SABRE: Assessment of safety and efficacy of ^{64}Cu-SAR-BBN in PSMA-negative biochemical recurrent prostate cancer patients

Luke T. Nordquist[1], Eva Lengyelova[2], Andrei Iagaru[3], Brandon R. Mancini[4], Hong Song[3], Medhat Osman[5], David Josephson[6], Frankis Almaguel[7], Daniel Saltzstein[8], Michelle Parker[2], Robert M. Miller[2], Neal D. Shore[9]

[1]XCancer, Omaha, NE; [2]Clarity Pharmaceuticals, Sydney, Australia; [3]Stanford University, Stanford, CA; [4]BAMF Health, Grand Rapids, MI; [5]SSM Health St. Louis University Hospital, St. Louis, MO; [6]Tower Urology, Los Angeles, CA; [7]Biogenixx Molecular/LLUH, Miami, FL; [8]Urology San Antonio, San Antonio, TX [9]Carolina Urologic Research Center, Myrtle Beach, SC

BACKGROUND

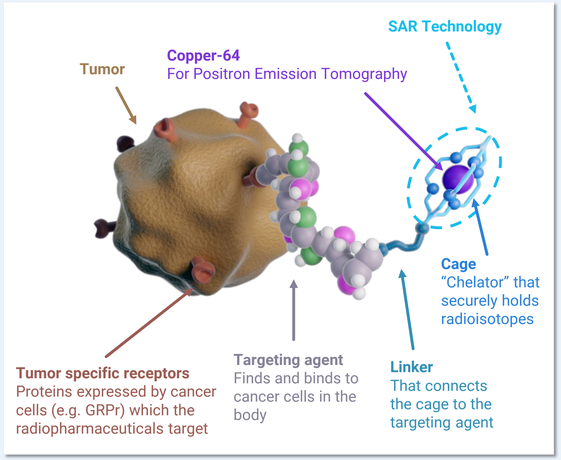
Between 20-40% of patients with prostate cancer (PC) will relapse within 10 years of their primary PC treatment, as identified through rising prostate-specific antigen (PSA) levels[1]. Most relapses will occur within 5 years after definitive therapy[2]. Early diagnosis of biochemical recurrence (BCR) with accurate staging is essential to informing optimal treatment decision-making.

Tumor expression of prostate-specific membrane antigen (PSMA) is not present or is low in up to 10% of primary PC, in 25% of men with castration-resistant PC, and in approximately 20-25% of men in BCR[3-6]. Consequently, these patients are unlikely to benefit from PSMA-targeted agents and represent a significant unmet need for both imaging and therapy.

The Gastrin Releasing Peptide receptor (GRPr) is a transmembrane G-protein coupled receptor that has various physiological functions in the gastrointestinal tract and nervous system[7]. It is also upregulated in many human cancers, including PC[8-11].

^{64}Cu-SAR-Bombesin (^{64}Cu-SAR-BBN, Figure 1), a GRPr-targeting agent, uses a radioactive form of copper, copper-64 (^{64}Cu), to image cancers using Positron Emission Tomography (PET). Translational data have shown a positive tumor-to-background ratio and increase tumor uptake over time by ^{64}Cu-SAR-BBN in PC3 tumor-bearing nude mice[12]. Initial clinical data have shown that ^{64}Cu-SAR-BBN was able to detect lesions in 32% (8/25) of patients with BCR of PC and negative/equivocal PSMA PET[13].

Figure 1. ^{64}Cu-SAR-BBN stylized structure



METHODS

Study Design

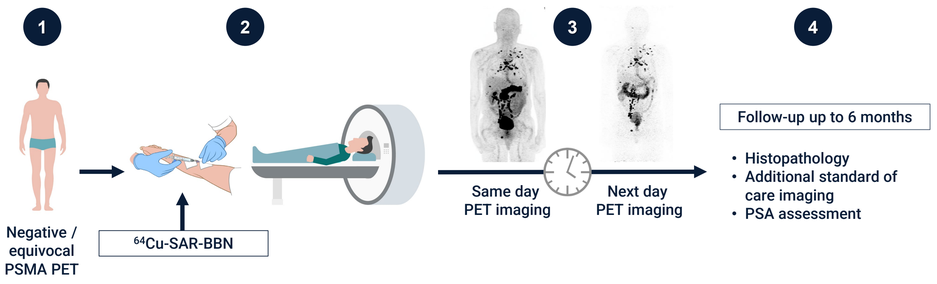
SABRE is a phase II, single arm, non-randomized, open-label study of ^{64}Cu-SAR-BBN administered to patients with BCR of PC following definitive therapy. Key eligibility criteria include confirmed adenocarcinoma of the prostate, recurrence of PC based on rising PSA after definitive therapy and negative or equivocal findings for PC on an approved PSMA PET.

Fifty-three patients were enrolled and imaged. The objectives are to assess the safety of ^{64}Cu-SAR-BBN (200 MBq/5.4mCi), and its ability to detect recurrent PC when traditional PSMA PET is not informative. Participants received a single administration of ^{64}Cu-SAR-BBN on Day 0, followed by a PET/CT scan at 1 to 4 hours post dose (Day 0 scan) and at 24 hours post dose (Day 1 scan) (Figure 2). We hypothesize that delayed imaging may allow the detection of additional lesions compared to the scan performed on the same day of the administration of the product. The safety endpoint includes the incidence and severity of treatment-emergent adverse events and serious adverse events following the administration of ^{64}Cu-SAR-BBN. Efficacy endpoints include correct detection rate (participant level) and positive predictive value (at participant and region level) at each scan timepoint independently.

^{64}Cu-SAR-BBN PET/CT scans will be evaluated for the presence of pathological ^{64}Cu-SAR-BBN uptake in the prostate bed/gland, pelvic lymph nodes (LN), extra pelvic LN, visceral/soft tissue and bone regions. Patients will be followed for up to 180 days to verify the findings. The ^{64}Cu-SAR-BBN PET/CT results will be determined by an independent, blinded, central expert panel, assessed against a composite Reference Standard (histopathology, conventional imaging, and/or PSA levels):

1. **Histopathology:** where feasible, obtaining histopathology from biopsy or surgery will be attempted for as many ^{64}Cu-SAR-BBN PET-positive lesions as possible within 180 days of Day 0.
2. **Follow-up conventional imaging:** all participants will undergo conventional imaging to allow for verification of the ^{64}Cu-SAR-BBN PET lesions at 90 days ± 15 days post Day 0 (and additionally at 180 days ± 15 days post Day 0 if the Day 90 scans are deemed to be negative or equivocal for PC recurrence based on central review).
3. **PSA response:** if radiation therapy or other salvage focal therapy (e.g. cryotherapy) is initiated during the study, PSA levels must be monitored every 4 weeks from the initiation of the therapy.

Figure 2. Study Design



1. Patients with BCR of PC who have a negative or equivocal PSMA PET scan and other available diagnostic imaging
2. ^{64}Cu-SAR-BBN administration followed by PET/CT scan
3. "Same day" and "next day" imaging
4. Conventional imaging at Day 90/180, histopathology of positive lesions, PSA assessment

Key Eligibility Criteria

1. Life expectancy ≥ 12 weeks
2. Histologically confirmed adenocarcinoma of prostate per original diagnosis and completed subsequent definitive therapy
3. Suspected recurrence of PC based on rising PSA after definitive therapy
4. Negative or equivocal findings for PC on (1) approved PSMA PET and (2) anatomical imaging (CT and/or magnetic resonance imaging) and (3) if available, any other conventional imaging performed as part of routine standard of care imaging workup within 60 days prior to Day 0
5. Participants must have adequate organ function and ECOG 0-2

Primary Objectives

- To investigate the safety and tolerability of ^{64}Cu-SAR-BBN
- To investigate the ability of ^{64}Cu-SAR-BBN PET/CT to correctly detect recurrence of PC

Secondary Objectives

- To investigate the biodistribution of ^{64}Cu-SAR-BBN
- To assess the participant-level positive predictive value of ^{64}Cu-SAR-BBN PET/CT
- To assess the participant-level detection rate of ^{64}Cu-SAR-BBN PET/CT
- To assess the false positive rate ^{64}Cu-SAR-BBN PET/CT
- To assess the discrepant PET negativity rate of the ^{64}Cu-SAR-BBN PET/CT scans
- To assess the true negative rate of ^{64}Cu-SAR-BBN PET/CT

Current Status

At the time of the meeting, the study has completed enrollment across 8 institutions in the United States.

ClinicalTrials.gov Identifier: NCT05407311. This study is sponsored by Clarity Pharmaceuticals Ltd.

References:

1. Ward and Moul. Rising prostate-specific antigen after primary prostate cancer therapy. Nat Clin Pract Urol . 2005
2. Pak et al. Time to biochemical relapse after radical prostatectomy and efficacy of salvage radiotherapy in patients with prostate cancer. Int J Clin Onc. 2019.
3. Bakht et al. Landscape of prostate-specific membrane antigen heterogeneity and regulation in AR-positive and AR-negative metastatic prostate cancer. Nat Cancer. 2023.
4. Vlachostergios PJ, Niaz MJ, Sun M, et al. Prostate-Specific Membrane Antigen Uptake and Survival in Metastatic Castration-Resistant Prostate Cancer. Frontiers in oncology. 2021.
5. Baratto and Iagaru et al. PSMA- and GRPR-Targeted PET: Results from 50 Patients with Biochemically Recurrent Prostate Cancer. J Nucl Med. 2021.
6. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of 68Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. Eur J Nucl Med Mol Imaging. 2017..
7. Jensen et al. International Union of Pharmacology. LXVIII. Mammalian bombesin receptors: nomenclature, distribution, pharmacology, signaling, and functions in normal and disease states. Pharmacol Rev. 2008;60(1):1-42.
8. Baratto et al. Imaging the Distribution of Gastrin Releasing Peptide Receptors in Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2020.
9. Fleischmann et al. High expression of gastrin-releasing peptide receptors in the vascular bed of urinary tract cancers: promising candidates for vascular targeting applications. Endocrine-related cancer. 2009.
10. Markwalder et al. Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. Cancer research. 1999.
11. Morgat et al. Expression of Gastrin-Releasing Peptide Receptor in Breast Cancer and Its Association with Pathologic, Biologic, and Clinical Parameters: A Study of 1,432 Primary Tumors. JNM. 2017.
12. Goumi et al. Copper-64 labeled macrobicyclic sarcophagine coupled to a GRP receptor antagonist shows great promise for PET imaging of prostate cancer. Molecular pharmaceutics. 2015.
13. Li and Emmett et al. Detection Rate of ^{64}Cu-SAR-Bombesin-PET/CT in men with biochemically recurrent prostate cancer and negative or equivocal ^{68}Ga-PSMA-11-PET/CT. EANM. 2023.