PSMA heterogeneity analysis in patients with metastatic castrate-resistant prostate cancer (mCRPC): Imaging versus CTCs

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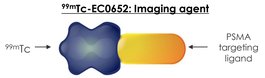
Background

- Prostate-specific membrane antigen (PSMA) is highly expressed on advanced, high grade mCRPC but expression is several hundred-fold lower in normal tissues, making it an ideal cancer biomarker and therapeutic target.
- The utility of the PSMA-targeted imaging agent ^{99m}Tc-EC0652 is being evaluated, along with biomarker analysis of circulating tumor cells (CTCs), in pts with mCRPC in a PSMA-targeted chemotherapeutic study.
- We now report the PSMA heterogeneity via CTC vs. imaging in the pt population treated to date.

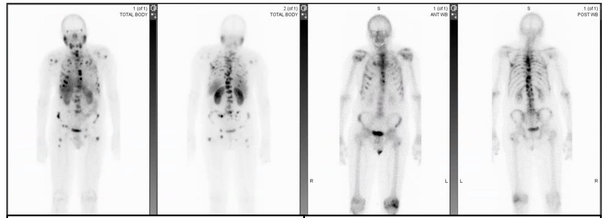
PSMA-Targeted Imaging Agents Target Both Soft Tissue and Bone Metastases

- ^{99m}Tc-EC0652 (SPECT/CT) TBR ratios in many lesions were greater than 50, which is higher than SUVs for FDG in other cancers
- High TBRs indicate specificity and potentially high drug delivery



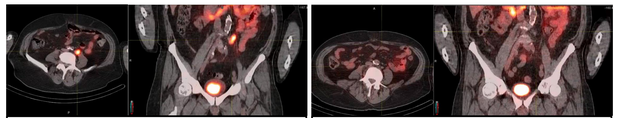
- ^{99m}Tc-EC0652 (SPECT/CT) was used during a PSMA-targeted therapeutic study to assess patients for the localization of PSMA expressing lesions.
- For this study being presented, a total lesion count was performed on a subset of 8 patients that were split into two cohorts of four patients that either responded well to treatment or responded poorly to treatment.

^{99m}Tc-EC0652 PSMA Imaging May Detect More Lesions than Traditional Bone Scans



Baseline ^{99m}Tc-EC0652 Scan | Baseline Bone Scan

PSMA Positive Disease Responded to PSMA Targeted Chemotherapy; Images of a Patient with a Confirmed PR



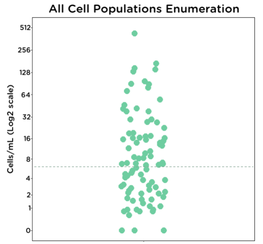
Baseline ^{99m}Tc-EC0652 SPECT/CT | Week 31 ^{99m}Tc-EC0652 SPECT/CT

Circulating Tumor Cell (CTC) Enumeration Analysis

- The CTC enumeration analysis was conducted on all patients in the study. Of the 63 patients on study, there were 95 samples analyzed.
- **91% (86/95)** of samples had at least 1 CTC if considering **All CTC Populations**
- **86% (82/95)** of samples had at least 1 CTC if considering **Traditional CTC Populations**

Traditional CTC Populations	CK+ Cells & Clusters
All CTC Populations	CK+ Cells & Clusters
	CK- Cells & Clusters
	Apoptotic Cells

Cell Type	Median	Mean	Min	Max
All Populations/mL	**6.6**	**23.8**	**0**	**426**
Traditional CTCs/mL	**4**	**19.6**	**0**	**416**
CK+ Cell/mL	3.9	18.2	0	393
CK+ Cluster/mL	0	1.4	0	22
CK- Cell/mL	0	1	0	18
CK- Clusters/mL	0	0.1	0	5.6
Apoptotic Cell/mL	0.8	3.1	0	59

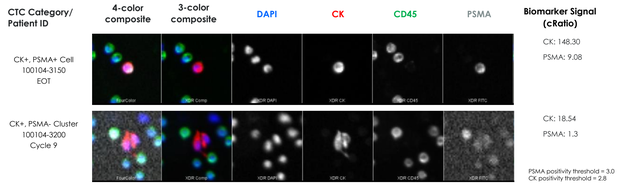


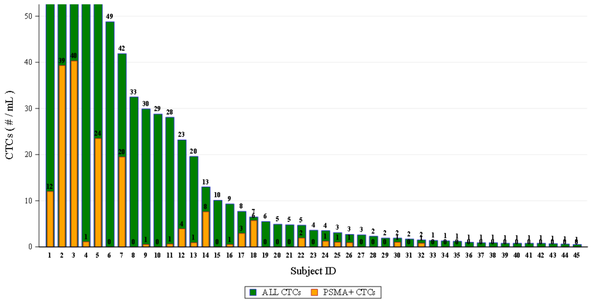
95 samples

Each dot indicates the calculated All Populations/mL per sample; Dotted line = median All Populations/mL

PSMA Expression in Patient Samples

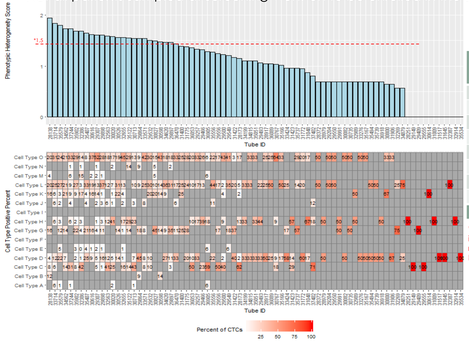
- Of the 50 patients enrolled in the study that were sampled at baseline for PSMA expression, 45 had samples that contained CTCs.
- 20 of these 45 samples (44%) had CTCs that contained PSMA-positive cells





Phenotypic Heterogeneity in Patient Samples

- 20/79 (25.3%) total samples collected had high phenotypic heterogeneity
- Only 16/63 (25.4%) of patient samples at screening had high phenotypic heterogeneity. Not all patients sampled at screening went on to be enrolled in the study.



Time Point	# Samples with High Phenotypic Heterogeneity (>1.5)
Screening	16/63 (25%)
Cycle 1	2/4 (50%)
Cycle 2	0/2 (0%)
Cycle 3	0/4 (0%)
Cycle 7	1/1 (100%)
Cycle 9	1/1 (100%)
Cycle 12	0/1 (0%)
End of Study	0/3 (0%)
Total	20/79 (25%)

*Phenotypic Heterogeneity Score of 1.5 is the cutoff associated with poor response to ARSi (cutoff for high Phenotypic Heterogeneity)

Among samples with high phenotypic heterogeneity (>1.5), 13/15 (87%) of cell subtypes were observed

- Most prevalent cell subtypes observed:
  - O, C, L
- Other cell subtypes observed:
  - K, H, G, D, M, J, E, N, A, B
- Most prevalent cell types tend to have:
  - MYC Gain (6-45%)
  - TP53 Loss (2-22%)
  - AR Gain (2-19%)
  - PTEN Loss (2-15%)
  - RB1 Loss (0-2%)

Cell Type	Phenotype Shorthand
A	Low cytokeratin, no AR, huge cell size
B	High CK expression, AR overexpression, large cytoplasm
C	No AR expression, large cytoplasm
D	Very small cell and nuclear size, high CK expression
E	Distinctly high AR expression, high nuclear entropy
F	High CK expression, AR expression, frequently in histological cluster of 2 CTCs
G	Very high CK expression and frequent high AR expression
H	Low AR expression, spindly cell shape
I	Low CK expression, Low AR expression, frequently found in histological CTC clusters
J	Very small cell size, high n/c ratio
K	Huge nucleus, high n/c ratio
L	Very small cell, frequent AR overexpression, high n/c ratio
M	Huge nuclear size, high nuclear entropy
N	Non-circular cell shape
O	Low AR expression, high nuclear entropy, large cell size

Predicted NEPC in Patient Samples

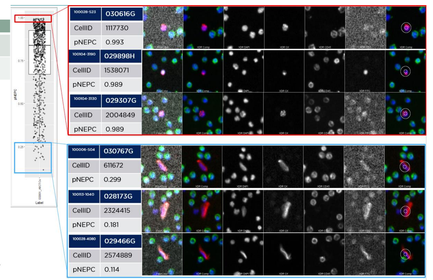
7/79 (9%) samples were positive for predicted (Neuroendocrine Prostate Cancer (NEPC)

pNEPC Scoring Criteria

Category	Scoring Criteria
Per Cell	If pNEPC+ ≥ 0.972, then cell pNEPC positive
Per Sample	If ≥ 3 pNEPC+ CTCs, then sample pNEPC positive

Time Point	# Samples positive for Predicted NEPC
Screening	6/63 (10%)
Cycle 1	0/4 (0%)
Cycle 2	0/2 (0%)
Cycle 3	0/4 (0%)
Cycle 7	0/1 (0%)
Cycle 9	0/1 (0%)
Cycle 12	0/1 (0%)
End of Study	1/3 (33%)
Total	7/79 (9%)

Cell Subtypes correlated to pNEPC: L, D, K and O
pNEPC+ CTC tend to be small and very circular



Comparative Lesion Detection by Imaging Modality

A total lesion count on a subset of 8 patients was performed to evaluate the concordance of ^{99m}Tc-EC0652 with conventional imaging modalities (CIM) which was defined as MDP based bone scans and CT scans.

Full Lesion Count (N = 8 patients)

	Bone Lesions						
	Bone Scan+	Bone Scan-	CT+	CT-	CIM+	CIM-	Total
^{99m}Tc-EC0652+	245	25	58	36	303	61	364
^{99m}Tc-EC0652-	0	0	2	0	2	0	2
Total	245	25	60	36	305	61	366
			Soft Tissue				
			CT+	CT-	CIM+	CIM-	Total
^{99m}Tc-EC0652+			6	2	6	2	8
^{99m}Tc-EC0652-			0	0	0	0	0
Total			6	2	6	2	8

Comparative Lesion Detection by Imaging Modality

High Responder Patients (N = 4 patients)

	Bone Lesions						
	Bone Scan+	Bone Scan-	CT+	CT-	CIM+	CIM-	Total
^{99m}Tc-EC0652+	33	0	33	0	66	0	66
^{99m}Tc-EC0652-	0	0	0	0	0	0	0
Total	33	0	33	0	66	0	66
			Soft Tissue				
			CT+	CT-	CIM+	CIM-	Total
^{99m}Tc-EC0652+			3	2	3	2	5
^{99m}Tc-EC0652-			0	0	0	0	0
Total			3	2	3	2	5

Low Responder Patients (N = 4 patients)

	Bone Lesions						
	Bone Scan+	Bone Scan-	CT+	CT-	CIM+	CIM-	Total
^{99m}Tc-EC0652+	212	25	25	36	237	61	298
^{99m}Tc-EC0652-	0	0	2	0	2	0	2
Total	212	25	27	36	239	61	300
			Soft Tissue				
			CT+	CT-	CIM+	CIM-	Total
^{99m}Tc-EC0652+			3	0	3	0	3
^{99m}Tc-EC0652-			0	0	0	0	0
Total			3	0	3	0	3

Conclusions

- PSMA-based imaging showed a high percentage of positive pts whereas CTC-based PMSA positivity is lower by comparison (44%).
- In the subset of patients that responded poorly, there was a higher osseous disease burden with one example of PSMA negative uptake by imaging.
- The evaluation of the imaging results & CTC-based biomarkers, and the relative therapeutic predictive value is ongoing.

Study is ongoing, therefore all data presented above are preliminary