Characteristics of de novo Resistance to Androgen Targeting Therapeutics (AR Tx) through Circulating Tumor Cells (CTCs) analyses in metastatic Castration Resistant Prostate Cancer (mCRPC) patients

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Background

- Novel, life extending therapies targeting the Androgen Receptor (AR) are now part of the standard of care in mCRPC.
- Response to these therapies is heterogeneous across patients.
- Prospective identification of patients with tumors that harbor de novo resistance to AR Tx could reduce morbidity and enable early exploration of alternative approaches.
- We examined total CTCs, specific CTC subpopulations and CTC AR protein expression from blood samples taken prior to Abiraterone Acetate + Prednisone (A), Enzalutamide (E) or taxane (T).

Results were correlated with response patterns shown in Figure A.

Methods

- 85 blood samples were collected from mCRPC pts immediately prior to treatment A, E, or T. Patients on A or E or T were classified according to Figure A as:
  - Responders (n=39) which included:
    - true response (n=15)
    - acquired resistance (n=24).
  - Non responder (n=46) de novo resistance
  - Baseline samples were processed utilizing the Epic Sciences platform.

Measurement of AR Ligand Binding Domain Alterations

CTCs were examined for AR Ligand Binding Domain (LBD) alterations utilizing a 2 target assay directed at AR N terminal protein expression and AR C terminal protein expression

Figure C: Example of CTC AR N-terminal to AR C terminal protein expression

Figure D: Schematic of Epic’s CTC collection and detection process: 1) Blood levy, nucleated cells from blood sample plated onto slides 2) Slides stained in CBC hematoxylin 3) Slides stained with CK, CD45, DAPI and AR 4) Slides scanned 5) Multi-parametric digital pathology algorithms run 6) Software and human reader confirmation of CTC & detection of biomarker expression

Figure E: Traditional CTCs

Figure F: Non-Traditional CTCs

Figure G: Prediction of A or E Resistant Disease

Figure H: CTC Characterization Predicts AR Tx de novo Resistance

Conclusions

1. CTC/7.5 mL or non-traditional CTC/7.5 mL frequency does not predict Abiraterone, Enzalutamide or Taxane resistance

2. Sensitivity to Abiraterone or Enzalutamide was assessable from baseline blood draw through the single cell CTC measurement of:
   1. CTC Heterogeneity
   2. Frequency of cdk4/5 positive, AR N-terminal positive CTCs with prominent nucleoli morphology
   3. AR C terminal loss

3. The CTC profile of sensitivity to Abiraterone and Enzalutamide resistant disease did not predict sensitivity to Taxane therapy, suggesting that the models may be useful to guide treatment selection.

4. Prospective validation of the predictive signatures in dedicated trials is planned.

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