DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

To: NCI CTEP UM1 Clinical Trials Investigators

From: Charles S. Kunos, M.D., Ph.D., IDB, CTEP, NCI
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Date: **December 20, 2019**

Re: ^{117m}Sn-DTPA Pre-Solicitation Applications: Notification to UM1 investigators including UM1 radiation oncologists

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As part of the ^{117m}Sn-diethylene triamine pentaacetic acid (DTPA) clinical development program, CTEP would like to request pre-solicitation applications from all interested UM1 investigators for a single study of this agent in men with metastatic castrate-resistant prostate cancer.

^{117m}Sn-DTPA is a conversion electron radiopharmaceutical formulation. Unlike the alpha particle–emitting ^{223}Ra, ^{117m}Sn emits conversion electrons of a long particle path length that results in deeper tissue penetration (~300 µm). ^{117m}Sn-DTPA affords clinical target engagement and dosimetry calculation by standard gamma imaging, has a 14-day half-life that supports patient treatment and logistical flexibility, and has radiotherapy characteristics that are very attractive for bone and dural-based metastatic lesion palliation therapy. Due to its limited particle range, myelosuppression or other toxic end-organ irradiation are unlikely to be encountered with this agent.

Pilot clinical trials in the 1990s of an injectable, 1:20 ^{117m}Sn:DTPA conjugate for patients with metastatic bone disease provided biodistribution, pharmacokinetic, and safety data as well as preliminary evidence of efficacy (pain relief) (Atkins *et al.* 1993; Radiology, 186(1):279-83). The majority (59%) of an administered ^{117m}Sn-DTPA dose localized to metastatic lesion-occupied bone surfaces, while the remainder was excreted by the urinary tract (37%) or compartmentalized in interstitial tissues (4%). This route of elimination by the urinary tract is distinct from bowel-excreted ^{223}Ra, and therefore, raises the monitoring of urinary tract adverse events to an Adverse Event of Special Interest for CTEP-sponsored clinical trials.

Based on the results of a phase 1/2 palliative trial (Srivastava *et al.* 1998; Clinical Cancer Research, 4:61-68) of the 1:20 ^{117m}Sn:DTPA formulation for bone metastases, Serene LLC (the pharmaceutical collaborator) now requests assistance from the NExT program to conduct a phase 2 study of a higher radioactivity, 1:5 ^{117m}Sn:DTPA formulation in bone-metastatic disease. Food & Drug Administration (FDA) Investigational New Drug (IND)-enabling studies of the 1:5 ^{117m}Sn-DTPA are not yet complete, and so, a three-step clinical development process is envisioned.

To begin the clinical development of ^{117m}Sn-DTPA in the NCI CTEP portfolio, CTEP proposes a 20-30 patient monotherapy trial of 1:20 ^{117m}Sn-DTPA (20 or 30 mCi q28 days for up to 2 cycles) in men diagnosed with castrate-resistant prostate cancer metastatic to at least two bone sites detected by ^{99m}Tc bone scintigraphy. ^{117m}Sn-DTPA gamma-camera dosimetry would be an anticipated primary correlative. In addition, applicants may propose genomic biomarkers, such as whole exome sequencing and RNA sequencing, as well as immune T-cell clonality assessments (to examine the potential for future immunotherapy combinations). Cumulative genitourinary toxicity and myelotoxicity would be adverse of events of special interest for this agent. CTEP would also like to explore the possibility to capture patient-reported outcomes and adverse events (PRO-CTCAE) captured by digital instruments in a radiopharmaceutical trial like the one proposed.

During accrual, CTEP would plan to engage the FDA in an end of phase 2 (EOP2) meeting to discuss plans for a bridging study to the 1:5 ^{117m}Sn-DTPA formulation. The monotherapy trial outlined above would be amended to study the 1:5 ^{117m}Sn-DTPA formulation per the FDA guidance.

The following criteria will be used to prioritize study assignment to investigators:

- Experience of the investigators and their support staff in conducting early phase studies of radiopharmaceuticals
- The documented ability of the site to achieve acceptable accrual rates in this patient population. If your submission includes other sites, it is recommended to include examples of their documented accrual rate as well. If prior accrual track record does not match projected accrual, please explain rationale for the projected accrual estimates.
- Competing trials. Please do not omit ongoing competing trials but explain mitigating factors (*e.g.* the trial will be finished, or the trial is accruing a non-competing patient subset).
- Early Career Investigator (ECI) trials led by an early-career Principal Investigator (PI) with appropriate and committed mentorship. The ECI-PI should have a major interest in clinical research and the intention to develop a career in that field. The ECI-PI should also be within 7 years of completion of fellowship training and be a faculty member at an institution with a successful track record in conducting clinical trials.

If you are interested in conducting a trial with ^{117m}Sn-DTPA in the above-described setting, please fill out the attached Pre-LOI form and submit it to PreLOIs@tech-res.com by COB 4 weeks after release date. Please note that in the case of an ECI application, the ECI-PI's curriculum vitae and letters of mentorship and institutional commitment must be submitted together with the Pre-LOI application via e-mail. The Investigational Drug Branch will review the submissions and make a formal request for a full LOI on or around 3 weeks after due date.

Should you have questions or concerns regarding this process or the solicited ^{117m}Sn-DTPA trials, please contact Dr. Charles Kunos at 240-276-6939 or charles.kunos@nih.gov.