**Elucidation of PARP Inhibitor Activity in BRCA-wt Recurrent Ovarian Cancer by HRR Mutational Gene Profile Analysis**

**Background**

Niraparib is an oral, selective poly(ADP-ribose) polymerase inhibitor approved for maintenance treatment of patients with BRCA-mutated (BRCAmut) and BRCA wild-type (BRCAwt) recurrent ovarian cancer who are in response to platinum-based chemotherapy.

In the non-gemcitabine BRCAmut (non-gBRCAmat) cohort of the ENGOT-OV16/NOVA trial, clinical benefit with niraparib was observed in patients regardless of their Myriad myChoice® HRD status (BRCAmut and homologous recombination deficiency (HRD) score), with a hazard ratio (HR) of 0.38 and 0.58 in HRD-positive (HRDpos) and HRD-negative (HRDneg) patients, respectively.

**Methods**

Archival ovarian cancer specimens were required for the 553 patients randomized in ENGOT-OV16/NOVA and were sequenced using the Myriad HRD assay to identify deleterious mutations in 43 DNA damage repair (DDR) genes.

- Tumor HRD score was detected by the Myriad myChoice® HRD assay.
- A retrospective, exploratory biomarker analysis was conducted using all available tumor samples from 331 patients enrolled in the ENGOT-OV16/NOVA non-gBRCAmat cohort.

Mutation status of HRD genes was evaluated using a 43-gene next-generation sequencing assay (Myriad Genetics), including BRCA1/2 and 16 additional HR genes. The 18 HR genes are:

- ATM, BAP1, BARD1, BRCA1, BRCA2, BRF1, MRE11A, NBN, PALB2, RAD50, RAD51B, RAD51C, RAD51D, WRAP53, RAD54L, ATR, XRCC2, and XRCC3.

**Results**

In this exploratory analysis of the non-gBRCAmat cohort, niraparib demonstrated clinical benefit in patients with somatic BRCA mutations (sBRCAmat; HR, 0.27) and in BRCAwt patients (HR, 0.47).

In addition, BRCAwt patients with other HRR gene mutations also derived benefit from niraparib (HR, 0.31), as did BRCA1/2HRHR wild-type (HRHwt) patients (HR, 0.49).

When BRCAwtHRHR patients were categorized by HRD score, clinical benefit was also observed in both HRDpos and HRDneg patients, with HRs of 0.33 and 0.60, respectively.

**Conclusions**

- This retrospective, exploratory analysis of the ENGOT-OV16/NOVA non-gBRCAmat cohort suggests that, although patients with somatic BRCA and other HRR mutations benefit from niraparib treatment, clinical benefit is also seen in HRDneg patients without HRR mutations, perhaps related to other genomic, epigenetic, or functional alterations within ovarian tumors yet to be defined.

- These results suggest that, although these biomarkers have good positive predictive value, they are not good negative predictors for niraparib benefit in this indication.

**References**


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