**ProstACT Global: A phase 3 study of Lutetium (Lu177) rosopatamab tetraxetan plus standard of care vs standard of care alone in patients with metastatic castration-resistant prostate cancer**

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**Background:** Targeted radionuclide therapy (TRT) can localize treatment to specific tumor cells to reduce or eliminate damage to normal tissue. Prostate-specific membrane antigen (PSMA) is an ideal therapeutic target as it is highly expressed by malignant prostate cancer (PC) cells. Prior studies have demonstrated a favorable safety profile & efficacy of the radio-antibody drug conjugate (rADC) lutetium (Lu 177) rosopatamab tetraxetan ($^{177}$Lu-rosopatamab) using a fractionated 2 dose regimen. $^{177}$Lu-rosopatamab is currently being investigated in this phase 3 study for treatment of patients with PSMA+ metastatic castration resistant PC (mCRPC) who have received prior treatment with one androgen receptor pathway inhibitor (ARPI).

**Methods:** This multinational, multicenter, prospective, randomized, open label phase 3 study (NCT06520345) has 2 parts: a dosimetry and safety lead-in (Part 1; n=30) & a randomized treatment expansion (Part 2; n=490). In Part 1, patients are divided into 3 groups (n=10 each) to receive 2 single intravenous injections of 76 mCi each, 14d apart, of $^{177}$Lu-rosopatamab with standard of care (SOC) combinations with abiraterone, enzalutamide, or docetaxel to characterize biodistribution & safety profiles of $^{177}$Lu-rosopatamab + SOC combinations. SOC received is determined prior to treatment with $^{177}$Lu-rosopatamab. In Part 2, patients will be enrolled 2:1 to receive SOC (determined pre-randomization) with or without 2 single injections of 76 mCi each of $^{177}$Lu-rosopatamab, given 14d apart.

Eligible patients must have PSMA-expressing mCRPC and have experienced disease progression on a minimum 12w prior therapy on their 1$^{st}$ ARPI (abiraterone, apalutamide, darolutamide, or enzalutamide) in metastatic castration-sensitive PC, non-metastatic CRPC, or mCRPC settings. Patients may have received docetaxel in mCSPC setting provided last dose was ≥6m prior to screening. Patients must have PSMA+ disease on $^{68}$Ga-PSMA-11 PET/CT imaging.

The primary endpoint is rPFS. Key secondary endpoint is OS. Additional secondary endpoints include 5-year OS, tumor ORR, time to symptomatic skeletal event, & health-related quality of life. An alpha control & 95% confidence intervals will be used; patients will be randomly assigned to receive $^{177}$Lu-rosopatamab + SOC or SOC alone.

**Results**: This study is currently enrolling; no results are available at the time of submission.

**Conclusions**: $^{177}$Lu-rosopatamab offers a novel approach with potential to meet current unmet needs by leveraging advantages of targeted radiotherapy and immunotherapy as an rADC, along with patient selection capabilities of $^{68}$Ga-PSMA-11 PET, warranting justification for evaluation in this Phase 3 study.

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**Conflicts of Interest:** ST is a paid consultant for Sanofi, Medivation, Astellas, Dendreon, Janssen, Genentech, Bayer, Endocyte, Eisai, Immunomedics, Karyopharm, Abbvie, Tolmar, Seattle Genetics, Amgen, Clovis, QED, Pfizer, AAA/Novartis, Clarity, Genomic Health, POINT Biopharma, Blue Earth, AIkido Pharma, Gilead, Telix Pharma, Convergent Therapeutics, EMD Serono, Myovant, Merck, Daiichi Sankyo, TransThera, Regeneron, Ambrx, Boston Scientific (DSMB). DC is an employee of Telix Pharmaceuticals.