3-Biomarker HRD Score versus Individual Biomarker (LOH, TAI, LST) Scores in Platinum Treated Serous Ovarian Cancer (SOC)

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BACKGROUND

- Previous studies have shown that tumors with defects in the homologous recombination (HR) pathway show improved response to DNA-damaging agents, such as platinum and niraparib (NOVA trial).1,2
- To identify tumors likely to benefit from these therapies, we developed a 3-biomarker HR deficiency (HRD) score that is an algorithmic assessment of 3 biomarkers of genomic instability:
  - Loss of heterozygosity (LOH)
  - Telomeric-allelic imbalance (TAI)
  - Large-scale state transitions (LST)
- Here we evaluate the ability of the 3-biomarker HRD score to approximate the biological phenomenon of HR deficiency relative to the individual biomarker scores.

HYPOTHESIS

- We hypothesize that a molecular score which approximates the biological phenomenon of HR deficiency will have a bimodal distribution that represents HR deficient and HR intact tumors.

METHODS

- The 3-biomarker HRD score and the individual score components were evaluated based regimens.8-11
- An HRD threshold (≥42) was developed in a training cohort of ovarian and breast tumors (N=1,058) to detect 95% of tumors with BRCA1/2 mutations.
- The HRD score is the sum of the 3 biomarker scores.
- Previous studies have shown that tumors with defects in the homologous recombination (HR) pathway show improved response to DNA-damaging agents, such as platinum and niraparib (NOVA trial).1,2
- To identify tumors likely to benefit from these therapies, we developed a 3-biomarker HR deficiency (HRD) score that is an algorithmic assessment of 3 biomarkers of genomic instability:
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RESULTS

- Only the 3-biomarker HRD score showed a bimodal distribution that corresponds to the two biological states being assessed (HR deficient and HR intact) (Figure 1).
- A larger proportion of wild type BRCA1/2 tumors above the TAI, LST, and LOH thresholds may correspond to a larger proportion of false positives.
- The correlation between the 3-biomarker HRD score and the component scores also shows that the individual TAI, LST, and LOH scores likely produce a substantial number of false positives as well as false negatives.
- Collectively, this suggests that the use of a single HR biomarker may misinform treatment decisions in SOC relative to the combined 3-biomarker HRD score.
- This supports previous validations of the combined 3-biomarker HRD score to predict response to platinum-containing regimens in women with TNBC and ovarian cancer.7 Validation with PARP inhibitors in ovarian cancer is ongoing (NOVA).5

CONCLUSIONS

- We hypothesize that a molecular score which approximates the biological phenomenon of HR deficiency will have a bimodal distribution that represents HR deficient and HR intact tumors.
- The 3-biomarker HRD score and the individual score components were evaluated based regimens.8-11
- An HRD threshold (≥42) was developed in a training cohort of ovarian and breast tumors (N=1,058) to detect 95% of tumors with BRCA1/2 mutations.
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REFERENCES