PARPs: All for One and One for All? Enhancing Diversity in Clinical Trials

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Summary: PARP inhibitors have revolutionized the management of ovarian cancer and are being licenced for other cancer indications. The clinical trials prompting licencing decisions in ovarian cancer were dominated by white participants or participant ethnicity was not documented. To compensate for this, replicative studies like L-MOCA can be run in specific ethnic groups. In the future, strategies such as mandatory collection and publication of race and ethnicity data are essential alongside concerted efforts to widen the inclusivity of trial recruitment.

In this issue of *Clinical Cancer Research*, Gao and colleagues present the results of the L-MOCA study, a non-randomized trial of maintenance olaparib given following chemotherapy to 225 Asian women with recurrent, platinum-sensitive, high-grade ovarian cancer [1]. It cannot be assumed that, worldwide, all cancer patients handle treatment similarly. This was exemplified in the JGOG 3016 study which showed that dose-dense paclitaxel-containing chemotherapy was superior to standard at prolonging survival in Japanese women with newly diagnosed ovarian cancer; a benefit that was not reproduced in the equivalent European study, ICON8. A likely pharmacogenomic explanation is that polymorphisms in the transporter gene *ABCB1* (also known as permeability-glycoprotein (P-gp)), enriched in Asian populations, allow higher and more intense paclitaxel dosing.

Metabolism of Poly ADP-ribose polymerase (PARP) inhibitors may also be subject to pharmacogenomic variability. Originally developed to induce synthetic lethality in germ-line *BRCA 1* or *2* mutation (*gBRCA1/2*)-driven tumours, olaparib, niraparib and rucaparib are PARP inhibitors that are licenced for use in primary or recurrent ovarian cancer. Each has a different affinity for the PARP1-3 isoforms and are metabolised either by carboxylesterases (niraparib) or cytochrome P450 enzymes (CYPs) such as CYP3A4/5 (olaparib) and CYP2D6/1A2/3A4 (rucaparib). When looking specifically at the four studies that led to their approval by US Food and Drug Administration (FDA) and European Medicines Agency (EMA) as post-chemotherapy maintenance for platinum-sensitive recurrent ovarian cancer: Study 19, SOLO2/ENGOT-OV21, ENGOT-OV16/NOVA and ARIEL3 [2-5], the three drugs appear to have similar levels of efficacy but distinct toxicity, pharmacodynamic and pharmacokinetic profiles. However, a lack of information about the ethnicity of participants limits further exploration or meta-analysis within specific ethnic or racial cohorts. In addition, where this data has been presented, the racial uniformity of participants - 80% and 95% were defined as "white" in ARIEL3 and Study-19 respectively - raises concerns that ethnic groups, particularly Asian

and Black/Afro-Caribbean women are under-represented and reflects the concentration of trial centres in Europe and North America [6]. In SOLO2, of the 126 study locations involved, 29 were centres in China, Japan or Korea, yet ethnicity information was not included in the patient characteristics, nor in the analyses (summarised in Table 1).

To address this knowledge gap, the NORA trial, conducted in 30 centres in China, was the first phase III randomised trial to demonstrate the safety and activity of maintenance niraparib in platinum-sensitive relapse in an exclusively Asian cohort. Responses were compared with the NOVA trial, conducted in a similar clinical context with a majority (87%) of white patients. Despite differences in the statistical design of the two trials, there were comparable outcomes in terms of reduction in risk of disease progression or death among the *BRCA1/2* mutation subgroups (NORA: HR = 0.22; NOVA: HR = 0.27) and gBRCA1/2 wild type group (NORA: HR = 0.40; NOVA: HR = 0.45).

Using a similar strategy to NORA, the L-MOCA investigators explored maintenance olaparib in an exclusively Asian population (91% from China and 9% from Malaysia) with recurrent, platinum-sensitive ovarian cancer. The existing approval for olaparib in this indication meant they could not institute a placebo-control arm. Instead, L-MOCA was run a single-arm trial, drawing on data from randomised PARP inhibitor studies for comparison. Patients with *gBRCA1/2* who received maintenance olaparib in the L-MOCA trial had similar median progression-free survival (PFS) as those in SOLO2 (olaparib) and with rucaparib in ARIEL3 (21.2 months in L-MOCA compared to 19.1 months in SOLO2 and 16.6 months in ARIEL3). Median PFS amongst BRCA 1/2 wild-type (wt) patients in L-MOCA was 11 months (8.3-15.8), which compared favourably with the 9.3 month PFS in non-germline BRCA/non-HRD patients treated with niraparib in NOVA and 7·4 months for the wt BRCA1/2 patients treated with olaparib in Study 19. While it would appear that olaparib has similar efficacy, toxicity was less equivalent; grade 3/4 anaemia was higher at 25% in L-MOCA compared to 19% in SOLO2 and 5.1% in Study-19 (where olaparib capsules rather than tablets were administered), neutropenia was equivalent and G1/2 nausea lower (53% in L-MOCA versus 73% SOLO2 and 66% in Study-19). Adverse-event driven dose adjustment or treatment discontinuation was also lower in L-MOCA at 44.6% and 9.4% respectively, compared to 61.5% and 16.9% in SOLO2. Collectively, these findings indicate that, compared to the four pivotal PARP inhibitor trials, olaparib had a broadly similar progression-free survival advantage amongst the exclusively Asian participants and provides benefit without foreknowledge of the patients' BRCA or HRD status. Toxicities, however, may differ.

PARP inhibitors will have an enduring place in the future management of ovarian cancer and other malignancies such as non-small cell lung and prostate cancer. They are also being evaluated in the treatment of neurogenerative diseases such as Parkinson's and Alzheimer's. It is therefore important that studies strive to represent the future patient population in which they will be administered. The FDA has recently reviewed the factors that may negatively impact recruitment of ethnic minority groups and released guidance to enhance diversity in clinical trial populations, including greater use of electronic communication and improving inclusion through public outreach, education and fostering community engagement. Ensuring that trial site distribution includes geographic locations with a higher concentration of racial and ethnic minority and indigenous populations would urgently address the drive for inclusivity. In the absence of inclusive recruitment to these registration trials, results of independent studies such as L-MOCA are required to delineate responses and refine treatment guidance in specific ethnic groups. However, they are disadvantaged by their need to draw cross-study comparisons leaving essential questions around efficacy and/or tolerability unanswered.

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Table 1: Summary of PARP inhibitor trials in platinum-sensitive relapsed ovarian cancer

Clinical Trial	PARP inhibitor	Locations of study sites	BRCA status of participants
L-MOCA [Phase 3] Platinum-sensitive maintenance. 225 with high grade ovarian cancer. NCT03534453	Olaparib tablet 300 mg b.d. [No placebo arm]	Asia **Ethnicities:** Chinese (91.5%) Malaysian (8.5%)	Unselected, of which 52.2% wt*BRCA,* 41% *gBRCA1/2* and 6.3% *sBRCA1/2*
ARIEL3 [Phase 3] Platinum-sensitive maintenance 564 with high grade serous or endometrioid ovarian cancer. NCT01968213	Rucaparib tablet 600 mg b.d or Placebo [2:1 randomisation]	Australia/NZ, Europe, Israel, USA/Canada **Ethnicities:** White (80%) Non-white (7%) Unknown (13%)	Unselected of which 65.2% *wtBRCA*, 23% *gBRCA1/2* and 10% *sBRCA 1/2*
SOLO2/ENGOT-OV21 [Phase 3] Platinum-sensitive maintenance 295 with high grade serous or endometrioid ovarian cancer. NCT01874353	Olaparib tablet 300 mg bd Or Placebo	Australia/NZ, Europe, S.America, USA/Canada, Asia, Israel **Ethnicities: not described**	*gBRCA* only
ENGOT-OV16/NOVA [Phase 3] Platinum-sensitive maintenance 553 with high grade serous or known gBRCA1/2 ovarian cancer NCT01847274	Niraparib tablet 300 mg o.d Or Placebo	Europe, USA/Canada, Israel **Ethnicities:** white (87%); Black/Asian/ other/ unknown (13%)	Unselected of which 37% *gBRCA1/2* 63% non-*gBRCA*
Study-19 [Phase 2] Platinum-sensitive maintenance 265 with high grade serous ovarian cancer. NCT00753545	Olaparib capsule 400 mg b.d Or Placebo	Europe, USA/Canada, Israel, Australia/New Zealand **Ancestries:** Jewish (14%) /non-Jewish (86%) **Ethnicities:** white 95%, black 1.5%, Asian 1.5% and Other 1.5%	Unselected of which 22% *gBRCA1/2* 13.2% non-*gBRCA1/2* 64% unknown