Changes in CTC burden and phenotypes in mCRPC patients (pts) receiving alpharadin (Ra-223) as single agent or in combination with other therapeutics (Tx)

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CTC Enumeration Changes on Ra-223 Single Agent and Combination Therapy

CTC Phenotypes Change During Ra-223 Single Agent Therapy

Phenotypes More Common in Baseline than On Tx Samples
- High Nuclear/Cytoplasmic Area Ratio
- Smaller Cytoplasmic Area

Phenotypes More Common in On Tx than Baseline Samples
- Low Nuclear/Cytoplasmic Area Ratio
- Larger Cytoplasmic Area
- Smaller Nuclear Area

Frequency of pts with CTC phenotype changes:

- Rise: 10% (1/10) pts had CTC gains
- Decline: 45% (4/9) pts had CTC drops
- Always Zero: 45% (4/9) pts had CTC drops

Baseline CTC Counts are Prognostic on Ra-223 Tx

CTC (log)

Category

Events

Average Alive Months

ALP Drop, Low CTC (<3/mL)
2 Alive, 5 Decesed (71% Decreased)
22

ALP Drop, High CTC (>3/mL)
1 Alive, 3 Decesed (75% Decreased)
13

ALP Rise, High CTC (>3)
4 Alive, 1 Decesed (20% Decreased)
25

CTCs changes occur in pts receiving single agent or combination Ra-223 therapy, supportive that characterization of CTCs may reflect changes to the bone compartment due to Ra-223
CTCs phenotypic changes occur in pts treated with Ra-223. Biological characterization of the specific cell types can potentially provide insights into treatment sensitivity
Measurement of baseline and on-therapy CTC counts and phenotypes are being evaluated in larger cohorts to further develop predictive and PD biomarkers in context to Ra-223 Tx

Combination of Baseline CTC Counts and Alkaline Phosphatase (ALP) Changes Potentially Improve Ra-223 Prognostics

Methods for CTC Detection

Blood samples were plated on microscope slides and every nucleated object imaged, with CTCs detected by a combination of: cytokeratin (CK), CD45, CD105, androgen receptor, and CD34 (blood lineage) staining, and malignant morphology.

Schematic of Epic CTC Platform CTC enumeration, morphology, and biomarker workflow:

1) Nucleated cells from blood sample placed onto slides and stored in a 4°C biorepository
2) Slides stained with cytokeratin (CK), CD45, CD105, androgen receptor
3) Slides scanned

4) CTC candidates detected by a multi-parametric digital pathology algorithm
5) Human reader confirmation of CTCs & quantification of biomarker expression

Patient Demographics

- This cohort represents a retrospective analysis of prospectively enrolled and banked samples (see above) and exploratory analyses
- Sample inclusion criteria: pts must have one draw before initiation of Ra-223, either as a single agent or in combination with abiraterone or enzalutamide, and one draw taken during therapy.
- 34 pts contributed two samples each
- 20 pts received Ra-223 alone
- 14 pts received a combination of Ra-223 and abiraterone or enzalutamide
- One patient excluded: abiraterone was added to Ra-223 after therapy initiation
- As of 25 May 2017, there are 22 death events among the 33 pts

Background

- In unselcted patient populations, Ra-223 (Xtigo) demonstrated an improvement in overall survival (OS). However, a lack of predictive and pharmacodynamic (PD) biomarkers to inform patient selection and confirm efficacy remain an unmet medical need.
- Ra-223 is being studied in combination with androgen receptor signaling inhibitors (ARSI), abiraterone, enzalutamide or taxane chemotherapy, further confirming the identification and validation of predictive and PD biomarkers.
- Pre-clinical data supports that Ra-223 may induce and sensitize tumors to DNA damaging agents and/or checkpoint inhibitors.
- We sought to evaluate the relationship between CTC counts and phenotypic changes for both single agent Ra-223 and combined Ra-223 + ARS from pre-treatment and on-therapy blood draws and patient outcomes.