TeNET Study: Phase 2 Study to Assess Safety and Efficacy of **Te**rbium-161 DOTATATE in Metastatic **Ne**uroendocrine **T**umors

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1. **Introduction:** Targeted radionuclide therapy (TRT) is a nuclear medicine technique that uses radiopharmaceuticals (RPs) with high affinity to receptors or antigens on the surface of tumor cells to achieve a therapeutic effect. TRT causes less collateral damage than external beam radiotherapy (EBRT) because the RPs are selectively taken up by tumors and their metastases, delivering high doses of radiation to cancer cells and minimizing doses to normal tissues.(1) NETTER-1 and 2 trials have already established PRRT (Peptide Receptor Radionuclide Therapy) with Lutetium-177 (Lu–177) DOTATATE as first line TRT in metastatic well-differentiated gastro-enteropancreatic neuroendocrine tumors(GEP-NETs).(2,3). At Tata Memorial Hospital, we are routinely treating patients with PRRT with Lu-177 DOTATATE since 2019 and have completed nearly 700 cycles of PRRT till date.

   While Lu-177 as a radioisotope is safe and indigenously produced by BARC, the recent global shortage of this isotope has led to development of Terbium-161 (Tb-161). Terbium-161 belongs to the same family of Lanthanides as Lu-177 and offers the same physical characteristics. (Table below)

Characteristics	Lutetium-177	Terbium-161
Half Life	6.7 days	6.9 days
Beta energy	134 keV	154 keV

Advantage of using Tb-161 over Lu-177: The superiority of Tb-161 over Lu-177 evolves from its basic property of emission of Auger electrons (AE).(4) Most important characteristics of radioisotopes in Nuclear Medicine or Radiation Oncology are linear energy transfer and range; which are determinants of cell-damage to the target cell and normal cell, respectively. Compared to beta-emissions (as in Lu-177), AEs are most lethal to cancer cells when emitted near the cell nucleus and especially when incorporated into DNA. AEs cause DNA damage both directly and indirectly via water

radiolysis. AEs can also kill targeted cancer cells by damaging the cell membrane and producing more targeted and lethal effects. Moreover, the important point is that since the range of delivery of this energy is relatively shorter as compared to beta-emitters, hence there is negligible bystander and crossfire effect, thereby causing no damage to surrounding cells.

Monte-Carlo simulations: Larauze et al assessed absorbed doses from simulations performed with CELLDOSE, (5)(6) which is a homemade Monte Carlo track-structure code for simulating the transport of electrons in water, based on differential and total interaction cross sections describing the elastic scattering, electronic excitation, and ionization. Absorbed doses to cell nuclei and cell membranes (with an intranuclear radionuclide location, only nuclear absorbed doses were assessed) were assessed. In this tumor cluster model, when all cells were targeted, and depending on the location of the radionuclide, Tb-161 delivered a 2- to 3-fold higher nuclear absorbed doses than Lu-11 but also 2- to 6-fold higher absorbed doses to cell membranes. Interaction of ionizing radiation with the cell membrane induces sphingomyelin hydrolysis to ceramide, initiating apoptosis. Since a number of radiopharmaceuticals reside on the membrane without being internalized (e.g., neuropeptide antagonist analogs and many antibodies), understanding the role of the cell membrane as a target becomes particularly important, specifically for TRT. ***With the radionuclide at the cell surface, absorbed doses to cell membranes were higher than nuclear doses, both with Lu-11 (7.4-fold higher: 38–41 vs. 4.7–7.2 Gy) and with Tb-161 (22-fold higher: 237–244 vs. 9.8–15.1 Gy).***

Cell survival studies: Spoormans et al performed cellular dosimetry to quantify the absorbed dose to the cell nucleus and compared dose–response curves to evaluate differences in relative biological effectiveness in vitro, between Tb-161 and Lu-177. (7) Tb-161-DOTATATE and delivered a 3.6 times higher dose to the nucleus, respectively, than their Lu-177-labeled counterparts on saturated receptor binding. This increased

nucleus-absorbed dose was mainly due to the additional emission of internal conversion electrons by Tb-161. When activity concentrations were considered, both Tb-161-DOTATATE showed a lower survival fraction than did labeling with Lu-177.When the absorbed dose to the nucleus was considered, no significant difference could be observed between the dose–response curves for Tb-161- and Lu-177-DOTATATE. Tb-161-DOTATATE showed only a linear dose response within the observed dose range, suggesting additional cell membrane damage by Auger electrons.

Tb-161 dosimetry: Verberg et al did a comparative dosimetric analysis of Lu-177 DOTATATE and Tb-161 DOTATATE by calculating the radiation absorbed dose to tumor as well as non-target organs of normal biodistribution, on adult human phantom models.(8) The substitution of Lu-177 with Tb-161 results in an increase in the delivered dose per unit of activity to tumour tissue by 40% (in a 10 g tumour: 2.9 Gy/GBq and 4.1 Gy/GBq, respectively) as well as to dose-limiting non-target tissue (kidneys: 39%(0.73 Gy/GBq and 1.01 Gy/GBq, respectively), bone marrow: 42% (0.04 Gy/GBq and 0.06 Gy/GBq, respectively)). If an equivalent non-target delivered dose is strived for in order not to increase toxicity, the registered standard activity of 7400 MBq [200 mCi]Lu-77-DOTATATE per therapy cycle should be replaced with a standard activity of 5400 MBq [145 mCi] Tb-161 DOTATATE.

First-In-Human Studies: After qualifying through the cell survival and dosimetry studies, Baum et al used Tb-161 DOTATATE in 2 patients, one with paraganglioma and other with metastatic neuroendocrine tumor, both of whom were refractory to Lu-177 DOTATATE therapy.(9) Patients formally consent to receive this treatment and Tb-161 DOTATATE was administered following the standard PRRT protocol. Post therapy SPECT/CT images were acquired which showed tracer localisation at the desired tumor locations. No adverse events and no changes in vital parameters were observed or reported by the patient during, immediately after or at follow-up review of the patient

after administration of Tb-161-DOTATATE. According to the Common Terminology Criteria for Adverse Events, there were no clinically significant changes in the relevant laboratory values (hematological, renal, and hepatic panel) at the subsequent follow up of the patient after administration of Tb-161-DOTATATE.

Current global trials of Tb-161 labeled radionuclide therapy:

VIOLET is an investigator-initiated, single-centre, phase 1/2 trial, conducted at the Peter MacCallum Cancer Centre (Melbourne, VIC, Australia), with progressive metastatic prostate cancer treated with Terbium-161 PSMA. It is important to note that the toxicity is primarily caused by radioisotope (Tb-161) and not due to ligand (PSMA), in our case DOTATATE. The initial results published (10) show that grade 3 treatment-related adverse events (TRAEs) were limited to pain (one [3%] of 30; the only serious TRAE) and lymphopenia (one [3%] of 30). No grade 4 TRAEs or treatment-related deaths occurred. No dose reductions or treatment discontinuation occurred for toxicity.

Current Indian scenario: As of today, Tb-161 DOTATATE is already commercially available in India and first therapy has already been administered, with multiple centers now starting this treatment. Dept of Nuclear Medicine, TMH and ACTREC has already obtained approval from Atomic Energy Regulatory Board (AERB), and has treated 2 patients of metastatic NET on compassionate basis with Tb-161 DOTATATE, who were refractory to Lu-177 DOTATATE.

We therefore would like to study the safety and efficacy of Tb-161 DOTATATE in patients in metastatic NET who have shown disease progression after treatment with Lu-177 DOTATATE PRRT.

2. **Aims and Objectives:**

   Aim: To evaluate the safety and efficacy of Terbium 161 DOTATATE PRRT in metastatic neuroendocrine tumors who have progressed on Lu-177 DOTATATE PRRT.

   Objectives:

   Primary:

   - To determine disease control rate in metastatic neuroendocrine tumors who have progressed on Lu-177 DOTATATE PRRT.

Secondary:

- To assess the safety profile expressed in terms of incidence of >grade 3 toxicity or proportion of patients developing > grade 3 in metastatic neuroendocrine tumors who have progressed on Lu-177 DOTATATE PRRT.

3. **Study End-point:** Safety and efficacy assessment
4. **Study Design:** Phase II (Simon Two Stage), Interventional, Single Arm, Open Label
5. **Study Sites:** Departments of Nuclear Medicine, TMH, Parel and RRU, ACTREC
6. **Pre-screening:** Patients of metastatic NET who have progressed on Lu-177 DOTATATE PRRT will be referred after discussion in Neuroendocrine Tumor Clinic, TMH or HPB-UGI Clinic at RRU, ACTREC.
7. **Screening:** Patients will be confirmed for disease progression on Ga-68 DOTATATE and/or FDG PET/CT imaging.
8. **Inclusion Criteria:**

- Male or female, age greater than 18 years
- Histopathological diagnosis of well-differentiated GEP-NET
- Positive Ga-68-DOTANOC PET/CT, Krennings score >/=3
- Locally advanced/inoperable disease or metastatic disease
- Patient who have shown disease progression with Lu-177 DOTATATE PRRT

- Karnofsky performance-status score of at least 60 or ECOG performance status </=2
- Life expectancy greater than 6 months

9. Exclusion criteria

- Serum creatinine level of more than 1.6 mg/dl or a creatinine clearance of less than 50 ml/min
- Hemoglobin level of less than 8.0 g per deciliter
- Red blood cell count less than 300,000/cubic millimeter
- White cell count of less than 2000 per cubic millimeter
- Platelet count of less than 75,000 per cubic millimetre
- Total bilirubin level of more than 3 times the upper limit of the normal range
- Serum albumin level > 3.0 g/dl
- Pregnancy and Lactation
- Patients with concurrent malignancies

10. Study Methodology: Patients referred from Neuroendocrine tumor clinic fulfilling the inclusion and exclusion criteria will be enrolled in the study for treatment with Terbium-161 DOTATATE. Since the physical characteristics of Tb-161 are same as Lu-177 and since the peptide is same (DOTATATE), principles and procedure of treatment is same as Lu-177 DOTATATE PRRT. This is a day care therapy and the patient shall be admitted and discharged on the same day. Patients will be administered 2 cycles of Tb-161 PRRT at intervals of 8-12 weeks. Pre-therapy investigations will be as per ‘standard of care’ work-up for PRRT. Even the therapy administration protocol will be same, which will be as follows:

PRRT administration protocol: (in sequence)

One day prior (Day 0)		Tablet Dexamethasone 4 mg BD oral
Day of therapy (Day 1)	Premedication	Tablet Aprepitant 125 mg oral Intravenous Dexamethasone 8 mg Intravenous Palonosetron 0.25 mg
Patient admitted	Amino Acid Infusion to be started (1 hour after pre-medication)	Intravenous infusion of lysine and arginine diluted in 500 ml of normal saline over 1 hour
	PRRT	Intravenous infusion of 145 mCi of Tb 161 DOTATATE diluted in 100 ml normal saline over 30 minutes
	After PRRT infusion is over, start amino acid infusion	Intravenous infusion of lysine and arginine diluted in 1500 ml of normal saline over 3 hours. **Patient discharged**
Day 2		Tablet Aprepitant 80 mg oral, in morning Oral Dexamethasone 4 mg BD
Day 3		Tablet Aprepitant 80 mg oral, in morning Oral Dexamethasone 4 mg BD

11. **Post-therapy scanning:** This involves looking at biodistribution of Tb-161 DOTATATE on post-therapy images, which are performed without any additional intervention (radiotracer injection) as Tb-161 also has gamma emission hence these images are acquired from the therapeutic tracer injection. Organ based dosimetry for tumor, kidney and bone marrow will be performed by acquiring whole body planar images at 4-, 24- and 72-hours following Tb-161 PRRT administration, on Dual head Gamma Camera in Dept of Nuclear Medicine at Tata Memorial Hospital/RRU, ACTREC. Images acquired will be processed on OLINDA XM software to calculate the target and non-target absorbed doses.

12. **Discharge and Follow-up:** After the post therapy scanning, patients will be discharged with summary document containing information about patient details, treatment received and advice at discharge, duly signed by Nuclear Medicine Physician authorized for the same. This is the standard practice in keeping with the radiation safety guidelines.

    Advice at discharge: There are no specific precautions to be followed with respect to radiation safety.

    Follow up: Patients will be followed up while on active treatment with cancer directed therapy as well as supportive care.

    a. Clinical and serological investigations like CBC, LFT, RFT, serum electrolytes will be done at 2 weeks, 4 weeks and at 6 weeks after each therapy session.

    b. After the completion of 2 sessions, participants will be followed up as per current standard institutional protocol as follows;

    c. Clinical and Quality of Life Assessment using EORTC QLQ C30 questionnaire before therapy, at 4 weeks and 8 weeks after each therapy session.

    d. Imaging Follow-up (as per established institutional standard-of-care) as follows: Ga-68 DOTANOC PET/CT will be performed at 4-6 weeks after each therapy session for documentation of response. After completion of protocol treatment, patients will be followed up as per standard institutional practices.

13. **Study Duration:** 2 years
14. **Follow-up Period:** 1 year
15. **Study Assessments:**

    Response assessment: Disease control rate will be measured as a primary endpoint. It is percentage of patients achieving complete or partial response or stable disease on Ga-68 DOTATATE PET/CT. Response assessment will be done using RECIST 1.1 for solid tumors. Non-PD (non-disease progression) after one session of Tb-161 therapy will be eligible for the second session. Patients showing CR with no

residual measurable disease will not undergo a second session of therapy. Patients with PD after 1 cycle of Tb-161 DOTATATE therapy will not continue in the study and will be referred to NET Clinic for further management. Currently there is no standard of care for treatment of refractory NET.

Safety Assessment: At each visit, the investigator will evaluate the subject to determine whether any AEs have occurred. CBC, LFT, RFT, Serum electrolytes will be done at 2 weeks, 4 weeks and 6 weeks after each therapy. AEs may be directly observed, reported spontaneously by the subject or by questioning the subject at each study visit. All laboratory values will be evaluated by the Investigator as to clinical significance. All post-baseline abnormal laboratory values considered clinically significant by the Investigator will be recorded as an AE. The NCI Common Terminology Criteria for Adverse Events version 5 (NCI CTCAE v5.0) will be used to classify and grade the intensity of adverse events during and after each treatment cycle. CTCAE will be used to grade all events regardless of attribution, in order to ensure objective reporting, and in order to report trial data according to accepted international guidelines. The highest grade of each observed toxicity will be recorded. The results will be computed in a tabular form in which the proportion of people having their highest grade of toxicity will be charted.

AEs are not required to be reported unless they meet SAE criteria.

Adverse events for Terbium are expected to be nausea (30-40%), vomiting (25-30%). Other common adverse events may include fatigue or asthenia and diarrhoea. Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia may be seen in 1%, 2%, and 9% of patients respectively.

Adverse event management: All adverse events will be managed as per institutional standards in concordance with gastrointestinal disease management group.

SAE reporting: All SAE will be reported within 24 working hours to the IEC, follow up will be given within 14 days and a final SAE will be submitted at resolution of the SAE.

16. Statistical Analysis for sample size calculation:

At the end of the study, we expect a disease control rate (DCR) of 87% in patients with metastatic NET progressed after Lu-177 DOTATATE PRRT.

Baseline assumption is DCR of 67% from historic control and addition of Terbium-161 DOTATATE therapy will improve DCR by 20%. The null hypothesis will be tested against a one-sided alternative with type I error rate of 0.05 & power of 0.80 in standard Simon two stage design. In the first stage, 6 patients will be accrued. If there are <4 responses, the study will be stopped. Otherwise, 14 additional patients will be accrued for a total of 20. The null hypothesis will be rejected if =/> 16 responses are observed in 20 patients.

17. Documentation and archives:

All patient-related data are recorded in a pseudonymized way. Each patient is unequivocally identified by a trial subject number, attributed at recruitment into the study. The investigator will keep a complete patient identification log, including the full name, address etc.

Patients who were screened in order to be entered into the study, but who could not be recruited for whatever reason will be recorded in a "patient reject log" with the reason for non-inclusion in study being specified. All the data retrieved during the conduct of the study are entered into the case record forms (CRF) by the investigator or co-investigator. All relevant forms and study documents including CRFs will be stored for 10 years at PI place with access to IEC, PI and designated personnel.

18. **Financing of study:** Budgeting details have been provided at the end of study protocol

19. **General ethics for the conduct of the study:** The study will be conducted in compliance with the ICMR Statement on Human Experimentation, and the Declaration of Helsinki principles.

    Declaration of Helsinki: The trial will be performed in accordance with the Declaration of Helsinki, as decided upon by the 18th World Medical Assembly, Helsinki, Finland, June 1964 (amended by subsequent World Medical Assembly Somerset West, South Africa, October 1996,).

20. **Informed consent:** The Investigator or a person designated by him/her will collect informed consent from all participants, prior to which the Investigator or co-investigator must inform each participant of the objectives, benefits, risks and requirements of the study. He/she will also provide the participant with an information sheet in clear, simple language. The study participant will be allowed ample time to inquire about details of the study and to decide whether or not to participate in the study. Moreover, the patient will receive a written “patient information”, containing all relevant information for the patient's decision and the course of the study. The consent of the patient to participate must be obtained in writing before recruitment into the study. The informed consent form must be dated and signed by the patient. Thereby, he declares his voluntary consent to participate in the study and his willingness to comply with the requirements of the trial and the instructions of the treating investigator during the course of the study. There are two copies of the informed consent form: one for the patient and one to be kept by the investigator in his study documents. The informed consent is only valid after receiving the patient’s signature. Thereafter, the patient can be entered into the study if he/she fulfils the selection criteria. The study will not commence until approval has been obtained from the Tata Memorial Hospital Human Ethics Committee.

21. **Protocol amendments:** Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by the investigators and then submitted to the IEC/IRB for acceptance.

    Administrative or technical changes of the protocol such as minor corrections and/or clarifications that have no effect on the way the study is to be conducted, nor on the risk-benefit ratio, will be agreed upon by all the investigators and will be documented in a memorandum to the protocol. The IEC may be notified of such changes at the discretion of the sponsor/coordinating investigator. The coordinating investigator has to assure, that all amendments have been added to the study documents at any site involved in the trial.

22. **Reimbursement:** The study budget shall include costs of blood investigations and imaging studies, Tb-161 therapy and post-therapy dosimetry scanning. Patients study visits will also be budgeted in the study.
23. **Compensation:** It will be as per the Institutional IEC policy

24. **Evaluation of Benefits and Risks/Discomforts:** There is potential benefit in the form of improved survival and quality of life from this study. No potential physical, psychological or social risks. There are no alternate treatment possible during the study
25. **Risks/Benefits Analysis:** The study poses minimal risk, i.e. the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of

routine physical or psychological examinations or tests.

26. **Consent and Assent Process and Documentation:** Consent shall be taken after giving adequate time to the patient and Legally Accepted Representative to understand the study design. Consent shall be signed and dated by the patient and countersigned by the investigator. **A copy of the consent shall be handed over to the patient and one copy shall be kept for records. Impartial** witnesses shall be present to overlook the consent administration process Participants' right to refuse to participate in the trial shall be respected. After the participant has entered into the trial, the clinician shall give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. The reason for doing so, shall be recorded; the participant will remain within the trial for the purpose of follow-up and for data analysis by the treatment option to which they have been allocated.

    Similarly, the participant must remain free to change their mind at any time about the protocol treatment and trial follow-up without giving a reason and without prejudicing his/her further treatment. Patients who are not able to give consent won't be included in the study. In case a patient loses his/her ability to give consent during the study, he/she will be dropped out of the study.
27. **Trial closure:** The trial will close when all patients have completed follow-up. Details about reporting of trial closure to the regulatory and ethical committees.
28. **Dissemination Of Results:** The trial results will be submitted for publication in international peer reviewed journals and presented at national/international conferences. No publication restrictions will be imposed by trial sponsors. The contribution of all investigators will be acknowledged in such manuscripts if they are not eligible for authorship. In addition the grant giving organizations will also be acknowledged in all publications.

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