

Testing for Homologous Recombination Deficiency – does it provide new insights for the use of veliparib?

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In the last decade treatment of ovarian cancer has shifted from a 'one size fits all' approach to biologically determined treatment options. This has been driven by an understanding of the importance of *BRCA* mutations to predict the benefit of PARP inhibitor treatment.

Mutations in the *BRCA* gene, whether germline or somatic are found in about 20-25% of women with high grade ovarian cancers. During the early PARP inhibitor studies with olaparib, it became clear that non-*BRCA*-related mechanisms may also be responsible for defects in the DNA homologous recombination repair pathway which are key to successful PARP inhibitor activity. An improvement in progression-free survival (PFS) after a recurrence was also seen in women with *BRCA wild-type* tumours when maintenance therapy with PARP inhibitors was used following a response to platinum-based therapy[1]. The hallmark of activity is HR deficiency (HRD) and is present in approximately 50% patients with high grade serous cancers[2]. However, in recurrent ovarian cancer HRD has been a less useful discriminant of PARP inhibitor benefit than a response to platinum-based therapy[3, 4]. Consequently, PARP inhibitors are licensed for maintenance treatment in recurrent ovarian cancer after a response to platinum-based therapy, irrespective of *BRCA* status[5]. Ovarian cancer research has now shifted to explore PARP inhibitor maintenance therapy in the first-line setting.

Following very successful results in patients with a *BRCA* mutation[6], three further studies were performed in a broader group of patients that included patients without *BRCA* mutations[7-9]. In two studies using either olaparib in combination with bevacizumab or niraparib, patients were enrolled following a partial or complete response (or no evidence of disease progression after surgery). The third study, VELIA/GOG-3005 used veliparib and differed from the other two trials in two important respects. It was a three-arm placebo-controlled study with veliparib given with chemotherapy in two of the arms, and then

continued as maintenance therapy in one arm. The control arm was carboplatin and paclitaxel, given either weekly or three-weekly according to physicians' choice. The second difference was that patients were not selected for maintenance therapy based on an initial response to the surgery/chemotherapy phase; they could continue provided there was no evidence of tumor progression. The primary results of the trial confirmed the benefit of veliparib maintenance in the three pre-planned cohorts of patients with a *BRCA* mutation (germline or somatic), HRD as determined by the Myriad MyChoice assay and the whole 'intention-to-treat' population[7]. In this group the median progression free survival in the veliparib throughout was 23.5 months and 17.3 months in the chemotherapy-placebo arm. The patient demographics, including neoadjuvant chemotherapy, chemotherapy scheduling and stage are similar to the ICON8 trial with 1566 patients. In ICON 8, the median PFS for the three chemotherapy arms with a weekly or three-weekly schedule ranged between 17.7- 21.0 months, like the control arm of VELIA in the ITT analysis[10]. From all the first-line PARP inhibitor studies the conclusions are that in patients with a *BRCA* mutation progression-free survival is significantly improved by maintenance with a PARP inhibitor and these extend to a lesser degree to *BRCA wild-type* tumours that have HRD. HRD needs to be carefully defined, as in some reports it includes patients with a *BRCA* mutation. However, subgroup analyses, excluding *BRCA* mutations, still show a benefit with PARP inhibitor maintenance. For those without HRD, the benefit of PARP inhibitors is less clear. In the PRIMA study with niraparib an improvement in progression-free survival was seen, but not in the PAOLA-1 the study which included bevacizumab and olaparib[8, 9]. Swisher et al [<https://doi.org/10.1016/j.vgyno.2021.12.003>] now present a subgroup analysis of progression-free survival 702 women without a *BRCA* mutation (germline or somatic) in tumors with or without HRD enrolled in the VELIA trial. The term HR proficiency

(HRP) is frequently and erroneously used instead of a lack of HRD, and it is particularly relevant when considering the veliparib study. Firstly, the definition ('cut off' score for GIS) for HRD in VELIA was different from PRIMA and PAOLA-1. Thus, the proficiency of DNA repair needed to circumvent PARP inhibitor activity differs in the three key studies even though the same Myriad MyChoice test was used. Furthermore, as Swisher and colleagues showed, the activity of veliparib in HRP tumors indicates some tumors are deficient, not proficient in the repair of DNA double strand breaks. As one might expect, patients in the HRP group had a lower PFS than those with HRD. These patients often have disease less sensitive to platinum-based therapy. However, the PFS hazard ratios were similar in the HRD and HRP groups (HR 0.76 [95% CI 0.53-1.09] and 0.77 [95% CI 0.56-1.4] respectively), leading the authors to conclude that a benefit of veliparib is seen irrespective of HR status. The difference in the median PFS among HRD and HRP patients was 3.1 and 3.5 months respectively. How should these results be interpreted? Differences in median PFS are easy to understand, but have less clinical importance than the hazard ratio, as they are point estimates and can be easily affected by the shape of the survival curve. Hazard ratios give a more meaningful difference of the separation of two curves if the hazards always remain proportional. A hazard ratio of 0.68 favoring niraparib in the HRP subgroup within the PRIMA trial has been used to support its use in the HRP group. In this subgroup the difference in median PFS was 2.7 months but the unadjusted PFS shows the curves coming together by 18 months. So, how clinically meaningful is a favorable hazard ratio? In the HRD and HRP subgroups of the VELIA trial the shape of the survival curves with similar hazard ratios is different. With a median follow up of 28 months, the PFS curve in HRD patients remains separate, but in the HRP group, the initial difference is lost and by 24 months after diagnosis, the curves join. The shape of this curve is typical of some other maintenance

studies, notably bevacizumab that leads to a brief improvement in PFS and favorable hazard ratio without a long-term benefit[11]. Thus, PFS, hazard ratios and the tail of the survival curves should all contribute to the evaluation of clinical benefit. Perhaps the similar hazard ratios in the HRD and HRP group in VELIA should also make us consider the limitations of current HRD assays, which in any case did not show a discrimination in outcome when GIS 'cut off' values of 33 or 42 were used. Do the results mean that veliparib could have a broader indication than other PARP inhibitors, including those with stable disease at the end of the surgery/chemotherapy phase? Stable disease after the chemotherapy phase was seen in 28% patients in the control arm and 21% of patients with veliparib throughout- a difference that may relate to factors to be discussed below. Median PFS was 13 months versus 16 months, respectively (hazard ratio 0.79; 95% CI 0.54 to 1.16), raising the possibility that veliparib with chemotherapy may help in situations where platinum-based therapy is less effective.

The second unique feature of the veliparib trial was the opportunity to assess its impact when combined with chemotherapy. In this analysis all patients (including *BRCAm* and *BRCAt*) were included, and the two veliparib and chemotherapy arms were pooled. Two activity parameters were investigated: CA125 and radiographic response in patients with measurable disease after primary surgery. The CA125 response was assessed to cycle 3, before interval surgery and over the duration of chemotherapy. Higher CA125 response rates were seen among patients receiving veliparib with chemotherapy to cycle 3, but this difference had largely disappeared by the end of chemotherapy. Similarly, there was a greater CA125 response among the neoadjuvant chemotherapy patients receiving veliparib (51% v37%) to cycle 3. However, this difference would only be clinically meaningful if it increased the percentage of patients undergoing complete cytoreduction at surgery. For

radiographic responses which were generally lower among HRP patients, the value of an improved response to veliparib would be the achievement of a better surgical outcome. That is not to state that all the benefit of veliparib was due to the maintenance phase, but without a pure maintenance arm it is difficult to apportion the relative contributions of the two phases of veliparib treatment. In other words, it is possible that early benefit of veliparib during chemotherapy could have been 'recovered' if the drug had been started after chemotherapy as in the other trials.

The VELIA trial with veliparib adds to our knowledge about the impact of PARP inhibitors in the first line treatment of ovarian cancer. This exploratory analysis demonstrates that veliparib is active in patients with HRP as well as HRD tumors, but these results remind us of the importance of evaluating the relative clinical benefit from different determinants of progression-free survival. Hazard ratios need to be assessed in context; similar values in HRP and HRD tumors do not imply that we should omit testing or ignore HRD test results, but rather that we should continue work to find better biomarkers of PARP sensitivity or resistance that have greater discriminatory power[12] to allow optimal use of PARP inhibitors to deliver the greatest incremental improvement in PFS.

References

- [1] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012;366:1382-92.
- [2] Konstantinopoulos PA, Ceccaldi R, Shapiro GI, D'Andrea AD. Homologous Recombination Deficiency: Exploiting the Fundamental Vulnerability of Ovarian Cancer. *Cancer Discov*. 2015;5:1137-54.
- [3] Coleman RL, Oza AM, Lorusso D, Aghajanian C, Oaknin A, Dean A, et al. Rucaparib maintenance treatment for recurrent ovarian carcinoma after response to platinum therapy (ARIEL3): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390:1949-61.
- [4] Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*. 2016;375:2154-64.
- [5] Mirza MR, Pignata S, Ledermann JA. Latest clinical evidence and further development of PARP inhibitors in ovarian cancer. *Ann Oncol*. 2018;29:1366-76.
- [6] Moore K, Colombo N, Scambia G, Kim B-G, Oaknin A, Friedlander M, et al. Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2018;379:2495-505.
- [7] Coleman RL, Fleming GF, Brady MF, Swisher EM, Steffensen KD, Friedlander M, et al. Veliparib with First-Line Chemotherapy and as Maintenance Therapy in Ovarian Cancer. *N Engl J Med*. 2019;381:2403-15.
- [8] Gonzalez-Martin A, Pothuri B, Vergote I, DePont Christensen R, Graybill W, Mirza MR, et al. Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer. *N Engl J Med*. 2019;381:2391-402.
- [9] Ray-Coquard I, Pautier P, Pignata S, Perol D, Gonzalez-Martin A, Berger R, et al. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. *N Engl J Med*. 2019;381:2416-28.
- [10] Clamp AR, James EC, McNeish IA, Dean A, Kim JW, O'Donnell DM, et al. Weekly dose-dense chemotherapy in first-line epithelial ovarian, fallopian tube, or primary peritoneal carcinoma treatment (ICON8): primary progression free survival analysis results from a GCIG phase 3 randomised controlled trial. *Lancet*. 2019;394:2084-95.

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- [11] Burger RA, Brady MF, Bookman MA, Fleming GF, Monk BJ, Huang H, et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med*. 2011;365:2473-83.
- [12] Chiang Y-C, Lin P-H, Cheng W-F. Homologous Recombination Deficiency Assays in Epithelial Ovarian Cancer: Current Status and Future Direction. *Frontiers in Oncology*. 2021;11.