Homologous recombination deficiency (HRD) score enriches for niraparib sensitive high grade ovarian tumors.

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In ovarian cancer, the loss of one specific DNA repair mechanism, the HR repair mechanism, results in a homologous recombination deficiency (HRD) and is associated with genomic instability, genetic perturbations (duplications, deletions and translocations of DNA) and ultimately tumor growth.1-3 Cells can develop HRD by a variety of mechanisms including the loss of function or inactivation of genes involved in DNA repair, such as BRCA1/2, RAD51 or ATM. Small molecules which inhibit PARP1 and PARP2 in a tumor cell already HR deficient, will effectively make the tumor cell non-viable and lead to tumor cell death through the rapid accumulation of genomic aberrations from low fidelity DNA repair.4-5 The HRD deficiency state is more common in ovarian cancer (40-50%) than the frequency of germline BRCA1/2 mutations (15%).6 A proportion of this HRD is accounted for by somatic BRCA1/2 mutations, methylation of the BRCA1 promoter (which inactivates the BRCA1 gene) and deleterious mutations in other known HR pathway genes.6,7 Therefore, biomarkers that can efficiently distinguish the HR status of a tumor would enable the identification of those that are not all ovarian cancer patients, who might respond to PARP inhibition. Toward this end we describe results in the application of a next generation sequencing test that detects variants in the BRCA1/2 genes and provides a quantitative measure of HRD in tumors from ovarian cancer patients. Selected patient derived xenografts (PDX) from breast and ovarian were used to confirm the ability of the test to enrich for responders of niraparib activity. Preliminary analysis of tumors obtained from the NOVA study is presented.

Introduction

In a series of ovarian tumors with associated tumor BRCA status and HRD score were implanted orthotopically in mice and evaluated for niraparib sensitivity by ultrasound imaging. A number of sensitive and resistant models were identified All sensitive models had an HRD score of 42 Response rate in BRCA+ was the same as in HRD+[BRCAwt]

Molecular Profile of Primary High Grade Serous Ovarian Cancer ~50% of tumors characterized by deficiencies in DNA repair6

Pre-clinical Patient Derived Xenografts

Archival FFPE tissue obtained from ovarian cancer patients enrolled in an ongoing Phase III clinical study [ENGOT-OV16/NOVA, NCT 01847724, Niraparib maintenance therapy after second platinum response in platinum sensitive HGSOC] and a living tumor bank was subjected to HRD testing as previously described.13 BRCA1/2 variants identified by the test are classified in accordance with the recommendations of the American College of Medical Genetics and Genomics (ACMG) for standards in the interpretation and reporting of sequence variation.8<br>

HRD score is a numerical range (0-100) resulting from the sum of the three component scores<br>

LOH: Loss of Heterozygosity<br>

TAI: Telomeric Allelic Imbalance<br>

LST: Large Scale-state Transitions

Analysis of HRD scores in ovarian tumors from Hennessey et al8 and TCGA shows a bimodal patient distribution (n=561) The cutoff value of 42 was determined to mutate 95% of BRCA+ and was therefore used to identify BRCA+ tumors

LOH, TAI and LST measurements on a scale from 0-100.13  Methods related to archival FFPE tumor tissue obtained from ovarian cancer patients enrolled in the NOVA study is presented.

Methods

In ovar...