Homologous recombination deficiency (HRD) of high grade serous ovarian tumors from the NOVA Phase III clinical study

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Introduction

Ovarian cancer is characterized by a high degree of genomic instability caused by deficiencies in DNA repair.

Cells can develop these homologous recombination (HR) deficiencies through the loss of function or inactivation of genes involved in DNA repair, such as BRCAl and BRCA2.

Ovarian cancers known to have these HR deficiencies have been shown to benefit from therapy with DNA-damaging agents, such as platinum and PARP-inhibitors.

Homologous recombination deficiency (HRD = defined as the sum of LOH, LST and TAI genomic defects), assessed across >500 ovarian tumors exhibits a bio-modal distribution allowing a clear differentiation of HR proficient and HR deficient tumors.

Methods

Patients: The NOVA study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of niraparib as maintenance in platinum sensitive ovarian cancer patients who have either gBRCAmut or a tumor with high grade serous histology and who have responded to their most recent chemotherapy containing a platinum agent.

Sample Analysis: DNA was extracted from formalin fixed paraffin- embedded (FFPE) tumor tissue and used to create libraries that were hybridized to a custom Agilent SureSelect capture array carrying probes for 54,031 single nucleotide polymorphism sites distributed across the human genome, as well as probes targeting 43 genes involved in DNA repair, including BRCAl and BRCA2. The captured and enriched DNA was sequenced on an Illumina HiSeq 2500 sequencer. Sequences covering SNP positions were used to generate allelic imbalance profiles. Measures of genomic instability, including determining allele frequencies (AFs) and score values, were calculated using allelic imbalance profiles and determination of loss of heterozygosity by ASCN.

HRD Score: The HRD score is the unweighted sum of LOH (number of subchromosomal LOH regions longer than 15 Mb), TAI (number of regions with allelic imbalance that extend to one of the subtelomeres but do not cross the centromere), and LST (the number of break points between regions longer than 10 Mb). HRD scores improve upon conventional approaches by weighting regions longer than 3 Mb.

HRD scoring was conducted, including 100% of the gBRCAmut cohort and 55% of the non-gBRCAmut cohort are HRD positive as defined by the Myriad HRD test.

The use of three algorithms of DNA damage allow a clearer differentiation of the HRD population in ovarian cancer than the use of the single LOH algorithm.

Deleterious or suspected deleterious mutations, with confirmed loss of both tumor alleles, were detected in 12 additional DNA damage response genes in 35 tumors.

HRD scores in tumors with DDR gene mutations showed a similar range of HRD scores to that observed in BRCAl/2 mutants (28-82 compared to 25-88).

Conclusions

• An assay has been developed that provides a quantitative continuous measure of genomic scoring and BRCA1/2 sequencing from tumor tissue in one test.

• Genomic analysis of 347/490 patient tumor samples in the NOVA study has been conducted, including 100% of the gBRCAmut cohort and 55% of the non-gBRCAmut cohort are HRD positive as defined by the Myriad HRD test.

• The use of three algorithms of DNA damage allow a clearer differentiation of the HRD population in ovarian cancer than the use of the single LOH algorithm.

• Deleterious or suspected deleterious mutations, with confirmed loss of both tumor alleles, were detected in 12 additional DNA damage response genes in 35 tumors.

• HRD scores in tumors with DDR gene mutations showed a similar range of HRD scores to that observed in BRCAl/2 mutants (28-82 compared to 25-88).

References


Evaluation of Phase 3 (NOVA) patient tumors

Non-gBRCAmut (n=211) analyzed to date

- gBRCAmut (n=136) analyzed to date

- Analysis of LOH score only from tumors obtained from gBRCAmut cohort patients indicates a broad score distribution.
- Utilizing the sum of three algorithms to score HRD (LOH, LST, TAI) results in a shift to higher HRD scores for BRCA2 tumours in NOVA.
- A cutoff of 7 or greater for LOH score alone captures 95% of gBRCAmut tumors in NOVA.
- A cutoff of ≥24 for gBRCAmut shows 95% of gBRCAmut tumors in NOVA.

HRD Score (LOH+LST+TAI)

- HRD score is defined as those with an HRD score of 24 or a deleterious or suspected deleterious mutation in BRCA2 as detected from tumor tissue.
- Patient eligibility criteria for the NOVA study are consistent with enrichment for patients with tumors having high HRD scores due to platinum sensitivity.
- Patients with HRD positive tumors consist of 100% of the patients in the gBRCAmut cohort and 55% of the patients in the non-gBRCAmut cohort based on this preliminary analysis of 347 pts.

Distribution of HRD scores in Samples with a Pathogenic Variant in a DDR Gene (BRCA1 or BRCA2) according to tumor stage:

<table>
<thead>
<tr>
<th>DDR Score</th>
<th>No. of Samples</th>
<th>% of BRCA1 Mutant Tumors</th>
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<tbody>
<tr>
<td>347</td>
<td>347</td>
<td>100%</td>
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HRD Score in NOVA Tumors (n=347 analyzed)

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