COMBAT: A study of ^{64}Cu-SAR-BBN and ^{67}Cu-SAR-BBN for identification and treatment of GRPr-expressing metastatic castrate-resistant prostate cancer

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BACKGROUND

Metastatic castrate-resistant prostate cancer (mCRPC) is an advanced and lethal form of prostate cancer (PC). Prostate-specific membrane antigen (PSMA)-targeted theranostic agents, ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617, have been approved by the Food and Drug Administration (FDA) for patient selection and therapy of patients with mCRPC, respectively.

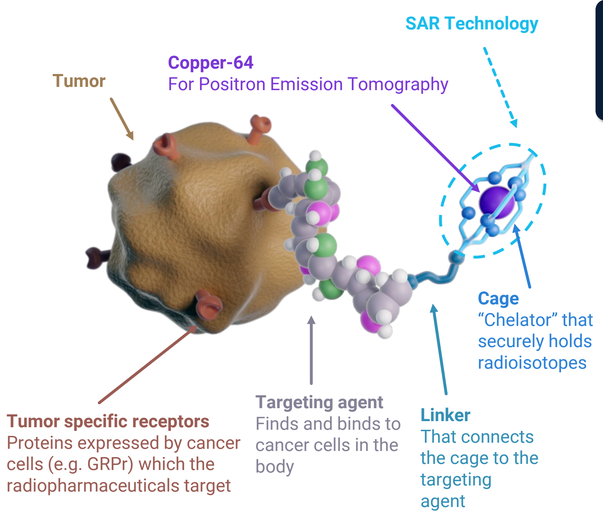
Tumor expression of PSMA is not present or is low in up to 10% of primary PC, in 25% of men with castration-resistant PC, and in approximately 20-25% of men in biochemical recurrence of PC[1-4]. Consequently, these patients are unlikely to benefit from PSMA-targeted agents and represent a significant 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[5]. It is also upregulated in many human cancers, including PC[6-9].

A promising new theranostic pair, consisting of ^{64}Cu-SAR-Bombesin (^{64}Cu-SAR-BBN, imaging) and ^{67}Cu-SAR-Bombesin (^{67}Cu-SAR-BBN, therapy), targets the GRPr (Figure 1). This may offer a potential imaging and treatment option for patients with low or no PSMA expression.

Translational data have shown inhibition of tumor growth and improved survival induced by ^{67}Cu-SAR-BBN in a PC3-xenograft mouse model[10]. These data led to the development of the COMBAT study, which aims to assess safety and anti-tumour efficacy of ^{67}Cu-SAR-BBN in mCRPC patients with GRPr-expressing disease.

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



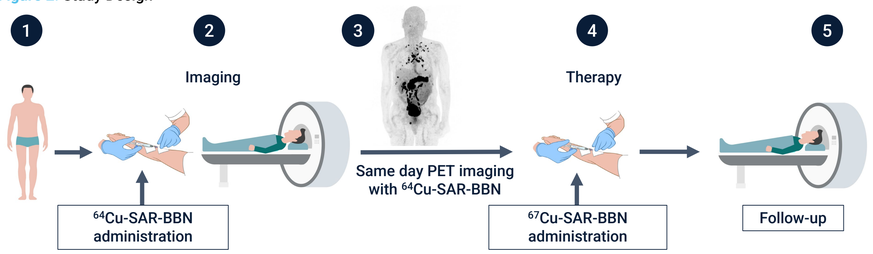
METHODS

Study Design

COMBAT is a multi-center, open-label, phase I/IIa dose-escalation and cohort expansion study of ^{64}Cu-SAR-BBN and ^{67}Cu-SAR-BBN administered to patients with mCRPC. Eligible patients will have progressive mCRPC, will be ineligible for ^{177}Lu-PSMA-617 therapy, and show a positive ^{64}Cu-SAR-BBN PET (Figure 2). The primary and key secondary objectives include assessment of safety of ^{64}Cu- and ^{67}Cu-SAR-BBN, determining the maximum tolerated dose (MTD) or maximum feasible dose (MFD) and anti-tumor efficacy of ^{67}Cu-SAR-BBN.

This study is being conducted in 2 phases: a Dose Escalation Phase (n=up to 24) and a Cohort Expansion Phase (n=14) (Figure 3). The ^{67}Cu-SAR-BBN dose levels investigated in the escalation phase include: 6 GBq (cohort 1, single dose with dosimetry assessment), 10 GBq (cohort 2, single dose), 14 GBq (cohort 3, single dose), and up to 28 GBq across two doses (cohort 4, two doses at MTD/MFD). Additional doses may be administered during both phases of the study.

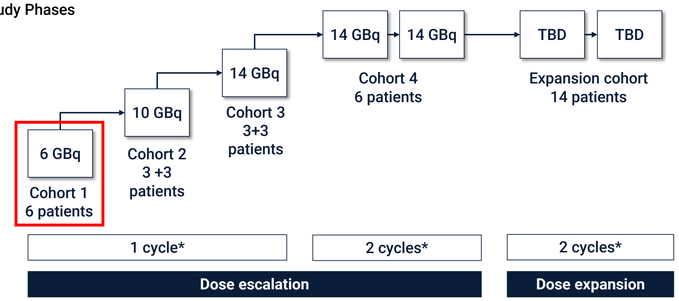
Figure 2. Study Design



1. Patients with progressive mCRPC, ineligible for PSMA-based therapy
2. ^{64}Cu-SAR-BBN administration followed by PET/CT scan
3. "Same day" imaging to select patients with a positive PET scan for therapy with ^{67}Cu-SAR-BBN
4. ^{67}Cu-SAR-BBN administration
5. Safety and efficacy follow-up. Additional doses of ^{67}Cu-SAR-BBN may be considered depending on safety/efficacy assessments

PET image illustrative only using ^{64}Cu-SAR-BBN, not from the COMBAT study.

Figure 3. Study Phases



Cohort 1 currently open for recruitment (red box). *If radiological non-progression, additional cycles of ^{67}Cu-SAR-bisPSMA may be offered (up to 4 cycles in each cohort). Dose escalation and expansion pending safety review. TBD: to be determined, dose based on safety review of previous cohorts.

Key Eligibility Criteria

1. Life expectancy >6 months
2. Histological, pathological, and/or cytological confirmation of PC
3. Positive ^{64}Cu-SAR-BBN PET/CT scan
4. Castrate level of serum/plasma testosterone (<50 ng/dL or <1.7 nmol/L)
5. ≥1 metastatic lesion that is present at screening CT, MRI, or bone scan imaging
6. Participants must have adequate organ function and Eastern Cooperative Oncology Group (ECOG) 0-2
7. Have progressive mCRPC despite prior androgen deprivation therapy and at least one androgen receptor pathway inhibitor. Progression based on least 1 of the following: serum/plasma PSA progression, soft-tissue progression and/or progression of bone disease
8. Participants must be ineligible for PSMA-based therapy as per investigator discretion (i.e. poor response expected OR participant has progressed after or stopped responding to PSMA-based radionuclide therapy)
9. Previous treatment with a systemic radionuclide is allowed after pre-specified washout period

Primary Objectives

Dose Escalation Phase

- To determine the MTD or MFD of a single dose of ^{67}Cu-SAR-BBN
- To determine the recommended dose of 2 doses of ^{67}Cu-SAR-BBN

Cohort Expansion Phase

- To investigate the anti-tumor efficacy of ^{67}Cu-SAR-BBN in terms of PSA and radiographic response

Dose Escalation and Cohort Expansion Phase

- To determine the safety and tolerability of ^{67}Cu-SAR-BBN
- To determine the safety and tolerability of ^{64}Cu-SAR-BBN

Secondary Objectives

Dose Escalation and Cohort Expansion Phase

- To investigate tumor response following treatment with ^{67}Cu-SAR-BBN based on RECIST V1.1 and PCWG3
- To investigate radiological progression-free survival following treatment with ^{67}Cu-SAR-BBN based on PCWG3
- To investigate change in biochemical markers following treatment with ^{67}Cu-SAR-BBN

Current Status

At the time of the meeting, study enrollment for cohort 1 is currently underway with 6 sites participating in the United States.

ClinicalTrials.gov Identifier: NCT05633160. This study is sponsored by Clarity Pharmaceuticals Ltd.

References:

1. Bakht et al. Landscape of prostate-specific membrane antigen heterogeneity and regulation in AR-positive and AR-negative metastatic prostate cancer. Nat Cancer. 2023.
2. 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.
3. Baratto and Iagaru et al. PSMA- and GRPR-Targeted PET: Results from 50 Patients with Biochemically Recurrent Prostate Cancer. J Nucl Med. 2021.
4. 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..
5. 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.
6. Baratto et al. Imaging the Distribution of Gastrin Releasing Peptide Receptors in Cancer. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2020.
7. 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.
8. Markwalder et al. Gastrin-releasing peptide receptors in the human prostate: relation to neoplastic transformation. Cancer research. 1999.
9. 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.
10. Huynh et al. Copper-67-Labeled Bombesin peptide for targeted radionuclide therapy of prostate cancer. Pharmaceuticals. 2022.