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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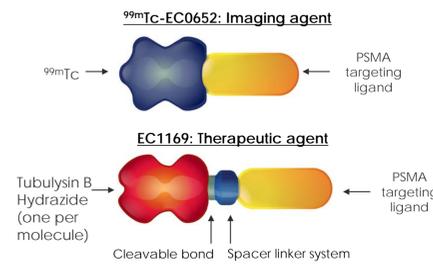
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Background

- 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.
- EC1169 is a novel, PSMA-targeted small molecule drug conjugate constructed of a PSMA-targeting ligand and a potent microtubule inhibitor (tubulysin B hydrazide).
- 99mTc-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.
- The Cohort Expansion Phase 1B of study EC1169-01 explored a dose of 6.5 mg/m² (days 1, 8 every 21 days) in two distinct mCRPC patient populations: one previously exposed to taxane therapy and the second taxane naive,
- This poster includes updated clinical information, 99mTc-EC0652 tumor to background ratio (TBR) data and exploratory biomarkers from this ongoing study.

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

- 99mTc-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
- In Ph1a, high TBRs suggested a trend in better outcome for subjects with a mean TBR > 5

99mTc-EC0652: Imaging agent
99mTc — PSMA targeting ligand

EC1169: Therapeutic agent
Tubulysin B Hydrazide (one per molecule) — PSMA targeting ligand
Cleavable bond — Spacer linker system

Phase 1b Patient and Disease Characteristics

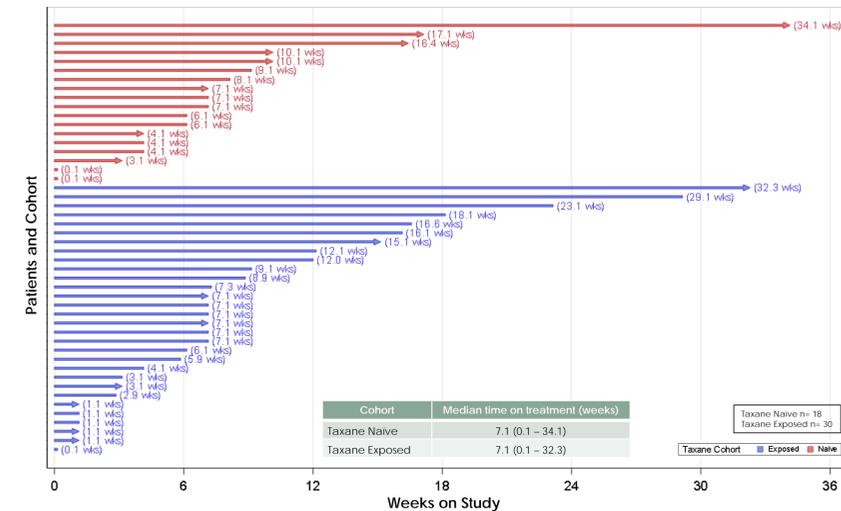|	Taxane Naive (n=18)	Taxane Exposed (n=30)	All Pts (n=48)
Gleason Score at diagnosis, N(%): 4-7; 8-10: Unk	10(55.6%): 7 (38.9%): 1 (5.6%)	9 (30.0%): 18 (60.0%): 3 (10.0%)	19 (39.6%): 25 (52.1%): 4 (8.3%)
Age (yrs), med (range)	72.0 (59 - 84)	67.5 (49 – 82)	68.5 (49 – 84)
Baseline PSA, med (range)	76 (2.6 – 1828)	117 (0.2 – 1550)	110 (0.2 – 1828)
Baseline Alkaline Phosphatase, med (range)	83 (47 – 1437)	131 (36 – 1231)	107 (36 – 1437)
Baseline LDH, med (range)	203 (148 – 279)	224 (123 – 4200)	208 (123 – 4200)
Prior Radiotherapy, med (range)	1 (1 – 4)	2 (1 – 3)	2 (1 – 4)
Prior Therapies (non-radiotherapy, med (range)	4.0 (2 – 11)	5 (1 – 10)	5 (1-11)
AR Directed	18 (100%)	29 (96.7%)	47 (97.9%)
Hormonal	12 (66.7%)	23 (76.7%)	35 (72.9%)
Chemotherapy	3 (16.7%)	30 (100.0%)	33 (68.8%)
Investigative or Supportive	7 (38.9%)	18 (60.0%)	25 (52.1%)
Biologic	2 (11.1%)	11 (36.7%)	13 (27.1%)
Radionuclide	3 (16.7%)	3 (10.0%)	6 (12.5%)
Patient Lesion types			
Visceral	1 (5.6%)	6 (20.0%)	7 (14.6%)
Lymph Node	8 (44.4%)	14 (46.7%)	22 (45.8%)
Bone	12 (66.7%)	25 (83.3%)	37 (77.1%)

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

| Adverse Event	All Grades (N=48)	Grade 1 (N=48)	Grade 2 (N=48)	Grade 3 (N=48)	Grade 4 (N=48)
Fatigue	16 (33.3%)	5 (10.4%)	9 (18.8%)	2 (4.2%)	0 (0.0%)
Decreased appetite	13 (27.1%)	11 (22.9%)	2 (4.2%)	0 (0.0%)	0 (0.0%)
Nausea	12 (25.0%)	10 (20.8%)	2 (4.2%)	0 (0.0%)	0 (0.0%)
Constipation	11 (22.9%)	7 (14.6%)	3 (6.3%)	1 (2.1%)	0 (0.0%)
Anaemia	9 (18.8%)	2 (4.2%)	6 (12.5%)	1 (2.1%)	0 (0.0%)
Alopecia	9 (18.8%)	8 (16.7%)	1 (2.1%)	0 (0.0%)	0 (0.0%)
Vomiting	8 (16.7%)	7 (14.6%)	1 (2.1%)	0 (0.0%)	0 (0.0%)
Abdominal pain	7 (14.6%)	5 (10.4%)	2 (4.2%)	0 (0.0%)	0 (0.0%)
AST increased	7 (14.6%)	4 (8.3%)	3 (6.3%)	0 (0.0%)	0 (0.0%)
Hypophosphataemia	6 (12.5%)	0 (0.0%)	5 (10.4%)	1 (2.1%)	0 (0.0%)
ALT increased	5 (10.4%)	3 (6.3%)	2 (4.2%)	0 (0.0%)	0 (0.0%)

Phase 1b Safety Overview

- 6.5 mg/m² was identified as the RP2 dose (established during Ph1a)
- 48 pts on Ph1b have received EC1169, administered days 1, 8 (QW) every 21 days: 18 taxane naive, 30 taxane exposed
- The median number of cycles for taxane naïve cohort is 3.0 (1 – 12) and taxane exposed is 3.5 (1 – 10)
- 36 (75%) patients have experienced drug related AEs, 6 (12.5%) grade 3 drug related AEs: fatigue (2), anaemia (1), constipation (1), hypophosphataemia (1), musculoskeletal pain (1). No grade 4 drug related AEs. No drug related SAEs or toxicity requiring dose reductions have occurred

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

Cohort	Median time on treatment (weeks)
Taxane Naive	7.1 (0.1 - 34.1)
Taxane Exposed	7.1 (0.1 - 32.3)

Taxane Naive n= 18
Taxane Exposed n= 30

Taxane Cohort — Exposed — Naive

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

99mTc-EC0652 PSMA imaging may detect more lesions than traditional bone scans
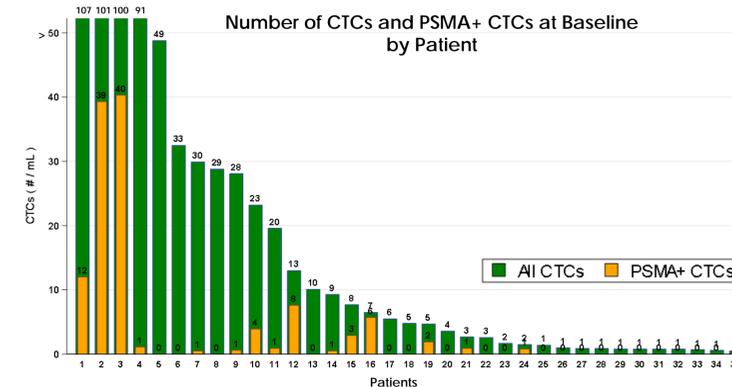

Baseline 99mTc-EC0652 Scan | Baseline Bone Scan
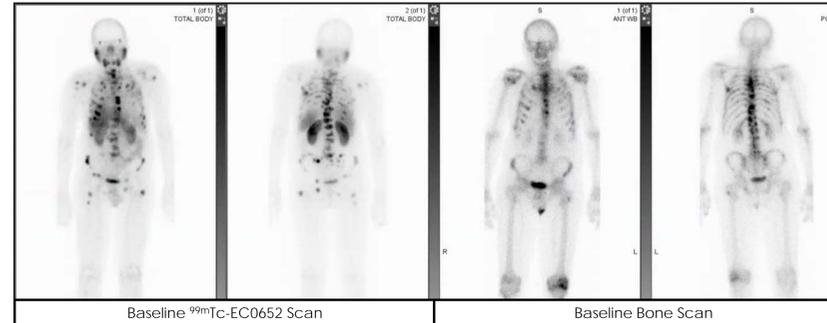
99mTc-EC0652 Lesion Uptake Intensity

Lesion Type	n*	TBR, Median (Range)
Bone	n=99	22.6 (2.9 – 126.2)
Soft Tissue	n=68	20.7 (0.9 – 119.8)
All lesions	n=167	21.9 (0.9 – 126.2)

*n signifies detected lesions selected by external radiologists for TBR analysis. Bone lesions selected max of 6 detected lesions per pt. Soft tissue lesions selected by modified RECIST 1.1 criteria.

- 99mTc-EC0652 detects both soft tissue and bone lesions
- TBRs are similar across lesion types

PSMA Positive Disease Responded to EC1169; Images of a Phase 1b Patient with a confirmed PR (Remains on Study)


Baseline 99mTc-EC0652 SPECT/CT | Week 31 99mTc-EC0652 SPECT/CT
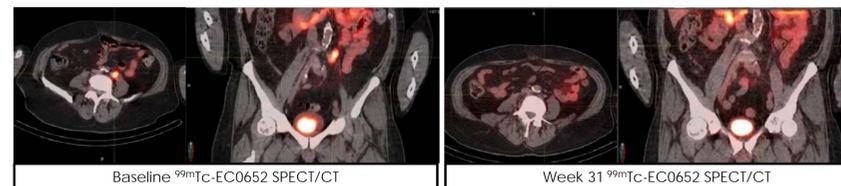
Phase 1b Circulating Tumor Cell (CTC) Analysis

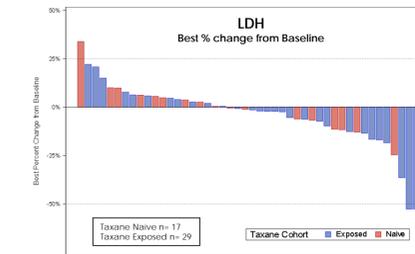Number of CTCs and PSMA+ CTCs at Baseline by Patient

All CTCs | PSMA+ CTCs

- 40/48 (83%) pts had a sample available for CTC analysis before their first treatment
- Baseline characteristics of this group were representative of the overall trial population
- 35/40 (88%) samples contained CTCs
- 15/35 (43%) samples containing CTCs contained PSMA-positive cells
- 4/29 (14%) were neuroendocrine positive (6 of 35 didn't have pNEPC samples)

Phase 1b Measurable Lesion Response and Exploratory Analyses

Best Percent Change From Baseline (Sum of All Measurable Lesions)

Taxane Cohort — Exposed — Naive
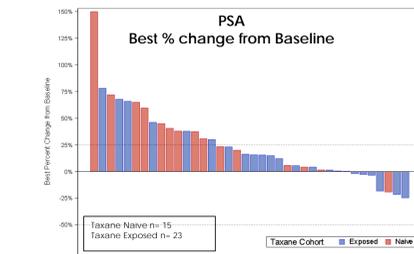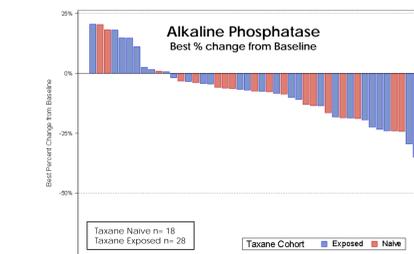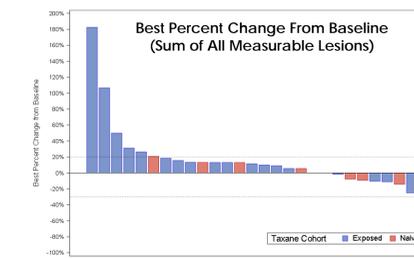
- **Taxane-naïve cohort:** 6 of the 18 patients (33%) had measureable soft tissue disease. 4/6 patients (67%) had stabilization of their measurable soft tissue disease: the remaining 2 patients have not reached their first follow-up assessment
- **Taxane-exposed cohort:** 16 of the 30 patients (53%) had measurable soft tissue disease. 1/16 patient (6%) had confirmed PR (partial response). 8/16 (50%) had stabilization of their measurable soft tissue disease: 1/16 (6%) had radiographic progression at the first follow-up assessment: 5/16 (31%) discontinued treatment prior to their first follow-up assessment; and 1 patient (6%) has not reached their first follow-up assessment.

Alkaline Phosphatase Best % change from Baseline

Taxane Naive n= 18, Taxane Exposed n= 28

LDH Best % change from Baseline

Taxane Naive n= 17, Taxane Exposed n= 29

PSA Best % change from Baseline

Taxane Naive n= 15, Taxane Exposed n= 23

- The correlatives that best match the treatment effect observed with EC1169 appear to be Alkaline Phosphatase and LDH when compared to PSA.
- This observation is similar to what is exhibited with bone targeted therapies.

Conclusions

- EC1169 continues to be well tolerated at the RP2D determined in Part A of the study.
- Both the taxane exposed cohort and taxane naive cohort received a median of 7.1 weeks of treatment to date with many patients still on treatment.
- 99mTc-EC0652 tumor to background ratio was on average 21.7 compared to muscle and similar in both bone and soft tissue.
- Treatment with EC1169 resulted in substantial declines in alkaline phosphatase and LDH levels, but not in PSA, indicating that PSA may not be the best measure of EC1169 anti-tumor effect, an observation similar to what is exhibited with bone targeted therapies.
- 43% of patients with enumerable CTCs contained PSMA-positive cells but also had CTCs that were not PSMA-positive, suggesting significant intra-patient heterogeneity of PSMA-positive disease, requiring further exploration.
- Low number of PSMA-positive cells may be related to late stage disease or site specific PSMA expression.