DNA repair protein expression and response of homologous recombination deficient ovarian cancer to the poly(ADP-ribose) polymerase (PARP) inhibitor rucaparib in the ARIEL2 Part 1 study

#3393

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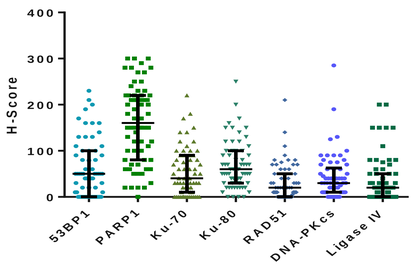
Introduction

- Poly (ADP-ribose) polymerase inhibitors (PARPi) are active in cancers with homologous recombination (HR) defects, such as mutations in BRCA1/2
- However, only 50% of cancers with germline HR mutations respond to PARPi therapy
- Preclinical studies have shown that secondary mutations or alterations in gene expression (e.g., downregulation of 53BP1, Ku70, Ku80, or DN-PKcs) restore HR and confer PARPi resistance
- Low PARP1 expression can diminish PARP trapping and cause PARPi resistance
- ARIEL2 Part 1 is a Phase 2 study of rucaparib in platinum-sensitive, relapsed, high grade ovarian cancer (OC).
- Hypothesis tested in ARIEL2 Part 1 pretreatment biopsies:
  - Sensitivity to PARP inhibitors is dependent on a disabled HR but intact non-homologous end joining (NHEJ) pathway
  - Lower PARP1 and/or lower expression of NHEJ components 53BP1, DNA-PKcs, Ku80, Ku70 or LIG4 expression may correlate shorter PFS following rucaparib treatment

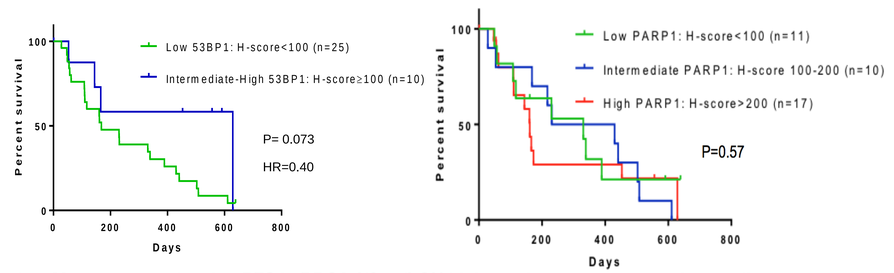
Methods

- Available pretreatment OC biopsies from ARIEL Part 1 were previously assayed for HR gene mutations and loss of heterozygosity (LOH), a genomic scar that reflects HR deficiency.
- Immunohistochemical assays were developed for 53BP1, DNA-PKcs, Ku-80, Ku-70, Ligase IV and PARP1
- The same pretreatment OC biopsies were stained and scored for % tumor nuclei that demonstrated negative, weak, moderate or strong staining
- Modified H scores were correlated with clinical characteristics and outcome measures low [<100], intermediate [100-200] or high [>200]
- Samples were categorized by BRCA wild type vs. mutated and LOH high or low

Modified H- Scores of DNA Repair Proteins

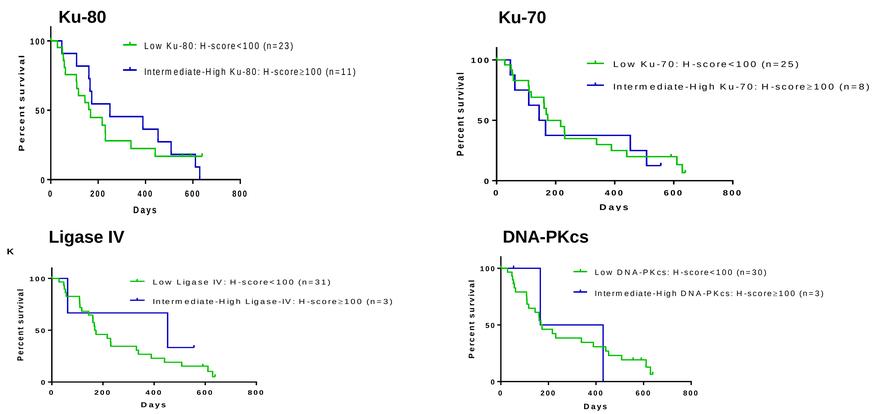


PFS According to 53BP1 and PARP1 Modified H- score



Kaplan–Meyer curves showing PFS in BRCA 1/2 wt/LOH high ovarian cancer grouped according to pretreatment modified H score for 53BP1 and PARP1.

PFS According to Ku-80, Ku-70, DNA PKcs and DNA ligase IV



Kaplan-Meyer curves showing PFS in *BRCA1/2* wt/LOH high ovarian cancers grouped according to pretreatment modified H score for Ku70, Ku80, DNA-PKcs and DNA ligase IV. Hazard ratios and p values were HR = 1.13 (p = 0.77), HR = 0.83 (p = 0.64), HR = 1.03 (p = 0.97) and HR = 0.55 (p = 0.41) for the four proteins, respectively.

Results

- Pretreatment biopsies from 62-68 patients were successfully stained for each repair protein
- Among the BRCA wt/LOH high group (n=38), there was no significant difference in PFS of patients with low, intermediate, or high PARP1 H-score (p=0.57).
- Expression of DNA-PKcs, Ku-70, Ku-80, and DNA Ligase IV was generally lower (median H-scores 20-60) and did not individually correlate with PFS
- There was a trend toward improved PFS in BRCA wt/LOH high OC pts expressing intermediate or high 53BP1 (H score > 100, n=10) compared to low 53BP1 (n=25) with a median PFS of 20.7 vs. 5.5 months (p=.073).

Conclusions

- In the BRCA wt/LOH high group, pretreatment PARP1 expression does not correlate with PFS duration following rucaparib treatment.
- BRCA wt/LOH high OC with low 53BP1 expression have a trend toward shorter PFS with rucaparib, suggesting that 53BP1 downregulation might correlate with clinical PARPi resistance in BRCA wt/LOH high OC.

Acknowledgments

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