Prediction of PARP inhibitor response and resistance utilizing a CTC phenotypic classifier in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC): Results from the NCI 9012 trial

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Background: PARP inhibitors (PARPi) have efficacy in mCRPC harboring homologous recombination DNA repair deficiencies (HRD), but there is no non-invasive assay to predict PARPi response. Previous work characterizing single CTCs from mCRPC pts has identified subclonal populations of CTCs with unique phenotypes and somatic genomic instability consistent with HRD and resulting in worse outcomes following abiraterone (A) treatment. NCI 9012 evaluated A alone with or without the PARPi Veliparib (V) in mCRPC pts. We now determine if the addition of V to A improves pts response and its association with phenotypic HRD CTC signature.

Methods: 84 baseline & 58 on-therapy blood samples from unique pts randomized to V + A vs A arms on NCI 9012 (baseline n=44 vs 40, follow-up n=34 vs 24, respectively) were analyzed with the Epic Sciences CTC platform. CTC analysis included digital pathology of 20 discrete phenotypic cell features inclusive of AR, CK, size and shape. 3323 single CTCs were characterized and analyzed for HRD+ signature utilizing the previously developed classifier and trained for a PARP resistant CTC subtype. A biomarker for PARPi sensitivity was developed, requiring HRD+ CTCs with no PARP resistance CTCs. A subset of CTCs (n= 434) from 48 samples (35 patients) were individually sequenced to concord to HRD genomics and a subset compared to tissue sequencing data.

Results: In baseline samples, the CTC biomarker occured in 35% (V + A) and 23% (A), and had a higher ORR (>50% PSA drop) in the V + A vs the A cohort (93% vs 22%, p=0.0007). No significant difference observed in V + A vs the A cohort (68% vs 80%, p=0.17) for Biomarker- patients. Time to PSA progression in Biomarker+ pts favored V+A vs. A alone (HR=0.45; p=0.12), whereas no selection biomarker showed little effect (HR=0.9, p=0.72). For pts with both baseline and short term follow up (<18 weeks) samples, the patient avg number of HRD+ CTCs increased 166% in A arm vs. decreased 82% in V + A arm (p<0.0001).

Conclusions: Prevelance of a unique morphologically derived CTC subtype predicts genomic HRD and sensitivity to V + A but not A alone. Further validation is ongoing to validate the utility of the CTC phenotypic classifier for patients selection and monitoring of therapeutic efficacy.
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