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Association of homologous recombination deficiency (HRD) with clinical outcomes in a phase III study of olaparib or cediranib and olaparib compared to platinum-based chemotherapy in recurrent platinum-sensitive ovarian cancer (PSOC): Biomarker analyses from NRG-GY004

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Background

HRD is associated with improved efficacy of PARP inhibitors (PARPi), but interaction between HRD and combined anti-angiogenics and PARPi is unclear. We explored several measures of HRD and clinical outcomes from NRG-GY004 (Liu, ASCO 2020).

Methods

NRG-GY004 is a randomized Phase 3 study evaluating olaparib (olap) or cediranib and olaparib (ced/olap) to platinum-based chemotherapy (chemo) in PSOC. BROCA-HR, a targeted next generation sequencing assay identifying all classes of mutations in 88 DNA repair or related genes was performed on germline and tumor DNA. Loss of heterozygosity (LOH) was calculated as a fraction of sub-chromosomal loss using allelic ratios of single nucleotide polymorphisms. Associations between clinical outcomes, homologous recombination repair (HRR) mutation status, and LOH were evaluated via standard statistical methods.

Results

BROCA-HR was evaluable in 491 of 565 randomized patients (pts). Core HRR genes were wild-type (HRRwt) in 323 pts, mutant (HRRmt) in 147, and not assessable (NA) in 21. >90% of HRRmt were *BRCA*mt. LOH was low in 147 pts, high in 79, and NA in 265, mostly due to inadequate tumor content. Across all pts, HRRmt was prognostic (median PFS 13.7 vs 8.3 mos HRRwt; HR 0.41, p <0.0001). In pts with HRRmt, median PFS was 12.3, 13.1, and 20.4 mos for chemo, olap, and ced/olap, with HR 0.78 (95% CI 0.48-1.27) for olap to chemo and HR 0.55 (0.32-0.95) for ced/olap. In pts with HRRwt, median PFS was 9.0, 6.4, and 8.5 mos for chemo, olap, and ced/olap, with HR 1.56 (1.15-2.12) for olap and 0.93 (0.68-1.27) for ced/olap. HRR status was predictive of olap response vs chemo (p = 0.0176) but not of ced/olap vs chemo (p = 0.1009). LOH was not independently prognostic after adjustment for *BRCA*mt. Median PFS was 10.6, 8.5, and 12.2 mos for chemo, olap, and ced/olap in LOH-high pts, and 8.1, 6.3, and 8.4 mos in LOH-low; LOH status was not predictive of olap or ced/olap response vs chemo.

Conclusions

In NRG-GY004 pts, HRR status was driven by *BRCA*mt, correlated with overall prognosis, and was predictive of olap response vs chemo.

Clinical trial identification

NCT02446600.

Legal entity responsible for the study

NRG Oncology.

Funding

National Cancer Institute.

Disclosure

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