

"Genomic Analysis of Circulating Tumor Cells to Evaluate Predictive Biomarkers"

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Abstract: We present an integrated program to qualify molecular profiles of circulating tumor cells (CTC) as biomarkers to guide treatment selection for patients with castration-resistant prostate cancer (CRPC). The program combines the expertise of investigators at MSKCC, CSHL and the MGH/Broad Institute and builds on the clinical activity of trials of two agents directed to specific molecular alterations common in CRPC tumor specimens: MDV3100, engineered by our group for activity against tumors with overexpressed androgen receptors (AR), and abiraterone acetate, a 17,20-lyase inhibitor of androgen synthesis. The all-or-none response seen clinically with these agents is consistent with molecular markers of sensitivity. To overcome the difficulty acquiring metastatic tumor tissue for molecular analysis, we have used different cell capture technologies under IRB-approved protocols and demonstrated these specific alterations in CTC. Our goal is to optimize two new CTC isolation technologies, fluorescence activated cell sorting (FACS) and a microfluidic enrichment device, that have enabled us to capture higher numbers of CTC from more patients than the current FDA-cleared approach. With FACS and microfluidic enrichment, cellular architecture and nucleic acids are preserved for the study of protein expression, DNA fluorescence *in situ* hybridization (FISH), and the expression of prostate cancer-specific genes. Next-generation deep sequencing of CTC for mutations, copy number alterations, and expression profiles is planned. The results will be used to design prospective trials that explore the relationship between specific molecular profiles in CTC and clinical outcomes. The first, a phase 3 trial of MDV3100 in CRPC patients, is under development.