Abstract 11516: Circulating tumor cells (CTCs) in SWOG S1216: A phase 3 multicenter trial in metastatic hormone sensitive prostate cancer (mHSPC)

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Abstract

Background: Novel hormonal therapies recently approved for metastatic castration resistant prostate cancer (mCRPC) are now being tested in hormone sensitive disease (mHSPC), prompting evaluation of new biomarkers to guide therapy in this earlier disease state. We are conducting CTC enumeration, sequencing, and gene expression studies in S1216, a SWOG-sponsored North American Intergroup phase 3 trial of androgen deprivation in combination with bicalutamide or orteronel, a CYP17,20 lyase inhibitor. Baseline CTC enumeration data are presented for 225 patients evaluated to date.

Methods: Four 7.5mL tubes of blood are collected for CTC analysis (enumeration, sequencing, gene expression) at study entry and at progression to mCRPC. Specimens are logged in the SWOG online specimen tracking system and sent overnight at room temperature to a central site (Goldkorn Lab) for analysis. One of the 4 tubes is a CellSave tube used for CTC enumeration on the FDA-cleared CellSearch platform (Janssen/J&J). CellSearch CTC counts are transmitted to SWOG Statistical Center for analysis and correlation with clinical data.

Results: From 11/2014 - 10/2015, CTCs were detected in 78 of 211 evaluable samples (37%), and detection was impacted by whether patients had already initiated therapy at the time of sample collection (29% detection in treated vs. 46% in treatment naïve, p=0.01). Median CTC count for patients with detectable CTCs was 2/7.5 ml blood (1st quartile =1, 3rdquartile =9), and median for the entire cohort was 0 (range 0-4000). Presence of baseline CTCs was associated with higher PSA (p=0.03), bony metastases (p=0.05), presence of extensive disease (p<0.001), and a trend toward worse performance status (p=0.06).

Conclusions: In this phase 3 trial, the largest prospective CTC cohort in mHSPC to date, baseline CTCs were detected in >1/3 of patients and nearly half of patients who had not yet initiated therapy. Presence of CTCs was associated with known baseline prognostic factors and therefore may predict clinical outcome with continued follow-up. Further CTC enumeration, sequencing and gene expression are ongoing in S1216 to maximize the prognostic and predictive benefit of CTC analysis in mHSPC.

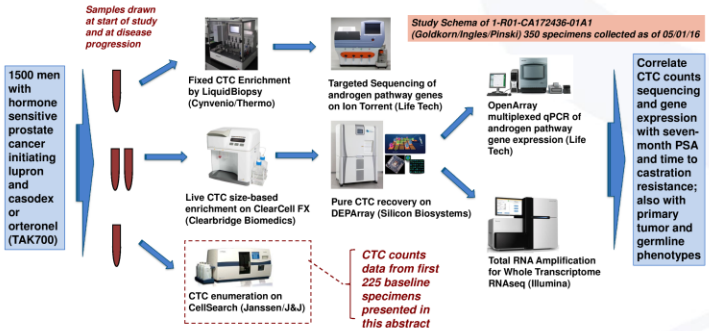
Introduction

- Prostate cancer is the most common non-skin malignancy in men
- Metastatic prostate cancer can be treated effectively as long as it remains sensitive to hormonal therapy (mHSPC), but the disease progresses more rapidly once it evolves to the castration resistant state (mCRPC)
- Informative prognostic and predictive biomarkers are needed to guide optimal therapy, to extend the mHSPC state and to delay progression to mCRPC
- Preliminary studies showed that sequence variants and expression levels of luteinizing hormone (LH), luteinizing hormone releasing hormone (LHRH), and other members of the androgen synthesis and signaling pathway are associated with response or resistance to androgen deprivation therapy

Hypothesis & Design

- S1216 is a SWOG-led intergroup Phase III multi-center trial in which men with mHSPC are randomized to lupron + bicalutamide or lurpon + orteronel (TAK700, cyp17,20 lyase inhibitor)
- We hypothesized that treatment response and resistance may be predicted and better understood by analyzing circulating tumor cells (CTCs) at baseline and at progression to mCRPC
- CTCs are enumerated and molecularly characterized (androgen pathway gene sequencing and expression analysis)
- Matched white blood cell pellets (all patients) and primary tumors (subset of patients) are collected for parallel analysis
- In this abstract, baseline CTC counts from the first 225 prospectively collected samples are presented

Methods



Results

Baseline Patient Characteristics

Age median (range)	67 (46-90)
Baseline PSA median (range)	35 (2-4809)
AST median (range)	23 (6-180)
ALT median (range)	24 (5-260)
Alkaline Phosphatase median (range)	86 (14-4800)
Hemoglobin median (range)	14 (9-21)
Gleason Score	
<= 6	8 %
7	30 %
>= 8	58 %
missing	4 %
Bone Pain	
Yes	24 %
No	76 %
Bone Metastases	
Yes	71 %
No	29 %
Visceral Metastases	
Yes	13%
No	87 %
Disease Severity	
Minimal	53 %
Extensive	47 %
Performance Status	
0-1	96 %
2-3	4 %
Pre-Registration LHRH Suppression	
Yes	49 %
No	51 %
Detectable CTCs	
Entire Cohort (N = 79 / 211)	37 %
Pre-registration LHRH suppression*	
Yes (N = 30 / 104)	29 %
No (N = 49 / 107)	46 %
CTC Count	
Entire Cohort: median (Q1, Q3)	0 (0, 2)
Subset with detectable CTCs: median (Q1, Q3)	2 (1, 9)

* p=0.01, Cochran-Mantel-Haenszel test N = 211

Baseline Prognostic Risk Factor Association with CTC Detection

Risk Factor	Detectable CTCs	p-value*
Age		0.61
<= 67	36 %	
> 67	39 %	
Baseline PSA		0.03
Low	25 %	
Medium	44 %	
High	43 %	
Gleason Score		0.84
<= 6	44 %	
7	32 %	
>= 8	36 %	
Bone Pain		0.15
Yes	46 %	
No	35 %	
Bone Metastases		0.05
Yes	42 %	
No	27 %	
Visceral Metastases		0.53
Yes	43 %	
No	37 %	
Disease Severity		<0.001
Minimal	26 %	
Extensive	51 %	
Performance Status		0.06
0-1	36 %	
2-3	67 %	

* Cochran-Mantel-Haenszel test N = 211

Association of baseline prognostic factors in S1216 with CTC Counts of 0 vs. 1-4 vs. >4

(previously identified cut points in mHSPC in SWOG S0925, *Yu E et al, JCO 2015*)

Risk Factor	p-value*
Baseline PSA	0.005
Gleason Score	0.42
Disease Severity (Minimal vs. Extensive)	0.001
Visceral Metastases (Yes vs. No)	0.54
Bone Metastases (Yes vs. No)	0.14
Bone Pain (Yes vs. No)	0.30
Performance Status (0-1 vs. 2-3)	0.08

* Fisher's Exact Test N=211

Conclusions

- In this largest prospective mHSPC cohort to date, CTCs were detected in a significant subset of patients, and detection was higher in men who had not yet initiated androgen deprivation therapy
- Baseline CTC detection was associated with worse PSA, bony metastases and disease severity
- Prior CTC cut points also were significantly associated with prognostic factors in S1216
- Baseline CTC counts may therefore predict clinical outcome with additional sample collection and longer follow-up (trial is ongoing)
- CTC characterization (sequencing, gene expression) is ongoing in S1216 and will be correlated with CTC counts, clinical outcomes, and parallel tumor and germline analyses