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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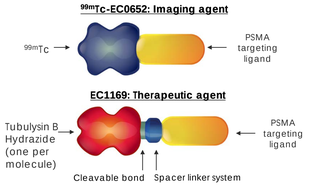
Background

- Prostate-specific membrane antigen (PSMA) is highly expressed on advanced, high grade 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).
- ^{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.
- The Cohort Expansion Phase 1B of study EC1169-01 explored a dose of 6.5 mg/m^2 (days 1, 8 every 21 days) in two distinct mCRPC patient populations: one previously exposed to taxane therapy and the second taxane naïve,
- This poster includes updated clinical information, ^{99m}Tc-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

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



Phase 1b Patient and Disease Characteristics

	Taxane Naïve (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%)

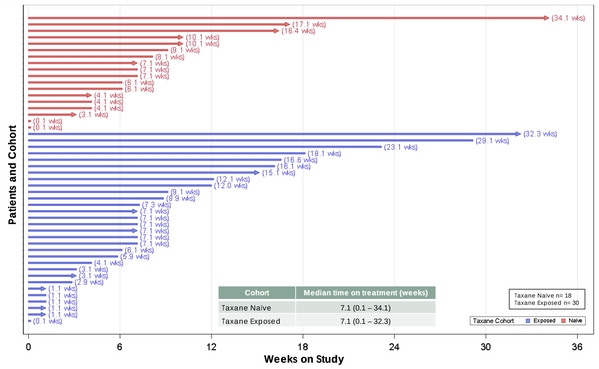
Phase 1b Drug-related Adverse Event in > 10% of Subjects

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

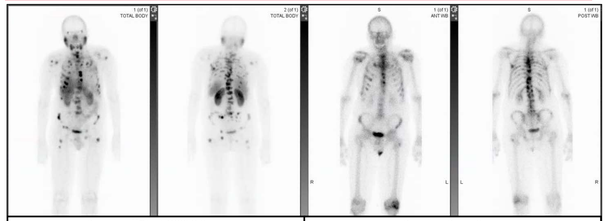
- 6.5 mg/m^2 was identified as the RP2 dose (established during Ph1a)
- 48 pts on Ph1b have received EC1169, administered days 1, 8 (QW) every 21 days: 18 taxane naïve, 30 taxane exposed
- The median number of cycles for taxane naïve cohort is 3.0 (1 – 12) and taxane exposed is 3.5 (1 – 10)
- 36 (75%) 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)



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

^{99m}Tc-EC0652 PSMA imaging may detect more lesions than traditional bone scans

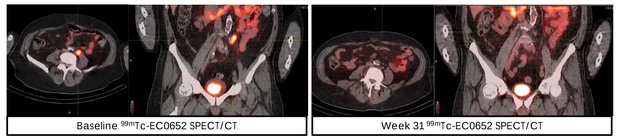


^{99m}Tc-EC0652 Lesion Uptake Intensity		
Lesion Type	n*	TBR, Median (Range)
Bone	n=99	22.6 (2.9 – 126.2)
Soft Tissue	n=68	20.7 (0.9 – 119.8)
All lesions	n=167	21.9 (0.9 – 126.2)

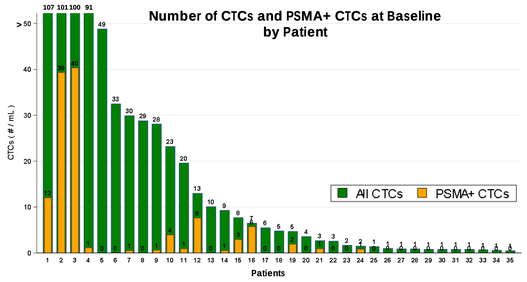
*n signifies detected lesions selected by external radiologists tor TBR analysis. Bone lesions selected max of 6 detected lesions per pt. Soft tissue lesions selected by modified RECIST 1.1 criteria.

- ^{99m}Tc-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)

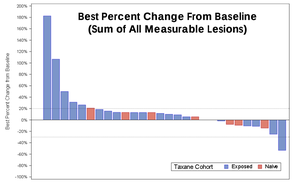


Phase 1b Circulating Tumor Cell (CTC) Analysis

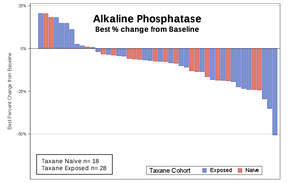


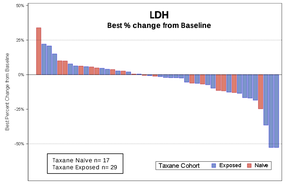
- 40/48 (83%) pts had a sample available for CTC analysis before their first treatment
- Baseline characteristics of this group were representative of the overall trial population
- 35/40 (88%) samples contained CTCs
- 15/35 (43%) samples containing CTCs contained PSMA-positive cells
- 4/29 (14%) were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

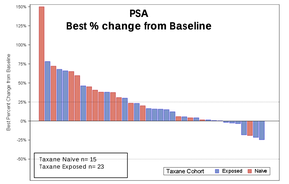
Phase 1b Measurable Lesion Response and Exploratory Analyses



- **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.







- 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 naïve cohort received a median of 7.1 weeks of treatment to date with many patients still on treatment.
- ^{99m}Tc-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.

Memorial Sloan Kettering Cancer Center

Study is ongoing, therefore all data presented above are preliminary