Title of Study:

PReCedeNT trial: Phase III randomised-controlled open-label trial of Lutetium - 177 Peptide Receptor Radionuclide Therapy (PRRT) Plus Chemotherapy Versus PRRT alone in FDG-avid, Well-Differentiated Gastro-Entero-Pancreatic Neuroendocrine Tumors (GEP-NETs)

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Clinical trial protocol Version 1.6

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Synopsis

Scientific background and rationale

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies ranging from well-differentiated, slowly growing tumors to poorly differentiated neoplasms, which are aggressive and less frequent (1). Neuroendocrine cells have the ability to express several peptide receptors in high volumes, especially somatostatin receptors, which are heptahelical G-protein–coupled glycoprotein transmembrane receptors. In the most recent SEER register (SEER-17), more than half of all NETs, i.e. 61%, were gastroenteropancreatic neuroendocrine tumors (GEP-NETs), with the highest frequency being found in the rectum (17.7%), the small intestine (17.3%), and the colon (10.1%) [2]. The tumor biology varies with the location of the primary tumors as well as with the grade and staging of the tumors. The malignant potential ranges from the most benign types of tumor to small intestinal tumors and up to neuroendocrine carcinoma (NEC) with very malignant behavior [3]. The tumors are graded according to the classification system of the World Health Organization (WHO), wherein a new classification system is just being accepted. The tumors are divided into grade 1 NET (NET-G1), with a proliferation <3%, NET-G2 with a proliferation between 3 and 20%, NET-G3, which is a new group with a Ki-67 >20%, and finally NEC-G3, exhibiting a Ki-67 of >20% as well (unpublished data). Of note, the difference between NET-G3 and NEC-G3 is mainly the degree of differentiation. NET-G3 are well-differentiated tumors, often with expression of somatostatin receptors. NEC-G3 are poorly differentiated tumors that usually lack expression of somatostatin receptors.

NETs are characterized by a general lack of symptoms until they are in advanced phase, and early biomarkers are not as available and useful as required. Heterogeneity is an intrinsic, pivotal feature of NETs that derives from diverse causes and ultimately shapes tumor fate. (4) The different layers that conform NET heterogeneity include a wide range of distinct characteristics, from the mere location of the tumor to its clinical and functional features, and from its cellular properties, to the core signaling and (epi)genetic components defining the molecular signature of the tumor. The importance of this heterogeneity resides in that it translates into a high variability among tumors and, hence, patients, which hinders a more precise diagnosis and prognosis and more efficacious treatment of these diseases. Heterogeneity can be assessed objectively by molecular imaging techniques. Patients with

well- differentiated GEP NETs undergo imaging with Ga-68-DOTATOC PET/CT (DOTA PET/CT), which is a somatostatin-receptor (SSTR)-specific imaging tracer. PET/CT with 68Ga-DOTA-peptides has been reported to present a higher sensitivity for the detection of well-differentiated, less aggressive NETs than

well tolerated with negligible grade 3/4 toxicities. After a median follow-up period of 36 months, the median OS was not achieved with a median PFS of 48 months. At 3 months after completion of combination of PRRT and chemotherapy, 2% of patients showed a complete anatomical response, 28% a partial response, 68% stable disease, and only 2% progression. On FDG PET/CT, 27% achieved a complete metabolic response during the follow-up period. A biochemical response (>25% fall in chromogranin-A levels) was seen in 45%. (16) These results established the effectiveness of the combination of PRRT and chemotherapy which is now practiced routinely. However, there is no prospective study to establish this treatment regime. We therefore propose to prospectively evaluate the combination of PRRT and chemotherapy in patients with well-differentiated NETs, in a systematic manner to generate reliable conclusions with regards to this treatment regimen for intermediate to high grade NETs.CT or scintigraphy (5,6). On the other hand, 18F-FDG PET/CT is preferred for more aggressive, less differentiated NETs as there is emerging evidence that the presence of increased expression of GLUT (glucose-transporter) receptors in NETs highlights an increased propensity for invasion and metastasis, and an overall poorer prognosis (7). In fact, a strong association has recently been shown between higher 18F-FDG uptake and worse outcome even in patients with well-differentiated or low-grade tumors, with provision of prognostic information independently of the mitotic rate (8). Accordingly, 18F-FDG has an important role in managing patients with NETs because of its high prognostic value and its higher sensitivity in delineating disease extent, especially in aggressive and high-grade and aggressive intermediate-grade tumors (9). While DOTA PET avidity is a feature of well-differentiated disease, FDG avidity tends to be associated with more aggressive, de-differentiated disease (10). Grade 1 NET tends to be DOTA-avid but negative on FDG PET, whereas grade 3 NEC generally shows the opposite imaging phenotype. Grade 2 NET may demonstrate uptake of both tracers. Irrespective of pathological grade, the distribution of these tracers may not be spatially concordant, with some lesions having either DOTA or FDG avidity, but not both. This highlights the limitations of relying on histopathological grade from a single biopsy site to predict disease behaviour. Despite the prognostic utility of pathological grading, FDG PET positivity has been consistently shown to be independently associated with a poor prognosis. (11) SSTR expression on the surface of NET enables the use of somatostatin analogues labelled with particle-emitting radionuclides for targeted peptide receptor radionuclide therapy (PRRT) NETTER-1 trial has established Lu-177 PRRT (Peptide Receptor Radionuclide

Therapy) as standard of care in treatment of metastatic well-differentiated GEP NETs. (12) However, FDG positivity in these tumors suggests presence of aggressive phenotypes and warrants simultaneous use of chemotherapy. (13) Strosberg et.al, have shown exceptionally high and durable response rate with combination of Capecitabine and temozolamide in metastatic well, or moderately differentiated pancreatic neuroendocrine tumor. Combination of PRRT and chemotherapy, that is, temozolomide-capecitabine (CAP-TEM) has been therefore effective in patients showing SSTR and GLUT receptor expression on Ga-68 DOTA PET and FDG PET respectively. (15) Kong et al studied a retrospective cohort of 52 patients selected for treatment on the basis of somatostatin-receptor imaging without spatially discordant FDG-avid disease. All patients received conventional PRRT regimen, in addition oral capecitabine was added after every PRRT cycle. Clinical, biochemical and imaging response was assessed after completion of induction.

treatment of combination of PRRT and chemotherapy. Combination of PRRT and chemotherapy was

Study objectives and endpoints

Primary endpoint

1. Progression-free survival (PFS) is defined as the time duration from the date of randomization to the tumor progression or death from any cause. Patients alive at last follow-up will be censored at the date of last follow-up visit

Secondary endpoints and objectives

2. Objective Tumor Response (complete + partial response) based on a Ga-68-DOTATOC PET/CT scan compared to baseline (pre-treatment) evaluation, and graded by RECIST 1.1 criteria and by Metabolic Criteria (EORTC) as defined below. This evaluation will be performed earlier in case of a suspected progression.
3. Quality of Life parameters using EORTC QLQ C-30 and EORTC G.I.NET-21

Overall Survival (OS) is defined as the time duration from the date of randomization to the date of death from any cause. Patients alive at last follow-up will be censored at the date of last follow-up visit

Study design

Type of study - Prospective, randomized,
open-label Patient number - 162
Time schedule - 8 years
Number of centres - Single Center, Tata Memorial Center, Mumbai

Histopathologically proven well-differentiated gastro-entero-pancreatic NEN patients who have been deemed inoperable on the basis of initial work-up, either in the form of cross-sectional imaging or ultrasonography and by consensus of multi-disciplinary NET Clinic will undergo Ga-68 DOTATOC PET/CT (if not done previously) and 18F-FDG PET/CT imaging which are as per the standard institutional protocol. Ga-68 DOTATOC PET/CT studies done elsewhere shall be uploaded on PACS and reviewed by the Dept of Nuclear Medicine at Tata Memorial Hospital.

Ga-68-DOTATOC PET/CT: Gallium-68 is a GMP-compliant generator produced isotope which is an in-house Hospital Radiopharmacy preparation in Department of Nuclear Medicine, Tata

Memorial Hospital. It is labeled to octreotide analogs (TOC/NOC/TATE) with a chelator - DOTA (tetraazacyclododecane - tetraacetic acid). Images are acquired on a PET/CT scanner after injection of 3- 4 mCi of radiotracer at 45-60 minutes after injection, from skull base to mid-thigh. Dedicated triphasic CT scan shall be performed with the abdomen in the field of view during arterial and portal phases, whereas venous phase shall be acquired from skull base to mid-thigh. Fused PET/CT Images will be evaluated. Krennings score will be assessed using a visual scale on MIP (Maximum Intensity Projection) image of Ga-68 PET.

Ga-DOTATOC PET/CT Image Interpretation based on Krennings score

1	Uptake < Liver
2	Uptake = Liver
3	Uptake > Liver < Spleen/kidneys
4	Uptake > spleen or kidneys

Score more than 3 will be interpreted as 'positive' study and these patients will undergo FDG PET/CT imaging.

FDG PET/CT: After 6 hours fasting, patients will be injected with 3-5 MBq/kg body weight of 18F- FDG intravenously and images will be acquired on a dedicated PET/CT scanner at 45-60 minutes, from skull base to mid-thigh.

FDG PET Image interpretation:

1	Uptake < liver
2	Uptake = liver
3	Uptake > liver

Score 3 uptake will be considered as positive FDG PET study.

All patients with positive Ga-68 DOTANOC and 18F-FDG PET/CT imaging will be recruited

in the study.

Patient selection

Inclusion criteria

- Male or female, age greater than 18 years
- Histopathological diagnosis of GEP-NET, necessarily satisfying all the the criteria below
- Well differentiated G2 (Ki67 : ≥3-20%) OR G3 (ki67- greater than 20-55%),

  OR

  Well-differentiated G1 (<3%) with disease progression in last 6 months

- Positive Ga-68-DOTANOC PET/CT, Krennings score >/=3
- Positive FDG PET imaging, grade 3 or 4 uptake
- Locally advanced/inoperable disease or metastatic disease
- Karnofsky performance-status score of at least 60 or ECOG performance status </= 2
- Life expectancy greater than 6 months

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 noty 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
- Treatment with more than 30 mg of octreotide LAR within 4 weeks before randomisation.
- Peptide receptor radionuclide therapy at any time before randomisation
- Pregnancy and Lactation
- Patients with concurrent malignancies

Treatment

Overview

Peptide Receptor Radionuclide Therapy involves use of beta-emitting radio-isotopes like Lutetium-177 (Lu-177) and Yttrium-90 (Y-90) labeled to somatostatin receptor specific peptide - DOTATATE. DOTA-TATE is a compound containing Tyrosine^3-octreotate, a somatostatin receptor (SSTR) antagonist, and the bifunctional chelator (BFC) DOTA. SSTRs are found with high density in numerous malignancies, including CNS, breast, lung, and lymphatics.The role of SSTR antagonists (i.e. somatostatin and its analogs such as octreotide, somatuline and vapreotide) in neuroendocrine tumours (NETs) is well established, and massive SSTR overexpression is present in several NETs. (Tyr^3)- octreotate binds the transmembrane receptors of NETs with highest activity for SSTR2 and is actively transported into the cell via endocytosis, allowing trapping of the radioactivity and increasing the probability of the desired double-strand DNA breakage (for tumour control). Trapping improves the efficacy of this effect due to the relatively short range of the beta particles emitted by Lu-177, which have a maximum range in tissue of <2 mm. Bystander effects include cellular damage by free radical formation.

Combination of PRRT with oral chemotherapy is popularly known as PRCRT (Peptide Receptor Chemo-radionuclide Therapy). CAPTEM (Capecitabine-Temozolomide) is one of the suggested
treatment regimens for progressive well-differentiated neuroendocrine tumors. Capecitabine is a prodrug that is converted from fluoropyrimidine to 5-fluorouracil upon oral intake. 5-Fluorouracil has anticancer activity that induces damage to DNA by inhibiting thymidylate synthase. Temozolomide is a lipophilic methylator derived from dacarbazine—an alkylating agent used as a chemotherapy drug. The pharmacologic rationale for Cap/Tem emerged from the hypothesis that slow-growing NETs might be more sensitive to cytotoxic drugs that have an extended G0 phase cycle. Consequently, a lipophilic methylator such as temozolomide under continuous exposure to an antimetabolite such as capecitabine could be beneficial.

Our study involves randomisation of patients into the PRRT Arm (Arm - A) and PRRT plus Chemotherapy arm

- Arm A (PRRT Arm)

  Peptide Receptor Radionuclide Therapy with Lu-177-DOTATATE, 180-200 mCi administered intravenously for 4 cycles, at interval duration of 8-12 weeks

- Arm B (PRRT plus Chemotherapy Arm)

  Peptide Receptor Radionuclide Therapy with Lu-177-DOTATATE, 180-200 mCi administered intravenously for 4 cycles, at interval duration of 6-8 weeks

  Plus

  CAP-TEM Protocol:

  Day 1: Oral Capecitabine 1500 mg/m2, per oral, twice daily within 15 min of food for 14 days, followed by 2 weeks rest period

  Day 10-D14: Oral Temozolamide 200 mg/m2 per oral, daily dose for 5 days as a single dose with a glass of water at bed time. To be taken empty stomach at least 30 min before or 2 hours after meal.

Distribution of study medications

All the radiopharmaceuticals and drugs used in this study will be considered as standard of care. Drugs will be prescribed by the treating physician, as this prescription is within the framework of standard usage.

Arm A (PRRT Arm):

- Overview and general principles
  Lutetium-1777-DOTATATE is FDA approved radiopharmaceutical produced by Board of Radiation and Isotope technology (BRIT). It is supplied in doses of 180-200 mCi and injected intravenously under radiation safety precautions. 4 cycles of PRRT are administered at an interval of 8-12 weeks.

Patient status before starting a new cycle of therapy

- Serum creatinine level should not be more than 1.6 mg/dl or a creatinine

clearance of less than 50 ml/min

- Hemoglobin level should not be less than 8.0 g per deciliter
- Red blood cell count not less than 300,000/cubic millimeter
- White cell count should not be less than 2000 per cubic millimeter
- Platelet count should not be less than 75,000 per cubic millimetre
- Total bilirubin level of should not be more than 3 times the upper limit of the normal range
- Serum albumin level should not be more than 3.0 g/dl
- Patient should not have been treated with more than 30 mg of octreotide LAR within 12 weeks

General Precautions

During the administration of the radiopeptide, a physician must remain nearby. A resuscitation cart as well as a trained emergency team must be available.

The radiopharmaceutical should be diluted with saline to a final volume of 100 ml.

The radiopharmaceutical should be administered via an indwelling catheter to ensure safe intravenous administration and prevent paravascular infiltration, and should be administered over 30 minutes·

The line should be flushed with saline after completion of radiopeptide infusion. PRRT may reproduce the syndromes of the respective functional tumours due to the sudden massive release of the hormones and stimulation of their corresponding receptors. The clinical manifestation is dependent on the specific hormone involved.

The following measures are therefore recommended. Vital signs (at least blood pressure and pulse) should be monitored before and after therapy infusion in symptomatic patients.

Amino Acid Infusion:

Renal uptake of radiolabelled somatostatin analogues can in part be attributed to the receptor-mediated endocytic renal transporter system involving megalin-mediated cubilin dependent endocytosis across the proximal epithelium.To counteract and reduce the high kidney retention of radiopeptides, positively charged amino acids, such as L-lysine and L-arginine, are co-infused to competitively inhibit the proximal tubular reabsorption of the radiopeptide. The coadministration of these amino acids leads to a significant reduction in the renal absorbed dose.

For renal protection, an intravenous amino acid solution 25g of lysine and 25g of arginine diluted in 2 liters of normal saline administered concomitantly for at least 4 hours, starting 30

minutes before infusion of radiopharmaceutical.

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
	Amino Acid Infusion to be started (1 hour after premedication)	Intravenous infusion of lysine and arginine diluted in 500 ml of normal saline over 1 hour
	PRRT	Intravenous infusion of 200 mCi of Lu- 177 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
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

Post-therapy scanning

Lutetium-177 being a gamma-emitting radio-isotope as well, patients can be imaged following administration of therapeutic dose of Lu-177. This is done to confirm localisation of tracer at the targeted sites. Post-therapy scans shall be acquired at 24, 48 and 96 hours after administration of therapy under Dual-head SPECT/CT Gamma Camera at Dept of Nuclear Medicine, Tata Memorial Hospital.

Radiation Safety Precautions

Therapy will be administered in a Isotope Therapy Facility located in Tata Memorial Center Complex that is, either at the 3rd floor or 9th floor of Annexe Building. Trained nursing personnel will be instructed in radiation safety. Any serious or life-threatening medical condition

will be noted and contingency plans put in place in case radiation precautions need to be breached to allow emergency medical care.

In a medical emergency, concerns about radiation exposure will not hinder the prompt delivery of appropriate medical care to the patient.

During the first 12 hours, patients will be advised to observe rigorous hygiene to avoid contaminating persons using the same toilet facilities. A double toilet flush will be followed after urination. Incontinent patients will be catheterized prior to PRRT and the catheter will be kept for 2 days thereafter. Urine bags will be emptied frequently. Standard Radiation Protection protocol will be followed.

Patient shall be discharged at 24 hours after the therapy, after documenting the exposure levels. No specific radiation safety precautions need to be followed thereafter.

Patients would undergo 48 and 96 hour post therapy scanning on an outpatient basis.

Arm B (PRRT plus chemotherapy)

PRRT will be administered as previously detailed with similar precautions**.** Post approximately 14-21 days of PRRT, patients will be started on chemotherapy with Capecitabine-Temozolomide.

Chemotherapy -Capecitabine-Temozolomide

Capecitabine

Formulation

Capecitabine is available as an oral tablet with a strength of 500mg

per tablet. Dispensing and handling

The tablets should be swallowed whole with water within 30 minutes after a meal. Capecitabine tablets should not be crushed or cut for administration.

Possible side effects

Nausea/vomiting, diarrhea, leukopenia, thrombocytopenia, anemia, increase of liver enzymes, hand-foot syndrome are common side effects seen.

Temozolamid

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Formulation

Temozolamide is available as an oral capsule with a strength of 5 mg, 20 mg, 100 mg, 140 mg, 180 mg, 250 mg per tablet.

Dispensing

Temozolamide capsules are swallowed with a glass of water. Temozolamide capsules should not be opened or chewed.

Possible side effects

Fatigue, headache, alopecia, skin rash, nausea, vomiting, constipation, anorexia, diarrhea, lymphocytopenia, thrombocytopenia, neutropenia, leukopenia are common side effects seen.

Modifications of therapy and dosage

Overview and general principles

Toxicity will be graded according to NCI CTCAE, version 5.0; the therapy modifications described below are applied according to this severity grading. Toxicities of severity grade 1 only will not lead to any dose reduction or cycle delay. The same holds for adverse reactions without any potential of serious or life- threatening complications according to the judgment of the physician (e.g. alopecia). If the toxicity is unequivocally caused by only one drug, a dosage modification of the other drugs is not required.

If more than one different type of toxicity occurs concurrently, the most severe grade will

determine the modification. In case of a necessary dose reduction the lower dose level will be applied throughout the rest of the therapy without re-escalation, if not stated otherwise.

In case of acute allergic reactions of grade 3 or 4, the respective agent should be discontinued permanently; in case of grade 1 or 2, it is up to the physician to continue treatment without dose modification, if this is in the best interest of the patient. Each dose modification or treatment delay has to be documented in the CRF, including the respective reason.

Due to logistic reasons arising out of non-availability of Lu-177-DOTATATE (PRRT), CAP-TEM regimen can be started till the availability of radio-pharmaceutical.

Baseline dose modification of chemotherapy – combination chemotherapy (Capecitabine-Temozolamide)

The following factors can be used for upfront dose modification (up to a maximum of 25% reduction) at discretion of treating physician -

- Albumin levels 3.0 – 3.5 mg%
- Creatinine clearance 40 ml/min – 50 ml/min
- ECOG PS 2
- Age > = 65

Modifications of chemotherapy – combination chemotherapy (Capecitabine and Temezolamide) from Cycle 2 of chemotherapy onwards

Dose adjustment/delay in case of myelosuppression

In case of myelosuppression persisting on the planned day 1 of the next cycle, the following measures should be taken:

ANC < 1.500/µL Therapy delay for at least 1 week

Platelets < 100.000/µL Differential blood counts at least weekly

In case of febrile neutropenia (despite secondary prophylaxis with G-CSF or peg GCSF as explained later) or thrombocytopenia with bleeding, temezolamide will be reduced to 75% of the initial dose. If these toxicities are observed again, a second reduction to 50% of the full

dose has to be performed. If the toxicity re-occurs, capecitabine will be reduced to 75% of the initial dose. If the toxicity still re-occurs, these 2 drugs will have to stop permanently.

Use of growth factors (GCSF or peg-GCSF) is allowed as per institution/physician choice. GCSF or peg- GCSF should not be used concurrently with capecitabine or temezolamide. GCSF or peg-GCSF may be used as an emergent measure during neutropenia or febrile neutropenia post cessation of oral chemotherapy.

Dose adjustment in case of febrile neutropenia

Occurrence of Febrile Neutropenia	Temezolamide dose reduction	Capecitabine dose reduction
1st appearance	75%	
2nd appearance	50%	
3rd appearance	50%	75%
4th appearance	50%	50%
5th appearance	Drug stopped permanently	Drug stopped permanently

Dose adjustment in case of diarrhoea / mucositis

In case of diarrhoea and/or mucositis ≥ grade 3, capecitabine have to be reduced to 75% of the initial dose. If these toxicities are observed again, a second reduction to 50% of the full dose has to be performed. If these toxicities are observed again, temezolamide have to be reduced to 75% of the initial dose. If these toxicities are observed again, a second reduction to 50% of the full dose has to be performed. If the toxicity re-occurs, these 2 drugs will have to stop permanently.

Dose adjustment in case of diarrhoea / mucositis

Occurrence of diarrhoea	Temezolamide dose reduction	Capecitabine dose reduction
and/or mucositis ≥ grade 3,		
1st appearance		75%
2nd appearance		50%
3rd appearance	75%	
4th appearance	50%	50%
5th appearance	Drug stopped	Drug stopped

Dose adjustment in case of nephrotoxicity

During the course of chemotherapy, if creatinine clearance drop to the range below 40 mL/min, but > 30 mL/min, hydration for 48 hours will be performed with a subsequent reassessment of the clearance. Following dosing modifications to take place –

Creatinine clearance 30 – 50 ml/min – Capecitabine to be continued at 75% doses; temezolamide can be continued at full doses or reduced doses as per physician decision.

Creatinine clearance below 30 ml/min – All drugs to be stopped.

Dose adjustments for capecitabine in case of hand-foot-syndrome

Grade of toxicity	Dose Adjustment for Next Cycle (% of starting dose)	Action during chemotherapy
Grade 1	Maintain dose level	Maintain dose level

Grade 2		
1st appearance	100 %	Interrupt until resolved to grade 0-1
2nd appearance	75%	Interrupt until resolved to grade 0-1
3rd appearance	50%	Interrupt until resolved to grade 0-1
4th appearance	--	Discontinue treatment permanently
Grade 3		
1st appearance	75%	Interrupt until resolved to grade 0-1
2nd appearance	50%	Interrupt until resolved to grade 0-1
3rd appearance, OR any evidence of Stevens-Johnson syndrome or Toxic epidermal necrolysis	---	Discontinue treatment permanently

Dose adjustment in case of other toxicities

If other toxicities of NCI CTC grade 3 to 4 occur, a dose adjustment of the cytostatic drug most probably responsible for the event should be reduced. Consultation of the PI is recommended.

Maximum doses

PRRT - 4 sessions maximum, in case the cumulative dose of 1000 MBq is not attained, 5th cycle can be given

Chemotherapy - 15- 18 cycles of chemotherapy. Chemotherapy will continue for 2-3 cycles post last dose of PRRT, assuming patient is feasible and satisfies criteria for administration of chemotherapy

Schedule of Events:

	Pre study	Cycle 1	15-21 days after PRRT	Pre therapy	Cycle 2	15-21 days after PRRT	Pre therapy	Cycle 3	15-21 days after PRRT	Pre therapy	Cycle 4	15-21 days after PRRT	Follow up
Lu-177 DOTATATE therapy (PRRT)		x			x			x			x		
CAPTEM Chemotherapy			x			x			x			x	
Informed Consent	x		x		x	x		x	x		x		
Demographics	x												
Medical history	x												
Concurrent meds	x												

Physical exam	x			x			x			x			x
Vital signs	x			x			x			x			x
Height/ Weight	x			x			x			x			x
Performance status	x			x			x			x			x
Hb	x			x			x			x			x
WBC	x			x			x			x			x
RBC	x			x			x			x			x
Platelet	x			x			x			x			x
GFR	x			x			x			x			x
DOTA PET	x						x						x
FDG PET	x						x						x
	Pre study	Cycle 1	15-21 days after PRRT	Pre therapy	Cycle 2	15-21 days after PRRT	Pre therapy	Cycle 3	15-21 days after PRRT	Pre therapy	Cycle 4	15-21 days after PRRT	Follow up
Adverse event evaluation	x			x			x			x			x
EORTC QLQ-C30	x			X			X			X			X
EORTC GI.NET21	x			X			X			X			X

Guidelines for therapy post progression

Once the patient has ceased therapy (either Arm A or Arm B), due to progressive disease, intolerable side effects or patient choice, further therapy is as per physician choice.

Patients who have temporarily ceased therapy (for a minimum of 2 months) (Arm A or Arm B) due to adverse events can be considered for restarting the same regimen after a delay/break based on discretion of the treating physician. The cessation of therapy will be labelled as an 'event', even if not progression and the date of cessation will be taken for calculation of event free survival.

Special situations:

- In patients with reduced renal function the following additional interventions are used:
  (a) Nephrourology consultation.
  (b) Extensive hydration (e.g. 2–3 l of fluid intake, if clinically appropriate) prior to PRRT.
  (c) Diuretics (e.g. furosemide) should be considered in case of dilated renal pelvis and delayed outflow.
- In patients with reduced haematological values the following additional interventions are used:
  (a) Haematologist consultation.
  (b) When required, packed red blood cells or platelet concentrate support may be given following PRRT.
- In patients randomized to the chemo-PRRT arm, in case there are certain unavoidable delays in administering PRRT, then patient may be started on chemotherapy as per plan and PRRT started at a later date based on PI decision.

Emergency management

In case of an emergency the principal investigator can be approached via phone or email. Serious adverse events or reactions observed during the conduct of the study, have to be reported to the IRB/IEC.

Enrolment

Subjects fulfilling all in- / exclusion criteria, having provided written informed consent on the approved informed consent form are eligible for participation in the study.

Premature withdrawal of an individual subject

Patients will be taken off the protocol treatment for the following reasons -

- Treatment delay more than three weeks post randomization.
- administration of any other anti-neoplastic medication or any other
- consent withdrawn by patient
- investigator decision in the best interest of the patient
- pregnancy or insufficient contraception
- loss to follow-up

The time point of and reason for removal of a patient must be documented on the case report form. The investigator will attempt to complete all discharge procedures at the time a patient is discontinued from study treatment and to record further follow-up data, if required.

Premature study termination by primary investigator and ethics committee

At any time, coordinating investigator of the study, or/and the ethics committee may terminate the trial participation of an individual patient, as well as the whole trial, provisionally or permanently, if this is required by stringent medical or legal reasons (including insufficient patient recruitment), especially if severe and/or frequent adverse events occur, requiring a new risk/benefit evaluation.

Study assessments

- Baseline assessment

  In the experimental and standard arm, the following procedures/assessments will be carried out at baseline within 2 weeks prior to start of study treatment

  - Physical exam and vital parameters
  - Echocardiography/MUGA
  - Hb, CBC, Liver Function Test (LFT)
  - Renal function test
  - Serum electrolytes
  - GFR (sampling method)/e-GFR and tubular function by 99m Tc – EC Renogram
- Assessment during and after study
  - Next day after conclusion of every cycle of PRRT: CBC, LFT and serum electrolytes
  - After 14 days: CBC, LFT and serum electrolytes
  - 1 week before starting every subsequent cycle of PRRT:

- Physical exam and vital parameters
- Echocardiography/MUGA
- Hb, CBC, Liver Function Test (LFT)
- Renal function test
- Serum electrolytes
- GFR (sampling method)/e-GFR and tubular function by 99m Tc – EC renogram

- Documentation at follow up

  Patients will be followed up while on active treatment with cancer directed therapy as well as supportive care. Investigations likely to be conducted are as follows (not all inclusive)

  - Physical examination including: weight, ECOG performance status
  - Vital signs: blood pressure, pulse rate and oral temperature
  - Evaluation of prolonged side effects as per NCI CTCAE
  - 2 D Echo/MUGA (Multi-Gated Acquisition)
  - Ga-68-DOTANOC PET/CT and/or FDG PET/CT, if deemed necessary
- Criteria for efficacy evaluation

  Tumor measurements are to be made using the same method at each protocol-defined assessment. If a patient has clinical signs of progression, then tumor evaluation can take place at that time.

  This tumor evaluation will be performed by the oncologist in collusion with radiologist as per the RECIST (Response Evaluation Criteria In Solid Tumors, V. 1.1, 2009) and EORTC criteria.

RECIST 1.1 Criteria:

Target Lesions:	
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	≥ 30% decrease in the sum of the longest diameters of target lesions compared with baseline

Stable Disease (SD)	Any case that does not qualify for PR or PD
Progressive Disease (PD)	≥ 20% increase in the sum of the longest diameter of target lesions compared with the smallest-sum longest diameter recorded or the appearance of one or more new lesions
Non-Target Lesions	
Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response, PD	Persistence of one or more non-target lesions and/or the maintenance of tumor marker level above the normal limits
Stable Disease (SD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions

EORTC Criteria:

Complete Metabolic Response (CMR)	Complete resolution of all lesions
Partial Metabolic Response (PMR)	Greater than or equal to 25% decrease in SUVmax
Stable Disease (SD)	Less than 25% change in SUVmax
Progressive Disease (PD)	Greater than/equal to 25% increase in SUV max

Progression free survival (PFS)

Progression-free survival (PFS) will be defined as the time from enrolment to the time of disease progression or death, or to the date of last tumor assessment without any such event (censored observation).

Time to deterioration (TTD) of ECOG PS

Time to deterioration (TTD) of ECOG PS is based on assessment of ECOG PS at baseline and then at every clinical visit while on active treatment. Worsening of ECOG-PS will be defined as an increase from 0 to ≥2, an increase from 1–2 to ≥3, or death (irrespective of cause).

Overall survival (OS)

The duration of overall survival (OS) will be determined by measuring the time interval from enrolment to the date of death or last observation (censored).

Study assessments (safety)

- At each visit, the investigator will evaluate the subject to determine whether any AEs have occurred. 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.

- All clinical AEs occurring after the subject signs the ICF and up to 30 days after the patient is taken off the active portion of the trial, whether observed by the investigator or reported by the subject, will be recorded as an AE. Medical conditions that exist prior to the informed consent will be recorded as part of the medical history and will not be an AE. Diagnosis to be reported as the AE or SAE term; when the diagnosis is unavailable, signs and symptoms as individual entries of AE or SAE to be entered until the diagnosis becomes available. Pre-planned procedure/hospitalization for pre-existing conditions which do not worsen in severity should not be reported as SAEs. Progressive disease is waived from SAE reporting. In addition, death due to progressive disease does not have to be reported as an SAE. The investigator should follow subjects with AEs until the event has resolved or the condition has stabilized. In case of unresolved

AEs including significant abnormal laboratory values at the end of treatment assessment, these events will be followed up until resolution or until they become clinically not relevant.

- The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.03) 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 worst 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.

II. Definitions

7.2.1 An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

1. All suspected adverse drug or device reactions

2. Apparently unrelated illnesses, including the worsening (severity, frequency) of pre- existing illnesses

3. Injury or accidents.

4. Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)

5. Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

6. Any untoward event that occurs after the protocol-specified reporting period

which the Investigator believes may be related to the drug or device.

AEs are not required to be reported unless they meet SAE

criteria. Documented Adverse Events are as follows:

CAP-TEM: The most common grade 3 or 4 hematological adverse events are thrombocytopenia (8–12%), lymphopenia (20-25%) and grade 1 or 2 neutropenia (~50%). Non-hematologic side effects, grade 1 or 2 palmar-plantar erythrodysesthesia is seen in approximately 12-15% with no treatment discontinuation, fatigue grade 1 or 2 upto 50%, severe nausea in a few cases, and grade 3 or 4 diarrhea (3%).

PRRT: The most common adverse events are nausea (30-40%) and vomiting

(25-30%). Other common adverse events included fatigue or asthenia and diarrhea.

Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia is seen in 1%, 2%,

and 9% of patients respectively.

III.A SERIOUS ADVERSE EVENT (SAE) are expected in less than 1% of patients.

SAE, if any, will be reported during the active period of the

trial. NOTES:

The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is

related to the drug or device and is unexpected (i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the

Subject Information Sheet and Informed Consent Form or elsewhere in the protocol. (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010)).

An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event (FDA, Safety Reporting Requirements for INDs and BA/BE Studies, draft guidance, September 2010).

For the purposes of this study, the following adverse events are not reported as SAEs:

-hospitalization or death as a result of or related to disease

progression. Procedure for reporting serious adverse events

SAE reports will be forwarded to the IEC in the IEC approved format within 24 hours.

- Pregnancy reporting
  Any pregnancy in a female subject diagnosed during the treatment period or within 6 months after last study treatment administration must be reported unhesitatingly to the IEC. Follow-up information on the subject and her pregnancy outcome should be communicated by the Investigator to the IEC as soon as available.

- Monitoring of subjects with adverse events
  Any AE that occurs in the course of the clinical study must be monitored and followed up until the end of treatment visits. It is the responsibility of the investigator that any necessary additional therapeutic measures and follow-up procedures are performed.

- Overdose
  In case of a significant overdose of a study drug, this has to be reported as a serious adverse event.

Assessment of quality of life

QOL analysis will be conducted using the following tools (with appropriate language translations)

· EORTC QLQ-30

· EORTC G.I.NET-21

QOL analysis will be conducted at the following time intervals (approximate)

- Baseline – 6-10 days before first cycle of PRRT, during pre-therapy work up (scheduled routine visit)
- 6-10 days before start of next cycle of PRRT, when the patient comes for pre-therapy work-up, (scheduled routine visit).
- 3 months after last cycle when patient comes for routine follow-up

It will be administered using the EORTC tools mentioned above through a face-to-face interview in language comfortable to the patient. Adequate time shall be given to patient to respond to questions.

As per the EORTC QOL scoring manual instructions for domains with multiple questions, if greater than 50% but less than 100% of questions are completed at a visit, then that visit will be deemed evaluable for that domain, and the average of the remaining assessed questions will be used in the analysis. Visits with less than 50% of questions missing for a particular domain shall be excluded from the analyses.

Data management and statistics

Based on the NETTER-1 trial, we assumed that PRRT will give a 2 year PFS of 60%, the experimental arm will improve the 2 year PFS by an absolute value of 15%. With a type 1 error (one-sided) of 5% and

Type 2 error of 20 %, with 10% lost to follow up, sample size of 162

patients For any statistical test performed, significance level will be

set to 5%.

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.

Financing of study:

Since both arms of the study are ‘standard-of-care’, there are no funding requirements Budgeting has been done only for personnel i.e. Trial Co-ordinator (Page 38) for the study.

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,).
- 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.

- 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.
- Reimbursement

  The patients receiving chemotherapy arm will have to pay for the chemotherapy, and for the blood investigations and imaging studies. For all patients, the cost of standard testing and therapy, like palliative radiation, stenting, analgesics, supportive medications, etc. will be borne by the patient.
- Compensation:

It will be as per the Institutional IEC policy

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

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.

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 patient and one copy shall be kept for records

Impartial witness 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.

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.

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Budget Sheet:

Year	1	2	3	4	5	6	7	8
Salary of Personnel (Co-ordinator)	18000	20000	22000	24000	26000	28000`	30000	32000

Total Budget: Rs 24,00,000/-