The PARP inhibitor niraparib demonstrates activity in patient-derived triple-negative breast cancer xenograft models with high homologous recombination deficiency (HRD) score

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Introduction

Triple-negative breast cancer (TNBC), has a poor prognosis and currently lacks effective treatment. TNBCs are highly proliferative, genomically unstable and share molecular characteristics with that of BRCA1/2 mutation driven breast cancer. Poly(ADP-ribose) polymerase-1 (PARP) is a key DNA repair enzyme that mediates single strand break (SSB) repair through the base excision repair (BER) pathway. PARP inhibitors have been demonstrated to selectively kill tumor cells that harbor BRCA1 and BRCA2 mutations. In addition, pre-clinical and preliminary clinical data suggest that PARP inhibitors are selectively cytotoxic for tumors with homologous recombination repair deficiency caused by dysfunction of genes other than BRCA1 or BRCA2.

Niraparib is a potent, orally active PARP inhibitor that is being evaluated in Phase 3 clinical studies for ovarian cancer and BRCA related breast cancer. Previously, we demonstrated that a subset of basal breast cancer (BBC) patient-derived xenograft (PDX) models responded robustly to single agent PARP inhibitor treatment (1). To understand the selectivity observed, the samples from a collection of 37 BBC PDX models have been subjected to homologous recombination deficiency (HRD) analysis. The MyChoice HRD assay is a DNA-based assay that is capable of detecting homologous recombination deficiency independent of its etiology.

Here, we show that Niraparib significantly inhibited the growth of 6 TNBC PDX models among the 20 tested. All six sensitive models had HRD scores higher than 42, the cut-off score defining homologous recombination deficiency in the MyChoice HRD assay.

Methods

Identification of HR Deficiency by MyChoice HRD™ Assay

- The MyChoice HRD™ assay measures genomic instability within tumor cells.
- It is a NGS based assay for FFPE tumor samples which includes both 50K SNPs covering whole genome to detect large scale rearrangements and BRCA1/2 sequencing to detect deleterious mutations.
- The HRD score is based on the number of large-scale rearrangements within the genome.
- HRD deficiency is defined as a HRD score ≥42 and/or presence of deleterious mutations in BRCA1/2.

Enrichment of Niraparib Sensitivity in High HRD Models

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References


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