Phase 1 study of the PSMA-targeted small-molecule drug conjugate EC1169 in patients with metastatic castrate-resistant prostate cancer (mCRPC)

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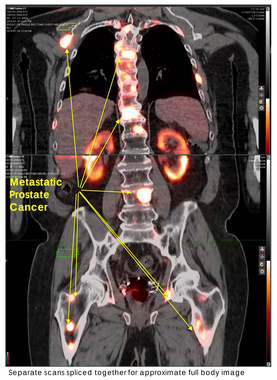
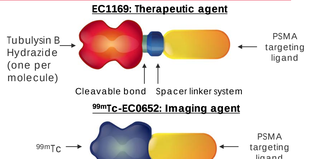
Background

- Prostate-specific membrane antigen (PSMA) is highly expressed on advanced, high grade, metastatic castration resistant prostate cancer (mCRPC) but several hundred fold less in normal tissues (Ghosh 2004), making it an ideal cancer biomarker and therapeutic target.
- ^{99m}Tc-EC0652 is a PSMA-targeted imaging agent being investigated as a non-invasive, real-time means to identify patients who may benefit from treatment with EC1169.
- EC1169 is a novel, small molecule drug conjugate (SMDC) of a PSMA-targeting ligand and a potent microtubule inhibitor (tubulysin B hydrazide; TubBH). EC1169 may avoid the hematologic toxicity of traditional chemotherapy.

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

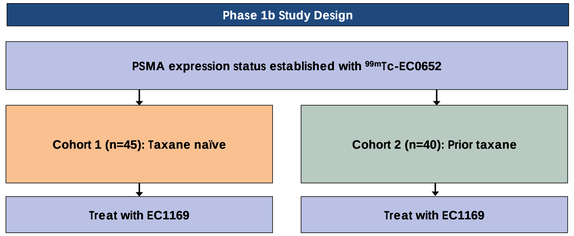


Separate scans spliced together for approximate full body image



- EC0652 (SPECT/CT) mean tumor-to-background (TBR) ratios in many lesions > 50
  - Higher than SUVs for FDG in other cancers
- High TBRs indicate potential high drug delivery
- In Ph1a, high TBRs suggested a trend in better outcome for subjects with a TBR > 5

EC1169 Phase 1b – Expansion Cohorts



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EC1169 Phase 1b Objectives and Study Design

- Primary objective: To assess time to radiographic progression (rPFS) per PCWG3
- Secondary objectives: To determine safety, PCWG3 defined NLCB (no longer clinically benefiting), median PFS, median OS, and to evaluate blood based markers and imaging biomarkers for efficacy correlation
- Exploratory objective: To explore the relationship between ^{99m}Tc-EC0652 uptake and patient response
- Study enrollment: Two distinct mCRPC patient populations
  - Cohort 1: No prior taxane-based therapy for mCRPC (taxane naïve)
  - Cohort 2: Prior treatment with taxane-based therapy for mCRPC (taxane exposed)

Phase 1b Patient and Disease Characteristics

	Taxane Naïve (n=16)	Taxane Exposed (n=24)	All Pts (n=40)
Gleason Score at diagnosis, N(%): 4-7; 8-10; Unk	8 (50.0%); 5 (31.3%); 3 (18.8%)	9 (37.5%); 12 (50.0%); 3 (12.5%)	17 (42.5%); 17 (42.5%); 6 (15.0%)
Age (yrs), med (range)	74 (59 - 84)	68 (49 – 82)	68.5 (49 – 84)
Baseline PSA, med (range)	69 (2.6 – 597)	110 (0.2 – 1550)	104 (0.2 – 1550)
Baseline Alkaline Phosphatase, med (range)	83 (47 – 1437)	138 (43 – 1231)	115 (43 – 1437)
Baseline LDH, med (range)	196 (17 – 279)	224 (123 – 4200)	207 (17 – 4200)
Prior Radiotherapy, med (range)	1.5 (1 – 3)	2 (1 – 3)	2 (1 – 3)
Prior Therapies (non-radiotherapy, med (range)	4 (1 – 11)	5 (1 – 8)	4 (1-11)
AR Directed	14 (87.5%)	20 (83.3%)	34 (85.0%)
Hormonal	10 (62.5%)	18 (75.0%)	28 (70.0%)
Chemotherapy	3 (18.8%)	21 (87.5%)	24 (60.0%)
Investigative or Supportive	3 (18.8%)	12 (50.0%)	15 (37.5%)
Biologic	1 (6.3%)	6 (25.0%)	7 (17.5%)
Radionuclide	2 (12.5%)	1 (4.2%)	3 (7.5%)

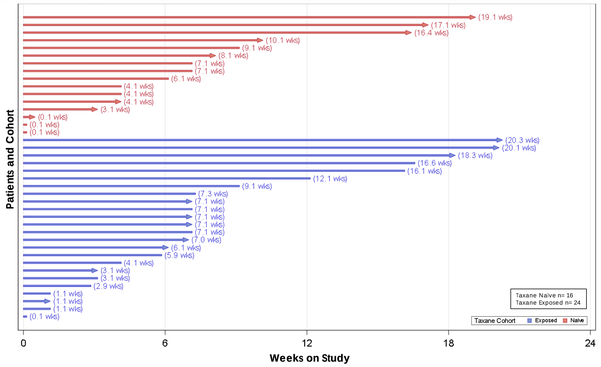
Phase 1b Safety Overview

- 6.5 mg/m^2 was identified as the RP2 dose (established during Ph1a)
- 40 pts on Ph1b have received EC1169 drug, administered days 1, 8 (QW) every 21 days: 16 taxane naïve, 24 taxane exposed
- The median number of cycles for each cohort is 3.0 (1.0 – 7.0)
- 31 (77.5%) patients have experienced drug related AEs, 2 (5.0%) grade 3/4 drug related AEs (Gr3 constipation and Gr3 musculoskeletal pain). No drug related SAEs or toxicity requiring dose reductions have occurred

Phase 1b Drug-related Adverse Event in > 10% of Subjects

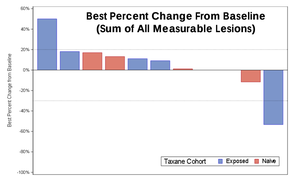
Adverse Event	All Grades (N=40)	Grade 1 (N=40)	Grade 2 (N=40)	Grade 3 (N=40)	Grade 4 (N=40)
Fatigue	13 (32.5%)	4 (10.0%)	9 (22.5%)	0 (0.0%)	0 (0.0%)
Decreased Appetite	11 (27.5%	9 (22.5%)	2 (5.0%)	0 (0.0%)	0 (0.0%)
Constipation	10 (25.0%)	6 (15.0%)	3 (7.5%)	1 (2.5%)	0 (0.0%)
Nausea	9 (22.5%)	8 (20.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)
Anemia	8 (20.0%)	2 (5.0%)	6 (15.0%)	0 (0.0%)	0 (0.0%)
Abdominal pain	7 (17.5%)	5 12.5%)	2 (5.0%)	0 (0.0%)	0 (0.0%)
Alopecia	7 (17.5%)	6 (15.0%)	1 (2.5%)	0 (0.0%)	0 (0.0%)
AST increased	6 (15.0%)	4 (10.0%)	2 (5.0%)	0 (0.0%)	0 (0.0%)
Vomiting	6 (15.0%)	6 (15.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Phase 1b Time On Study by Cohort (Taxane naïve vs. Taxane exposed)



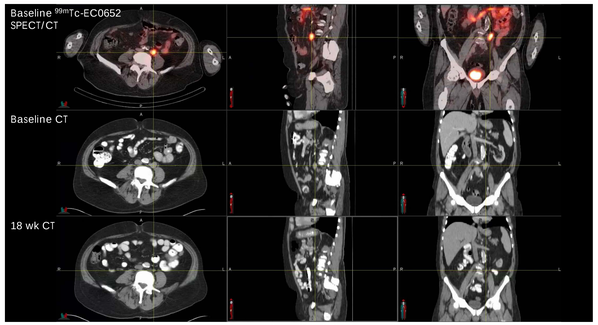
Note: An arrow shows that the patient is still active on study treatment. A solid stop shows that the patient has discontinued treatment.

Phase 1b Patient Response (Measurable Soft Tissue Disease)

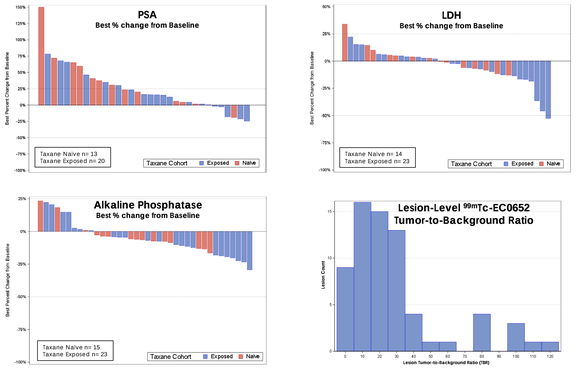


- **Taxane-naïve cohort:** 6 of the 16 patients (38%) had measurable soft tissue disease. 4/6 patients (67%) had stabilization of their measurable soft tissue disease; the remaining 2 patients have not reached their first follow-up assessment.
- **Taxane-exposed cohort:** 13 of the 24 patients (54%) had measurable soft tissue disease. 1/13 patient (8%) had confirmed PR (partial response). 5/13 patients (38%) had stabilization of their measurable soft tissue disease; 1/13 (8%) had radiographic progression at the first follow-up assessment; 5/13 (38%) discontinued treatment prior to their first follow-up assessment; and 1 patient has not reached their first follow-up assessment.

PSMA Positive Target Disease Responded to EC1169; Phase 1b Pt had confirmed PR



Phase 1b Exploratory Analyses



Phase 1b Circulating Tumor Cell (CTC) Analysis

CTC status		PSMA Positive	PSMA Negative	Total
13 of 20 pt specimens had enumerable CTCs • 13 pt CTCs were evaluated for PSMA • 10 pt CTCs were evaluated for positive probability of belonging to neuroendocrine prostate cancer (pNEPC)	pNEPC Positive	3	0	3
	pNEPC Negative	2	5	7
	pNEPC not tested	1	2	3
	Total	6	7	13

- 13/20 (65%) of specimen CTCs were enumerated. 6/13 (46%) of enumerable specimens were PSMA positive, of which 3/6 (50%) were pNEPC positive. These CTCs show a heterogeneous mixture of both PSMA and pNEPC expression.

Conclusions

- mCRPC is a phenotypically diverse disease with high unmet need as not all patients are suitable for chemotherapy, reinforcing the need for predictive biomarker co-development.
- EC1169 has been found to be well tolerated in patients with recurrent mCRPC without causing the dose-limiting hematologic toxicity that is often associated with traditional prostate chemotherapy.
- ^{99m}Tc-EC0652 non-invasively characterizes in real time an individual patient's PSMA expression in both soft tissue and bone lesions, and is therefore being co-developed to select patients most likely to benefit from PSMA-targeted EC1169.
- An early assessment of Ph1b pts treated with EC1169 monotherapy have experienced tumor shrinkage, durable stabilization of disease, improvements in disease-related symptoms and decreases in disease-related markers such as lactate dehydrogenase and alkaline phosphatase.

Study is ongoing, therefore all data presented above is preliminary