Study protocol of LANTana: a phase Ib study to investigate epigenetic modification of somatostatin receptor-2 with ASTX727 to improve therapeutic outcome with [177Lu]Lu-DOTA-TATE in patients with metastatic neuroendocrine tumours, UK

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ABSTRACT

Introduction Suability for peptide receptor radionuclide therapy (PRRT) for neuroendocrine neoplasia (NENs) depends on presence of somatostatin receptor-2 (SSTR2) determined by [68Ga]Ga-DOTA-peptide-positron emission tomography (PET). Some patients have low or no uptake on [68Ga]Ga-DOTA-peptide-PET, precluding PRRT. The upstream promoter region of SSRT2 is methylated, with percentage of methylation correlating with SSTR2 expression. Demethylating agents increase uptake on PET imaging in vivo such that tumours previously negative on PET become positive, correlating with a dose dependent increase in tumorous SSTR2 expression. LANTana will determine whether treatment with the demethylating agent, ASTX727, results in re-expression of SSTR2 using [68Ga]Ga-DOTA-peptide-PET to image epigenetic modification of the SSTR2 locus, allowing subsequent PRRT.

Methods and analysis 27 participants with a histological diagnosis of NEN (Ki67<55%) with no or low uptake on baseline [68Ga]Ga-DOTA-TATE-PET/CT will be recruited. Patients will receive 5 days of ASTX727 (fixed dose 35 mg decitabine +100 mg cedazuridine). [68Ga]Ga-DOTA-peptide-PET/CT will be repeated day 8±2; where there is significant uptake greater than liver in most lesions, PRRT will be administered. Primary objective is to determine re-expression of SSTR2 on PET imaging. Tolerability, progression-free survival, overall response and quality of life will be assessed. Methylation in peripheral blood mononuclear cells and tumorous methylation will be evaluated.

Ethics and dissemination LANTana has ethical approval from Leeds West Research Ethics Committee (REC Reference: 21/YH/0247). Sponsored by Imperial College London and funded by Advanced Accelerator Applications pharmaceuticals. Results will be presented at conferences and submitted to peer-reviewed journals for publication and will be available on ClinicalTrials.gov.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Will investigate epigenetic modification to resensitise tumours to somatostatin receptors (SSTR2) targeting radiotheranostic drugs.
⇒ Prospective trial using a demethylation strategy to re-express SSTR2 using [68Ga]Ga-DOTA-PET as a biomarker of response
⇒ May potentially allow treatment with [177Lu]Lu-DOTA-TATE in a group of patients who otherwise would be excluded.

Trial registration numbers EUDRACT number: 2020-003800-15, NCT05178693.

INTRODUCTION

While thought to be a rare cancer, the incidence of neuroendocrine neoplasias (NENs) has increased dramatically (approximately 500 fold) over the past 30 years, and unlike most other solid tumours, the incidence continues to rise.1 NENs are a heterogeneous group of tumours derived from peptide and amine producing cells of the neuroendocrine system, characterised by neurosecretory granules containing a variety of hormones and biogenic amines. NENs can arise anywhere in the body, commonly midgut (40%) and pancreas (8%).2 NENs can also arise in the lung and often the primary is unknown.1 Some release vasoactive substances into systemic circulation, causing diarrhoea, flushing and wheezing, having a negative impact on quality of life (QoL). However, the majority (>80%) are non-secretory, and often present with widespread metastatic disease.
The management and prognosis of NENs are determined by both stage and grade. For patients with localised or limited disease, the primary modality of therapy is surgery, aiming to cure. However, in patients with metastatic disease, the only option is systemic therapy, administered with palliative intent. Tumour grade is determined by mitotic count or Ki67 proliferation index: low-grade or grade 1: Ki67<3%, moderate or grade 2: Ki67 between 3% and 20% (collectively termed neuroendocrine neoplasia, NENs), and high-grade or grade 3: Ki67>20%. There is increasing recognition of heterogeneity in grade 3 NENs such that poorly differentiated tumours with Ki67>55% are defined as neuroendocrine carcinomas (NECs), and have an average survival of 5 months while well-differentiated grade 3 NENs have a treatment response and outcome analogous to grade 2 NENs.3 4 The prognosis for metastatic NENs varies from 25% 5-year survival in grade 1 NENs to<12 months in NECs. 5

NENs are characterised by the presence of somatostatin receptors (SSTRs) on the tumour surface.6 The SSTR family comprises five widely distributed G-protein coupled receptors that mediate intracellular signalling pathways with roles in cell proliferation, cell differentiation and angiogenesis.7 The expression of the SSTRs on NENs can be exploited for therapeutic benefit with somatostatin analogues (SSAs) and Peptide Receptor Radionuclide Therapy (PRRT). Indeed, the long-acting SSA preparations octreotide and lanreotide are considered standard of care for the treatment of grade 1 and 2 NENs within the current European Neuroendocrine Tumour Society Consensus Guidelines, with proven antiproliferative protein pathways with roles in cell proliferation, cell differentiation and angiogenesis. The expression of the SSTRs on NENs can be exploited for therapeutic benefit with somatostatin analogues (SSAs) and Peptide Receptor Radionuclide Therapy (PRRT). Indeed, the long-acting SSA preparations octreotide and lanreotide are considered standard of care for the treatment of grade 1 and 2 NENs within the current European Neuroendocrine Tumour Society Consensus Guidelines, with proven antiproliferative and outcome analogous to grade 2 NENs.3 4 The prognosis for metastatic NENs varies from 25% 5-year survival in grade 1 NENs to<12 months in NECs.5

PRRT consists of a SSA linked to a long-acting beta-emitting radionuclide, such as lutetium 177, which has a half-life of 140 days and particle range of up to 2 mm ([177Lu]Lu-DOTA-0-Tyr3-Octreotate, [177Lu]Lu-DOTA-TATE). The radiolabelled SSA binds specifically to SSTR2 on the tumour surface. The complex is internalised delivering selective, targeted radiotherapy. The efficacy of [177Lu]Lu-DOTA-TATE was highlighted in the NETTER-1 trial which has arguably provided the biggest clinical impact in the treatment of SSTR2-expressing NENs in terms of improvement in clinical outcomes.11 In NETTER-1, patients with metastatic grade 1–2 NENs were randomised to receive either high dose octreotide or [177Lu]Lu-DOTA-TATE. The trial reported a significant reduction in progression or death, 79%, with [177Lu]Lu-DOTA-TATE over SSAs (HR 0.21, 95% CI 0.13 to 0.34; p<0.001).11 Importantly, treatment with PRRT improved QoL.12 The use of PRRT is approved by most healthcare systems for the management of unresectable or metastatic, progressive, well-differentiated (grade 1 or grade 2), SSTR-positive NENs.

Selection for treatment with PRRT is based on the presence of SSTR2 on the tumour as illustrated by positive receptor imaging; typically using [68Ga]Ga-labelled SSAs ([68Ga]Ga-DOTA-peptides) PET/CT imaging.13 The only validated predictor of response to PRRT is positive SSTR2 imaging, such that patients with no tumorous uptake or tumorous uptake below that of background liver on imaging are not suitable for PRRT.14 15 While grade 1 tumours are well differentiated and retain tumour expression of SSTR2, some intermediate and high-grade NENs either have low or no uptake on [68Ga] Ga-DOTA-peptide-PET/CT or heterogeneous expression. In contrast, these patients have positive uptake on 2-[fluorine-18]fluoro-2-deoxy-d-glucose PET/CT and are indicative of a group of patients with poor prognosis who do not benefit from PRRT.16 17

Previous studies have demonstrated that the expression of the SSTR2 receptor is controlled by epigenetic modifications of a novel SSTR2 upstream promoter.18 This putative upstream promoter area for SSTR2 is conserved across species and is responsible for between 40% and 60% of total SSTR2 expression across multiple cell lines representing different cancer types. Methylation of this promoter was demonstrated to be reversible in vitro with the first-generation DNA methyltransferase inhibiting agent decitabine.19 These findings were extended by Veenstra et al and Taelman et al who illustrated that treatment of NEN cell lines with decitabine, not only resulted in re-expression of SSTR2 but importantly resulted in enhanced uptake of radiolabelled octreotide.19 20 In order to assess if re-expression of SSTR2 results in improved cytotoxicity of [177Lu]Lu-DOTA-TATE, Taelman incubated cells with [177Lu]Lu-DOTA-TATE following treatment with decitabine. The authors report increased cytotoxicity with combination therapy compared with [177Lu]Lu-DOTA-TATE alone.19 We extended these findings into a mouse model of NEN using BON-1 cells (low basal expression SSTR2) and QGP-1 cells (high basal expression SSTR2) using guadecitabine to illustrate a 70% increase in the SSTR2-directed radioligand, [18F]-FET-BβAG-TOCA in BON-1 tumour model.21 22 We therefore demonstrated that PET imaging can be used as a biomarker of demethylation of SSTR2.23 Taken together, this suggests that SSTR2 epigenetic silencing can be reversed, opening a novel therapeutic approach for patients with no or marginal uptake on [68Ga]Ga-DOTA-PET scans who are currently not suitable for PRRT, using [68Ga]Ga-DOTA-PET as a biomarker of SSTR2 re-expression.

The primary aim of the LANTana is to determine whether pretreatment with the demethylating agent ASTX727 results in re-expression of SSTR2 in patients with metastatic NENs who have no or low expression of SSTR2 on [68Ga]Ga-DOTA-peptide-PET/CT. [68Ga] Ga-DOTA-peptide-PET/CT will be used to image epigenetic modification of the SSTR2 locus allowing subsequent treatment with [177Lu]Lu-DOTA-TATE. The biological relevance of this approach will be assessed through tumour response. ASTX727 is an oral fixed-dose combination of 100mg cedazuridine and 35mg decitabine. Cedazuridine inhibits cytidine deaminase increasing
the oral bioavailability and half-life of decitabine. The key dose-limiting toxicities with demethylating agents is myelosuppression and there is concern that this may be additive with the use of [177Lu]Lu-DOTA-TATE in a safe manner.23 The recommended dosing for ASTX727 100/35 mg daily for 5 days 28 days. In this trial, patients will receive treatment for 5 days every 2 months and with this regimen we would not anticipate the degree of side-effects reported in the phase I/II studies. However, myelotoxicity will be evaluated prior to and following each cycle of ASTX727. Our preclinical combination studies lend support to this regimen being safe in a clinical setting.

LANtana proposes to explore this concept in a phase I clinical trial. If successful, LANtana will represent a step change in the management of NENs, allowing patients who currently cannot be treated with [177Lu]Lu-DOTA-TATE access to an effective treatment regimen. This trial will also be the first to show the novel manipulation of receptor expression through the use of demethylating agents which may be applicable to other tumour types as illustrated by others preclinically.

**METHODS AND ANALYSIS**

**Trial objectives**

**Primary objective**

The primary objective is to evaluate the uptake of [68Ga]Ga-DOTA-peptide-PET/CT in patients with NENs who have no or low tumorous uptake on baseline [68Ga]Ga-DOTATATE-PET/CT imaging, as a mean to image changes in epigenetic regulation of SSTR2 in response to ASTX727.

**Secondary objectives**

Objective response rate (ORR) to combination treatment will be assessed according to RECIST 1.1. The incidence of adverse and serious adverse events (AEs/SAEs) overall and by severity, graded by the National Cancer Institute—Common Toxicity Criteria (NCI-CTC V.5.0) will be assessed. Other secondary objectives are to determine progression-free survival (PFS) defined as the time from the date of treatment to the date of the first documentation of disease progression as determined by RECIST V.1.1 or death, and to assess QoL using the European Organisation for Research and Treatment of Cancer (EORTC) questionnaires QLQ-C30 and QLQ-GI.NET21 at baseline and every 2 months until disease progression. Several translational endpoints will be explored. Expression of SSTR2 on baseline tumour biopsies, as determined by immunohistochemistry, will be correlated with baseline PET uptake parameters (SUV<sub>max</sub>). Promoter methylation status of the SSTR2 locus in the tumour will be correlated with baseline PET uptake parameters (SUV<sub>max</sub>), and any changes in the methylation status will be determined on repeat biopsy following 1 cycle of ASTX727 in the first five recruited patients. Changes in methylation will be correlated with changes in PET uptake. Bloods will be taken at baseline, prior to and following each cycle of ASTX727. Changes in LINE-1 methylation status in peripheral blood mononuclear cells (PBMC) will be correlated with changes in PET uptake parameters (SUV<sub>max</sub>), and treatment response.

**Trial design**

LANtana is a phase Ib study that will investigate a demethylating strategy to re-express tumorous SSTR2 as visualised on [68Ga]Ga-DOTA-TATE-PET/CT in patients with NENs that have no or low uptake on [68Ga]Ga-DOTA-TATE-PET who would otherwise be unsuitable for PRRT.

**Eligibility criteria**

Participants will be recruited from Hammersmith Hospital, Imperial College Healthcare NHS Trust. Patients will be provided with a verbal and written explanation of the trial and given the opportunity to discuss all aspects of the trial with both the clinician and the research nurse (online supplemental file 1). Patients who provide written consent to participate in the trial after at least 24 hours of consideration will be registered and therefore eligible to proceed to further assessments.

To be eligible patients will have a confirmed histologic diagnosis of well differentiated grade 1–3 NENs (Ki67<55%) with tumour uptake less than background liver (modified Krenning score<2, table 1)24 on [68Ga]Ga-DOTA-TATE-PET at the majority of sites. NEN of any site will be included in the study.25 26 Patients must have progressed through at least one line of therapy. Detailed inclusion and exclusion criteria are outlined in table 2. A total of 27 patients will be recruited. Recruitment to the study commenced November 2022 and will be completed by December 2024.

**Study procedures**

Patients will undergo baseline standard of care imaging with [68Ga]Ga-DOTA-TATE-PET/CT, contrast CT scan of the chest, abdomen and pelvis, or contrast MRI. Archival tumour biopsies will be obtained or pretreatment biopsy undertaken under ultrasound guidance. Patients will then receive cycle 1 ASTX727 days 1–5 (fixed dose 35 mg decitabine+100 mg cedazuridine), orally. [68Ga]Ga-DOTA-TATE-PET/CT will be repeated post cycle 1, day 8±2 to assess SSTR2 re-expression. In a subset of patients (n=5), repeat tumour biopsy will be undertaken following 5 days.

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**Table 1 Modified Krenning Score**

<table>
<thead>
<tr>
<th>Krenning Score</th>
<th>Findings at [68Ga]Ga-DOTA-TATE-PET/CT imaging</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>No uptake</td>
</tr>
<tr>
<td>1</td>
<td>Minimal uptake</td>
</tr>
<tr>
<td>2</td>
<td>Uptake slightly less than or equal to that of liver</td>
</tr>
<tr>
<td>3</td>
<td>Uptake greater than that of liver but less than that of spleen</td>
</tr>
<tr>
<td>4</td>
<td>Uptake greater than that of spleen</td>
</tr>
</tbody>
</table>

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**Table 2 Inclusion and exclusion criteria**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
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<tbody>
<tr>
<td>Written consent from the patient (whom must be 18 years or older)</td>
<td>Previous treatment with either study medication and/or known hypersensitivity to the study medication</td>
</tr>
<tr>
<td>Histological or cytologic confirmed diagnosis of NEN</td>
<td>History of organ transplantation or serious concurrent medical illness</td>
</tr>
<tr>
<td>Disease that can be biopsied via ultrasound guidance</td>
<td>Known history of HIV or active Bacillus Tuberculosis or active CNS metastases and/or carcinomatous meningitis. Participants with previously treated brain metastases must display radiologically stability.</td>
</tr>
<tr>
<td>Ki67&lt;55% (well differentiated grade 1–3 NETs only as poorly differentiated grade 3 carry a prognosis&lt;6 months)</td>
<td>Bleeding or thrombotic disorders or subjects at risk for severe haemorrhage</td>
</tr>
<tr>
<td>Progression or intolerance to first line therapy including somatostatin analogues</td>
<td>Participating in or previously participated in a study with the investigational medicinal product</td>
</tr>
<tr>
<td>Eastern Cooperative Oncology Group Performance status 0–2</td>
<td>Additional malignancy requiring active treatment or that is progressing (excluding basal cell carcinoma or squamous cell carcinoma of the skin that has undergone curative therapy or in situ cervical cancer)</td>
</tr>
<tr>
<td>No tumorous uptake on(68Ga)GaDOTA-TATE or uptake less than background liver</td>
<td>Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject’s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating Principal Investigator (PI).</td>
</tr>
<tr>
<td>Measurable disease based on RECIST V.1.1. Lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions</td>
<td>Known psychiatric or substance abuse disorders that would interfere with the requirements of the trial</td>
</tr>
<tr>
<td>Highly effective method of contraception for women of childbearing potential and an adequate method of contraception for men starting with first dose of the investigational medicinal product through to 6 months of the last dose of the study.</td>
<td>Is pregnant or breast feeding, or expecting to conceive or father children within the projected duration of the trial, starting with screening visit through to 6 months after the last dose of the investigational medicinal product</td>
</tr>
</tbody>
</table>
| Criteria for bloods:  
  ► Absolute neutrophil count≥1500 cells/μL  
  ► Platelets≥100 000/μL  
  ► Haemoglobin≥9.0 g/dL  
  ► Creatinine≤1.5× upper limit of normal (ULN)  
  ► Creatinine clearance≥60 mL/min for subject with creatinine levels>1.5 × ULN  
  ► Bilirubin≤1.25 × ULN  
  ► AST and ALT≤2.5 × ULN (Patients with documented liver metastases: AST and/or ALT<5 × ULN)  
  ► International normalised ratio or prothrombin time (PT), activated partial thromboplastin time (aPTT) (≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants) | Received any live vaccine within 30 days of first dose of ASTX727 |
| Received prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis. A 1-week washout is permitted for palliative radiation (≤2 weeks of radiotherapy) to non-CNS disease and stereotactic radiotherapy to the CNS |  
  ► Any other comorbidities that could compromise the subject’s participation in the study  
  ► Kidney failure with creatinine clearance<30 mL/min |
of ASTX727 to assess the impact of the demethylating agent on SSTR2 gene promoter methylation within the tumour. If there is a significant change (defined below) in tumour uptake on repeat [68Ga]Ga-DOTA-TATE-PET/CT, patients will receive cycle 2 of ASTX727 after 28 days, days 1–5 followed by cycle 1 of [177Lu]Lu-DOTA-TATE, day 8+2. Combination treatment will be continued for a total of four cycles administered every 2 months.

If there is not a significant change in uptake on repeat [68Ga]Ga-DOTA-TATE-PET/CT, the patient will be withdrawn from the study. Necessary levels of SSTR expression on [68Ga]Ga-DOTA-TATE-PET/CT have not been clearly defined, but lesion uptake should exceed background hepatic uptake. Study procedures are outlined in figure 1. To proceed with [177Lu]Lu-DOTA-TATE, uptake on [68Ga]Ga-DOTA-TATE-PET/CT should be visually greater than that of background liver in most (>50%) of lesions using the modified Krenning score (Krenning score ≥3). Patients will be reviewed at baseline, prior to each cycle of ASTX727 and on a 3-monthly basis until disease progression, withdrawal from the trial or death (whichever comes first). Blood tests will be performed at the start of each cycle of ASTX727 for safety and research. Repeat research bloods will be taken at day 8 of each ASTX727 cycle. Tumour imaging will be repeated after 2 and 4 cycles of combination therapy and then 3 monthly until tumour progression. The same method used for assessment at baseline must then be used at all subsequent time points. RECIST V.1.1 criteria will be used to determine patient response to treatment, PFS and ORR. Participants will be assessed every 3 months thereafter for disease assessment and survival. QoL questionnaires (EORTC QLQ-C30 and EORTC QLQ-GINET21) will be completed at baseline, prior to each cycle of combination therapy and 3 monthly post [177Lu]Lu-DOTA-TATE until tumour progression.

Figure 1  Trial schema. 1CT chest, abdomen and pelvis or MRI (physician’s choice), routine bloods, history, physical examination, AE data collected - baseline and every 3 months until disease progression.
Table 3  Dose modifications for [177Lu]Lu-DOTA-TATE

<table>
<thead>
<tr>
<th>Adverse drug reaction</th>
<th>Severity of adverse drug reaction</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>Grade 2 (platelets&lt;75–50 × 10^9/L) 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Grade 3 (platelets&lt;50–25 × 10^9/L)</td>
<td>Withhold dose until complete or partial resolution (grade 0 to 1).</td>
</tr>
<tr>
<td></td>
<td>Grade 4 (platelets&lt;25 × 10^9/L)</td>
<td>Resume(177Lu)Lu-DOTA-TATE at 3700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in grade 2, 3 or 4 thrombocytopenia, administer(177Lu)Lu-DOTA-TATE at 7400 MBq (200 mCi) for next dose. Permanently discontinue(177Lu)Lu-DOTA-TATE for grade 2 or higher thrombocytopenia requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent grade 2, 3 or 4 Permanently discontinue(177Lu)Lu-DOTA-TATE.</td>
</tr>
<tr>
<td>Anaemia and neutropenia</td>
<td>Grade 3 (Hb&lt;8.0 g/dL) 1; transfusion indicated</td>
<td></td>
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<tr>
<td></td>
<td>Grade 4 (life threatening consequences)</td>
<td></td>
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<tr>
<td></td>
<td>Grade 3 (absolute neutrophil count (ANC)&lt;1.0–0.5× 10^9/L)</td>
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<tr>
<td></td>
<td>Grade 4 (ANC&lt;0.5 × 10^9/L)</td>
<td>Withhold dose until complete or partial resolution (grade 0, 1, or 2).</td>
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<tr>
<td></td>
<td></td>
<td>Resume(177Lu)Lu-DOTA-TATE at 3700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in grade 3 or 4 anaemia or neutropenia, administer(177Lu)Lu-DOTA-TATE at 7400 MBq (200 mCi) for next dose. Permanently discontinue(177Lu)Lu-DOTA-TATE for grade 3 or higher anaemia or neutropenia requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent Grade 3 or 4 Permanently discontinue(177Lu)Lu-DOTA-TATE.</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Defined as:</td>
<td>Withhold dose until complete resolution or return to baseline.</td>
</tr>
<tr>
<td></td>
<td>Creatinine clearance less than 40 mL/min 1; calculate using Cockcroft Gault with actual body weight, or</td>
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<td></td>
<td>40% increase in baseline serum creatinine, or</td>
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<tr>
<td></td>
<td>40% decrease in baseline creatinine clearance; calculate using Cockcroft Gault with actual body weight.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume(177Lu)Lu-DOTA-TATE at 3700 MBq (100 mCi) in patients with complete resolution or return to baseline. If reduced dose does not result in renal toxicity, administer(177Lu)Lu-DOTA-TATE at 7400 MBq (200 mCi) for next dose. Permanently discontinue(177Lu)Lu-DOTA-TATE for renal toxicity requiring a treatment delay of 16 weeks or longer.</td>
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<tr>
<td></td>
<td></td>
<td>Recurrent renal toxicity Permanently discontinue(177Lu)Lu-DOTA-TATE.</td>
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<tr>
<td>Hepatotoxicity</td>
<td>Defined as:</td>
<td>Withhold dose until complete resolution or return to baseline.</td>
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<td></td>
<td>Bilirubinaemia greater than 3 times the upper limit of normal (grade 3 or 4), or</td>
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<td>Hypoalbuminaemia 2 less than 30 g/L with a decreased prothrombin ratio less than 70%</td>
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<tr>
<td></td>
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<td>Resume(177Lu)Lu-DOTA-TATE at 3700 MBq (100 mCi) in patients with complete resolution or return to baseline. If reduced(177Lu)Lu-DOTA-TATE dose does not result in hepatotoxicity, administer(177Lu)Lu-DOTA-TATE at 7400 MBq (200 mCi) for next dose. Permanently discontinue(177Lu)Lu-DOTA-TATE for hepatotoxicity; requiring a treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent hepatotoxicity. Permanently discontinue(177Lu)Lu-DOTA-TATE.</td>
</tr>
<tr>
<td>Any other CTCAE* grade 3 or grade 4 toxicity possibly related to(177Lu)Lu-DOTA-TATE</td>
<td>Grade 3 or 4</td>
<td>Withhold dose until complete or partial resolution (Grade 0 to 2).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resume(177Lu)Lu-DOTA-TATE at 3700 MBq (100 mCi) in patients with complete or partial resolution. If reduced dose does not result in grade 3 or 4 toxicity, administer(177Lu)Lu-DOTA-TATE at 7400 MBq (200 mCi) for next dose. Permanently discontinue(177Lu)Lu-DOTA-TATE for grade 3 or higher toxicity requiring treatment delay of 16 weeks or longer.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recurrent grade 3 or 4 Permanently discontinue(177Lu)Lu-DOTA-TATE.</td>
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</tbody>
</table>
Safety

ASTX727 is a fixed dose combination of 35 mg decitabine+100 mg cedazuridine and no dose reductions will be possible in the event of toxicity. However, changes in dose duration are permitted in the advent of grade 3 related AEs. Dose duration can be reduced to 4 days and 3 days as clinically indicated. Treatment delays are permitted for up to 28 days following which patients will be withdrawn from the study.

Dose modifications of [177Lu]Lu-DOTA-TATE are permitted (table 3) and dose delays up to 16 consecutive weeks is permitted for resolution of toxicities. If the drug-related toxicity resolves within 16 weeks, the subsequent cycle will be administered with a 50% dose reduction. If no further dose modifying toxicities occur, full dose can be administered on the subsequent cycle, otherwise patients will be withdrawn from the study.

All AEs will be reported in a timely fashion. AEs whether expected or not, will be collected and recorded during clinical assessments prior to each ASTX cycle and 3 months thereafter as well as at the time of progression. WhenSAEs occur, an SAE form will be completed within 24 hours. The Chief Investigator will determine whether SAEs were ‘related’ (resulting from administration of the study treatment or procedure) or ‘unexpected’ (an event not listed in the study protocol as an anticipated occurrence) and report this to the Research Ethics Committee. Any questions concerning AE reporting will be directed to the Chief Investigator in the first instance. The Chief Investigator will notify the sponsor of all SAEs that occur. Potential related SAEs are included in online supplemental data.

Data collection

Data will be collected using paper case report forms and entered into a validated trial database by the Cancer Research Team, Imperial College NHS Healthcare Trust, where data quality will be monitored. Automatic and manual validation of entered data will be conducted. Data items relating to the safety and rights of individual participants will be dealt with as a priority. Missing data will be chased until it is either received or confirmed as not available at the trial analysis stage. For the primary analysis, there will be no data imputation for missing data in the primary end point.

Statistical analysis

The Simon’s minimax two-stage design of phase II clinical trials will be used. The primary endpoint of clinical benefit rate (CBR) in this trial is defined as percentage of patients with 20% increase in SUV$_{\text{max}}$ on[68Ga]Ga-DOTA-TATE-PET/CT at days 8–10 compared with baseline. Assuming maximum unacceptable CBR (p0) for the experimental treatment of 5% and minimal acceptable CBR (p1) of at least 20%, the trial will need to recruit 27 patients in total with an interim data review after 13 patients to have 80% power and one-sided type-I error of 0.05. In the interim review, at least 1 patient with response (defined below) to ASTX727 among the first 13 patients should have been observed to move the second stage, where 14 additional patients will be accrued for a total of 27. If the trial passes interim analysis, at least 4 patients with response among the total 27 patients will have to be reported to claim the treatment effective.

Planned analyses

Image analysis. Image analysis shall be performed by two experienced PET readers in consensus (TB and MN). Visual analysis using the modified Krenning score will be performed (table 1). Quantitative analysis with lesion SUV$_{\text{max}}$ and tumour to liver ratio (T/L, SUV$_{\text{max}}$ tumour/ SUV$_{\text{mean}}$ liver) will be determined (tumour SUV$_{\text{max}}$/liver SUV$_{\text{mean}}$) using a 2–3 cm volume of interest in normal background liver. Changes in [68Ga]Ga-DOTA-TATE-PET/CT uptake parameters (SUV$_{\text{max}}$ and T/L) will be calculated on a per-lesion basis. A maximum of 5 lesions per organ or at least 50% of lesions per organ, whichever is greater, will be used for quantitative analysis.

Post treatment response assessments. Response will be assessed by CT imaging (RECIST V.1.1). CR, PR and SD (response) will be collapsed into a response category while PD, missing and non-evaluable cases will be deemed to be non-response. Any changes in PBMC DNA methylation will be assessed across each cycle of therapy and associations with tumour response explored using non-parametric tests. Scores from the EORTC QLQ-C30 and GI.NET 2 questionnaires will be analysed in accordance with EORTC guidelines. Kaplan-Meier and Cox regression test will be used for survival analyses.

Patient and public involvement

The design and protocol was developed with patient and public input (PPI). All patient facing materials were reviewed by PPI representatives. As part of the trial conduct PPI representatives will be part of the trial steering committee where they will provide a unique perspective on the trial conduct and reporting of endpoints.

Ethics and dissemination

This study has Clinical Trials Authorisation from the UK Competent Authority, MHRG. The Study Coordination Centre has obtained approval from the Leeds West Research Ethics Committee and Health Regulator Authority (IRAS 237279). The study has received confirmation of capacity and capability from Imperial College NHS Healthcare Trust. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. Participants’ identification data will be required for the registration process. The Study Coordination Centre will preserve the confidentiality of participants taking part in the study and is registered under the Data Protection Act. Full results will be published once recruitment is complete. The Standard Protocol Items:
Recommendations for Interventional Trials reporting guidelines were used for this study.29

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Contributors
RM: study doctor; contribution to manuscript. GC: contribution to manuscript. MM: project manager; coordination of trial set-up, contribution to protocol and manuscript. CW: project manager; coordination of trial set-up, contribution to protocol and manuscript. SRK: coinvestigator, contribution to manuscript. TB: coinvestigator; contribution to protocol, trial preparations and manuscript. EA: contribution to protocol, trial preparations and manuscript. RS: principal investigator; concept, preparation of trial, writing of protocol and manuscript. All authors read and approved the final manuscript.

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Competing interests
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Patient and public involvement
Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not applicable.

Supplemental material
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