

## Correspondence



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### Conflict of Interest

Eduardo Paulino (P.E.) reports honoraria (AstraZeneca, MSD, and Roche), consulting or advisory role (AstraZeneca, MSD, and Roche), speakers' bureau (MSD, AstraZeneca, and Roche), and travel, accommodations, expenses (AstraZeneca, Roche, and MSD). Andreia Cristina de Melo (D.M.A.C.) reports honoraria (MSD Oncology, Novartis, and Bristol Myers Squibb Brazil), speakers' bureau (Bristol Myers Squibb Brazil and MSD Oncology), research funding (Roche [Inst],

# Olaparib and bevacizumab in front-line maintenance of ovarian cancer: an over reliance in unpowered subgroup analysis of the PAOLA-1 trial?

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Epithelial ovarian cancer (EOC) is usually diagnosed as a locally advanced disease (International Federation of Gynecology and Obstetrics 2018 stages III/IV) and is the most lethal gynecological cancer in developed countries [1]. Primary treatment usually consists of debulking surgery followed by adjuvant platinum/taxane therapy [2]. In the 80s and 90s, a marked gain in overall survival (OS) was observed with the introduction of cisplatin and paclitaxel in the treatment of EOC, respectively. Since then, the development and approval of new drugs has not been as impressive as those seen in other malignancies, such as lung, breast cancer and melanoma.

High grade EOC, especially serous histology, is characterized by genomic instability due to homologous recombination deficiency (HRD) [3]. This is mainly caused by mutated BRCA (mBRCA) but could also occur by alterations in other homologous recombination repair (HRR) genes such as RAD51. HRD causes genomic scar signatures (loss of heterozygosity [LOH], telomeric imbalance and large-scale transitions) and a score can be calculated using these parameters [4-6]. HRD score is correlated to the sensitivity to platinum and poly (ADP-ribose) polymerase (PARP) inhibitor [7]. Recently, this understanding of tumors harboring mBRCA and with HRD as the best predictive biomarkers of PARP inhibitors has taken the treatment of EOC to a new level.

PARP inhibitors (olaparib, niraparib, and rucaparib) have been approved by the U.S. Food and Drug Administration (FDA) for high grade EOC in different settings: in platinum sensitive recurrence (PSROC) as maintenance after a new response to platinum rechallenge, regardless of HRD status; as treatment for those with recurrent mBRCA (olaparib and rucaparib) or HRD tumors (niraparib); and in front-line as maintenance for mBRCA tumors [8]. All of these approvals are in accordance with the primary end point of each trials.

More recently, with the presentation and publication of others practice changing clinical trials with PARP inhibitors in front-line settings (PRIMA and PAOLA-1 trials), the FDA approved niraparib as maintenance regardless of BRCA and HRD status, which is in line with the primary endpoint of PRIMA trial—progression free survival (PFS) in HRD and in overall population - but the combination of olaparib/bevacizumab only in patients with HRD tumors with the Myriad myChoice CDx as a companion test, based on a subgroup analysis of the PAOLA-1 trial—primary endpoint was PFS in the intention to treat population (**Table 1**) [8]. It is assumed that about 50% of patients with high grade EOC have HRD, including 20% of patients with somatic/germline mBRCA, and it seems clear that the magnitude of benefit for

**Olaparib and bevacizumab in front-line maintenance of ovarian cancer**
**Table 1.** Studies that led FDA approval of iPARP in frontline maintenance for ovarian cancer

	SOLO-1	PRIMA	PAOLA-1
Patient population	Stage III/IV High grade serous or endometrioid BRCA mutated	Stage III/IV High grade serous or endometrioid All comers	Stage III/IV High grade serous or endometrioid All comers
Primary endpoint	PFS	PFS in HRD and in those in the overall population, as determined on hierarchical testing	PFS in ITT
Intervention	2:1 Olaparib vs. placebo	2:1 Niraparib vs. placebo	2:1 Olaparib/bevacizumab vs. placebo/bevacizumab
Primary endpoint result	PFS at 3 years: 60% vs. 27% (HR=0.30; 95% CI=0.23–0.41, p<0.001)	PFS HRD: 21.9 mo vs. 10.4 mo (HR=0.43; 95% CI=0.31–0.59; p<0.001) PFS overall: 13.8 mo vs. 8.2 mo (HR=0.62; 95% CI=0.50–0.76; p<0.001)	PFS ITT: 22.1 mo vs. 16.6 mo (HR=0.59; 95% CI=0.49–0.72; p<0.001)
Subgroup analysis	-	HRD/wtBRCA: HR=0.50 (95% CI=0.31–0.83) HRP: 8.1 mo vs. 5.4 mo (HR=0.68; 95% CI=0.49–0.94).	HRD/wtBRCA: 28.1 vs. 16.6 mo (HR=0.43; 95% CI=0.28–0.66) HRP: 16.9 mo vs. 16.0 mo (HR=0.92; 95% CI=0.72–1.17)
FDA approval	Olaparib approved for mBRCA	Niraparib approved for all comers	Olaparib/bevacizumab approved for HRD population only

CI, confidence interval; FDA, U.S. Food and Drug Administration; HR, hazard ratio; HRD, homologous repair deficiency; HRP, homologous repair proficient; iPARP, no description; ITT, intention to treat population; mBRCA, mutated BRCA; PFS, progression free survival; wtBRCA, wild-type BRCA.

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**Author Contributions**

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Methodology: P.E., D.M.A.C.; Supervision: P.E.;  
Writing - original draft: P.E., D.M.A.C.; Writing -  
review & editing: P.E., D.M.A.C.

PARP inhibitor is different in all subgroups: higher in mBRCA, lower in HRD without mBRCA (HRD/wild-type BRCA [wtBRCA]) and the least benefit seem in homologous recombination proficient (HRP) group [3,9,10]. In subgroup analysis of PSROC studies, although different assays were used to evaluate HRD score (myChoice in NOVA trial and Foundation Medicine LOH in ARIEL3 trial), both HRD/wtBRCA and HRP showed a benefit for PARP inhibitor therapy, demonstrating that we do not have a biomarker of no benefit for PARP inhibitor in high grade PSROC. In these trials, mBRCA derived the greatest benefit as expected followed by those HRD tumors including mBRCA. In the subgroup of patients with HRD/wtBRCA the benefit was lower, but still seen (in NOVA trial hazard ratio [HR]=0.38, 95% confidence interval [CI]= 0.23–0.63 and in ARIEL3 trial HR=0.55, 95% CI=0.35–0.89) as well as in HRP subgroup (in NOVA trial HR=0.58, 95% CI=0.36–0.92 and in ARIEL3 trial HR=0.47, 95% CI=0.31–0.71) [9,10]. In the front-line setting, PRIMA showed a benefit for all molecular subgroups [11]. In PAOLA-1, however, the HRP subgroup seemed not to have the same benefit for the combination of olaparib to bevacizumab as seen in the PRIMA trial, but retained the benefit for the HRD/wtBRCA subgroup [12]. A third trial, VELIA, studied veliparib concomitant and as maintenance, and showed benefit only for patients with mBRCA or HRD/mBRCA [13]. These studies were different in many aspects such as patient population (higher risk patients in PRIMA trial than PAOLA-1/VELIA trial), the use an active drug in the control group (PAOLA-1 used bevacizumab and PRIMA/VELIA placebo), time to randomization (after chemotherapy in PRIMA/PAOLA1 but concomitant to chemotherapy in VELIA), duration of maintenance (2 years in PAOLA1/VELIA and 3 years in PRIMA), cutoff of the HRD assay (42 in PRIMA/PAOLA1 and 33 in VELIA), among others. Regarding HRD score, it is important to remember that the cutoff of 42 came from trials that included not only ovarian cancer patients but also breast cancer. Takaya et al. [14] analyzed the Atlas of Cancer Genome of ovarian cancer and identified the scores of telomeric allelic imbalance, LOH and large-scale state transitions to calculate the HRD score. They showed that, probably, the best cutoff for ovarian cancer patients should be 63, and it is enriched by patients with mBRCA (38% of mBRCA). Patients with more or equal than 63 had better OS compared to those less than 63, and it was not different between 42–63 and less than 42. In a very interesting analysis of VELIA trial presented at Annual Meeting of the Society of Gynecologic Oncology this year,

Swisher et al. [15] compared different cutoffs in the subgroups of HRD and non-HRD. The results suggested PFS benefit for both HRD and non-HRD subgroups (myChoice) without a clear cutoff. Changing the cutoff of 33 to 42 in the HRD/wtBRCA subgroup did not modify the results seen in VELIA and has the same magnitude seen in the HRP subgroup (HR=0.76 for both HRD/wtBRCA and HRP, respectively) [15]. Another interesting finding was the fact that even in patients with the cutoff of 0–10 the benefits from veliparib can be seen. These findings highlight that, unfortunately, we do not have a cutoff of no benefit from PARP inhibitor. Reinforcing this concept, an extrapolatory analysis of SOLO1 trial showed that 23% of mBRCA patients were LOH low (score less than 16) and they derived the same magnitude of benefit of olaparib as those with LOH high (HR of 0.29 for both groups) [16].

Except for VELIA, the studies discussed here in the recurrent setting or in front-line have an important similarity: clinical response to platinum. In PRIMA and all trials in PSROC response to platinum before entry in the study was mandatory while in PAOLA-1 almost 70% had platinum response—30% of patients were not assessed for response since they had an upfront complete cytoreduction before adjuvant therapy. In VELIA, patients were randomized regardless of assessment of platinum sensitivity. Platinum response is an important marker for PARP inhibitor efficacy and maybe a better biomarker than the current HR assays available in the market [17].

Another important issue to be considered is who will be responsible to pay one expensive assay (such as the Myriad myChoice) for the decision-making process. Although it is a companion test in US, in many parts of the world patients will not have access to do it. In Brazil, as example, health insurance only covers the germline BRCA mutation (gBRCA) and in this population it is expected that 16.8% have gBRCA in high grade serous ovarian tumors [18]. In the case of olaparib/bevacizumab approval only for those with HRD tumors, we are sparing another 30% with HRD who could benefit from this combination. Although it is not validated and is still a matter of debate, evaluating mutations in other non-BRCA HRR genes could have a role in the decision-making process since it has been also suggested to be predictive for PARP inhibitor outcomes. Recently, analyzing a small subgroup from ARIEL3, O'Malley et al. [19] showed that rucaparib improved outcomes (PFS, chemotherapy free interval, time to first and second subsequent therapy) in patients with mutation in non-BRCA HRR genes, and some genes such as RAD51 may confer a higher sensitivity to PARP inhibitor. It is undeniable that many questions still need to be answered with PARP inhibitor in EOC as better biomarkers for selecting patients; if we can reserve its use for the recurrent setting instead of frontline; what is the role of re-challenge patients with PARP inhibitor; the best combination drug with PARP inhibitor and the economic burden related to this strategy.

Although the risk benefit-ratio and the magnitude of benefit must be considered and discussed, patients should not be denied the offer of a drug based on an unpowered subgroup analysis of a trial. Physician must have a frank discussion of the data with the patient, weighting adverse events and magnitude of benefit, and rely the decision of prescribe or not based on a shared decision. If an eligible patient with HRP based in the PAOLA-1 trial does not have the option to receive the proposed olaparib/bevacizumab combination in front line scenario, she can recur as platinum resistant disease and will lose the only opportunity to use an active drug.

In the opposite direction of FDA approval, the latest National Comprehensive Cancer Network guideline (NCCN v1.2020) for ovarian cancer leads to a more rigorous interpretation

of the data giving doctors and patients, regardless of HRD status, the option to discuss maintenance with olaparib/bevacizumab after platinum response and bevacizumab use in the front line (category 1 for mBRCA and 2A for BRCA wild type or unknown) [2]. It's noteworthy that niraparib is an option with the same grade of recommendation for BRCA wild type or unknown (category 2A). NCCN guidelines endorses that in absence of mBRCA, HRD status may provide information on the magnitude of benefit of PARP inhibitor therapy (category 2B). This option in the NCCN guidelines is welcome and intriguing: to what extent can we rely on our decision in underpowered subgroups? It will be interesting to see how other international regulatory agencies, such as the European Medicines Agency, will interpret these data and make their approval decisions.

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