REVIEW ARTICLE

Pharmacokinetics and Pharmacodynamics of PARP Inhibitors in Oncology

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Abstract

Olaparib, niraparib, rucaparib, and talazoparib are poly (ADP-ribose) polymerase (PARP) inhibitors approved for the treatment of ovarian, breast, pancreatic, and/or prostate cancer. Poly (ADP-ribose) polymerase inhibitors are potent inhibitors of the PARP enzymes with comparable half-maximal inhibitory concentrations in the nanomolar range. Olaparib and rucaparib are orally dosed twice a day, extensively metabolized by cytochrome P450 enzymes, and inhibitors of several enzymes and drug transporters with a high risk for drug–drug interactions. Niraparib and talazoparib are orally dosed once a day with a lower risk for niraparib and a minimal risk for talazoparib to cause drug–drug interactions. All four PARP inhibitors show moderate-to-high interindividual variability in plasma exposure. Higher exposure is associated with an increase in toxicity, mostly hematological toxicity. For talazoparib, exposure–efficacy relationships have been described, but for olaparib, niraparib, and rucaparib this relationship remains inconclusive. Further studies are required to investigate exposure–response relationships to improve dosing of PARP inhibitors, in which therapeutic drug monitoring could play an important role. In this review, we give an overview of the pharmacokinetic properties of the four PARP inhibitors, including considerations for patients with renal dysfunction or hepatic impairment, the effect of food, and drug–drug interactions. Furthermore, we focus on the pharmacodynamics and summarize the available exposure–efficacy and exposure–toxicity relationships.

Key Points

The approved poly (ADP-ribose) polymerase inhibitors olaparib, niraparib, rucaparib, and talazoparib show moderate-to-high interindividual variability in plasma exposure.

Olaparib and rucaparib have a high potential for drug–drug interactions, while this risk is lower for niraparib and minimal for talazoparib.

Exposure has been associated with toxicity for all poly (ADP-ribose) polymerase inhibitors, mainly with hematological toxicity.

Exposure–efficacy relationships have been described for talazoparib, but remain inconclusive for olaparib, niraparib, and rucaparib.

1 Introduction

A relatively new class of targeted anticancer agents are the poly (ADP-ribose) polymerase (PARP) inhibitors. Poly (ADP-ribose) polymerase inhibitors primarily inhibit the catalytic activity of PARP-1 and PARP-2 enzymes, which are involved in base excision repair of DNA single-strand breaks. Poly (ADP-ribose) polymerase inhibition leads to accumulation of single-strand breaks, ultimately resulting in double-strand breaks (DSBs) [1]. In addition to catalytic inhibition, PARP inhibitors trap the PARP enzyme-DNA complex on single-strand breaks resulting in DSBs [2]. Poly (ADP-ribose) polymerase trapping is considered the major mechanism of anti-tumor activity [3]. While PARP inhibition is not effective in healthy cells, as they alternatively

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can utilize the functional homologous recombination repair mechanism for repair of DSBs, it is particularly effective in cells harboring homologous recombination deficiencies (HRD), such as pathogenic breast cancer (BRCA)-1 or BRCA-2 mutations [2]. This concept is called synthetic lethality: simultaneous loss of function of two or more key molecules results in cell death, while a deficiency in only one is not lethal (Fig. 1) [1].

The introduction of PARP inhibitors has accomplished many breakthroughs in the treatment of ovarian, breast, pancreatic, and prostate cancer. It improved progression-free survival (PFS) and quality of life, but there are still challenges to overcome. Drug resistance and adverse effects are common and can limit long-term treatment. Poly (ADP-ribose) polymerase inhibitors are orally administered, given in a fixed dose, and are substrates for different metabolizing enzymes and drug transporters [4–7]. Consequently, large variability in pharmacokinetic exposure between patients is not exceptional. Low exposure may lead to suboptimal efficacy, while high exposure can cause toxicities. This gives the opportunity for precision dosing, for example, by therapeutic drug monitoring [8–11]. Indications of PARP inhibitors are rapidly expanding from monotherapy in patients with BRCA mutations, to patients with other HRD and no HRD, to combination therapy with DNA-damaging agents, radiation, targeted therapies, and immunotherapy [1, 12]. In this review, we aim to summarize the available pharmacokinetic and pharmacodynamic data for the approved PARP inhibitors olaparib, niraparib, rucaparib, and talazoparib.

2 Methods

A comprehensive literature search was performed using PubMed and EMBASE. The term 'pharmacokinetics' was combined with the different PARP inhibitors and relevant studies were selected. The snowballing method was used to find additional relevant studies. The Committee for Medicinal Products for Human Use Assessment Reports from the European Medicines Agency (EMA) and the US Food and Drug Administration Clinical Pharmacology and Biopharmaceutics review of niraparib, olaparib, rucaparib, and talazoparib were consulted as well.

3 Pharmacokinetics and Pharmacodynamics of PARP Inhibitors

Table 1 gives an overview of the EMA-approved PARP inhibitors and indications. Information on the preclinical pharmacology of PARP inhibitors is shown in Table 2. The clinical pharmacokinetics at steady state is summarized in Table 3. Tables 4 and 5 describes the impact of renal and hepatic impairment, respectively, and other potential factors

Fig. 1 Mechanism of action of poly (ADP) ribose polymerase (PARP) inhibitors. Single-strand breaks in DNA are repaired through base excision repair mediated by PARP enzymes. Inhibition of PARP or trapping of PARP on the DNA by PARP inhibitors, result in double-strand breaks in DNA. In normal cells harboring the homologous recombination repair mechanism, double-strand breaks are repaired and the cell survives. In cells with an homologous recombination deficiency (HRD), including breast cancer (BRCA) 1 and 2 mutations, this repair mechanism is absent leading to accumulation of double-strand breaks and cell death
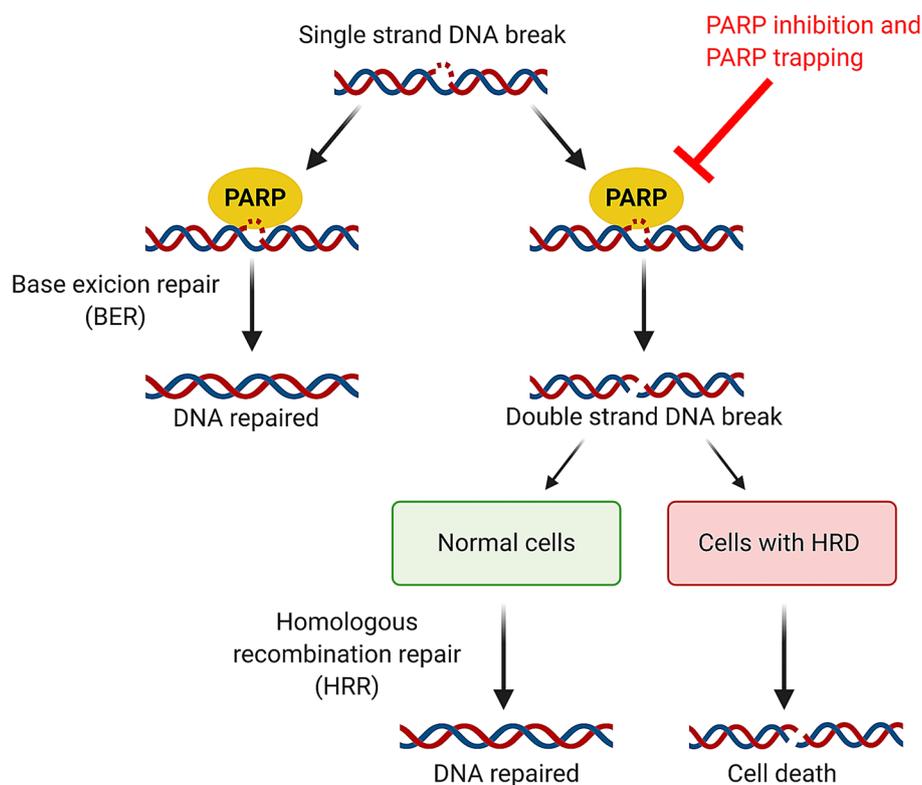
influencing the pharmacokinetics of PARP inhibitors are discussed as well. The results of food-effect studies are shown in Table 6 and drug–drug interaction (DDI) studies are summarized in Table 7. The data and the implications of the data presented in the tables are further discussed for each compound.

3.1 Olaparib

Olaparib was the first approved PARP inhibitor by the EMA in 2014 (Table 1). In study 19, maintenance treatment of olaparib capsules in patients with platinum-sensitive, relapsed, high-grade epithelial ovarian cancer, in response to platinum-based chemotherapy, improved median PFS in the overall population compared with placebo (8.4 vs 4.8 months; hazard ratio [HR] 0.35 (95% confidence interval [CI] 0.25–0.49), $p < 0.0001$) [13]. The greatest benefit was found in germline (g) or somatic (s) BRCA1/2 mutated patients [11.2 vs 4.3 months; HR 0.18 (95% CI 0.10–0.31), $p < 0.0001$] with a lower benefit for patients with wild-type BRCA (BRCA variants of unknown significance and no known or reported BRCA mutation) [7.4. vs 5.5 months; HR 0.54 (95% CI 0.34–0.85), $p < 0.0075$] [14]. The approved dose of 400 mg twice a day was the maximum tolerated dose (MTD) [15]. The high administration burden of the 50-mg capsules has led to the development of an alternative solid dispersion tablet formulation (100 and 150 mg). Because capsules and tablets are not bioequivalent, Study 24 was performed resulting in an optimal tablet dose of 300 mg BID [16]. The tablet formulation was approved in 2018 based on the SOLO2 trial with prolonged PFS in patients using olaparib compared with placebo [19.1 vs 5.5 months; HR 0.30 (95% CI 0.22–0.41), $p < 0.0001$] [17]. Approval was granted regardless of BRCA status, as overall survival in study 19 was prolonged irrespective of BRCA status [HR 0.73 (95% CI 0.55−0.95), $p = 0.02138$] [18]. Indications expanded to breast, pancreas, and prostate cancer. The tablet formulation will mainly be discussed in this review, as capsules are being phased out of the marked.

3.1.1 Preclinical Pharmacology

The in vitro interaction of olaparib with enzymes and transporters is shown in Table 2. Olaparib inhibits the organic cation transporter (OCT) 2, multidrug and toxin extrusion protein (MATE) 1 and MATE2K involved in the tubular secretion of creatinine. Inhibition by olaparib has been associated with increased creatinine levels without affecting renal function. Therefore, the creatinine-derived estimated glomerular filtration rate can underestimate the renal function and an alternative marker such as cystatin C should be used to assess renal function [19, 20]. Furthermore, olaparib penetrates the brain in vivo, but is rapidly cleared from

the brain, probably owing to P-glycoprotein (P-gp) efflux transporters [10].

Olaparib is mainly metabolized by cytochrome P450 (CYP) 3A4/5 with three major metabolites formed (M12, M15, and M18). Their potency to inhibit growth of BRCA1 mutant cells and PARP-1 is 30-fold, 30-fold, and four-fold lower, respectively, than olaparib itself [21]. In addition to being a substrate to CYP3A, olaparib inhibits and induces CYP3A. The net effect on CYP3A is weak inhibition, possibly increasing exposure to CYP3A substrates, which could be important for drugs with a narrow therapeutic window [22]. In vivo, olaparib exerts single-agent activity in BRCA1-deficeint and BRCA2-deficient cells, but is less effective in ovarian and/or breast cancer wild-type models [10, 23].

3.1.2 Clinical Pharmacokinetics

Steady-state pharmacokinetic parameters of olaparib capsules and tablets are summarized in Table 3. Formulations of capsules and tablets are not bioequivalent [16]. The 300-mg tablet formulation with improved bioavailability has a 13% higher mean relative exposure (area under the curve [AUC]) at steady state than the 400-mg capsule formulation [24]. Absolute bioavailability has not been investigated, but is probably low, as olaparib is classified as a Biopharmaceutical Classification System (BCS) class IV compound (low solubility, low permeability) [23]. Mean protein binding (albumin and alpha-1 acid glycoprotein) is high (89%), which decreases to 82% at concentrations of $>10,000$ ng/mL in vitro [5, 25]. Olaparib has an apparent volume of distribution of 167 L (capsules) and 158 L (tablets) [23, 26]. Olaparib is metabolized by CYP enzymes with three major metabolites (M12, M15, and M18) accounting for 9–14% of plasma radioactivity [23]. Considering preclinical data (Sect. 3.1.1), the clinical activity of these metabolites is negligible [21]. Olaparib is hepatically and renally cleared, with 44% (15% unchanged) of the radioactive dose recovered in urine and 42% (6% unchanged) in feces [25, 27].

3.1.3 Pharmacokinetics in Special Populations

3.1.3.1 Patients with Renal Impairment The impact of renal impairment on the pharmacokinetics of olaparib is shown in Table 4. Area under the curve and maximum concentration (C_{max}) are significantly increased in patients with renal impairment. Although no increase in adverse events were observed, higher exposure might eventually result in increased toxicity, mainly hematological toxicities [28]. Dose adjustments are required in patients with moderate renal impairment and olaparib is not recommended in patients with severe renal impairment [28–30]. Dose adjustments during olaparib treatment should be considered care-

Table 1 Overview of the approved PARP inhibitors and indications by the EMA

PARP inhibitor	Registered trade name	Company	Year of approval	Indication	Mutation	Setting	Approved EMA indication	Approved dose
Olaparib (AZD-2281)	Lynparza	AstraZeneca	2014	Ovarian	g/sBRCAm	Maintenance treatment	Platinum-sensitive, relapsed, high-grade serous EO, FT, PP cancer in complete or partial response to platinum-based chemotherapy	400 mg BID (capsules)
			2018	Ovarian	–	Maintenance treatment	Platinum-sensitive, relapsed, high-grade serous EO, FT, PP cancer in complete or partial response to platinum-based chemotherapy	300 mg BID (tablets)
			2019	Breast	gBRCAm and HER2-	Treatment	Locally advanced or metastatic breast cancer previously treated with an anthracycline and taxane in the (neo)adjuvant or metastatic setting unless not suitable for these treatments. Patients with HR-positive breast cancer should have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy	300 mg BID (tablets)
			2019	Ovarian	g/sBRCAm	Maintenance treatment	Advanced high-grade EO, FT, PP cancer in complete or partial response following completion of first-line platinum-based chemotherapy	300 mg BID (tablets)
			2020	Pancreas	gBRCAm	Maintenance treatment	Metastatic pancreatic adenocarcinoma without progression after a minimum of 16 weeks of platinum treatment within a first-line chemotherapy regimen	300 mg BID (tablets)
			2020	Ovarian	HRD+	Maintenance treatment	Advanced high-grade EO, FT, PP cancer in complete or partial response following completion of first-line platinum-based chemotherapy	300 mg BID (tablets)
			2020	Prostate	g/sBRCAm	Treatment	Metastatic castration-resistant prostate cancer who have progressed following prior therapy that included a new hormonal agent	300 mg BID (tablets)
			2020	Ovarian	HRD+	Maintenance treatment icm bevacizumab	Advanced high-grade EO, FT, PP cancer in complete or partial response following completion of first-line platinum based chemotherapy with bevacizumab	300 mg BID (tablets)
Rucaparib (AG014699)	Rubraca	Clovis Oncology	2018	Ovarian	g/sBRCAm	Treatment	Platinum-sensitive, relapsed, or progressive high-grade serous EO, FT, PP cancer previously treated with two or more prior lines of platinum-based chemotherapy and unable to tolerate further platinum-based chemotherapy	600 mg BID
			2018	Ovarian	–	Maintenance treatment	Platinum-sensitive, relapsed, high-grade serous EO, FT, PP cancer in complete or partial response to platinum-based chemotherapy	600 mg BID
Niraparib (MK-4827)	Zejula	Tesaro/GSK	2017	Ovarian	–	Maintenance treatment	Platinum-sensitive, relapsed, high-grade serous EO, FT, PP cancer in complete or partial response to platinum-based chemotherapy	300 mg QD
			2020	Ovarian	–	Maintenance treatment	Advanced high-grade EO, FT, PP cancer in complete or partial response following completion of first-line platinum-based chemotherapy	300 mg QD
Talazoparib (BMN 673)	Talzenna	Pfizer	2019	Breast	gBRCAm and HER2-	Treatment	Locally advanced or metastatic breast cancer previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced, or metastatic setting unless patients were not suitable for these treatments. Patients with HR-positive breast cancer should have progressed on or after prior endocrine therapy, or be considered unsuitable for endocrine therapy	1 mg QD

BID twice a day, *BRCA* Breast Cancer, *EO* epithelial ovarian, *FT* fallopian tube, *g* germline, *HR* hormone receptor, *HRD* homologous recombination deficiency, *HRR* homologous recombination repair, *HER2* human epidermal growth factor receptor 2, *m* mutation, *PARP* poly (ADP-ribose) polymerase, *PP* primary peritoneal, *QD* once a day, *s* somatic

fully, as the creatinine-derived estimated glomerular filtration rate can underestimate renal function with the risk of underdosing [20].

3.1.3.2 Patients with Hepatic Impairment

The impact of hepatic impairment on olaparib exposure is shown in Table 5. Olaparib exposure was not significantly altered in patients with mild or moderate hepatic impairment and therefore no dose adjustments are required [31]. Physiologically based pharmacokinetic simulations estimated an negligible increase in AUC for patients with severe hepatic impairment [32]. Until a dedicated clinical study is performed, olaparib is not recommended in patients with severe hepatic impairment [31].

3.1.4 Other Factors Influencing the Pharmacokinetics of Olaparib

Olaparib exposure was 50% higher in patients with advanced solid tumors [15, 33] compared with patients having a non-advanced disease state (patients with breast cancer scheduled for elective surgery). This can partly be explained by the fed versus fasted state, in these studies, but also the disease state might influence the pharmacokinetics [34]. The impact of body weight, age, sex, race, serum creatinine, creatinine clearance, line of treatment, Eastern Cooperative Oncology Group performance status, and tumor type on the pharmacokinetics of olaparib was evaluated in two population pharmacokinetic models. Only Eastern Cooperative Oncology Group performance status had a significant effect on olaparib clearance without a clear biological explanation [24, 35]

3.1.5 Food Effect

The results of the two food-effect studies are described in Table 6. A small significant increase in olaparib exposure was observed when olaparib tablets were administered with a high-fat meal. The inter-patient variability was not affected and no important differences between adverse events were observed under fed/fasted conditions. The current advice is that olaparib can be administered with or without food [36].

3.1.6 Drug–Drug Interactions

Table 7 gives an overview of the performed DDI studies. Olaparib is metabolized by CYP3A4, and exposure is significantly changed when combined with strong CYP3A4 inhibitors or inducers [37]. It is advised to reduce the olaparib tablet dose to 100 and 150 mg BID when co-administered with strong and moderate CYP3A4 inhibitors, respectively, if avoidance is not possible. Moderate and strong CP3A4 inducers should be avoided. Furthermore, clinically relevant interactions between olaparib and CYP3A4 substrates with a narrow therapeutic index (e.g., cyclosporine, tacrolimus) occur [32]. However, this was not observed for the CYP3A4 substrates anastrazole and letrozole [38]. Inhibition is probably weak, as olaparib is an inhibitor and inducer of CYP3A4 with a net effect of weak inhibition (Sect. 3.1.1) [22]. Additionally, interactions with olaparib as a perpetrator could occur with substrates to OCT1, OCT2, OATP1B1, OAT3, MATE1, and MATE2K (Table 2) [39].

3.1.7 Clinical Pharmacodynamics

3.1.7.1 Exposure Efficacy

Inhibition of PARP in peripheral blood mononuclear cells is highly variable [34]. Maximum PARP inhibition (> 90% from baseline) is reached at doses of $\geq$ 60 mg BID (capsules) and tumor responses are observed at doses $\geq$ 100 mg BID [15, 40].

Dose–efficacy relationships were demonstrated; the objective response rate (ORR) was 41% versus 22% with a median PFS of 5.7 months versus 3.8 months in patients with BRCA-mutated breast cancer receiving 400 mg BID and 100 mg BID, respectively [41]. A similar result was observed in patients with BRCA-mutated ovarian cancer (ORR: 33% vs 13%, median PFS: 5.8 months vs 1.9 months, for 400 mg BID and 100 mg BID, respectively) [42].

Exposure–efficacy relationships are not very clear. In patients with prostate cancer (PROfound study, $n = 74$), Cox proportional hazard modeling showed no significant correlation between exposure and PFS [AUC: HR 0.98 (95% CI 0.97–1.00), C_{max}: HR 0.89 (95% CI 0.75–1.02), minimum concentration: HR 0.77 (95% CI 0.56–1.06)]. However, patient numbers were small [43]. Results from an exposure-PFS Cox proportional hazard model using data from patients with solid tumors ($n = 410$) indicate that 300 mg BID (steady state C_{max} 7.67 µg/mL) is superior to 200 mg BID ($C_{max,ss}$ 6.99 µg/mL) [HR 0.96 (95% CI 0.94–0.99)], but the difference is small [44]. In summary, the olaparib dose is related to efficacy, but looking at exposure within the registered doses, no clear exposure–efficacy relationship has been demonstrated.

3.1.7.2 Exposure Toxicity

Hematological toxicities were more frequently reported with the 300-mg tablet formulation compared with the 400-mg capsule formulation [24]. As exposure of the 300-mg tablet formulation is 13% higher, an exposure–toxicity relationship is apparent.

An exposure–toxicity analysis with data from multiple clinical trials showed an exposure–toxicity relationship between the probability of grade 1–4 anemia and steady-state minimum concentrations ($p = 0.001$) and predicted C_{max} ($p = 0.013$) of the 400-mg capsule

Table 2 Preclinical pharmacology: the in vitro interaction of PARP inhibitors with their target, enzymes, and transporters and average unbound steady-state concentrations in patients at clinical doses

PARP inhibitor	Average unbound steady-state C_{min} in patients at clinical doses (nM)[a]	Average unbound steady-state C_{max} in patients at clinical doses (nM)[b]	Target	Target IC_{50} (nM)	Catalytic inhibition[c] (IC_{50}, nM)	Cytotoxicity[d] (EC_{50}, nM)	PARP trapping potency[e]	Metabolized by	Inductor of	Inhibitor of	Down regulator of	Substrate to	References
Olaparib *Capsules Tablets*	460 672	2825 3779	PARP1 PARP2 PARP3 TNKS1	5 1 4 1500	6	259	1	CYP1A1[a] CYP2A6[a] CYP3A4	CYP2B6 CYP3A4	CYP3A4 MATE1 MATE2K OATP1B1 OAT3 OCT1 OCT2 P-gp UGT1A1	–	P-gp	[22, 23, 25, 26]
Niraparib	364	937	PARP1 PARP2 PARP3	3.8 2.1 1300	60	650	2	CES CYP1A2[f] CYP2D6[f] CYP3A4/5[f] UGT	CYP1A2[g]	BCRP DAT MAO-B MATE1 MATE2-k NET SERT	–	BCRP P-gp	[51]
Rucaparib	1702	2010	PARP1 PARP2 PARP3	0.5 0.8 28	21	609	1	CYP1A2 CYP2D6 CYP3A4	CYP1A2	BCRP CYP1A2 CYP2C9 CYP2C19 CYP2D6 CYP3A4 MATE1 MATE2-k Non-selective sigma channel OCT1 OCT2 P-gp Several kinases[h] Sodium channel 2 UGT1A1	CYP3A4 CYP2B6	BCRP P-gp	[75, 80, 88, 92]

Table 2 (continued)

PARP inhibitor	Average unbound steady-state C_{min} in patients at clinical doses (nM)[a]	Average unbound steady-state C_{max} in patients at clinical doses (nM)[b]	Target	Target IC_{50} (nM)	Catalytic inhibition[c] (IC_{50}, nM)	Cytotoxicity[d] (EC_{50}, nM)	PARP trapping potency[e]	Metabolized by	Inductor of	Inhibitor of	Down regulator of	Substrate to	References
Talazoparib	2.5	14.4	PARP1 PARP2 PARP3 TNKS1 TNKS2	0.6 0.3 22.0 13.5 4.7	4	5	100	–	–	–	–	BCRP P-gp	[102]

CES carboxylesterase, C_{max} maximum plasma concentration, C_{min} minimum plasma concentration, *CYP* cytochrome P450, *BCRP* breast cancer resistance protein, *DAT* dopamine transporter, EC_{50} half-maximal effective concentration, IC_{50} half-maximal inhibitory concentration, *MAO-B* monoamine oxidase inhibitor B, *MATE* multidrug and toxin extrusion protein, *NET* norepinephrine transporter, *OAT* organic anion transporter, *OATP* organic anion transporting polypeptide, *OCT* organic cation transporter, *PARP* poly (ADP-ribose) polymerase, *P-gp* P-glycoprotein, *SERT* serotonin transporter, *TNKS* tankyrase, *UGT* uridine 5'-diphospho-glucuronosyltransferase (UDP)-glucuronosyltransferase

[a]Calculated based on protein binding and weighed average C_{min} levels at steady state reported in Table 3

[b]Calculated based on protein binding and weighed average C_{max} levels at steady state reported in Table 3

[c]Measured as PAR level inhibitions in DT40 cells [114, 115]

[d]Measured in the human Capan-1 cell line, which is BRCA2 deficient [3, 100]

[e]Relative to olaparib

[f]Minimal contribution

[g]Weak inhibitor

[h]CDK16/cyclin Y (PCTAIRE), PASK, CDK17/cyclin Y (PCTK2), PIM3, DYRK1/DYRK1A, DYRK1B, CDK18/cyclin Y (PCTK3), MYO3b, MYO3A, PIM1, CDK6/cyclin D1

Table 3 Pharmacokinetic parameters at steady state

PARP inhibitor	N	Dose (mg)	T_{max} (h) Mean (range)	C_{min} (ng/mL)	C_{max} (ng/mL)	$AUC_{0–tau}$ (ng/mL*h) [a]	$t_{1/2}$ (h)	References
Olaparib capsules	6	400 BID	2.0 (1.5–3.0)	1290 (76%)	7650 (27%)	44,900 (39%)	NR	[15]
	17	400 BID	1.25 (1.0–8.0)[b]	1040 (230–8490)	6360 (3880–13,300)	41,500 (18,700–147,000)	11.9 ± 4.82[b]	[16]
	10	400 BID	1.25 (1.0–8.0)[b]	1860 (530–6670)	5700 (2380–10,9000)	43,100 (18,100–98,600)	11.9 ± 4.82[b]	[16]
	5[c]	400 BID	2.1 (1.5–4.0)	NR	5900 (19.7%)	33,300 (22.3%) [d]	10.7 (3.8–18.9)[e]	[33]
	6	400 BID	2.0 (1.5–3.0)	NR	7900 (26%)	44,000 (38%)	NR	[25]
	4	400 BID	2.0 (2.0–3.0)[f]	1600 (46.1%)	9100 (27.2%)	58,100 (29.4%)	NR	[128]
Olaparib tablets	17	300 BID	NR	1840 (340–3830) (67%)	9370 (2280–14,700) (47%)	58,400 (23,100–96,000) (47%)	NR	[16, 25]
	15[g]	300 BID	1.50 (0.97–3.00)	800 (118%)	8270 (35.0%)	44,000 (48.4%)	6.52 ± 1.35[h]	[129]
	6[c]	300 BID	3.00 (1.50–3.93)	1290 (157.6%)	8430 (35.05%)	52,340 (68.17%)	9.43 (6.45–14.7)[i]	[130]
	29	300 BID	NR	2000 (89.8%)[j]	9500 (41.5%)[j]	62,100 (51.6%)[k]	NR	[38]
Niraparib	10	300 QD	3.5 (2.0–4.2)	687 ± 303 (44%)[l]	1399 ± 608 (43%)[l]	21,407 ± 9168 (43%)[l]	36.2 ± 14.6	[46]
	12[g]	300 QD	3.05 (2.9–6.1)	NR	2070 (29.3%)[l]	27,852 (28.6%)[l]	36.45 ± 17.21	[59]
	4[c]	300 QD	3.7 ± 1.6	592.3 ± 138.2	1167 ± 194.9	19,540 ± 3117	NR	[131]
Rucaparib	7	600 BID	4 (2.53–10)	NR	2420 (45%)	21,400 (61%)[m]	NR	[71]
	196	600 BID	NR	2026 ± 1147 (57%)	NR	NR	NR	[72]
	16	600 BID	2.5 (0.5–3.1)	NR	2650 (57%)	25,800 (57%)	NR	[92]
	18	600 BID	1.92 (0–5.98)	NR	1940 (54%)	16,900 (54%)[n]	12.6 (54%)[n]	[91]
	375	600 BID	NR	1754 ± 805 (46%)	2169 ± 890 (41%)	47,507 ± 20,436 (43%)	NR	[88]
Talazoparib	6	1.0 QD	1.02 (0.75–2.00)	3.720 ± 1.590 (43%)	21.000 ± 7.990 (38%)	202 ± 54 (27%)	50.0 ± 16.6 (33%)	[99]
	27	1.0 QD	2.00 (0.97–6.00)	4.950 (56%)	16.400 (32%)	208 (37%)	NR	[132]
	6[c]	1.0 QD	1.03 (0.7–1.9)	3.650 (49%)	32.840 (14%)	244.7 (21%)	50.73 ± 10.1 (20%)[o]	[133]

AUC area under the plasma concentration–time curve, $AUC_{0–tau}$ AUC from time zero to the end of the dosing interval (tau), *BID* twice a day, C_{max} maximum plasma concentration, C_{min} minimum plasma concentration, *CV%* percentage coefficient of variation, *N* number of subjects, *NR* not reported, *SD* standard deviation, $t_{1/2}$ elimination half-life, T_{max} time to maximum plasma concentration, *QD* once a day

Variability is reported as ± SD, (CV%), (range)

[a] For olaparib and rucaparib, AUC from 0 to 12 hours, for niraparib and talazoparib AUC from 0 to 24 hours

[b] Based on 6 patients receiving a single dose of 400 mg

[c] Japanese patients

[d] AUC from 0 to 10 hours

[e] Based on 6 patients receiving a single dose of 400 mg

[f] Median (range)

[g] Chinese patients

[h] Based on 16 patients receiving a single dose of 300 mg

[i] Based on 7 patients receiving a single dose of 300 mg

[j] Based on 27 patients

[k] Based on 26 patients

[l] Calculated based the molecular weight of 320.4 g/mol

[m] Based on 4 patients

[n] Based on 12 patients

[o] Based on 6 patients receiving a single dose of 1.0 mg

Table 4 Impact of renal impairment on the pharmacokinetics of PARP inhibitors

PARP inhibitor	Method	Renal impairment	PK parameter	GLS mean ratio	90% CI	Effect on PK parameter	Advice	References
Olaparib tablets	Clinical study[a,b]	Mild	C_{max}	1.15	1.04–1.27	↑ 15%	No dose adjustments required	[28, 29]
			$AUC_{0-\infty}$	1.24	1.06–1.47	↑ 24%		
		Moderate	C_{max}	1.26	1.06–1.48	↑ 26%	Decrease the dose to 200 mg BID	
			$AUC_{0-\infty}$	1.44	1.10–1.89	↑ 44%		
	PBPK model[a]	Mild	C_{max}	1.04	1.03–1.04	↑ 4%	No dose adjustments required	[29, 32]
			AUC	1.40	1.39–1.40	↑ 40%		
		Moderate	C_{max}	1.09	1.07–1.10	↑ 9%	Decrease the dose to 200 mg BID	
			AUC	1.89	1.89–1.90	↑ 89%		
		Severe	C_{max}	1.11	1.10–1.12	↑ 11%	Olaparib is not recommended	
			AUC	2.21	2.19–2.22	↑ 121%		
Olaparib capsules	PBPK model[a]	Mild	C_{max}	1.21	1.19–1.24	↑ 21%	No dose adjustments required	[30, 32]
			AUC	1.48	1.44–1.52	↑ 48%		
		Moderate	C_{max}	1.28	1.26–1.31	↑ 28%	Decrease the dose to 300 mg BID	
			AUC	1.95	1.92–1.98	↑ 95%		
		Severe	C_{max}	1.31	1.28–1.33	↑ 31%	Olaparib is not recommended	
			AUC	1.27	2.25–2.29	↑ 27%		
Niraparib	PopPK model[c]	Mild	Exposure[d]	NR	NR	↔	No dose adjustments required	[51, 54, 134]
		Moderate	Exposure[d]	NR	NR	↔	No dose adjustments required	
Rucaparib	PopPK model[c]	Mild	AUC_{ss}	NR	NR	↑ 15%	No dose adjustments required	[84, 88]
		Moderate	AUC_{ss}	NR	NR	↑ 32%	No dose adjustments required	
Talazoparib	Clinical study[c,e]	Mild	C_{max}	1.11	0.74–1.66	↔	No dose adjustments required	[107]
			AUC	1.12	0.80–1.57	↔		
		Moderate	C_{max}	1.32	0.89–1.94	↔	Decrease the dose to 0.75 mg QD	
			AUC	1.43	1.03–1.98	↑ 43%		
		Severe	C_{max}	1.89	1.27–2.83	↑ 89%	Decrease the dose to 0.5 mg QD	
			AUC	2.63	1.88–3.69	↑ 163%		
	PopPK model[c]	Mild	CL/F	NR	NR	↓ 15%	No dose adjustments required	[106]
		Moderate	CL/F	NR	NR	↓ 38%	Decrease the dose to 0.75 mg QD	

AUC area under the plasma concentration–time curve, $AUC_{0-\infty}$ AUC from zero to infinity, AUC_{ss} AUC at steady state, AUC_{0-24} AUC from 0 to 24 hours, *BID* twice a day, *CI* confidence interval, *CL/F* apparent oral clearance, C_{max} maximum plasma concentration, *GLS mean* geometric least-squares mean, *NR* not reported, *PARP* poly (ADP-ribose) polymerase, *PBPK* physiologically based pharmacokinetic, *PK* pharmacokinetic, *PopPK* population pharmacokinetic, *QD* once a day, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no change

[a]Classification for renal impairment based on the Committee for Medicinal Products for Human Use guidance (CHMP/EWP/225/02 [135]). Normal renal function: creatinine clearance >80 mL/min; mild renal impairment: creatinine clearance 51–80 mL/min; moderate renal impairment: creatinine clearance 31–50 mL/min; severe renal impairment: creatinine clearance ≤30mL/min

[b]Creatinine clearance calculated according to the Cockcroft–Gault equation

Classification for renal impairment based on the Committee for Medicinal Products for Human Use guidance (EMA/CHMP/83874/2014 [136]). Normal renal function: creatinine clearance ≥90 mL/min; mild renal impairment: creatinine clearance 60–89 mL/min; moderate renal impairment: creatinine clearance 30–59 mL/ min; severe renal impairment: creatinine clearance ≤30 mL/min

[d]Not specified

[e]Estimated glomerular filtration rate, calculated using the Modification of Diet in Renal Disease formula

formulation [25]. In addition, an exposure–safety (categorical adverse events and hemoglobin) model has been developed using data from multiple clinical trials ($n = 757$). The probability of safety events and hemoglobin decrease were comparable in all exposure groups [300-mg BID capsules (C_{max} 7.67 µg/mL), 400-mg BID capsules (C_{max} 6.99 µg/mL), 200-mg BID tablets (C_{max} 6.18 µg/mL)], suggesting a minimal effect of olaparib exposure on safety [44].

Table 5 Impact of hepatic impairment on the pharmacokinetics of PARP inhibitors

PARP inhibitor	Method	Renal impairment	PK parameter	GLS mean ratio	90% CI	Effect on PK parameter	Advice	References
Olaparib tablets	Clinical study[a]	Mild	C_{max}	1.13	0.82–1.56	↔	No dose adjustment required	[31]
			$AUC_{0-\infty}$	1.15	0.72–1.93	↔		
		Moderate	C_{max}	0.87	0.63–1.22	↔	No dose adjustment required	
			$AUC_{0-\infty}$	1.08	0.66–1.74	↔		
	PBPK model[a]	Mild	C_{max}	1.06	1.05–1.07	↑ 6%	No dose adjustment required	[32]
			AUC	1.26	1.26–1.28	↑ 26%		
		Moderate	C_{max}	0.78	0.77–0.80	↓ 22%	No dose adjustment required	
			AUC	1.26	1.15–1.32	↑ 26%		
		Severe	C_{max}	0.59	0.58–0.59	↓ 41%	Olaparib is not recommended	
			AUC	1.06	1.03–1.08	↑ 6%		
Olaparib capsules	PBPK model[a]	Mild	C_{max}	1.16	1.15–1.16	↑ 16%	No dose adjustment required	[32]
			AUC	0.95	0.94–0.97	↓ 5%		
		Moderate	C_{max}	1.27	1.26–1.28	↑ 27%	No dose adjustment required	
			AUC	1.54	1.52–1.56	↑ 54%		
		Severe	C_{max}	1.04	1.03–1.06	↑ 4%	Olaparib is not recommended	
			AUC	2.20	2.13–2.28	↑ 120%		
Niraparib	PopPK model[b]	Mild	Exposure[c]	NR	NR	↔	No dose adjustment required	[51, 54]
	Clinical study[b]	Moderate	C_{max}	0.93	0.64–1.36	↔	Decrease the dose to 200 mg QD	[57]
			$AUC_{0-\infty}$	1.56	1.06–2.30	↑ 56%		
Rucaparib	PopPK model[b]	Mild	C_{min}	NR	NR	↔	No dose adjustment required	[75, 84, 88]
			AUC_{ss}	NR	NR	↔		
		Moderate	C_{min}	NR	NR	↔	No dose adjustment required	
			AUC_{ss}	NR	NR	↑ 32%		
	Clinical study[b]	Moderate	C_{max}	0.91	0.61–1.36	↔	No dose adjustment required	[87]
			$AUC_{0-\infty}$	1.45	0.67–3.13	↔		
Talazoparib	Clinical study/ PopPK[b]	Mild	Exposure[c] and CL/F	NR	NR	↔	No dose adjustment required	[108]
		Moderate	Exposure[c] and CL/F	NR	NR	↔	No dose adjustment required	
		Severe	Exposure[c] and CL/F	NR	NR	↔	No dose adjustment required	
	PopPK model[b]	Mild	CL/F	NR	NR	↔	No dose adjustment required	[106]

AUC area under the plasma concentration–time curve, $AUC_{0-\infty}$ AUC from zero to infinity, AUC_{ss} AUC at steady state, *CI* confidence interval, *CL/F* apparent oral clearance, C_{max} maximum plasma concentration, *GLS mean* geometric least-squares mean, *NR* not reported, *PARP* poly (ADP-ribose) polymerase, *PBPK* physiologically based pharmacokinetic, *PopPK* population pharmacokinetic, *PK* pharmacokinetic, *QD* once a day, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no change

[a]Classification for hepatic impairment based on the Committee for Medicinal Products for Human Use guidance (CHMP/EWP/2339/02) [137]. Mild hepatic impairment: Child-Pugh class A; moderate hepatic impairment: Child-Pugh class B; severe hepatic impairment: Child-Pugh class C

[b]Classification for hepatic impairment defined by National Cancer Institute Organ Dysfunction Working Group Criteria criteria [138]

[c]Not specified

In a retrospective study ($n = 27$), olaparib exposure was significantly associated with early adverse events in patients with BRCA1/2-mutated ovarian cancer. A trough concentration of 2500 ng/mL was identified as a threshold that can help to guide dose adjustments [11].

3.2 Niraparib

In 2017, niraparib has been approved by the EMA for the maintenance treatment of platinum-sensitive, recurrent, high-grade epithelial ovarian cancer regardless of BRCA

Table 6 Effect of food on the pharmacokinetics of PARP inhibitors after a single dose

PARP inhibitor	Condition	N	Dose (mg)	$t_{1/2}$ (h)	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-last} (ng × h/mL)	$AUC_{0-\infty}$ (ng × h/mL)	Result meal vs fasted state	References
Olaparib capsules	High-fat meal	31	400	12.20 ± 4.53^a	$4.03 (2.00–8.03)^a$	$6,070 (45.1\%)^a$	$64,620 (63.3\%)^a$	$65,440 (64.2\%)^a$	$\downarrow t_{1/2}$ 34% $\uparrow T_{max}$ 134% $\leftrightarrow C_{max}$ $\uparrow AUC_{0-last}$ 22% $\uparrow AUC_{0-\infty}$ 19%	[139]
	Standard meal	31	400	15.42 ± 5.92^a	$4.00 (1.00–8.00)^b$	$6,970 (45.9\%)^b$	$67,710 (86.4\%)^c$	$70,190 (80.5\%)^a$	$\downarrow t_{1/2}$ 16% $\uparrow T_{max}$ 133% $\uparrow C_{max}$ 10% $\uparrow AUC_{0-last}$ 20% $\uparrow AUC_{0-\infty}$ 21%	
	Fasted	31	400	18.39 ± 6.99^b	$1.72 (0.92–4.05)^d$	$6,350 (40.9\%)^d$	$58,400 (75.6\%)^d$	$61,060 (78.1\%)^b$		
Olaparib tablets	High-fat meal	54	300	11.1 ± 4.09^e	4.00 (1.00–12.0)	5,480 (40.5%)	$46,000 (56.6\%)^e$	$45,400 (57.1\%)^e$	$\leftrightarrow t_{1/2}$ $\uparrow T_{max}$ 167% $\downarrow C_{max}$ 21% $\uparrow AUC_{0-last}$ 8% $\uparrow AUC_{0-\infty}$ 8%	[36]
	Fasted	55	300	12.2 ± 5.31^f	1.50 (0.50–5.85)	7,000 (35.0%)	$43,600 (54.3\%)^f$	$43,000 (55.2\%)^g$		
Niraparib	High-fat meal	15	300	47.9 ± 17.5^h	8.0 ± 4.9^i	582.1 (39%)	27,186.4 (52%)	$31,194 (54\%)^h$	$\leftrightarrow t_{1/2}$ $\uparrow T_{max}$ 128% $\downarrow C_{max}$ 27% $\leftrightarrow AUC_{0-last}$ $\leftrightarrow AUC_{0-\infty}$	[61]
	Fasted	16	300	50.5 ± 17.9	3.5 ± 1.2^i	803.7 (50%)	28,638.1 (63%)	$29,016.1 (63\%)^j$		
Rucaparib	High-fat meal	26	600	16.8 ± 9.5^k	7.83 (1.5–24.45)	959 (73%)	$13,900^l (74\%)$	NR	$\leftrightarrow t_{1/2}$ $\uparrow T_{max}$ 95% $\uparrow C_{max}$ 20% $\uparrow AUC_{0-24h}$ 38%	[91]
	Fasted	26	600	18.7 ± 9.9^m	4.02 (0.53–24.83)	819 (84%)	$10,000^l (76\%)$	NR		
Talazoparib	High-fat meal	18	0.5	113.6 ± 38.3	4.00 (0.75–5.00)	0.996 (22%)	58.215 (19%)	61.065 (19%)	$\leftrightarrow t_{1/2}$ $\uparrow T_{max}$ 300% $\downarrow C_{max}$ 46% $\leftrightarrow AUC_{0-last}$ $\leftrightarrow AUC_{0-\infty}$	[102]
	Fasted	18	0.5 g	116.7 ± 31.9	1.00 (0.50–1.52)	1.849 (41%)	59.694 (19%)	62.551 (18%)		

AUC area under the plasma concentration–time curve, *AUC*$_{0–24h}$ AUC from zero to 24 hours, *AUC*$_{0–last}$ AUC from zero to the last measurable timepoint, *AUC*$_{0–∞}$ AUC from zero to infinity, *C*$_{max}$ maximum plasma concentration, *CV%* percentage coefficient of variation, *N* number of subjects, *NR* not reported, *PARP* poly (ADP-ribose) polymerase, *SD* standard deviation, *t*$_{1/2}$ elimination half-life, *T*$_{max}$ time to maximum plasma concentration, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no change

Data are presented as mean (CV%) for C$_{max}$, AUC$_{0–last}$ and AUC$_{0–∞}$, as median (range) for t$_{max}$ and mean ± SD for t$_{1/2}$

[a]Based on 27 patients

[b]Based on 29 patients

[c]Based on 28 patients

[d]Based on 30 patients

[e]Based on 51 patients

[f]Based on 54 patients

[g]Based on 52 patients

[h]Based on 14 patients

[i]t_{max} is presented as mean ± SD

[j]Based on 15 patients

[k]Based on 11 patients

[l]AUC$_{0–24h}$,[m] based on 19 patients

status (Table 1). In the phase III NOVA trial, niraparib maintenance treatment resulted in a prolonged median PFS in the gBRCA-mutated cohort [21.0 vs 5.5 months; HR 0.27 (95% CI 0.173–0.410), *p* < 0.001], the cohort with an HRD deficiency [12.9 vs 3.8 months; HR 0.38 (95% CI 0.243–0.586), *p* < 0.001], and the non-gBRCA-mutated cohort [9.3 vs 3.9 months; HR 0.45 (95% CI 0.338–0.607), *p* < 0.001] [45]. The approved dose of 300 mg once a day (QD) was the MTD with fatigue, pneumonitis, and thrombocytopenia as dose-limiting toxicities [46]. Niraparib was additionally approved in 2020 as maintenance treatment following first-line platinum therapy based on the PRIMA trial with prolonged PFS in the overall niraparib population [13.8 vs 8.2 months; HR 0.62 (95% CI 0.50–0.76), *p* < 0.001] [47].

3.2.1 Preclinical Pharmacology

In Table 2, the in vitro interaction of niraparib with enzymes and transporters is summarized. Niraparib has the potential to cause off-target effects on the cardiovascular and central nervous systems, as it inhibits the neuronal dopamine, norepinephrine, and serotonin transporters. Except for the inhibition of MATE-1 and MATE-2 and being a substrate to P-gp and breast cancer resistance protein (BCRP), niraparib is no substrate to, or inhibitor of other important enzymes or transporters [48].

In vivo, niraparib treatment resulted in tumor regression in a BRCA-1 mutant mouse xenograft model [49], as well as BRCA wild-type models [10]. Although niraparib is substrate of P-gp and BCRP, it is able to permeate the blood–brain barrier with sustainable brain exposure in mice. The high permeability might overcome the transporter-mediated efflux of niraparib [10, 49]. Concentrations in

tumor tissue (subcutaneous breast and ovarian cancer xenograft models) three times higher than in plasma have been reported. However, niraparib also has the unfavorable property of distributing into the bone marrow where platelets are generated [10, 49].

3.2.2 Clinical Pharmacokinetics

Table 3 shows the steady-state pharmacokinetic parameters of niraparib. Niraparib is classified as a BCS class II compound (low solubility, high permeability) with a high bioavailability and protein binding (73% and 83%, respectively). It has a high volume of distribution of 1220 L and preferably distributes into red blood cells with a blood-to-plasma ratio of 1.6 [48, 50–52]. The intra-individual variability in exposure is 36.9%, which has been determined in a population pharmacokinetic (PopPK) model [48, 51]. Metabolism mainly takes place by carboxylesterases with M1 as the main metabolite. M1 undergoes glucuronidation by uridine 5′-diphospho-glucuronosyltransferase to form M10. The M1 and M10 metabolites are inactive. Niraparib and its metabolites are eliminated by hepatic and renal routes, with 32% and 40% of total administered dose being recovered in feces and urine, respectively [51, 53].

3.2.3 Pharmacokinetics in Special Populations

3.2.3.1 Patients with Renal Impairment The effect of renal impairment on the pharmacokinetics of niraparib was investigated in a PopPK model (Table 4). As no differences were observed in exposure between patients with a normal, mild, and moderate renal function, no dose adjustments are

Table 7 Overview of drug–drug interaction studies

PARP inhibitor	Method	Compound	Enzymatic target	Effect on PARP inhibitor	PARP inhibitor effect on compound	Conclusion	References
Olaparib capsules	PBPK model	Itraconazole	Strong CYP3A4 inhibitor	↑ C_{max} 33% ↑ AUC 152%	–	Strong CYP3A4 enzyme inhibitors should be avoided during olaparib treatment. If coadministration cannot be avoided, the olaparib dose should be reduced from 400 mg to 150 mg BID.	[32]
		Fluconazole	Moderate CYP3A4 inhibitor	↑ C_{max} 17% ↑ AUC 98%	–	Moderate CYP3A4 enzyme inhibitors should be avoided during olaparib treatment. If coadministration cannot be avoided, the olaparib dose should be reduced from 400 mg to 200 mg BID.	
		Fluvoxamine	Weak CYP3A4 inhibitor	↔ C_{max} ↔ AUC	–	Co-administration of olaparib with weak CYP3A4 inhibitors is permitted with olaparib treatment.	
		Rifampin	Strong CYP3A4 inducer	↓ C_{max} 45% ↓ AUC 71%	–	Strong CYP3A4 enzyme inducers should be avoided during olaparib treatment	
		Efavirenz	Moderate CYP3A4 inducer	↓ C_{max} 34% ↓ AUC 53%	–	Strong CYP3A4 enzyme inducers should be avoided during olaparib treatment	
		Dexamethasone	Weak CYP3A4 inducer	↔ C_{max} ↔ AUC		Co-administration of olaparib with weak CYP3A4 inducers is permitted with olaparib treatment.	
		Midazolam	CYP3A4 substrate	–	↑ C_{max} 11% ↑ AUC 45%	Caution should be exercised when CYP3A4 substrates with a narrow therapeutic window are combined with olaparib	
		Simvastatin	CYP3A4 substrate	–	↑ C_{max} 27% ↑ AUC 47%	Caution should be exercised when CYP3A4 substrates with a narrow therapeutic window are combined with olaparib	
		Digoxin	P-gp substrate	–	↔ C_{max} ↔ AUC	Clinically relevant interactions with P-gp substrates cannot be excluded. Appropriate clinical monitoring is advised	
		Raltegravir	UGT1A1 substrate	–	↔ C_{max} ↔ AUC	No clinical relevant interaction	
Olaparib tablets	In vivo	Itraconazole	Strong CYP3A4 inhibitor	↑ C_{max} 42% ↑ AUC_{0-last} 166% ↑ $AUC_{0-\infty}$ 170% ↔ $t_{1/2}$	-	Strong CYP3A4 enzyme inhibitors should be avoided during olaparib treatment	[37]
		Rifampin	Strong CYP3A4 inducer	↓ C_{max} 71% ↓ AUC_{0-last} 88% ↓ $AUC_{0-\infty}$ 87% ↔ $t_{1/2}$	–	Strong CYP3A4 enzyme inducers should be avoided during olaparib treatment	
	PBPK model	Itraconazole	Strong CYP3A4 inhibitor	↑ C_{max} 20% ↑ AUC 255%	–	Strong CYP3A4 enzyme inhibitors should be avoided during olaparib treatment. If coadministration cannot be avoided, the olaparib dose should be reduced from 300 mg to 100 mg BID	[32]

Table 7 (continued)

PARP inhibitor	Method	Compound	Enzymatic target	Effect on PARP inhibitor	PARP inhibitor effect on compound	Conclusion	References
		Fluconazole	Moderate CYP3A4 inhibitor	↑C_{max} 14% ↑AUC 121%	–	Moderate CYP3A4 enzyme inhibitors should be avoided during olaparib treatment. If coadministration cannot be avoided, the olaparib dose should be reduced from 300 mg to 150 mg BID	
		Fluvoxamine	Weak CYP3A4 inhibitor	↔C_{max} ↔AUC	–	Co-administration of olaparib with weak CYP3A4 inhibitors is permitted with olaparib treatment	
		Rifampin	Strong CYP3A4 inducer	↓C_{max} 44% ↑AUC 75%	–	Strong CYP3A4 enzyme inducers should be avoided during olaparib treatment	
		Efavirenz	Moderate CYP3A4 inducer	↓C_{max} 31% ↓AUC 60%	–	Strong CYP3A4 enzyme inducers should be avoided during olaparib treatment	
		Dexamethasone	Weak CYP3A4 inducer	↔C_{max} ↔AUC	–	Co-administration of olaparib with weak CYP3A4 inducers is permitted with olaparib treatment	
		Midazolam	CYP3A4 substrate	–	↑C_{max} 18% ↑AUC 61%	Caution should be exercised when CYP3A4 substrates with a narrow therapeutic window are combined with olaparib	
		Simvastatin	CYP3A4 substrate	–	↑C_{max} 33% ↑AUC 54%	Caution should be exercised when CYP3A4 substrates with a narrow therapeutic window are combined with olaparib	
		Digoxin	P-gp substrate	–	↔C_{max} ↔AUC	Clinically relevant interactions with P-gp substrates cannot be excluded. Appropriate clinical monitoring is advised	
		Raltegravir	UGT1A1 substrate	–	↔C_{max} ↔AUC	No clinical relevant interaction	
	In vivo	Tamoxifen	CYP3A4 inducer	↓C_{max} 20% ↓AUC_{0-tau} 27%	↑C_{max} 13% ↑AUC_{0-tau} 16% *N-DMT* ↔C_{max} ↓AUC_{0-tau} 8% *Endoxifen* ↔C_{max} ↔AUC_{0-tau}	Co-administration of olaparib with tamoxifen shows no clinical relevant interaction	[38]
		Anastrazole	CYP3A4 substrate	↔C_{max} ↔AUC_{0-tau}	↓C_{max} 10% ↓AUC_{0-tau} 14%	Co-administration of olaparib with anastrazole shows no clinical relevant interaction	
		Letrozole	CYP3A4 substrate	↔C_{max} ↑AUC_{0-tau} 15%	↓C_{max} 6% ↓AUC_{0-tau} 5%	Co-administration of olaparib with letrozole shows no clinical relevant interaction	
	PBPK model	Grapefruit juice (bergamottin)	CYP3A4 inhibitor	↑C_{max} 1.04-fold ↑AUC 1.11-fold		No clinically relevant interaction	[140]
		St. John's wort (hyperforin)	CYP3A4/5 inducer	↓C_{max} 0.84-fold ↓AUC 0.54-fold		No clinically relevant interaction	
		Turmeric (curcumin)	CYP3A4/5 inhibitor	↑C_{max} 1.22-fold ↑AUC 1.40-fold		No clinically relevant interaction	

Table 7 (continued)

PARP inhibitor	Method	Compound	Enzymatic target	Effect on PARP inhibitor	PARP inhibitor effect on compound	Conclusion	References
Rucaparib	In vivo	Caffeine	CYP1A2 substrate		↔ C_{max}; ↑ AUC_{0-72h} 126%	Dose adjustments should be considered for CYP1A2 substrates with a narrow therapeutic window (e.g., tizanide, theophylline) when concomitantly used with rucaparib	[83, 92]
		S-warfarin	CYP2C9 substrate		↔ C_{max}; ↑ AUC_{0-96h} 49%	Dose adjustments should be considered for CYP2C9 substrates with a narrow therapeutic window (e.g., warfarin, phenytoin) when concomitantly used with rucaparib	
		Omeprazole	CYP2C19 substrate		↔ C_{max}; ↑ AUC_{0-72h} 55%	The risk for a relevant effect on the exposure of PPIs is small. No dose adjustments are required for CYP2C19 substrates	
		Midazolam	CYP3A4 substrate		↔ C_{max}; ↑ AUC_{0-72h} 39%	Dose adjustments should be considered for CYP3A4 substrates with a narrow therapeutic window (e.g., cyclosporine, tacrolimus) when concomitantly used with rucaparib	
		Digoxin	P-gp substrate		↔ C_{max}; ↑ AUC_{0-72h} 20%	No clinically relevant interaction	
		Rosuvastatin	BCRP substrate		↑ C_{max} 29%; ↑ AUC_{0-last} 34%	Dose adjustments are not necessary when concomitantly used with rucaparib	
		Ethinylestradiol	CYP3A and CYP2C9 substrate		↔ C_{max}; ↑ AUC_{0-last} 43%	Dose adjustments are not necessary when concomitantly used with rucaparib	
		Levonorgestrel	CYP3A substrate		↔ C_{max}; ↑ AUC_{0-last} 56%	Dose adjustments are not necessary when concomitantly used with rucaparib	
	PopPK model	PPI	P-gp inhibitor	↑ FI 15%	–	Rucaparib exposure is not affected by the concomitant use of proton pump inhibitors. No dose adjustments are required	[75]
		NR	P-gp inhibitor CYP1A2 inhibitor CYP2D6 inhibitor	↔ Exposure	–	Concomitant use of strong P-gp, CYP1A2, or CYP2D6 inhibitors has no impact rucaparib pharmacokinetics	
Talazoparib	PopPK model	P-gp inhibitors		↑ FI 45%	–	A dose reduction from 1 to 0.75 mg is required in patients taking potent P-gp inhibitors	[106]
		Acid-reducing agents (PPI, H₂-receptor antagonists)		↔ Exposure	–	No dose adjustments are required	

Table 7 (continued)

PARP inhibitor	Method	Compound	Enzymatic target	Effect on PARP inhibitor	PARP inhibitor effect on compound	Conclusion	References
	In vivo	Itraconazole	P-gp inhibitor	↑C_{max} 40% ↑AUC_{0-last} 51% ↑AUC_{0-inf} 56%	–	Coadministration of talazoparib with potent P-gp inhibitors should be avoided. If coadministration cannot be avoided, the talazoparib dose should be reduced from 1 to 0.75 mg QD	[109]
		Rifampicin	P-gp inducer	↑C_{max} 37% ↔AUC_{0-last} ↔AUC_{0-inf}	–	The effect on rucaparib exposure is limited. No dose adjustments are required	

AUC area under the plasma concentration–time curve, *AUC_{0-last}* AUC from zero to the last measurable time point, *$AUC_{0-\infty}$* AUC from zero to infinity, *AUC_{0-tau}* AUC from time zero to the end of the dosing interval (tau), *BID* twice a day, *C_{max}* maximum plasma concentration, *CV%* percentage coefficient of variation, *CYP* cytochrome P450, *F1* relative bioavailability, *H_2* histamine 2, *N* number of subjects, *NR* not reported, *PARP*, *PBPK* pharmacologically based pharmacokinetic, *P-gp* P-glycoprotein, *PopPK* population pharmacokinetic, *PPI* proton pump inhibitor, *QD* once a day, *SD* standard deviation, *$t_{1/2}$* elimination half-life, *T_{max}* time to maximum plasma concentration, *UGT* uridine 5′-diphospho-glucuronosyltransferase (UDP)-glucuronosyltransferase, ↑ indicates increase, ↓ indicates decrease, ↔ indicates no change

required [51, 54]. The effect of severe renal impairment has not been assessed. Niraparib itself can mildly affect the estimated glomerular filtration rate. This is probably not an effect of inhibition of the tubular creatinine secretion, like olaparib [20, 39, 55], but of hemodynamic impairment due to dopamine and norepinephrine transporter inhibition. As the effect is mild and reversible in most cases, this is not an indication of treatment discontinuation [56].

3.2.3.2 Patients with Hepatic Impairment Niraparib exposure was significantly increased in patients with moderate hepatic impairment (Table 5). Therefore, a starting dose of 200 mg is recommended [57]. In a PopPK model, exposure in patients with mild hepatic impairment ($n = 27$) was not different from exposure in patients with a normal hepatic function ($n = 351$), thus no dose adjustments are advised in this group [51, 54]. The effect of severe impaired hepatic function on niraparib pharmacokinetics has not been established.

3.2.4 Other Factors Influencing the Pharmacokinetics of Niraparib

In a PopPK model, the impact of age, sex, ethnicity, and body weight on niraparib pharmacokinetics was evaluated. These variables could not explain the moderate-to-high interindividual variability (e.g., 52.5% for oral clearance) [51, 54]. However, clinical studies demonstrated low body-weight (< 77 kg) to be correlated with a higher exposure (C_{max} and AUC). These patients might benefit from a lower starting dose of 200 mg/day, which is currently advised [58, 59]. No effect of age was demonstrated in the PopPK model, which was confirmed in an efficacy and safety analysis. Patients aged > 70 years ($n = 61$) had comparable PFS benefits and incidence of adverse events, compared to patients aged < 70 years ($n = 311$) [60].

3.2.5 Food Effect

The results of the food-effect study are shown in Table 6. A high-fat meal delays the time to C_{max} and decreases the C_{max} of niraparib significantly, but the extent of absorption was not altered. The efficacy and safety profile of niraparib was not affected, therefore niraparib can be taken with or without food [61].

3.2.6 Drug–Drug Interactions

No in vivo DDI studies are performed. The risk of DDIs with CYP enzyme inhibitors or inducers is minimal, as the major route of metabolism is mediated by carboxylesterases. Additionally, gastric-reducing agents are unlikely to alter exposure because niraparib solubility is independent of a pH

below its pKa of 9.95 [51]. Co-administration of niraparib with substrates to MATE-1 or MATE-2 (e.g., metformin) could potentially result in increased plasma concentrations of the co-administered drug [48].

3.2.7 Clinical Pharmacodynamics

3.2.7.1 Exposure Efficacy In patients, efficacious PARP inhibition (> 90% inhibition of PARP in tumor tissue) was reached at doses of 80 mg/day and above and durable responses measured by Response Evaluation Criteria in Solid Tumors (RECIST) were observed at doses of 60 mg/day [46, 62]. Dose–efficacy relationships were investigated using data from two clinical trials. In the retrospective analysis of the NOVA safety population ($n = 553$), PFS was similar in patients using 100, 200, and 300 mg/day in gBRCA-mutated and non-gBRCA-mutated patients. However, dose modifications (80%) and interruptions (73%) were common [58]. This is in line with the results of the QUADRA study ($n = 463$). Clinical benefit rate (ORR), disease control rate, and clinical benefit rate at 24 weeks (CBR24) was similar between patients receiving a mean niraparib dose of ≤ 200 mg/day (8%, 58%, and 19%, respectively) and patients receiving > 200 mg/day (7%, 39%, and 15%, respectively) [63].

A pharmacokinetic model was developed using phase I and III data (NOVA trial, $n = 512$) to investigate exposure–efficacy relationships. A trend towards increased PFS with increased exposure (AUC) was observed in the non-gBRCA group [11.5 vs 7.5 months; HR 0.70 (95% CI 0.49–0.99)], while this relationship was absent in the gBRCA group [> 15.7 vs 15.9 months; HR 0.91 (95% CI 0.54–1.52)] [48, 64]. More research should be conducted to investigate a possible exposure–efficacy relationship, as these data are inconclusive.

3.2.7.2 Exposure Toxicity In the phase I dose-escalation trial, hematological toxicities were more often observed at higher doses and seemed dose proportional [46]. The incidence of nausea, thrombocytopenia, and fatigue was 74%, 61%, and 59%, respectively, in patients using the recommended dose of 300 mg/day in the phase III NOVA trial ($n = 367$) [45]. The incidence was significantly lower in patients initiating niraparib at 200 mg/day (16%, 14%, and 24% respectively) in a real-world cohort ($n = 153$) [65]. Furthermore, 66.5% of the patients in the phase III NOVA trial needed a dose reduction and 68.9% had dose interruptions. Dose reductions reduced the incidence of grade 3 and 4 thrombocytopenia, anemia, and neutropenia [45, 66].

A PopPK model was developed to investigate exposure–response relationships using data from the NOVA trial. Exposure (AUC, C_{max}, minimum concentration) was

significantly associated with any grade of thrombocytopenia and other hematologic and non-hematologic treatment-emergent adverse events [67].

In addition, patients with a low bodyweight (< 77 kg) or low platelet counts (< 150.000/mL) at baseline had a higher risk of grade > 3 thrombocytopenia (35% vs 12%) [58]. Bodyweight was correlated with higher exposure (C_{max} and AUC) [59] and it is recommended to start with a dose of 200 mg/day for patients with a bodyweight < 77 kg and/or baseline platelets of < 150.000/mL [58, 59]. This individualized dosing strategy was further investigated in the PRIMA trial ($n = 733$) [47, 68] and NORA trial ($n = 177$) [69], with safety being significantly improved while efficacy not being affected. This was confirmed in two real-life cohorts [62, 67]. In summary, data clearly show a relationship between the dose and exposure of niraparib and toxicity.

3.3 Rucaparib

In the ARIEL2 study and study 10, rucaparib treatment of patients with g/sBRCA-mutated platinum-sensitive, relapsed, high-grade ovarian cancer resulted in an ORR, complete response, and partial response of 53.8%, 8.5%, and 45.3%, respectively, leading to the accelerated first approval of rucaparib in 2016 (Table 1) [71–73]. The recommended dose of 600 mg BID was selected based on toxicity and clinical activity with no MTD [71]. Additional approval was granted for the maintenance treatment of platinum-sensitive, relapsed, high-grade ovarian cancer regardless of BRCA status with a prolonged median PFS in the BRCA group [16.6 vs 5.4 months; HR 0.23 (95% CI 0.16–0.34), $p < 0.0001$], HRD group [13.6 vs 5.4 months; HR 0.32 (95% CI 0.24–0.42), $p < 0.0001$], and total group [10.8 vs 5.4 months; HR 0.36, (95% CI 0.30–0.45), $p < 0.0001$] [74].

3.3.1 Preclinical Pharmacology

Table 2 shows the in vitro interaction of rucaparib with enzymes and transporters. Rucaparib inhibits many enzymes and transporters, causing a high risk for DDIs in patients (Sect. 3.3.6). Inhibition of the renal transporters OCT2, MATE-1, and MATE-2K have been related to an increase in creatinine levels without affecting renal function [19, 20]. Furthermore, the antagonistic activity towards the non-selective sigma receptor and several kinases [75] are likely to cause off-target side effects (e.g., increase in cholesterol), but are unlikely to exert anti-tumor activity [76].

P-glycoprotein and BCRP are restricting oral availability and brain accumulation in mice, causing tumor resistance and limiting the use against brain metastasis [77]. Despite limited brain penetration in glioblastoma xenografts [78],

antitumor activity was still observed in an intracranial BRCA1-mutated model [79].

3.3.2 Clinical Pharmacokinetics

Steady-state pharmacokinetic parameters of rucaparib are shown in Table 3. Rucaparib is a BCS class IV compound (low solubility and low permeability). Bioavailability is low (36%) with a concentration-independent protein binding of 70.2% in vitro [80]. Rucaparib has a mean volume of distribution of 211 L [81] and preferentially distributes into red blood cells with an average blood-to-plasma ratio of 1.83 [80]. Rucaparib is extensively metabolized by CYP enzymes (Table 2), undergoing phase I and phase II reactions with M324 as the major metabolite. M324 is 30 times less potent compared with rucaparib and mainly eliminated by the kidneys. In a mass balance study, the mean recovery of the administered dose was 17.4% and 71.9% for urine and feces, respectively (7.6% and 63.9% unchanged) [82, 83].

3.3.3 Pharmacokinetics in Special Populations

3.3.3.1 Patients with Renal Impairment The effect of renal impairment on the pharmacokinetics of rucaparib is summarized in Table 4. Although exposure of rucaparib was slightly higher in patients with mild and moderate renal impairment, no dose adjustments are required because the side effects and efficacy were not affected [84]. In patients with severe renal impairment or in patients undergoing dialysis, rucaparib is not recommended [7, 75, 85]. However, rucaparib therapy was safe in a single patient with dialysis-dependent renal failure using trough concentrations for dose optimization [86]. Therefore, therapeutic drug monitoring might be useful in patients with severe renal impairment or patients undergoing dialysis.

3.3.3.2 Patients with Hepatic Impairment The effect of hepatic impairment on rucaparib exposure is shown in Table 5. No dose adjustments are required in patients with mild or moderate hepatic impairment, but the advice is to monitor patients for adverse events [75, 84, 87, 88]. Until the effect of severe hepatic impairment is investigated, rucaparib is not recommended in patients with severe hepatic impairment [7].

3.3.4 Other Factors Influencing Pharmacokinetic Parameters

Bodyweight [75, 89], body mass index, race, alpha-1 acid glycoprotein, and age have no significant effect on pharmacokinetic parameters of rucaparib [75]. Efficacy and safety were similar in age subgroups, indicating no effect of age on rucaparib pharmacokinetics [90]. Steady-state exposure

(AUC) at 600 mg BID was not different between CYP2D6 phenotypes (poor metabolizers, $n = 9$; intermediate metabolizers, $n = 71$; normal metabolizers, $n = 76$; ultra-rapid metabolizers, $n = 4$) or CYP1A2 phenotypes (normal metabolizers, $n = 28$, hyper-inducers, $n = 136$). Therefore, no dose adjustments are needed [84].

3.3.5 Food Effect

The results of the food-effect study are summarized in Table 6. A high-fat meal delays the time to C_{max} and increases the AUC and C_{max} significantly. This was confirmed in a PopPK model with an increase in bioavailability from 32.7 to 51.7% when rucaparib was taken with a high-fat meal [84]. Food might increase intestinal solubility, as rucaparib is poorly water soluble. The increase in exposure is clinically insignificant because pharmacokinetic variability is not reduced and efficacy and safety are acceptable [91]. Therefore, rucaparib can be taken with or without food.

3.3.6 Drug–Drug Interactions

The results of DDI studies are summarized in Table 7. Rucaparib is extensively metabolized by CYP enzymes; however, CYP1A2 or CYP2D6 inhibitors did not impact rucaparib exposure. As rucaparib is metabolized by CYP3A4, the effect of strong CYP3A4 inhibitors and inducers should be explored [75]. Concomitant use of proton pump inhibitors showed no meaningful effect on rucaparib pharmacokinetics [85].

In addition, dose adjustments should be considered for CYP1A2, CYP2C9, and CYP3A4 substrates with a narrow therapeutic window when administered with rucaparib [92]. Rucaparib had a marginal effect on digoxin exposure, but the effects could be underestimated, as digoxin is not the most selective P-gp probe [75, 93, 94]. Rucaparib weakly increased exposure to oral contraceptives and rosuvastatin. As hormone levels vary widely between individuals, it is unlikely that efficacy is affected and toxicity increased. Although no dose adjustments are recommended for rosuvastatin, attention should be used in case of genetic polymorphisms in genes for BCRP and when extrapolating to other BCRP substates [95]. Furthermore, there is a high potential for DDIs when rucaparib is co-administered with substrates of MATE-1, MATE2-l, OCT1, and OCT2 (e.g., metformin) (Table 2) [75].

3.3.7 Clinical Pharmacodynamics

3.3.7.1 Exposure Efficacy Mean PARP inhibition in peripheral blood lymphocytes in patients was > 90% and not dose dependent between doses of 92 mg QD and 600 mg BID [96]. A PopPK model was developed using data from Study

10 and ARIEL2 to explore exposure–efficacy relationships in patients with BRCA-mutated ovarian cancer ($n = 121$). The AUC averaged by the actual dose received over time was correlated with an investigator radiologist review-assessed RECIST response in the subgroup of platinum-sensitive recurrent disease ($n = 75$, $p = 0.017$). Other efficacy endpoints were not correlated. Sample size was small, thus no definite conclusion can be drawn [89, 97].

3.3.7.2 Exposure Toxicity In patients taking the recommended dose of 600 mg BID in the phase I/II ARIEL2 study and study 10, adverse events were common and frequently led to dose reductions (69%) and treatment interruptions (64%) [71]. In addition, dose-limiting toxicities were reported in patients receiving doses above 480 mg BID, while doses below were well tolerated [96].

In an exposure–safety analysis with data from Study 10 and ARIEL2 in patients with BRCA-mutated ovarian cancer ($n = 393$), $C_{max,ss}$ was associated with grade ≥ 2 creatinine ($p < 0.001$), grade ≥ 3 alanine aminotransferase ($p = 0.033$), grade ≥ 3 aspartate aminotransferase ($p = 0.027$), fatigue ($p = 0.029$), platelet decrease ($p = 0.04$), and a maximum hemoglobin change from baseline ($p < 0.001$) [89, 97]. The rise in creatinine levels is likely a result of inhibition of renal transporters without an impacting renal function [55]. These results indicate a relationship between exposure and toxicity.

3.4 Talazoparib

Talazoparib approval was granted in 2019 by the EMA for the treatment of gBRCA-mutated, human epidermal growth factor receptor-2 negative metastatic breast cancer (Table 1). In the phase III EMBRACA trial, talazoparib treatment resulted in a significantly longer median PFS [8.6 vs 5.6 months; HR 0.54 (95% CI 0.41–0.71), $p < 0.001$] and a higher ORR (62.6% vs 27.2%; OR 5.0, $p < 0.001$) compared with standard therapy [98]. The approved dose of 1.0 mg QD was also the MTD [99].

3.4.1 Preclinical Pharmacology

In Table 2, the in vitro interaction of talazoparib with enzymes and transporters is summarized. Talazoparib is the most potent catalytic PARP inhibitor with the highest trapping potency [100–102]. It inhibits tankyrase 1 and tankyrase 2 (PARP5a and b) causing an anti-cancer and anti-fibrotic effect, but also the induction of bone loss with increased osteoclasts [103]. Talazoparib has no effect on enzymes and transporters, but is a substrate to P-gp and BCRP. This is confirmed in vivo, with 1.9 times and 15 times higher plasma and brain concentrations, respectively, in P-gp and BCRP knockout mice [102].

3.4.2 Clinical Pharmacokinetics

Pharmacokinetic parameters of talazoparib at steady state are described in Table 3. Talazoparib is a BCS class II or IV compound (low solubility, moderate permeability) with an estimated bioavailability of at least 55% based on a mass balance study and protein binding of 74% (in vitro) [104, 105]. The apparent volume of distribution is 420 L [102, 104] with no preferable distribution into red blood cells [105]. Metabolism of talazoparib is minimal and the major route of elimination is renal excretion. Mean recovery of the total administered dose is 68.7% (54.6% unchanged) in urine and 19.7% (13.6% unchanged) in feces [104, 105].

3.4.3 Pharmacokinetics in Special Populations

3.4.3.1 Patients with Renal Impairment The effect of renal impairment on the pharmacokinetics of talazoparib is summarized in Table 4. Dose adjustments are recommended for patients with moderate or severe renal impairment, as clearance is decreased [106] and exposure significantly increased [107].

3.4.3.2 Patients with Hepatic Impairment

The effect of hepatic impairment on talazoparib exposure is shown in Table 5. No effect of mild, moderate, or severe hepatic impairment was observed on talazoparib pharmacokinetics. Therefore, no dose adjustments are required [106, 108].

3.4.4 Other Factors Influencing Pharmacokinetic Parameters

The effect of several covariates on the pharmacokinetics of talazoparib was explored by a PopPK model. Age, sex, and body weight had no clinical relevant effect on talazoparib exposure. Talazoparib clearance was 24.7% higher and exposure approximately 20% lower in Asian patients compared with non-Asian patients. P-glycoprotein and BCRP polymorphisms are ethnicity dependent with a higher frequency of single nucleotide polymorphisms in Asian individuals compared with white individuals. This might contribute to the lower exposure in Asian individuals, but no dose adjustments are recommended, as 1 mg QD is the MTD [106].

3.4.5 Food Effect

The effect of food on talazoparib pharmacokinetics is shown in Table 6. A high-fat meal delays the time to C_{max} and decreases the C_{max} significantly, but does not influence the extent of absorption [102]. These findings are consistent

with a PopPK analysis where the absorption rate is decreased (Ka) without any change in the extent of absorption (F1) [106]. In conclusion, talazoparib can be taken with or without food.

3.4.6 Drug–Drug Interactions

Table 7 summarizes the results of DDI studies. Concomitant use of potent P-gp inhibitors increases bioavailability and exposure of talazoparib significantly. Therefore, a reduced dose of 0.75 mg is advised when talazoparib is co-administered with potent P-gp inhibitors. Gastric-reducing agents had no effect on talazoparib exposure, which was expected based on the pH-independent solubility [106, 109]. As talazoparib is a substrate to BCRP, the effect of BCRP inhibitors cannot be excluded and should be further investigated.

3.4.7 Clinical Pharmacodynamics

3.4.7.1 Exposure Efficacy Talazoparib shows a dose-dependent and exposure-dependent PARP activity in peripheral blood mononuclear cells with sustained PARP inhibition at and above doses of 0.6 mg/day [99]. Exposure–efficacy relationships were demonstrated in the EMBRACA and ABRAZO trials. In the EMBRACA trial ($n = 281$), the time-varying average talazoparib concentration ($C_{avg,t}$, [to account for dose modifications]) was significantly associated with longer PFS [110]. Dose reductions resulted in a trend towards a marginally less favorable PFS outcome compared with patients without dose reductions. However, dose reductions itself could lead to a shorter PFS, but it could also be a marker of worse prognosis and therefore a shorter PFS [111]. An exposure–efficacy analysis using data from the phase II ABRAZO trial ($n = 81$) found a trend towards a higher ORR with higher exposure, but no relationship with PFS. However, patient numbers were small [112]. These data suggest an exposure–efficacy relationship is apparent.

3.4.7.2 Exposure Toxicity An exposure–safety analysis was performed with pooled data from the EMBRACA ($n = 285$) and ABRAZO trials ($n = 82$). Patients above the median exposure ($C_{avg,t}$) experienced more events of anemia and thrombocytopenia. In the final Cox proportional hazard model, a higher $C_{avg,t}$ was associated with a higher risk for anemia and thrombocytopenia and there was a trend towards a higher log-transformed $C_{avg,t}$ and risk for neutropenia [111, 113]. These results indicate an exposure–toxicity relationship.

4 Discussion

We provided an overview of the (pre)-clinical pharmacology, clinical pharmacokinetics, and clinical pharmacodynamics of the four approved PARP inhibitors. This review reveals that PARP inhibitors have overlapping characteristics and unique properties as well. While all four PARP inhibitors are potent inhibitors of PARP enzymes with comparable half-maximal inhibitory concentration values, they differ in their PARP-trapping potency. Talazoparib has the most rigid structure with two chiral centers, which likely accounts for its potent trapping ability (50–100 times higher) compared with olaparib, niraparib, and rucaparib [103]. Cytotoxicity of PARP inhibitors as a single agent is correlated with PARP trapping and not with catalytic inhibition of PARP [114, 115]. Talazoparib shows the greatest PARP trapping potency, which is also correlated with increased toxicity in normal cells. Therefore, the MTD of talazoparib is much lower than other PARP inhibitors [116, 117]. Furthermore, the approved dose of talazoparib is in the range of the half-maximal inhibitory concentration for PARP inhibition, and therefore the only PARP inhibitor showing a dose-dependent and exposure-dependent inhibition of PARP in peripheral blood mononuclear cells. Unbound steady-state concentrations of olaparib, niraparib, and rucaparib exceed the half-maximal inhibitory concentration for PARP inhibition, which probably means that maximal PARP inhibition is reached at doses far below the recommended dose in patients.

Interestingly, olaparib and niraparib have similar catalytic activities and cytotoxicity against BRCA mutant cells and xenograft models [114], but niraparib is more efficacious in BRCA wild-type models [10]. This is also observed in patients with BRCA wild-type ovarian cancer, with a 5.4-month improvement in PFS for niraparib [45] compared with 1.9 months for olaparib. [14]. BRCA wild-type cells might require higher concentrations of the PARP inhibitor than BRCA-mutated cells, which explains the greater efficacy of niraparib; niraparib concentrations in wild-type tumors in mice were ten times higher compared with olaparib at therapeutic and comparable doses [118]. Initially, PARP inhibitor treatment was restricted to BRCA-mutated patients. As BRCA wild-type patients with HRD-positive tumors and no mutations in homologous recombination repair genes also benefit from PARP inhibitor treatment (but to a lesser extent), indications are expanding. It becomes more clear that biomarkers beyond BRCA, like other deficiencies in homologous recombination repair, play a role in the susceptibility to PARP inhibitors [119, 120].

Olaparib and rucaparib are substrates and inhibitors of several enzymes and transporters. Both PARP inhibitors increase creatinine without affecting renal function and have a high risk for DDIs. Niraparib has less effect on enzymes and transporters and the contribution of talazoparib is minimal. This can be an advantage for patients with comorbidities using multiple drugs. All four PARP inhibitors are substrates of the P-gp efflux transporter causing interactions and limiting the brain penetration. However, niraparib is classified as a BSC II compound with a high permeability that might (partly) overcome the P-gp-mediated efflux that could justify its use in the case of brain metastasis.

Poly (ADP-ribose) polymerase inhibitors differ in the way they are metabolized and excreted. While olaparib and rucaparib are metabolized by CYP enzymes, metabolism of niraparib is mainly mediated by carboxylesterase enzymes and metabolism of talazoparib is minimal. Poly (ADP-ribose) polymerase inhibitors are hepatically and renally cleared with no preferred route for olaparib and niraparib and the liver being the main route of excretion for rucaparib and the kidneys for talazoparib. Dose adjustments are necessary in patients with renal dysfunction for olaparib and talazoparib and for niraparib in patients with hepatic impairment.

Exposure is dose proportional for all PARP inhibitors, except for olaparib capsules because of limited solubility. The improved tablet formulation increased bioavailability and decreased the high administration burden. Niraparib and talazoparib have convenient long half-lives allowing QD dosing while olaparib and rucaparib have shorter half-lives and are dosed BID. All PARP inhibitors are classified as BCS class II or IV compounds with low solubility [23, 48, 75, 121]. This might contribute to the moderate-to-high interindividual variability in exposure; however, exposure is not drastically affected by intake with food.

While a PARP exposure–efficacy relationship is present for talazoparib, this relationship remains inconclusive for olaparib, niraparib, and rucaparib. Average unbound steady-state concentrations of rucaparib at the recommended dose of 600 mg BID are much higher than the required exposure for durable anti-tumor response in preclinical models [75] and exceed the half-maximal effective concentration for cytotoxicity. Based on these data and because dose findings of targeted anti-cancer agents are still mostly based on toxicity, rather than efficacy, the optimal dose of rucaparib might be lower than the current recommended dose. However, further clinical studies should investigate and confirm efficacy at lower dose levels.

Although PARP inhibitors have the same mechanism of action, they differ in their toxicity profile. Rucaparib has the most reported adverse drug reaction, which could be expected based on its many off-target effects (Table 2) [122]. Hypercholesterolemia is specific for rucaparib mediated through off-target kinase inhibition [76]. Hypertransaminasemia

has been reported for rucaparib and niraparib and less for olaparib [123]. Niraparib is the only PARP inhibitor causing hypertension, due to off-target inhibition of neuronal dopamine, norepinephrine, and serotonin transporters, increasing neurotransmitters with inotropic effects on the heart. These neurotransmitters are involved in the psychiatric and nervous system disorders as well, which explains the association with niraparib. Gastrointestinal adverse events are very common and a class effect of PARP inhibitors. Furthermore, hematological toxicities, such as anemia, thrombocytopenia, and neutropenia are frequently reported and an on-target class effect. PARP-1 trapping is not only related to cytotoxicity in cancer cells with HRD, but also drives bone marrow toxicity [124]. Additionally, inhibition of PARP-2 is directly related to anemia, due to impaired differentiation of erythroid progenitors and a shortened lifespan of erythrocytes [125]. Awareness of the delayed adverse events of myelodysplastic syndrome and acute myeloid leukemia is important, as these adverse events can be lethal and occur after several months [126]. Niraparib has the highest number of reported hematological toxicities followed by rucaparib and olaparib, related to the volume of distribution [123]. Dose reductions and treatment interruptions occurred frequently with niraparib, but efficacy was not affected [58]. Therefore, the recommended dose of 300 mg/day is possibly higher than necessary for sufficient efficacy, especially for gBRCA-mutated patients, and lower doses of niraparib might be justified. While BRCA status is predictive for efficacy, it is not related to toxicity [127]. Higher exposure is associated with an increase in efficacy for talazoparib and with an increase in hematological toxicities for all PARP inhibitors and thereby might be a rationale for therapeutic drug monitoring.

5 Conclusions

Poly (ADP-ribose) polymerase inhibitors are valuable anticancer agents with rapidly expanding indications. The understanding of the overlapping and unique pharmacokinetic and pharmacodynamic properties of PARP inhibitors can guide the choice of the PARP inhibitor, support treatment optimization, and improve clinical outcomes.

Declarations

Ethics Approval Not applicable.

Consent to Participate Not applicable.

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