study with Niraparib Versus Placebo in Patients with Platinum Sensitive Ovarian Cancer	Phase III
	GDC40002502	A Study of Niraparib Maintenance Treatment in Patients with Advanced Ovarian Cancer Following Response on Front-Line Platinum-Based Chemotherapy (PRIMA)	Phase III
Olaparib	EudraCT-2015- 000734-30	To Assess the Efficacy and Safety of Olaparib Maintenance Monotherapy in the Treatment of Ovarian Cancer (ORZORA)	Phase IV
	NCT02489058	A Study of Long-term Responders on Olaparib (OLALA)	Phase IV
	NCT02503436	Non-interventional Study (NIS) to Collect Clinical and Patient Reported Outcome Data in an Olaparib Treated BRCAm+ PSR Ovarian Cancer Population (C-PATROL)	Phase IV
	GDCT0301653	A Phase IIIb, Single-arm, Open-label Multicentre Study of Olaparib Maintenance Monotherapy in Platinum Sensitive Relapsed non-Germline BRCA Mutated Ovarian Cancer Subjects who are in Complete or Partial Response Following Platinum Based Chemotherapy (OPINION)	Phase III
	NCT01844986	Olaparib Maintenance Monotherapy in Patients With BRCA Mutated Ovarian Cancer Following First Line Platinum Based Chemotherapy (SOLO1)	Phase III
	NCT02282020	Olaparib Treatment in Relapsed Germline Breast Cancer Susceptibility Gene (BRCA) Mutated Ovarian Cancer Patients Who Have Progressed at Least Six Months After Last Platinum Treatment and Have Received at Least Two Prior Platinum Treatments (SOLO3)	Phase III
	NCT03106987	A Study to Examine Olaparib Maintenance Retreatment in Patients with Epithelial Ovarian Cancer (OReO)	Phase III
	NCT02477644	Randomized, Double-Blind, Phase III Trial of Olaparib vs. Placebo in Patients with Advanced FIGO Stage IIIB - IV High Grade Serous or Endometrioid Ovarian, Fallopian Tube, or Peritoneal Cancer treated with standard First-Line Treatment, Combining Platinum-Taxane Chemotherapy and Bevacizumab Concurrent with Chemotherapy and in Maintenance (PAOLA)	Phase III
Rucaparib	GDC20006738	A Study of Rucaparib Versus Chemotherapy in BRCA Mutant Ovarian, Fallopian Tube, or Primary Peritoneal Cancer Patients (ARIEL4)	Phase III
	NCT01891344	A Study of Rucaparib in Patients with Platinum-sensitive, Relapsed, High-grade Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer (ARIEL2 expansion study)	Phase II
	GDC30013293	Phase II Study of Rucaparib in Combination with Bevacizumab as a First-line Maintenance Therapy in Advanced Ovarian Cancer	Phase II

Appendix II: PARPi in late stage development in solid tumours (excluding ovarian)

Compound	Trial ID	Trial title	Phase
Niraparib [Tesaro]	NCT01905592	A Phase III Trial of Niraparib Versus Physician's Choice in Her2 Negative, Germline BRCA Mutation-positive Breast Cancer Patients (BRAVO)	Phase III
Olaparib [AstraZeneca]	NCT02184195	Olaparib in gBRCA Mutated Pancreatic Cancer Whose Disease Has Not Progressed on First Line Platinum-based Chemotherapy (POLO)	Phase III
	NCT01924533	Efficacy and Safety Study of Olaparib in Combination with Paclitaxel to Treat Advanced Gastric Cancer	Phase III
	NCT02032823	Olaparib as Adjuvant Treatment in Patients with Germline BRCA Mutated High Risk HER2 Negative Primary Breast Cancer (OlympiAD)	Phase III
	NCT02810743	Substantially Improving the Cure Rate of High-risk BRCA1-like Breast Cancer (Subito)	Phase III
	NCT01682772	A Phase II Trial of Olaparib in Patients With Advanced Castration Resistant Prostate Cancer (TOPARP)	Phase II
Rucaparib [Clovis Oncology]	GDC20006736	A Study of Rucaparib Verses Physician's Choice of Therapy in Patients with Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON3)	Phase III
	NCT02042378	A Study of Rucaparib in Patients with Pancreatic Cancer and a Known Deleterious BRCA Mutation	Phase II
	GDC20006737	Phase II Study of Rucaparib in Treatment of De Novo Metastatic tBRCAmut and BRCA-like Prostate Cancer	Phase II
	NCT02952534	A Study of Rucaparib in Patients with Metastatic Castration-resistant Prostate Cancer and Homologous Recombination Gene Deficiency (TRITON2)	Phase II
	GDC20006740	Proof of Concept Study of Rucaparib in the treatment of tBRCAmut and BRCA-like Gastroesophageal Cancer	Phase II
Talazoparib [Pfizer]	NCT01945775	A Study Evaluating Talazoparib (BMN 673), a PARP Inhibitor, in Advanced and/or Metastatic Breast Cancer Patients with BRCA Mutation (EMBRACA Study)	Phase III
	GDC30009592	A Pivotal Study of Talazoparib (MDV3800) in Small Cell Lung Cancer	Phase III
	GDC30009409	A Pivotal Study of Talazoparib (MDV3800) in non-BRCA Breast Cancer	Phase III
	GDC30009411	A Pivotal Study of Talazoparib (MDV3800) in Prostate Cancer	Phase III
	NCT02034916	A Phase II, Two-stage, Two-cohort Study of Talazoparib (BMN 673), in Locally Advanced and/or Metastatic Breast Cancer Patients with BRCA Mutation (ABRAZO Study)	Phase II
	NCT02282345	Neoadjuvant Talazoparib for Patients with a BRCA Deleterious Mutation	Phase II
	NCT02401347	Talazoparib Beyond BRCA (TBB) Trial	Phase II
	GDC30009384	A Phase II Study of Talazoparib in Subjects with Colorectal Cancer	Phase II
	GDC30009385	A Phase II Study of Talazoparib in Glioblastoma Multiforme Subjects Undergoing Surgical Resection	Phase II
	EudraCT-2016 -002036-32	A Study of Talazoparib in patients with DNA Repair Defects and Metastatic Castration-Resistant Prostate Cancer	Phase II
Veliparib [AbbVie]	NCT02163694	A Randomized, Placebo-Controlled Trial of Carboplatin and Paclitaxel With or Without the PARP Inhibitor Veliparib (ABT-888) in HER2 Negative Metastatic or Locally Advanced Unresectable BRCA-Associated Breast Cancer	Phase III
	NCT01149083	Veliparib with or without Carboplatin in Treating Patients with Stage III or Stage IV Breast Cancer	Phase II
	NCT01657799	A Clinical Study Conducted in Multiple Centers Comparing Veliparib and Whole Brain Radiation Therapy (WBRT) Versus Placebo and WBRT in Subjects with Brain Metastases From Non Small Cell Lung Cancer (NSCLC)	Phase II
	NCT02890355	FOLFIRI or Modified FOLFIRI and Veliparib as Second Line Therapy in Treating Patients with Metastatic Pancreatic Cancer	Phase II
	NCT03044795	Response to PARP Inhibitor Predicted by the RAD51 Assay (REPAIR)	Phase II

Other PARPi compounds in earlier clinical development

Generic Name [Company Name]	Indication	Highest Development Stage
E-7449 [Eisai Co Ltd]	B-Cell Chronic Lymphocytic Leukemia; BC; Diffuse Large B-Cell Lymphoma; Follicular Lymphoma; Lung Cancer; Malignant Mesothelioma; Mantle Cell Lymphoma; Melanoma; Metastatic Ovarian Cancer; Neuroendocrine Tumours; Pancreatic Cancer; Solid Tumour	Phase II
Compounds in Phase I	ABT-767 [AbbVie Inc]; BGB-290 [BeiGene Ltd]; CK-102 [Checkpoint Therapeutics]; Fluzoparib [Jiangsu Hengrui Medicine]; SC-10914 [Shanghai De Novo Pharmatech]; SOMCL-9112 [Shanghai Acebright Pharma]	