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REVIEW

The forefront of ovarian cancer therapy: update on PARP inhibitors

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Background: In recurrent ovarian cancer, poly(ADP-ribose) polymerase (PARP)-inhibiting agents have transformed the treatment of platinum-sensitive disease. New data support use of PARP inhibitors earlier in the treatment algorithm.
Design: We review results from recent phase III trials evaluating PARP inhibitors as treatment and/or maintenance therapy for patients with newly diagnosed ovarian cancer. We discuss the efficacy and safety of these agents in the all-comer and biomarker-selected populations studied in clinical trials, and compare the strengths and limitations of the various trial designs. We also consider priorities for future research, with a particular focus on patient selection and future regimens for populations with high unmet need.
Results: Four phase III trials (SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26 and VELIA/GOG-3005) demonstrated remarkable improvements in progression-free survival with PARP inhibitor therapy (olaparib, niraparib or veliparib) for newly diagnosed ovarian cancer. Differences in trial design (treatment and/or maintenance setting; single agent or combination; bevacizumab or no bevacizumab), patient selection (surgical outcome, biomarker eligibility, prognosis) and primary analysis population (intention-to-treat, *BRCA* mutated or homologous recombination deficiency positive) affect the conclusions that can be drawn from these trials. Overall survival data are pending and there is limited experience regarding long-term safety.
Conclusions: PARP inhibitors play a pivotal role in the management of newly diagnosed ovarian cancer, which will affect subsequent treatment choices. Refinement of testing for patient selection and identification of regimens to treat populations that appear to benefit less from PARP inhibitors are a priority.
Key words: PARP inhibitor, ovarian cancer, olaparib, niraparib, veliparib, phase III

INTRODUCTION

For many years, treatment of patients with newly diagnosed ovarian cancer centred on cytoreductive surgery followed by carboplatin and paclitaxel. Changes to the paclitaxel schedule have been explored with sometimes conflicting results.[1–5] In the past decade, the addition of bevacizumab to chemotherapy following debulking surgery has become standard of care in many countries,[6] supported by the progression-free survival (PFS) benefit observed in the randomised phase III GOG-0218 and ICON7 trials.[7,8] In some countries, bevacizumab is restricted to stage IV or high-risk disease, or patients with residual disease, but PFS benefit is also observed in patients with no residual disease[9] and National Comprehensive Cancer Network guidelines have no restriction according to risk.[10] The European Society for Medical Oncology-European Society of Gynaecological Oncology (ESMO-ESGO) guidelines state that bevacizumab should be considered in addition to carboplatin and paclitaxel, but that evidence for bevacizumab in the neoadjuvant setting is less clear and there is no Level I evidence for additional improvement in efficacy.[11–13] Thus, there remained a high unmet need for new and/or improved treatments for patients with advanced disease, especially those with clinical characteristics associated with a poor prognosis, such as stage IV disease, macroscopic residual disease after primary debulking surgery (PDS), and neoadjuvant chemotherapy (NACT).

The ovarian cancer treatment landscape was transformed in 2014 with the first approval of poly(ADP-ribose) polymerase (PARP) inhibitors. These agents exploit *BRCA* mutations and DNA damage response (DDR) deficiencies. Inhibition of PARP leads to propagation of single-strand

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DNA breaks and accumulation of double-strand breaks, which require repair by homologous recombination (HR) repair mechanisms. In ovarian cancer, PARP inhibitors were initially developed as maintenance therapy in patients with sustained complete or partial response after platinum-based chemotherapy for recurrent disease. The remarkable improvement in PFS in three randomised phase III trials — NOVA/ENGOT-OV16, SOLO-2/ENGOT-OV21 and ARIEL3[14–16] — led to regulatory approval of niraparib, olaparib and rucaparib, respectively, as maintenance therapy for platinum-sensitive recurrent ovarian cancer, irrespective of biomarker status. Development up to this point has been described in detail in our previous review article.[17] Olaparib, rucaparib and niraparib monotherapy are also approved in various guises in the treatment (rather than maintenance) setting for pretreated recurrent ovarian cancer.[18–20]

In addition to extensive evaluation in the recurrent setting, clinical development of PARP inhibitors has included randomised phase III trials in the front-line setting. These trials evaluated olaparib, niraparib and another PARP inhibitor, veliparib, which is still investigational. In this article, we review the results and implications of trials evaluating PARP inhibitors in the front-line setting, and aim to define the optimal positioning of these agents in the treatment algorithm for ovarian cancer.

LATEST DATA: PARP INHIBITORS IN THE FRONT-LINE SETTING

Trial designs and patient populations

Four phase III trials evaluating PARP inhibitors in the front-line setting have been published: SOLO-1, PAOLA-1/ENGOT-OV25, PRIMA/ENGOT-OV26 and VELIA/GOG-3005.[21–24] The trial designs are summarised in Table 1. Although all four trials were in the front-line setting and had a primary end point of PFS, there are considerable differences between them, particularly in relation to the control arms (placebo or active drug), patient populations (notably regarding sensitivity to induction platinum and residual disease), timing of PARP inhibitor initiation (concomitant with chemotherapy versus maintenance only), and planned duration of PARP inhibitor therapy, making meaningful comparisons an almost impossible challenge. The differences between trials are evident when comparing the control arms of the trials, which performed quite differently in the various study populations. Each of the trials was designed with a specific hypothesis in mind, reflecting divergence in clinical development and target populations for these agents. Conversely, each of the trials has limitations to generalisability and applicability, which we discuss below.

In the maintenance setting, the SOLO-1 trial compared maintenance olaparib (for up to 2 years, or beyond in patients with partial response at 2 years) versus placebo in patients with newly diagnosed advanced ovarian cancer with a *BRCA1* and/or *BRCA2* mutation.[21] All but three patients had germline *BRCA1/2* mutations. Most patients (82%) had no evidence of disease (NED) after chemotherapy and a normal cancer antigen-125 (CA-125) level, as well as a good performance status. An obvious limitation to general applicability of the SOLO-1 results is the restriction of eligibility to patients with *BRCA*-mutated tumours. The results do not inform on patients with non-*BRCA*-mutated tumours. In addition, the trial lacked bevacizumab-containing therapy and prior bevacizumab was not permitted.

PRIMA/ENGOT-OV26 evaluated niraparib for up to 3 years in patients with disease at high risk of treatment failure.[23] Patients with stage III ovarian cancer and no residual disease after PDS were excluded and 67% of patients had received NACT. Thus, PRIMA/ENGOT-OV26 enrolled a population with disease characteristics where arguably a bevacizumab-containing regimen could be considered standard of care, and the lack of bevacizumab is considered a weakness (while acknowledging that the evidence for concomitant bevacizumab in patients receiving NACT is limited). Exclusion of patients with no visible residuum at PDS, which is the goal of cytoreductive surgery, also limits the applicability of the results to a number of patients in routine oncology practice.

The PAOLA-1/ENGOT-OV25 trial[22] included bevacizumab in both treatment arms, and the absence of an olaparib-alone arm is a limitation, as it is not possible to determine the contribution of bevacizumab to the combination regimen's activity. Olaparib was continued for up to 2 years (or beyond in patients with partial response at 2 years) but bevacizumab was discontinued after 15 months' treatment (including bevacizumab given in combination with chemotherapy before initiation of olaparib). Although the design reflects the current and approved usage of bevacizumab, results from the BOOST/AGO-OVAR 17 trial (NCT01462890) comparing 15 versus 30 months of bevacizumab in the front-line setting may affect interpretation and implementation of the PAOLA-1/ENGOT-OV25 results. Finally, regarding generalisability, results from PAOLA-1/ENGOT-OV25 are not applicable to patients considered ineligible for bevacizumab.

The VELIA/GOG-3005 trial[24] evaluated PARP inhibition from the start of systemic treatment, concomitantly with chemotherapy as well as in the maintenance setting, with veliparib continued for up to 2 years in the concomitant arm. The trial design was very similar to that of the GOG-0218 trial evaluating bevacizumab as concomitant-only therapy or concomitant and maintenance therapy with chemotherapy,[7] and some of the criticisms made of GOG-0218 may also be levelled at VELIA/GOG-3005. In particular, the contribution of veliparib during the concomitant chemotherapy phase is difficult to define in the absence of a fourth arm evaluating veliparib given only as maintenance therapy after chemotherapy. In addition, similar to the SOLO-1 and PRIMA/ENGOT-OV26 trials, the lack of bevacizumab may be regarded as a limitation of the trial.

Efficacy

The main efficacy findings from each trial are summarised in Table 2. Taken together, these four positive trials provide strong evidence for the pivotal role of PARP inhibitors in the

Table 1. Overview of randomised phase III trials of PARP inhibitors in the front-line ovarian cancer setting

Trial	Maintenance			With chemotherapy
	PRIMA/ENGOT-OV26 ($N = 733$)[23]	SOLO-1 ($N = 391$)[21]	PAOLA-1/ENGOT-OV25 ($N = 806$)[22]	VELIA/GOG-3005 ($N = 1140$)[24,25,a]
Treatment arms	Niraparib vs placebo	Olaparib vs placebo	Olaparib + bevacizumab vs placebo + bevacizumab	Veliparib + CP → veliparib vs veliparib + CP → placebo[a] vs placebo + CP → placebo
PARP inhibitor duration	36 months or until PD	Until PD (up to 2 years if NED, continued in patients with PR at 2 years)	Up to 24 months or until PD or unacceptable toxicity	Up to 24 months
Randomisation	2:1	2:1	2:1	1:1[a]:1
Patient population	Stage III with visible residual tumour after PDS, inoperable stage III, or any stage IV ovarian cancer CR or PR (investigator assessment) to 6–9 cycles of platinum-based chemotherapy	*BRCA1/2* mutated, CR or PR (≥30% decrease in tumour volume, or NED on imaging but CA-125 >ULN) to platinum-based chemotherapy (without bevacizumab)	Newly diagnosed stage III/IV high-grade ovarian cancer or other non-mucinous ovarian cancers with *BRCA1/2* mutation, regardless of surgical outcome NED or CR or PR after first-line platinum + taxane + bevacizumab	Newly diagnosed stage III/IV high-grade serous ovarian cancer in patients undergoing PDS or IDS
Primary end point	PFS (BICR assessed) in HRD and ITT populations (hierarchical testing)	PFS (investigator assessed)	PFS (investigator assessed)	PFS (investigator assessed) in the veliparib-throughout vs control arms ($N = 757$) in *BRCA*-mutated, HRD and ITT populations (sequentially)
Stage IV	35%	17%	30%	22%
PDS	33%	63%	51%	68%
R0 after PDS	Excluded	47% (75% of those undergoing PDS)	30% (60% of those undergoing PDS)	32% (47% of those undergoing PDS)
Neoadjuvant chemotherapy	67%	35%	42%	27%
R0 after IDS	Excluded	29% (82% of those undergoing IDS)	30% (70% of those undergoing IDS)	13% (48% of those undergoing IDS)
BRCA mutated	30%	100%	30%	26%
CR to platinum	69%	82%	20% (+53% NED)	22%[b] (46% CR or NED) [R. Coleman, personal communication]
ECOG PS 0	70%	78%	70%	60%
HRD testing	myChoice® test (Myriad Genetics): *BRCA* deleterious mutation and/or HRD score ≥42	NA (*BRCA* testing using BRACAnalysis® test; Myriad Genetics)[c]	myChoice® HRD Plus assay (Myriad Genetics): tumour *BRCA* mutation or HRD score ≥42	myChoice® HRD CDx assay (Myriad Genetics): *BRCA* mutation by BRACAnalysis® CDx (Myriad Genetics) or HRD score ≥33

BICR, blinded independent central review; CA-125, cancer antigen-125; CP, carboplatin + paclitaxel; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; HRD, homologous recombination deficiency; IDS, interval debulking surgery; ITT, intention-to-treat; NA, not applicable; NED, no evidence of disease; PARP, poly(ADP-ribose) polymerase; PD, disease progression; PDS, primary debulking surgery; PFS, progression-free survival; PR, partial response; ULN, upper limit of normal.

[a] The design including all three arms of the trial is described, but data are reported only for the veliparib-throughout and control arms, excluding the veliparib combination-only arm.

[b] Among 290 patients with measurable disease after primary surgery.

[c] Or *BRCA1/2* genetic testing assay (BGI) at Chinese sites.

front-line treatment of ovarian cancer. Secondary endpoints typically showed supportive results, although overall survival results are not yet mature for any of the trials. Of note, the population predefined for the primary endpoint analysis differed between trials, thus findings from subgroup analyses in some trials are more robust than in others. This is important when considering interpretation of specific patient populations, as the main conclusions should be based on the predefined primary analysis population for which each trial was powered.

All four trials demonstrated significantly improved PFS in the intention-to-treat population. In the SOLO-1 trial, this comprised only *BRCA*-mutated cancers as patients without *BRCA*-mutated tumours were excluded. In PAOLA-1/ENGOT-OV25, the all-comer population represented the primary endpoint population. In PRIMA/ENGOT-OV26, the primary analysis population was the HR deficiency (HRD)-positive population, followed hierarchically by the all-comer population. In SOLO-1 and VELIA/GOG-3005, the primary end point (SOLO-1) or first population in the hierarchical testing (VELIA/GOG-3005) was the *BRCA*-mutated cancer population. In VELIA/GOG-3005, hierarchical testing of the HRD-positive cohort (which included the *BRCA*-mutated cohort) also demonstrated a statistically significant benefit; passage through the *BRCA* and HRD cohorts led to the all-comer analysis mentioned previously.

In exploratory analyses of HRD-positive non-*BRCA*-mutated populations, the hazard ratio favoured the PARP inhibitor-containing regimen in PRIMA/ENGOT-OV26 and PAOLA-1/ENGOT-OV25. In VELIA, there was a numerical trend in the same direction. These patients were excluded from SOLO-1.

The final row of Table 2 shows results in patients testing negative for HRD using the Myriad myChoice® assay

Table 2. Summary of efficacy in randomised phase III trials of PARPis in the front-line ovarian cancer setting

Trial	Maintenance			With chemotherapy
	PRIMA/ENGOT-OV26 niraparib ($N = 733$)[23]	SOLO-1 olaparib ($N = 391$)[21]	PAOLA-1/ENGOT-OV25 olaparib + bevacizumab ($N = 806$)[22]	VELIA/GOG-3005 veliparib ($N = 1140$)[24,26,a]
Median duration of follow-up, months (PARPi vs control)	14	41 vs 41	23 vs 24	28
All comers	**($N = 733$)**	NA	**($N = 806$)**	($N = 757$)
PFS HR (95% CI)	**0.62 (0.50–0.76)**		**0.59 (0.49–0.72)**	0.68 (0.56–0.83)
Median PFS, months (PARPi vs control)[b]	**13.8 vs 8.2**		**22.1 vs 16.6**	23.5 vs 17.3
BRCA mutated	($N = 223$)	**($N = 391$)**	($N = 237$)	**($N = 200$)**
PFS HR (95% CI)	0.40 (0.27–0.62)	**0.30 (0.23–0.41)**	0.31 (0.20–0.47)	**0.44 (0.28–0.68)**
Median PFS, months (PARPi vs control)[b]	22.1 vs 10.9	**(NE vs 13.8)**	37.2 vs 21.7	**34.7 vs 22.0**
HRD test positive	**($N = 373$)**	NR	($N = 387$)	($N = 421$)
PFS HR (95% CI)	**0.43 (0.31–0.59)**		0.33 (0.25–0.45)	0.57 (0.43–0.76)
Median PFS, months (PARPi vs control)[b]	**21.9 vs 10.4**		37.2 vs 17.7	31.9 vs 20.5
HRD test positive non-*BRCA* mutated	($N = 150$)	NA	($N = 152$)	($N = 221$)
PFS HR (95% CI)	0.50 (0.31–0.83)		0.43 (0.28–0.66)	0.74 (0.52–1.06)
Median PFS, months (PARPi vs control)[b]	19.6 vs 8.2		28.1 vs 16.6	(22.9 vs 19.8)[c]
HRD test negative (proficient)	($N = 249$)	NR	($N = 277$)	($N = 249$)
PFS HR (95% CI)	0.68 (0.49–0.94)		1.00 (0.75–1.35)	0.81 (0.60–1.09)
Median PFS, months (PARPi vs control)[b]	8.1 vs 5.4		16.6 vs 16.2	15.0 vs 11.5

Results in bold represent primary end points.

CI, confidence interval; HR, hazard ratio; HRD, homologous recombination deficiency; NA, not applicable; NE, not evaluable; NR, not reported; PARPi, poly(ADP-ribose) polymerase inhibitor; PFS, progression-free survival.

[a] Data are reported only for the veliparib-throughout and control arms, excluding the veliparib combination-only arm.

[b] Median PFS was calculated from the time of randomisation after completion of platinum-based chemotherapy in PRIMA/ENGOT-OV26, SOLO-1 and PAOLA-1/ENGOT-OV25, but from the start of chemotherapy in VELIA/GOG-3005.

[c] The non-*BRCA*-mutated/HRD-positive cohort in VELIA/GOG-3005 was defined by a myChoice® CDx score of ≥33.

(Myriad Genetics, Inc., Salt Lake City, UT, USA; referred to as 'HR proficient' in some trials). In the PRIMA/ENGOT-OV26 trial, there was an effect with niraparib treatment in this population but median PFS was short in both treatment arms. In the PAOLA-1/ENGOT-OV25 trial there was no signal of effect (hazard ratio 1.00 vs the active bevacizumab control arm). Results in this population in the VELIA/GOG-3005 trial fell somewhere between PRIMA/ENGOT-OV26 and PAOLA-1/ENGOT-OV25 (albeit defined by a lower cut-off, thus including patients who were 'more proficient'). The absolute medians should not be compared because of the different starting points for the definition of PFS and differences in enrolled patient populations. While these results are provocative, it is important to recognise that these are hypothesis-generating exploratory analyses and therefore no definitive conclusions should be drawn.

When the PAOLA-1/ENGOT-OV25 trial was designed, it was anticipated that bevacizumab and olaparib might show synergy in non-*BRCA*-mutated tumours. There are several hypotheses why the bevacizumab and olaparib combination did not demonstrate synergy in patients with non-*BRCA*-mutated HRD-negative cancers. Firstly, in PAOLA-1/ENGOT-OV25, 60% of patients had no visible residual disease (R0) after PDS, and therefore were not selected based on a documented platinum-associated response. Furthermore, the olaparib/bevacizumab combination was given as maintenance therapy rather than definitive treatment. This contrasts with previous trials evaluating PARP inhibitor/anti-angiogenic combinations in the recurrent setting,[27–29] which enrolled well-defined populations selected on the basis of previous sustained response to platinum. Secondly, it is possible that the efficacy of the control arm may have made it difficult to discern a subtle treatment effect. Thirdly, in PRIMA/ENGOT-OV26, patients were profoundly platinum sensitive (CA-125 level close to normal, baseline residual disease reduced to <2 cm), which is hypothesised to predict benefit from PARP inhibition. Fourthly, anti-vascular endothelial growth factor (VEGF)-mediated hypoxia can be heterogeneous in distribution and has been documented to induce DDR kinases other than *BRCA1/2* in some experimental models.[30] Indeed, selective targeting of phosphorylated checkpoint kinase (CHK)1/2 and ataxia telangiectasia and RAD3-related protein (ATR)/ATM effectors demonstrated synthetic lethality in hypoxic conditions.[30] Thus, PARP inhibitors may not have taken advantage of this tumour microenvironmental potentiation under bevacizumab. Finally, retrospective analyses of bevacizumab trials in the front-line setting suggest that *BRCA* status does not predict for the magnitude of bevacizumab effect.[31] In PAOLA-1/ENGOT-OV25 we cannot address the hypothesis regarding bevacizumab-induced hypoxia affecting PARP inhibitor efficacy as both arms contain bevacizumab.

Safety

Differences in tolerability and safety among the four trials are summarised in Table 3. The incidence of grade ≥3 adverse events was notably higher in the experimental versus the control arm of the PRIMA/ENGOT-OV26 trial and, to a lesser extent, the SOLO-1 trial. In PRIMA/ENGOT-OV26, this elevated incidence was driven by frequent grade 3/4 haematological adverse events. In SOLO-1, anaemia was the most common grade 3/4 adverse event. In the PAOLA-1/ENGOT-OV25 trial, incidences of grade ≥3 adverse events exceeded 50% in both arms, reflecting an active rather than placebo maintenance control regimen. However, the

Table 3. Summary of safety in randomised phase III trials of PARPis in the front-line ovarian cancer setting

Trial	Maintenance						VELIA/GOG-3005 veliparib[24,a]			
	PRIMA/ENGOT-OV26 niraparib ($N = 728$)[23]		SOLO-1 olaparib ($N = 390$)[21]		PAOLA-1/ENGOT-OV25 olaparib + bevacizumab ($N = 802$)[22]		Maintenance-only phase ($N = 621$)		Entire treatment phase ($N = 748$)	
	PARPi ($N = 484$)	Control ($N = 244$)	PARPi ($N = 260$)	Control ($N = 130$)	PARPi ($N = 535$)	Control ($N = 267$)	PARPi ($N = 310$)	Control ($N = 311$)	PARPi ($N = 377$)	Control ($N = 371$)
Any grade, *N* (%)	478 (99)	224 (92)	256 (98)	120 (92)	531 (99)	256 (96)	294 (95)	290 (93)	377 (100)	371 (100)
Grade ≥3[b], *N* (%)	341 (70)	46 (19)	102 (39)	24 (18)	303 (57)	136 (51)	138 (45)	99 (32)	332 (88)	285 (77)
AE leading to treatment discontinuation, *N* (%)	58 (12)	6 (2)	30 (12)	3 (2)	109 (20)	15 (6)	53 (17)	3 (1)	NR	NR
AE leading to dose reduction, *N* (%)	343 (71)	20 (8)	74 (28)	4 (3)	220 (41)	20 (7)	74 (24)	12 (4)	NR	NR
Treatment ongoing at data cut-off, *N* (%)	177 (37)	69 (28)	13 (5)	1 (1)	56 (10)	20 (7)	NR	NR	NR	NR
Selected grade ≥3, *N* (%)										
Fatigue/asthenia	9 (2)	1 (<1)	10 (4)	2 (2)	28 (5)	4 (1)	19 (6)	3 (1)	31 (8)	12 (3)
Anaemia	150 (31)	4 (2)	56 (22)[c]	2 (2)[c]	93 (17)[c]	1 (<1)[c]	23 (7)	3 (1)	144 (38)[c]	97 (26)[c]
Thrombocytopenia	139 (29)	1 (<1)	2 (1)[d]	2 (2)[d]	9 (2)[d]	1 (<1)[d]	20 (6)	1 (<1)	105 (28)	30 (8)
Neutropenia	62 (13)	3 (1)	22 (8)[e]	6 (5)[e]	32 (6)[e]	8 (3)[e]	16 (5)	12 (4)	218 (58)	183 (49)

AE, adverse event; NR, not reported; PARPi, poly(ADP-ribose) polymerase inhibitor.
[a] Data are reported only for the veliparib-throughout and control arms, excluding the veliparib combination-only arm.
[b] Excludes grade 5 in SOLO-1 and VELIA/GOG-3005.
[c] Includes anaemia, decreased haemoglobin level, decreased haematocrit, decreased red cell count, erythropenia, macrocytic anaemia, normochromic anaemia, normochromic normocytic anaemia and normocytic anaemia.
[d] Includes thrombocytopenia, decreased platelet production, decreased platelet count and decreased plateletcrit.
[e] Includes neutropenia, febrile neutropenia, neutropenic sepsis, neutropenic infection, decreased neutrophil count, idiopathic neutropenia, granulocytopenia, decreased granulocyte count and agranulocytosis.

addition of olaparib to bevacizumab did not exacerbate bevacizumab-associated toxicity. Hypertension was the most frequent grade ≥3 adverse event in PAOLA-1/ENGOT-OV25, yet olaparib did not seem to increase this typical bevacizumab-associated toxicity; indeed, the olaparib-containing arm was associated with lower incidences of all-grade and grade ≥3 hypertension compared with the bevacizumab-alone arm. The reason for this unexpected finding is unclear. The incidence of grade 3/4 adverse events was highest in VELIA/GOG-3005 in both control and experimental arms, driven by high incidences of haematological toxicity; however, comparison should take into account that the VELIA/GOG-3005 trial included initial platinum—taxane chemotherapy treatment. The majority of adverse events occurred during chemotherapy; however, if only the maintenance phase is considered, the incidence of grade ≥3 adverse events, including haematological toxicities, in the veliparib-containing arm is within the range reported with PARP inhibitors in the three maintenance trials.

In all four trials, the proportion of patients with adverse events leading to treatment discontinuation was at least threefold higher in the PARP inhibitor-containing arm than the control arm, and was highest in PAOLA-1/ENGOT-OV25. Similarly, dose reduction was substantially more common with PARP inhibitors. However, differences in planned treatment duration should be considered when assessing this finding.

Overall, the safety profiles of niraparib, olaparib and veliparib in the four front-line trials were consistent with previously reported observations in the recurrent platinum-sensitive setting for niraparib, olaparib and rucaparib.[32] When comparing PAOLA-1/ENGOT-OV25 (olaparib plus bevacizumab) with SOLO-1 (olaparib monotherapy), a higher proportion of patients discontinued treatment because of adverse events in both treatment arms of PAOLA-1/ENGOT-OV25; however, discontinuation at the patient's request with minor adverse events was reported as toxicity in PAOLA-1 (but not in SOLO-1). Haematological toxicities, particularly anaemia, were the most common adverse event and in the PRIMA/ENGOT-OV26 trial of niraparib, there was a substantially higher incidence of thrombocytopenia. Of note, the niraparib starting dose was reduced during conduct of the PRIMA/ENGOT-OV26 trial, from 300 mg in all patients to 200 mg in patients with a baseline body weight <77 kg and/or a platelet count <150 000/mm^3 based on analyses from the NOVA trial.[33] Safety improved with the implementation of individualised dosing.

TREATMENT DECISION-MAKING

Despite the clear positive outcome of these four trials and the consistent message supporting use of PARP inhibitors in the front-line setting, the numerous differences, subtleties and nuances of both the designs and the results are challenging when trying to develop an updated algorithm for the front-line treatment of ovarian cancer. In *BRCA*-mutated tumours, there is no doubt that all patients should receive a PARP inhibitor. But with which regimen? Should we offer a doublet (bevacizumab/olaparib) or should we save bevacizumab until relapse? PAOLA-1/ENGOT-OV25 reported the longest median PFS in a setting where unfortunately 70% of patients will die from their disease. Of note, in the

PRIMA/ENGOT-OV26 trial, 75% of patients in the control arm (all of whom had achieved a complete or partial response on chemotherapy) had experienced progression or died within 18 months of randomisation. In these high-risk patients, bevacizumab is often used, although evidence specifically in patients with interval debulking surgery is limited.[3] Confounding the decision further, veliparib, as dosed in VELIA/GOG-3005, was also administered to a 'high-risk' population, with approximately 23% having stage IV disease and 60% having bulky unresectable disease (NACT population) or suboptimal PDS.

In patients with a positive HRD test but without *BRCA* mutation, should we offer a doublet or is single-agent PARP inhibitor or bevacizumab sufficient? Given the modest or absent treatment effect in patients with no *BRCA* mutation and a negative HRD test, is it justified to delay PARP inhibitor therapy until relapse and if so, what is the potential for long-term survival in patients receiving PARP inhibitors only for recurrent disease? In patients with HR-proficient disease, the potential risk of PARP-inhibitor therapy may outweigh the modest benefit. In this situation, bevacizumab-containing regimens upfront may be considered, with the option to administer a PARP inhibitor in later lines; however, this approach will need to demonstrate a subsequent response to platinum in these poor-prognosis patients. On the other hand, bevacizumab could be postponed to the second line based on data for patients with platinum-sensitive and platinum-resistant relapse. There is a substantial unmet need for patients with neither *BRCA* mutation nor HRD and an urgent requirement for novel combinations offering better outcomes. Furthermore, a more robust and reliable HRD (or ideally HR-proficient) test is required, not least because of the notable proportion of patients with exquisitely platinum-sensitive tumours selected for PRIMA/ENGOT-OV26 who nevertheless tested negative for HRD. Uncertainty with HRD testing is also illustrated by the 15—18% of patients recorded with HRD status 'not determined', most often because tumour tissue was lacking or of insufficient quality.

The decision about which PARP inhibitor to use is influenced by numerous factors, which may include potential differences in the potency of PARP trapping and PARP inhibitor concentrations in preclinical models, pharmacokinetics, pharmacodynamics and other preclinical data. However, from a practical perspective, the choice is driven predominantly by the available clinical data in each setting and the relevance to each individual patient, the need to combine with bevacizumab or not, as well as access, availability and reimbursement considerations and dosing schedule. Another important consideration relates to subsequent treatment. We have attempted to construct a treatment algorithm taking into account clinically critical questions, such as surgical approach (which some may consider parallel to the need for bevacizumab) and *BRCA* status (Figure 1). However, we strongly advise against cross-trial comparisons within subsets of the four trials evaluating front-line PARP inhibitors, as over-interpretation and extrapolation of results in very specific populations and excluding certain clinical settings is likely to lead to inappropriate conclusions, given the variation in patient populations enrolled, end points and assessments, and lack of data in certain populations. Making conclusive statements on subgroups that are neither controlled nor statistically powered is hazardous, and needs to be confirmed by higher levels of evidence. Table 4 reflects the opinions of the authors, underscoring the settings where data are more provocative and further evaluation is a priority. The authors' opinions on reserving PARP inhibition until relapse in some situations are also presented.

HRD TESTING

Since the arrival of PARP inhibitors in the clinic, *BRCA* testing has become routine in ovarian cancer[11] and is included in guidelines in many countries,[34,35] but HRD testing lags behind. Initial approvals of PARP inhibitors were restricted to patients with *BRCA* mutations, therefore the testing infrastructure was developed and implemented rapidly. In the platinum-sensitive setting, PARP inhibitors are approved irrespective of HRD status. HRD status is not routinely tested in many countries, at least in Europe, and sometimes raises more questions than it answers. Does the status quo change given the recent FDA approval of olaparib with bevacizumab only in patients testing positive for HRD, versus the approval of niraparib in all-comers irrespective of HRD status?

The first commercially available HRD assay was myChoice® CDx (Myriad Genetics), which was designed to determine HRD status through detection and classification of *BRCA1* and *BRCA2* (sequencing and large rearrangement) variants and assessment of genomic instability combining three parameters: loss of heterozygosity (LOH), telomeric-allelic imbalance and large-scale state transitions. By combining these three independent measures of HRD, prognostic power is increased compared with any of the individual components.[36] Of the four front-line trials reviewed in this article, three (PRIMA/ENGOT-OV26, PAOLA-1/ENGOT-OV25 and VELIA/GOG-3005) used the commercially available myChoice® test to determine HRD status, making this the most relevant for evidence-based decision-making according to HRD status. The definitions of HRD positivity varied between the trials. Initially, all three trials used an HRD score cut-off of $\geq$42 to define HRD positivity, but in the VELIA/GOG-3005 trial, this was subsequently revised to $\geq$33 to increase the sensitivity of detecting a response to PARP inhibitors after retrospective analyses from previous clinical trials.[37—39] This difference in thresholds has a slight impact on the reported prevalence of HRD status, which appeared marginally higher in VELIA/GOG-3005 (55%) than in PRIMA/ENGOT-OV26 (51%) or PAOLA-1/ENGOT-OV25 (48%). In SOLO-1, eligibility criteria required all patients to have *BRCA*-mutated tumours.

The second commercially available test is Foundation Medicine's FoundationFocus® CDx (Foundation Medicine, Inc., Cambridge, MA, USA), which tests tumour DNA to detect mutations in *BRCA1/2* genes and the percentage of

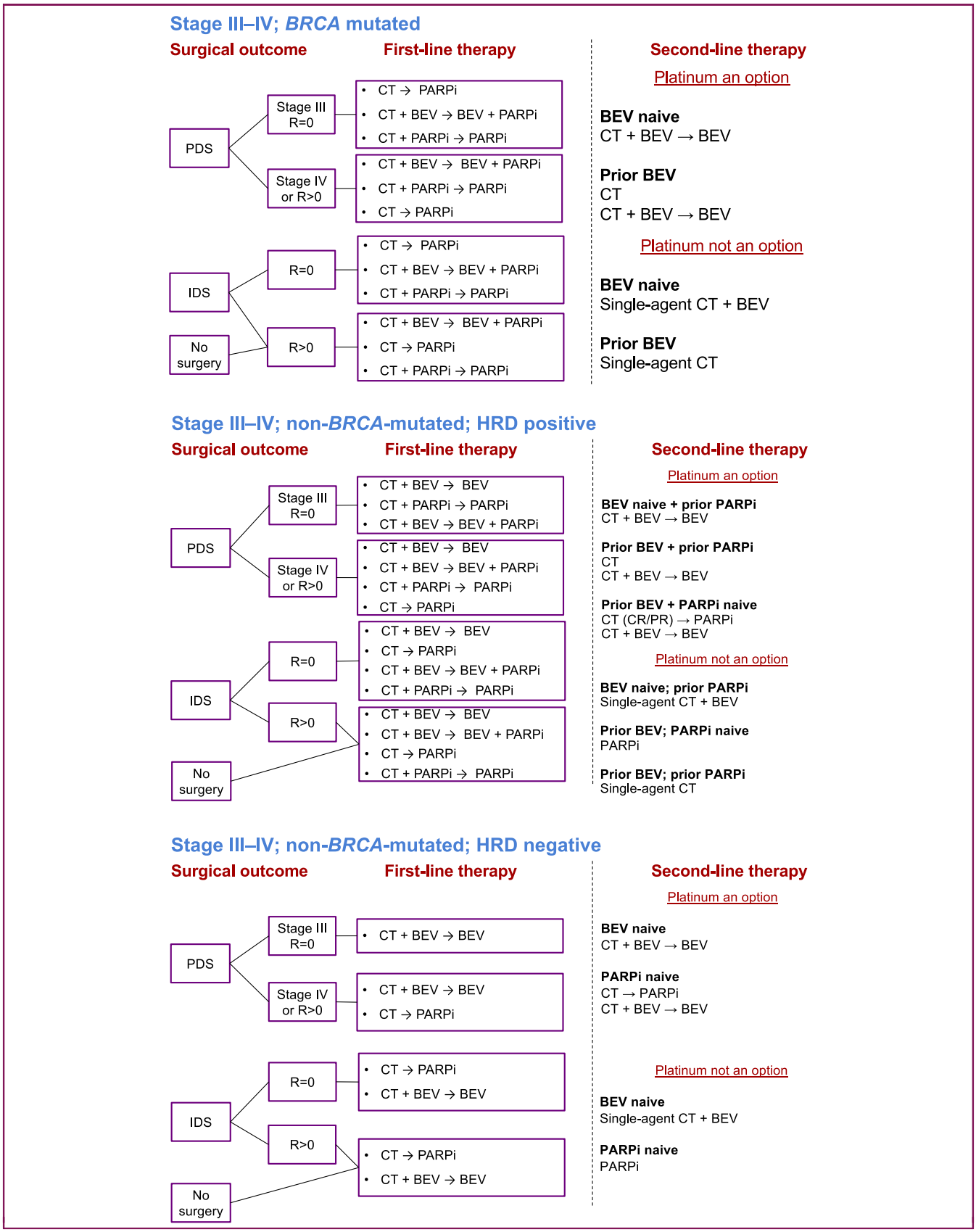

Figure 1. Evidence-based options in advanced ovarian cancer. The algorithms presented represent suggested considerations for treatment approach based on existing data and inference from analysed subgroups. The authors acknowledge that subgroup inference should be considered with caution as they have not been validated or formally tested in a prospective phase III setting. Table 4 represents the consensus of opinions among the authors. See text for details.

BEV, bevacizumab; CR, complete response; CT, chemotherapy; HRD, homologous recombination deficiency; IDS, interval debulking surgery; PARPi, poly(ADP-ribose) polymerase inhibitor; PDS, primary debulking surgery; PR, partial response; R, residual disease.

the genome affected by LOH.[40] Tumours are considered to be HRD positive if the LOH score is ≥16%. In the SOLO-1 population, an exploratory analysis of LOH showed that, despite *BRCA* mutation, 16% and 23% of samples evaluable for genome-wide LOH score would have been classified as LOH low using the Foundation Medicine FoundationOne companion diagnostic assay and a cut-off of 14% and 16%, respectively.[41]

Limitations of currently available options include the proportion of samples returned with 'unknown' status (as mentioned above), the possibility of false negatives, cost, frequent use of NACT (which in turn lessens the chance of obtaining adequate tumour samples for HRD testing) and unavailability/lack of access to testing. Newer assays under evaluation include those identifying somatic mutations in HR genes, array-based genomic hybridisation to identify genomic scars (large genomic aberrations), next-generation sequencing to identify mutational signatures or single nucleotide polymorphisms, HRD transcriptional profiles and functional assays.[42] Several academic groups have attempted or are attempting to develop HRD tests to identify patients with mutations in HR genes.[43–45] Tumiati et al. described a functional HRD test developed in ovarian cancer samples, which reliably predicted treatment response and outperformed other clinical and pathological parameters.[46] The test identified tumours with HRD-related mutational signature 3 and LOH, but also appeared to identify more patients with HRD than available genetic screening. Such tests require validation in larger cohorts, but show promise as a faster, less expensive alternative to sequencing. Phenotypic testing also avoids some of the challenges of currently available genotype testing, such as interpretation of variants of uncertain significance or non-actionable mutations.[47] Knowledge of HRD status — and consequently prediction of treatment response before completing primary chemotherapy — could guide treatment decisions. Availability of a reliable, easy-to-implement HRD test is essential to avoid administering PARP inhibitors in the front-line setting to patients considered unlikely to benefit. An ENGOT-led project is aiming to explore new HRD tests, and several, including *RAD51* foci, are currently being evaluated using tumour samples from the PAOLA-1/ENGOT-OV25 trial. In addition, there are ongoing efforts to capture exosomal DNA from blood to enable a real-time HR compliancy test. These are being evaluated in the veliparib-containing arms of VELIA/GOG-3005 and in the ongoing ATHENA trial (NCT03522246).

Another challenge of testing is tumour heterogeneity, both spatial and temporal. Samples reported as HRD negative may be HRD positive in other areas, and subclonal tumour populations may emerge.[48] Therefore, in the future it will be important to consider testing throughout the disease course and consider testing multiple metastatic lesions. In addition, tests should be able to detect restoration of HR repair and/or reversion of HR by chemotherapy. Chemotherapy administered between lines of PARP inhibition has a significant impact on HR, and platinum-based chemotherapy has previously been shown to restore *BRCA1/2* function in a notable number of patients, possibly due to selective pressure for secondary *BRCA* mutations. It has been suggested that these and other mechanisms restore HR and lead to resistance to PARP inhibitors (reviewed by Mweempwa and Wilson[49]). Repeat assessment of HRD might be used to guide PARP inhibition after platinum-based chemotherapy, but can be challenging in practice as most patients have a complete response or NED before maintenance therapy begins.

Currently available tests allow an indication that HRD is not present, but this is very different from a test designating a tumour to be HR proficient with an assay representative of the tumour microenvironment. Practically, a test determining HR proficiency is needed. It seems unlikely that cancers with functional DDR elements would benefit from PARP inhibition at achievable plasma levels. Mechanistically, if HR is functional, there are few reasons that a PARP inhibitor alone would cause cancer cell death. The primary mechanism would be release of non-homologous end joining, but even this would be a competitive environment for HR. A test that reliably determines HR proficiency would eliminate unnecessary exposure to PARP inhibitors unless administered with a combination that has documented efficacy.

PRIORITIES FOR FUTURE RESEARCH

Better identification and treatment of patients with HR-proficient tumours and the development of more effective treatments for these patients are a priority. Building on a foundation of anti-angiogenic therapy, perhaps immunotherapeutic agents will be more important in these patients with high unmet need, either as doublets, or as triplets combining anti-angiogenic, PARP inhibition and immunotherapeutic strategies.[50] Supplementary Table S1 (available at *Annals of Oncology* online) summarises ongoing phase III trials in the front-line setting (BOOST, IMagyn050, ATHENA, DUO-O, ENGOT-OV43, FIRST, MAMOC), any of which may change our interpretation of the existing front-line trials in a rapidly changing treatment landscape. While the JAVELIN OVARIAN trials failed to show any benefit from avelumab[51,52] and were prematurely terminated, other trials of immunotherapeutic agents in combination with targeted approaches are ongoing. If cure is achievable, the strategy of administering all available active agents together in rational upfront combinations has merit, although the financial impact cannot be underestimated. On the other hand, it begs the question of how to treat patients if disease recurs. To date, while re-treatment with bevacizumab is supported by results from the MITO16B-MaNGO OV2B-ENGOT OV17 randomised phase III trial,[53] we await results from the OReO/ENGOT-OV38 randomised phase III trial (NCT03106987) evaluating re-treatment with a PARP inhibitor, which will be critical to our understanding of subsequent therapy.

Beyond re-treatment options, there is a mechanistic rationale for combining PARP inhibitors with agents targeting other DDR pathways to promote synthetic lethality (reviewed by Taylor Veneris et al.[54]). These include WEE1,

Table 4. Preferred treatment strategy by subgroup.

Population	Treatment sequence (front-line → recurrence)
Stage III–IV, *BRCA* mutated	• Olaparib maintenance → chemotherapy + bevacizumab • Platinum + paclitaxel followed by olaparib maintenance → platinum-based chemotherapy + bevacizumab • Olaparib maintenance → carboplatin + PLD + bevacizumab with bevacizumab maintenance • Olaparib or niraparib maintenance (equal preference) → chemotherapy (platinum based or not, depending on the relapse) + bevacizumab • Carboplatin + paclitaxel followed by olaparib with or without bevacizumab → platinum doublet followed by PARP inhibitor if PARP inhibitor naive or did not progress on prior PARP inhibitor • Olaparib + bevacizumab maintenance → chemotherapy • Olaparib maintenance → PLD + carboplatin with rucaparib maintenance
Stage III–IV, non-*BRCA* mutated; HRD unavailable/unvalidated/unknown	• Niraparib maintenance → carboplatin + PLD + bevacizumab with bevacizumab maintenance • Niraparib maintenance → chemotherapy (platinum based or not, depending on the relapse) + bevacizumab • Carboplatin + paclitaxel followed by niraparib → platinum doublet followed by PARP inhibitor if PARP inhibitor naive or platinum doublet + bevacizumab followed by bevacizumab if previously treated with PARP inhibitor • Niraparib maintenance → chemotherapy + bevacizumab • Olaparib + bevacizumab maintenance → chemotherapy • Carboplatin + paclitaxel + bevacizumab with bevacizumab maintenance → carboplatin + paclitaxel + bevacizumab with bevacizumab maintenance • Platinum + paclitaxel + bevacizumab → platinum-based chemotherapy followed by PARP inhibitor
Stage III–IV; non-*BRCA* mutated; HRD positive	• Olaparib + bevacizumab maintenance → chemotherapy • Olaparib + bevacizumab maintenance → chemotherapy + bevacizumab • Platinum + paclitaxel + bevacizumab followed by bevacizumab + olaparib → platinum-based chemotherapy • Carboplatin + paclitaxel + bevacizumab with bevacizumab + olaparib maintenance → carboplatin + PLD with rucaparib maintenance • Niraparib maintenance → carboplatin + PLD + bevacizumab with bevacizumab maintenance • Niraparib maintenance → chemotherapy (platinum based or not depending on the relapse) + bevacizumab • Carboplatin + paclitaxel followed by niraparib → platinum doublet followed by PARP inhibitor if PARP inhibitor naive or platinum doublet + bevacizumab followed by bevacizumab if previously treated with PARP inhibitor
Stage III–IV; non-*BRCA* mutated; HRD negative	• Bevacizumab → chemotherapy followed by PARP inhibitor • Bevacizumab → chemotherapy + PARP inhibitor • Platinum + paclitaxel + bevacizumab → platinum-based chemotherapy followed by PARP inhibitor • Carboplatin + paclitaxel + bevacizumab followed by bevacizumab → platinum doublet + bevacizumab followed by bevacizumab • Paclitaxel + carboplatin + bevacizumab followed by bevacizumab → carboplatin + paclitaxel + bevacizumab followed by bevacizumab • Bevacizumab concomitant and maintenance → carboplatin + PLD with niraparib maintenance • Niraparib maintenance → chemotherapy (platinum based or not, depending on the relapse) + bevacizumab

While all agree that biomarker status should be the main driver in treatment decision-making, some authors consider additional clinical variables (e.g., primary versus interval debulking surgery, residual/stage IV disease versus no residual disease, quality of response to platinum, disease burden at diagnosis) to be important factors for decision-making in daily clinical practice.

HRD, homologous recombination deficiency; PARP, poly(ADP-ribose) polymerase; PDS, primary debulking surgery; PLD, pegylated liposomal doxorubicin.

ATR and CHK1.[55] In preclinical models derived from *BRCA*-mutant patient-derived xenograft models, the combination of a PARP inhibitor with ATR or CHK1 inhibition was more effective than PARP inhibition alone.[56] Evaluation of mechanisms of resistance is a priority for future research. A recent MITO study showed that among patients treated with maintenance olaparib for platinum-sensitive ovarian cancer, only 22% responded to subsequent therapy,[57] suggesting that resistance to platinum is a real clinical challenge after PARP inhibition. The main mechanisms described to date relate to restoration of homologous recombination repair and stabilisation of replication forks.[58–62] Several authors have reviewed mechanisms of resistance to PARP inhibitors and therefore this topic is not reviewed here in detail. Drugs showing promise in overcoming these mechanisms of resistance include inhibitors of ATR, CHK1, WEE1 and RAD51 (RI-1) and these approaches are being explored in combination with PARP inhibitors.[63] For example, the three-arm randomised phase II DUETTE trial (NCT04239014) is combining a PARP inhibitor re-treatment strategy with CHK1 inhibition in patients previously treated with a PARP inhibitor, comparing the efficacy of placebo versus olaparib versus olaparib plus the ATR inhibitor ceralasertib.

CONCLUSION ON THE ROLE OF PARP INHIBITORS IN THE FRONT-LINE SETTING

There is little doubt that the landscape of ovarian cancer management has changed dramatically with the introduction of PARP inhibitors into standard-of-care therapy. Ovarian cancer has been transformed into a chronic disease and there is a place for optimism that some patients may be cured. Factors affecting patient selection and treatment choice in the front-line setting include clinical risk factors, stage, comorbidities, clinical condition, timing of surgery (interval versus primary debulking), residual disease, the need for bevacizumab, and *BRCA* results. In addition, access to PARP inhibitors in specific populations may influence treatment decisions and may vary between Europe and the USA, according to regulatory approval, and even between different European countries, according to reimbursement. This is more likely to influence choice between different PARP inhibitors than any potential difference between the agents based on pharmacokinetic data, unless the different agents are ever compared head-to-head. In the recurrent setting, the importance of platinum sensitivity, which seems to be one of the most reliable biomarkers for sensitivity to PARP inhibitors, is clear, but this information is not available at the start of chemotherapy for newly diagnosed disease and we may need to rely more on *BRCA* and HRD status.

Knowledge of HRD status seems to be important in treatment decision-making for newly diagnosed ovarian cancer and indeed is important for access to olaparib in the USA, where the approval of maintenance olaparib after front-line chemotherapy is restricted to *BRCA*-mutated disease if given alone and HRD-positive disease if given in combination with bevacizumab. However, the accuracy and reliability of currently available tests leave room for improvement; developing more robust tests is a priority. On the other hand, niraparib is FDA-approved as maintenance therapy after front-line platinum-based therapy irrespective of HRD status, providing an option for 'all comers' and perhaps lessening the need for HRD testing.

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