Association of RAD51 and efficacy outcomes in patients with HER2-negative breast cancer and homologous recombination deficiency: post-hoc analysis of the GeparOla trial

266P

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1. Background

The randomized GeparOla trial (NCT02789332) evaluated neoadjuvant olaparib versus carboplatin togehter with antrhacycline/taxane chemotherapy in patients with early HER2-negative breast cancer who had homologous recombinant deficiency (HRD) assessed by Myriad myChoice or g/t BRCA1/2 mutations. The primary analysis showed that both study arms achieved comparable pathological complete response (pCR) rates in both study arms (55.1% vs 48.6%), with olaparib demonstrating a better safety and tolerability profile.

Given the potential safety implications of chemotherapeutic agents, efforts have been made to identify biomarkers that can select patients who might benefit from less aggressive treatment regimen. We evaluated the feasibility and effectiveness of the HRD-RAD51 test in identifying patients with different clinical outcomes within a pre-selected population.

2. Methods

This is a post-hoc, blinded, biomarker analysis from the randomized GeparOla trial.

- **HRD-RAD51 testing**:

RAD51 nuclear foci were manually stained and quantified using an immunofluorescence assay (**Figure 1**). RAD51 foci were quantified by scoring the percentage of geminin-positive tumor cells with 5 or more RAD51 nuclear foci.

HRD-RAD51 was evaluated both as a continuous score (ranging from 0 to 100) and as grouped categories (low vs. high, with a pre-defined cut-off of 10%). The RAD51 test was retrospectively evaluated in a blinded manner, with results centrally analyzed and subsequently linked to clinical data.

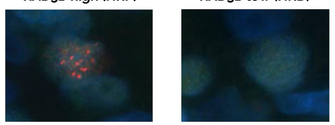

Figure 1. RAD51 assay

- **Objectives and statistical methods**

The primary objective of this study was to evaluate the association between HRD-RAD51 groups and pCR, both in the overall population and within each treatment arm. Univariable and multivariable logistic regression models were used to investigate the association for each variable with pCR in terms of odds-ratios (ORs) with 95% CI. The C-statistics was used to calculate the discrimination. Kaplan-Meier method was used to estimate survival outcomes.

3. Results

3.1 Descriptive analysis

A total of 90 out of the 97 samples available (92.8%) were evaluable for RAD51 testing and were included in this study. Briefly, mean age was 46.8 years, the representation of clinical T1 disease was 46.7%, clinical N0 (76.2%), tBRCA-mutated tumor (48.3%) and TNBC (76.7%). Most of patients were classified as HRD-RAD51 positive (72/90, 80.0%). The RAD51 test identified 8.7% of tBRCA1/2-mutated tumors and 30.2% of the non-tBRCA1/2 mutant cases as not harboring functional HRD-RAD51.

3.2 pCR endpoint

The pCR rate in patients with HRD-RAD51 positive tumors was 66.7% (48/72), while it decreased to 22.2% (4/18) in non-HRD+ tumors (**Figure 2**). In the multivariable model, which include clinicopathological factors and treatment, the HRD-RAD51 score remained significantly associated with pCR (OR = 0.11, 95% CI 0.03–0.43, p=0.002).

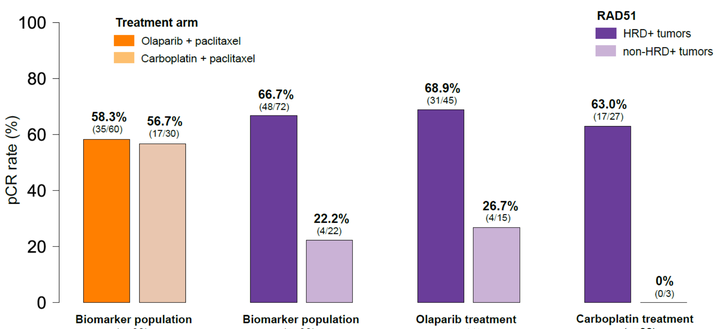

Figure 2. pCR rates according treatment and RAD51 groups

3.3 RAD51 and sTILs to predict pCR rates

HRD+ tumors by RAD51 with high sTILs had a pCR rate of 75.0% (27/36), while the rate decreased to 10.0% (1/10) in patients with non-HRD+ tumors and high sTILs (**Figure 3**). The C-statistic with the combination of RAD51 and sTILs was 0.70.

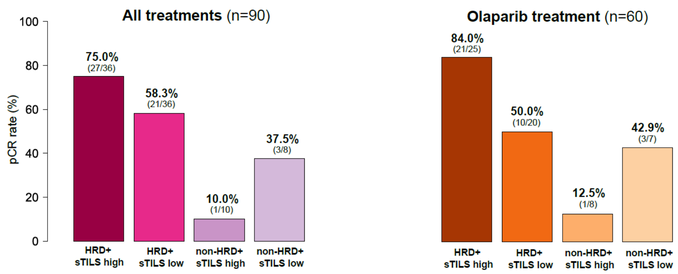

Figure 3. pCR rates according RAD51 and sTILs

3.4 Survival outcomes

No differences were observed between RAD51 groups in disease-free survival (DFS) (non-HRD+ vs. HRD+: HR = 0.85, 95% CI 0.25–2.97) (**Figure 4**).

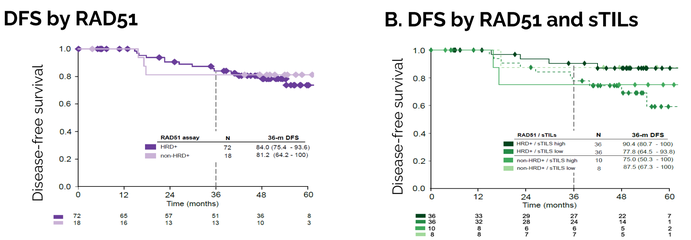

Figure 4. Kaplan-Meier curves of RAD51 groups

4. Conclusions

In a pre-selected population, the HRD-RAD51 assay identifies patients with different pCR rates under PARPi or platinum-based therapies. The association was independent of sTILs. Future biomarker-driven studies should consider this information to improve patient selection.

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