

PSMA-targeted PET imaging and radionuclide therapy for prostate cancer: Development of a platform agent.

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Background: PSMA is overexpressed on a majority of prostate cancers and is especially prevalent in late-stage, androgen-independent and metastatic tumors. Limited or no expression in normal prostate and other tissues makes PSMA an excellent biomarker for prostate cancer as well as a target for diagnostic imaging and therapy. We present herein first-in-man PET imaging results of our recently completed Phase 1 trial for CTT1057, a fluorine-18 labeled phosphoramidate small molecule with high PSMA affinity, and preclinical evaluation of CTT1403, a lutetium-177 labeled analog for PSMA-based radiotherapy.

Methods: Phase 1 patient cohorts: A) known prostate cancer pre-prostatectomy within 12 weeks of PET scan; and B) castrate-resistant disease on ADT with metastases by CT or bone scan were injected intravenously with 10 mCi CTT1057 (prepared from succinimidyl-¹⁸F]fluorbenzoate coupled to CTT1298) and imaged on a GE SIGNA PET/MR. SUV_{mean} (normal organs) and SUV_{max} (metastases up to 5 per subject) were recorded.

For radiotherapy a ¹⁷⁷Lu-chelate and an albumin-binding moiety were tethered to CTT1298 producing CTT1403. Specificity and efficacy were evaluated *in vitro* in PC3-PIP (PSMA+) cells and pharmacokinetics and therapeutic efficacy were determined *in vivo* in xenografted mice.

Results: Five cohort A patients imaged for dosimetry with CTT1057 had an average effective dose of 0.0228 mSv/MBq. Fourteen patients (PSA 0.73-1239; Age 35-85) imaged in cohort B had PSMA avid disease. Nine patients had osseous metastases with SUV_{max} = 15.78 ± 12 and 7 patients had lymph node metastases (SUV_{max} = 18.16 ± 14.66).

CTT1403 displayed excellent uptake and retention properties in PC3-PIP tumors. The albumin binding moiety increased bioavailability and tumor uptake - up to 50% injected dose per gram in PSMA+ tumors. Therapeutic efficacy was observed in 5 out of 8 mice with survival greater than 200 days versus 42 days for the control group.

Conclusions: CTT1057 was safe and well tolerated with prominent tumor and metastatic accumulation. Focal CTT1057 uptake was observed in lesions not seen by conventional imaging. CTT1403 showed impressive therapeutic efficacy (>60% survival at 200 days) with the albumin binding moiety conferring enhanced circulation half-life and tumor uptake.

CTT1057 and CTT1403 demonstrate significant promise as a clinical imaging agent and targeted radiotherapeutic for prostate cancer management.

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