GETNE-1408 (SUNINET)

A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated metastatic pancreatic neuroendocrine tumours (pNET) previously untreated

STATISTICAL ANALYSIS PLAN

MFAR CLINICAL RESEARCH

GETNE Grupo Español de Tumores Neuroendocrinos y Endocrinos

12th of November 2018 (version 1.1)

Written by: [redacted]

GENERAL INFORMATION

TITLE

A phase II trial to assess the activity and safety of TH-302 in combination with sunitinib in patients with well- and moderately-differentiated Metastatic Pancreatic Neuroendocrine Tumours (pNET) previously untreated.

STUDY DESIGN

A phase II, open-label, non-controlled, multicenter prospective clinical trial.

TREATMENT

Single arm of TH-302 administered at 340 mg/m2 by intravenous infusion on days 8 and 22 in combination with sunitinib given orally at doses of 37.5 mg per day continuously in 28-day cycles.

Pharmaceutical form:

- Sunitinib: hard gelatin capsules of 25 and 12.5 mg. Oral administration.
- TH-302: the dose will be adjusted according to body surface area and will be administered by intravenous infusion over 30 to 60 minutes. In the event of weight variation > 10%, the body surface area will be recalculated and the dose readjusted.

The physical and chemical properties of sunitinib and TH-302, as well as the list of excipients, are included in the Investigator's Brochure.

SPONSOR

Spanish Task Force Group For Neuroendocrine Tumours (Grupo Español de Tumores Neuroendocrinos - GETNE)

[redacted]

STUDY CHIEF INVESTIGATOR

[redacted]

MONITORING ORGANISATION (CRO)

MFAR Clinical Research

[redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Explanation
AE	Adverse events
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myeloid leukaemia
ANC	Absolute neutrophil count
AOC	Advanced ovarian cancer
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the curve
bd	twice a day
CHO	Chinese hamster ovary
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CRA	Clinical research associate (monitor)
CTCAE	Common terminology criteria for adverse events
DSBs	Double strand breaks
E-code	Enrolment code
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOC	Epithelial ovarian cancer
EU	European Union
G-CSF	Granulocyte colony-stimulating factor
GMI	Growth modulation index
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
HRD	HR deficiencies

HRR	Homologous recombination repair
IB	Investigator's brochure
ICH-GCPs	International Committee Harmonization – Good Clinical Practice
INR	International normalized ratio
MDS	Myelodysplastic syndrome
MedDRA	Medical dictionary for regulatory activities
mg	milligrams
MTD	Maximum tolerated dose
NCI	National Cancer Institute from United States of America
OC	Ovarian cancer
OS	Overall survival
PFS	Progression-free survival
PFS6m	Progression-free survival rate at 6 months
PFS	Progression-free survival rate
Pgx	Pharmacogenetics
PLD	PEGylated liposomal doxorubicin
PPE	Palmar-plantar erythrodysesthesia
PRO	Patient reported outcome
QoL	Quality of life
RECIST	Response Evaluation Criteria In Solid Tumours
RR	Response rate
SAEs	Serious adverse events
SEER	NCI Surveillance, Epidemiology and End Result Program
SmPC	Summary of product characteristic
SOC	System organ class
SOPs	Standard operational procedures
SSBs	Single strand breaks
t-AML	therapy-related acute myeloid leukaemia
TDT	Time from randomization to study of Discontinuation of Treatment or death
TEAE	Treatment-emergent adverse events

TFST Time from randomization to first subsequent therapy or death

TSST Time from randomization to second subsequent therapy or death

ULN Upper limit of normal

WBC White blood cells

1. MATERIAL AND METHODS

1.1. INTRODUCTION

1.1.1. BACKGROUND

Epidemiology

pNETs represent a heterogeneous tumour group classified according to their functional capacity and histological differentiation (1) (Annex 2). The prevalence of neuroendocrine tumours (NET) has increased in recent years at an estimated rate of 35/100,000/year, of which approximately 30% are pNET. In particular, the incidence of pNET is 0.32/100,000/year (2). Most are non-functioning tumours. Those that are functioning are identified according to the hormone secreted, and some are found outside the pancreas.

The 5-year survival rate is 80%; 60-100% for localised disease, 40% for locally advanced disease and 25% for metastatic disease (which can reach 60% in reference sites).

Therapeutic options for managing metastatic pancreatic neuroendocrine tumours (pNET)

Treatment goals in the management of pNETs are symptom control and limiting tumour growth in order to positively affect patient survival.

In the context of cytotoxic drugs, it appears that pNETs are more sensitive to chemotherapy than other NETs, including carcinoid tumours. For decades, cytotoxic therapy was the only available treatment option, with streptozotocin as the first drug to demonstrate NET activity, being approved in 1976 by the FDA (Food and Drug Administration). Its combination with fluoropyrimidines, particularly doxorubicin, further increased its activity, and it became the standard treatment for well- and moderately-differentiated tumours. These combinations achieved a pNET response rate of between 35-69%, with median overall survival of up to 26 months (3), (4). However, this goal was not always measured according to radiological assessments, but also clinical ones, so its interpretation was limited and no definite correlation was found between these data and those obtained in reviews of routine clinical practice (5). A second cytostatic agent that is key in the treatment of pNETs is temozolomide, an alkylating agent, the benefit of which appears to be correlated with MGMT enzyme deficiency. The combination of temozolomide and capecitabine studied in retrospective reviews, such as the one published in 2011 with 30 treatment-naïve patients with pNET (6), showed an objective response rate of 70%, a median progression-free survival (PFS) of 18 months and an overall 2-year survival rate of 92%.

In high-grade, poorly-differentiated tumours, the standard treatment regimen comprises the combination of platinum and etoposide, which, in retrospective reviews and prospective studies, achieves a high response rate of between 56-67%, but they are unfortunately not as durable as expected (7).

The pNET population was represented in the CLARINET phase III study, which randomised 204 patients with G1/G2 non-functioning GEP-NETs, to receive lanreotide Autogel 120 mg (N = 101) versus placebo (N = 103) (8). The first endpoint - PFS - was achieved by showing a 53% reduction in the risk of progression in favour of somatostatin analogues (HR 0.47; 95% CI 0.30-

0.73, p = 0.0002). Subgroup analysis according to the location of the primary demonstrated a PFS for pNET patients (N = 91) that had not been achieved in the arm with lanreotide Autogel and 12.1 months in the placebo arm (HR 0.58; 95% CI 0.32-1.04, p = 0.0637).

In recent years, data from two phase III studies with targeted therapy against vascular endothelial growth factor receptor (VEGFR), sunitinib, and the mammalian target of rapamycin (mTOR), everolimus, in pNET patients, has broadened the therapeutic horizon for these patients. The improved PFS demonstrated led to the approval of both drugs by the EMA and the FDA.

The PI3K/AKT/mTOR pathway is also key in tumour development, as it regulates the metabolism, growth, cell proliferation and angiogenesis, integrating multiple signalling pathways. Its activation can be responsive to VEGFR, PDGFR and insulin-like growth factor receptor (IGFR) stimulation, and it is regulated through two tumour suppressor genes (TSG) - TSC2 and PTEN. As everolimus deregulates this molecular pathway in pNET, use of the drug should be developed against these tumours. Thus, based on the phase II results published in 2008 with two cohorts of 60 patients treated with octreotide and everolimus at doses of 5 and 10 mg daily, a response rate of 27% was observed in pNET patients with a median PFS of 63 weeks (9). Based on these results, a second phase II study was developed, called RADIANT-1, targeting pNET patients who had progressed during or after chemotherapy and who received everolimus 10 mg/day, being stratified according to prior treatment with octreotide (115 patients in monotherapy and 45 patients in combination) (10). The results for both strata showed a response rate of 9.6% and 4.4%, respectively, and PFS was 9.7 vs. 16.7 months, respectively, for both arms. In a third phase III study, RADIANT-3, 410 pNET patients were randomised to receive everolimus 10 mg/day vs. placebo (11). The results of the study demonstrated significantly improved PFS with everolimus of 11.4 months versus 5.4 months (HR 0.34; p<0.0001).

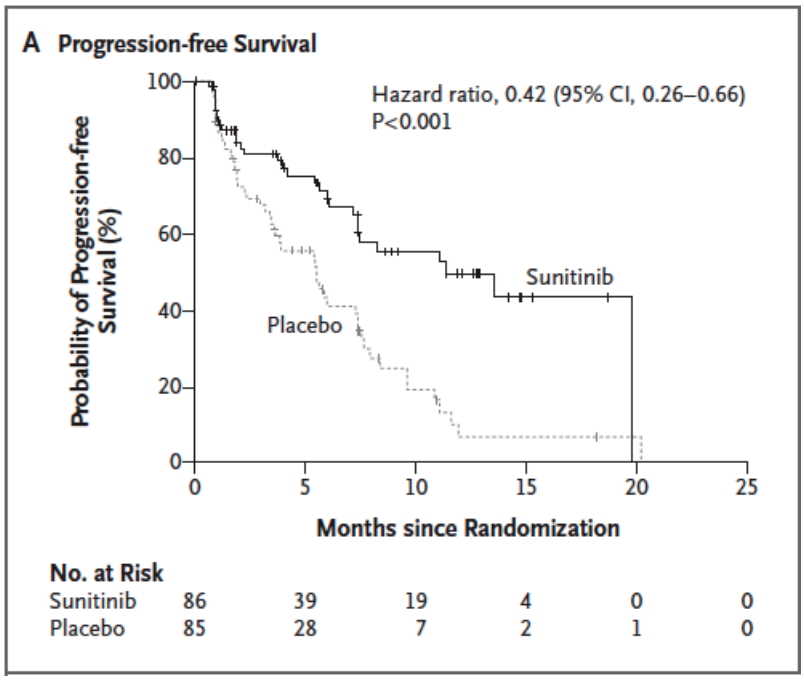
Unfortunately, patients ultimately progress and the development of new active drugs, as well as the development of predictive biomarkers of progression, is vital. The first study to analyse the sequence of therapeutic targets was the PAZONET study, the results of which were presented at ESMO 2012 (12). A total of 44 patients were enrolled who had previously received treatment with a tyrosine-kinase inhibitor (TKI) and/or mTOR inhibitor, and who were treated with pazopanib 800 mg/day allowing concomitance with somatostatin analogues. The results showed that pazopanib was active in this patient arm with a clinical benefit of 83% for those previously treated with TKI, 89% with an mTOR inhibitor and 60% with both drugs. The PFS in these three subgroups was 12.1 months, 6.8 months and 4.1 months, respectively. For the overall population it was 9.5 months.

Sunitinib in Pancreatic Neuroendocrine Tumours

In pNET, there is a high expression of VEGF and VEGFR2-3, PDGFR alpha and beta, cKIT and EGFR, and hypoxia are a key event in the regulation of tumour angiogenesis. This constitutes a strong rationale when it comes to developing anti-angiogenic drugs for these tumours. In clinical studies, the activity of sunitinib on NET was first demonstrated in a phase I study where the 3 enrolled NET patients, all of whom had been previously treated, showed reduced tumour lesions to varying degrees, being exceptional in one patient with a higher partial response (21 weeks) and two long-lasting minor responses (13). Thereafter, a multicenter, phase II study was conducted in patients with carcinoid tumours and pNET (14). Results from the 66 pNET

patients showed an objective response rate of 16.7% and a stable disease rate of 68%. The time to progression and overall survival at one year was 7.7 months and 81.1%, respectively. To definitively confirm this benefit, a phase III study versus placebo was developed, in which 171 patients of the 340 initially estimated were finally randomised against independent data monitoring (15). The benefit in terms of PFS was 11.4 months for the sunitinib arm at a dose of 37.5 mg/day versus 5.5 months for the placebo arm (HR 0.42; p<0.001). Efficacy data on patients in routine clinical practice treated with sunitinib were consistent with those obtained on selected populations in clinical trials (16).

Figure 1 PFS results of the phase III study of sunitinib vs. placebo in pNET patients.



TH-302 (Preclinical and Clinical Development in Solid Tumours)

- **Introduction**

(1-methyl-2-nitro-1H-imidazole-5-yl) methyl N, N'-bis (2-bromoethyl) diamidophosphate (also known as TH-302) is a nitroimidazole-triggered prodrug of a brominated version of isophosphoramide mustard (Br-IPM) (17). TH-302 is able to diffuse into hypoxic tissues without activation by NADP (H) quinone oxidoreductase (DT-diaphorase). It is preferentially activated under severe hypoxic conditions that are unlikely to be present in healthy tissue but in solid tumours (18).

The molecule TH-302 is activated by a process that involves a one electron reduction at the 2-nitroimidazole site of the prodrug, mediated by ubiquitous cellular reductases such as the NADPH-cytochrome P450, to generate a radical anion prodrug (RP). In the presence of oxygen (normoxia) the radical anion prodrug reacts rapidly with oxygen to generate the original prodrug and superoxide (SO). In these situations, TH-302 is relatively inert, remaining intact as a prodrug. However, under hypoxic conditions, (<0.5% O2), the radical anion prodrug can either fragment directly or undergo further reduction at the nitroimidazole site of the prodrug, causing Br-IPM to be released (Figure 2). Br-IPM can then act as a DNA alkylating agent and

form DNA crosslinks, causing damage through the presence of γH2AX. Br-IPM can diffuse through normoxic tissues and act as a cytotoxic agent in these regions. Previously, other alkylating mustards such as ifosfamide or cyclophosphamide had already demonstrated activity in many tumours.

Tumours often contain highly hypoxic regions that are known to be resistant to chemotherapy and radiotherapy. These regions develop due to the creation of irregular and aberrant blood vessels that prevent adequate oxygenation and penetration of the majority of chemotherapy treatments, which act on highly proliferating cells adjacent to the blood vessels, but not on the relatively quiescent cells found in the hypoxic regions. For this reason, they are resistant to these regimens of cytostatic drugs (19). In contrast, the prodrug TH-302 is activated in conditions of severe hypoxia, and not in the majority of normal tissues with a similar structure (20). Recent preclinical findings support the hypothesis of the induction of hypoxia within the tumour developed by anti-angiogenic drugs, which could constitute a synergistic effect with TH-302.

The molecular formula of TH-302 is C9H16Br2N5O4P and the molecular mass is 449 g/mol.

Figure 2 TH-302 activation pathway diagram

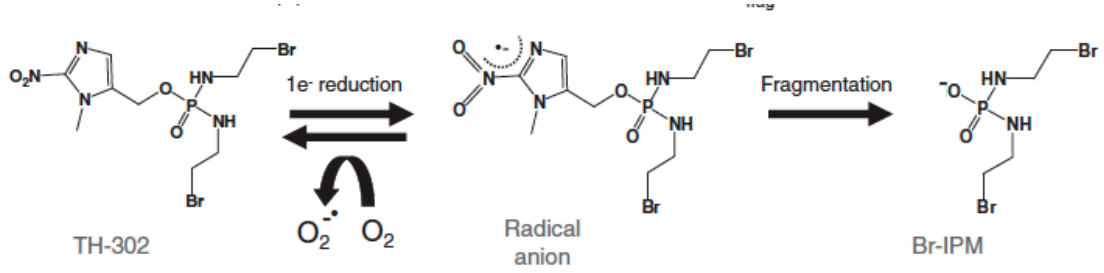


Figure obtained from Meng, F., et al. Molecular and cellular pharmacology of the hypoxia-activated prodrug TH-302. Mol Cancer Ther. 2012;11:740–51

- **Preclinical Data**

In preclinical investigations, TH-302 as monotherapy or in combination with numerous cytotoxic drugs has shown broad activity in murine models (21). In particular, TH-302 has shown consistent activity in cell lines from neural crest derived tumours such as melanoma and glioblastoma/astrocytoma (TH-302 Investigator's Brochure).

TH-302 is very active in vitro, as demonstrated in proliferation studies of H460 lung carcinoma cells (22), where TH-302 activity is related to dose-exposure and oxygen dependence, which practically achieves linearity (23). This activity is also observed in H69 small-cell lung cancer cells (SCLC), B16-F10 melanoma, SKMEL-5 melanoma, HT-29 colon cancer, HCT116 colon cancer, MES-SA uterine cancer, DX5 uterine cancer, ACHN renal cancer and PC-3 prostate cancer in anoxic conditions (CI50 from 0.1 to 10 µM) and weakly cytotoxic in the presence of air (CI50 > 80 µM). Consistent results are obtained in clonogenic models.

In vivo studies demonstrate activity both as monotherapy and in combination with other cytostatic drugs (cisplatin, paclitaxel or 5-fluorouracil) (22).

The effect of TH-302 has been studied in many murine xenograft models (H82 small-cell lung cancer, H460 and Calu-6 non-small cell lung cancer, A375 and Stew2 melanoma, 786-0 renal

cell and PLC/PRF/5, Hs766t and BxPC-3 pancreatic cancer). The cytotoxic activity of TH-302 increases in vivo in hypoxic conditions, as shown by excision methods and tumour growth models. Acute (single dose) or chronic (for 2 weeks) treatment with TH-302 demonstrates selective reduction in tumour volume of the hypoxic regions in xenograft models, with their corresponding increase in necrotic compartments (20). TH-302 achieves a significantly greater benefit in combination with chemotherapy, and even the complete eradication of some tumours, including metastatic ones (24).

With regard to the combination with anti-angiogenic drugs, the rationale starts from the knowledge of hypoxia induced by these agents that, in tumour progression, provide a more aggressive phenotype. The study of murine xenograft models in human 786-O renal cell carcinoma, melanoma A375, H460 non-small cell lung cancer and hepatocellular carcinoma PLC/PRF/5, investigated the synergistic activity of TH-302 in combination with sunitinib or sorafenib (25). Both anti-angiogenic drugs increased hypoxia detected in the tumour tissue, and were time and dose-dependent. In the 786-O renal cell model, the activity of sunitinib (40 mg/kg) increased when combined with TH-302 (50 mg/kg) in terms of tumour growth control, from 38% to 75%. In addition, no significant weight loss was identified when combining anti-angiogenic drugs with TH-302, which is an indicator of toxicity. In conclusion, the synergism reached in terms of the anti-tumour efficacy of the combination of sunitinib or sorafenib with TH-302 by selective action on hypoxic tissue induced by anti-angiogenic drugs, forms the basis for the future clinical development of this combination.

1.2. STUDY OBJECTIVES

1.2.1. PRIMARY OBJECTIVE

Objective response rate (ORR).

1.2.2. SECONDARY OBJECTIVES

Secondary endpoints are:

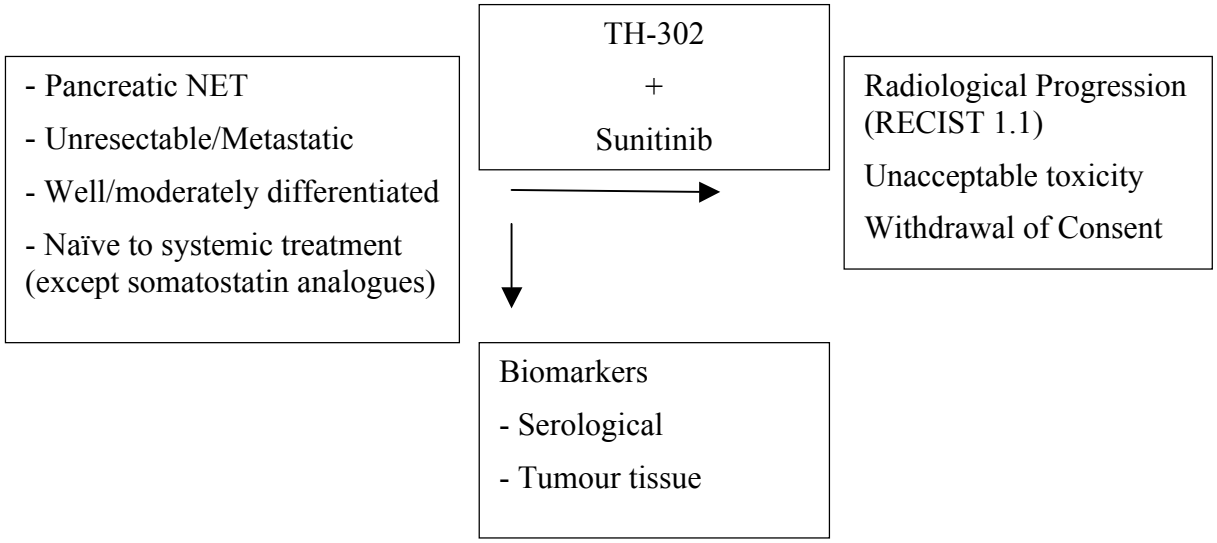
- Progression-free survival (PFS)
- Time to progression (TTP)
- Response duration (RD)
- Overall survival (OS)
- Safety
- Serological and tumour tissue biomarkers

1.2.3. SAFETY OBJECTIVE

To determine the safety of TH-302 in combination with sunitinib.

1.3. STUDY FLOWCHART

Figure 3 Trial Schema



1.4. STUDY POPULATION

1.4.1. Selection criteria

Patients with a well- or moderately-differentiated metastatic pancreatic neuroendocrine tumour (pNET) (grade 1-2 of histological differentiation and Ki67 ≤ 20%) who are naïve to systemic treatment, with the exception of somatostatin analogues, will be eligible for the trial if they meet all the inclusion criteria and none of the exclusion criteria, as described below.

1.4.1.1 Inclusion criteria

For inclusion in the study subjects should fulfil the following criteria:

1. Age ≥ 18 years capable of giving informed consent.
2. ECOG performance status (Eastern Cooperative Oncology Group) 0 or 1
3. Pancreatic neuroendocrine tumours (pNET) diagnosed histologically with a Ki67 ≤ 20% (well- or moderately-differentiated tumours).
4. Evidence of unresectable or metastatic disease. Locally advanced disease must not be amendable to surgical resection or radiation therapy with curative intent.
5. Prior systemic therapy is not permitted. Patients may be treated with somatostatin analogues prior to or during the trial. Concomitant or prior interferon (IFN) treatment is not permitted.
6. Tumour progression documented by CT scan, MRI or octreoscan within 12 months prior to the baseline visit.

7. Measurable disease by RECIST 1.1 criteria. Measurable lesions that have been previously radiated will not be considered target lesions unless increase in size has been observed following completion of radiation therapy.
8. The patient must be able to consume the medication orally.
9. Life expectancy more than 12 weeks.
10. The required laboratory values corresponding to adequate organ function and bone marrow are as follows.

    • Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN), or AST and ALT ≤ 5 x ULN if liver function abnormalities are secondary to underlying malignancy.

    • Total serum bilirubin ≤ 1.5 × ULN

    • Serum albumin ≥ 3.0 g/dl

    • Absolute neutrophil count ≥ 1500/µl.

    • Platelets ≥ 100,000/µl

    • Haemoglobin ≥ 5.6 mmol/l (9 g/dl)

    • Creatinine clearance > 40 ml/min (Cockroft and Gault Formula)
11. Suitable cardiac function:

    • 12-lead ECG with no pathological findings (non-clinically significant abnormalities are permitted)

    • Normal echocardiogram/MUGA normal (LVEF ≥ 50%)
12. Informed consent with date and signature indicating that the patient (or legal representative) has been informed of all study aspects prior to enrolment.
13. The patient must be able to comply with the required study visits, treatment, laboratory tests and other study procedures.

1.4.1.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

Patients must NOT meet any of the following exclusion criteria:

1. Previous treatments with chemotherapy, anti-VEGF monoclonal antibodies, tyrosine kinase inhibitors (TKI), mTOR inhibitors or interferon (IFN) administered for advanced disease.
2. Prior treatment with another hypoxia-activated drug under clinical trial.
3. Major surgery, radiotherapy or systemic therapy within 4 weeks prior to study enrolment, except palliative radiotherapy for non-target metastatic lesions.
4. Prior high-dose chemotherapy requiring haematopoietic stem cell rescue.
5. Immunosuppressive drugs such as cyclosporine, tacrolimus, azathioprine, or long-term corticosteroids taken concurrently or within 3 months prior to study enrolment.

6. Treatment, within 7 days prior to study enrolment, with known strong CYP3A4 inhibitors or inducers, or drugs that prolong the QT interval.
7. Prior radiation therapy to > 25% of the bone marrow.
8. Treatment within another clinical trial.
9. Uncontrolled brain metastatic disease, spinal cord compression, carcinomatous meningitis or leptomeningeal disease. Patients should have completed surgery or radiation therapy for existing brain lesions, should not have documented increase in size of said lesions over the three months prior to the first study treatment dose, and should be asymptomatic.
10. Diagnosis of any second malignancy within the last 3 years, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
11. Clinically significant cardio/cerebrovascular disease within 12 months prior to treatment initiation, including:
    - Myocardial infarction
    - Severe/unstable angina
    - Coronary/peripheral artery bypass graft
    - Congestive heart failure NYHA (New York Heart Association) Class III or IV, or patients with a history of congestive heart failure NYHA class III or IV, unless an echocardiogram or MUGA scan within 3 months prior to screening shows a left ventricular ejection fraction ≥ 45%.
    - Significant cardiac valvular heart disease.
    - Cerebrovascular accident including transient ischaemic attack.
    - Pulmonary thromboembolism.
12. Cardiac arrhythmias (NCI CTCAE version 4.0 grade ≥ 2), atrial fibrillation of any grade, or QTc interval > 450 msec for males or > 470 msec for females.
13. Hypertension that cannot be controlled despite optimal medical therapy (> 150/100 mmHg)
14. Chronic obstructive pulmonary disease (COPD) or any lung disease accompanied by hypoxaemia or oxygen saturation < 90% after a 2-minute walk.
15. Current treatment with therapeutic doses of acenocoumarol (administration of low doses of acenocoumarol up to 2 mg/24 h for deep vein thrombosis prophylaxis is permitted).
16. Known human immunodeficiency virus (HIV) infection.

17. Pregnant or breast-feeding. All female patients of childbearing age must have a negative pregnancy test (blood or urine) prior to study enrolment.
18. Prior allergic reaction to ingredients structurally similar to TH-302 or sunitinib or to any of the drugs' excipients.
19. Non-healing wound, fistulae, active stomach ulcer or bone fractures.
20. Any condition (medical or psychiatric) or reason that, in the opinion of the investigator, would interfere with the patient's ability to participate in the clinical trial, by placing the patient at excessive risk or by complicating the interpretation of the safety data, therefore being unsuitable for enrolment in the study.

1.5. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

1.5.1. DESCRIPTION OF ANALYSIS SETS

1.5.1.1 Total analysis population

All safety and efficacy analyses will be based in the total analysis population. Any patient fulfilling all the inclusion criteria and none of the exclusion criteria will be included the total analysis population.

1.5.2. EFFICACY ASSESSMENT

Objective response rate (ORR)

This will be assessed according to RECIST version 1.1 criteria, to be performed every 8 weeks, regardless of treatment delays caused by treatment toxicity.

The ORR is defined as the percentage of patients in which there is confirmation of a complete response (CR) or a partial response (PR) according to RECIST criteria, in relation to the total analysis population.

A response is confirmed for patients in whom the response persists in an imaging test repeated ≥ 4 weeks after initial documentation of response.

Progression-free survival (PFS)

This is defined as the time between the start of study treatment to the date of first objective evidence of radiological progression or patient death from any cause; whichever comes first.

Time to progression (TTP)

This is defined as the time between the start of study treatment to the date of first objective evidence of radiological progression.

Response duration (RD)

This is defined as the time between the first recorded objective response (CR or PR), which is subsequently confirmed, to the first objective evidence of radiological progression or death from any cause.

RD will only be calculated in the subgroup of patients with objective response (CR + PR).

Overall survival (OS)

This is defined as the time between the start of study treatment to the date of death from any cause.

If confirmation of death could not be obtained, survival will be censored with the date of the last visit at which time the patient was known to be alive.

Safety

See Safety Assessment section below.

Biomarkers:

They assess the correlation between radiological response and the patient's clinical course and the following expression levels:

- ENO1 (enolase 1) in plasma (it will be performed locally at the same time as chromogranin at each participating site)
- SNPs (single nucleotide polymorphisms) related to the activity and metabolism of sunitinib and TH-302 VEGFR2 (rs2305948 and rs1870377), VEGFR3 (rs307826), IL8 (rs1126647), CYP3A4 (rs35599367 and rs67666821), CYP3A5 (rs776746), ABCB1 (rs1045642, rs1128503 and rs2032582), POR (rs1057868 and c.1705_1706insG). If a polymorphism of particular relevance and related to the effectiveness of sunitinib or TH-302 appears in the literature as the study progresses, its inclusion in the study could be considered.
- Hypoxia markers related to paraffin-embedded tumour tissue (HIF1- α, CYP2W1 and c-Myc).

1.5.3. SAFETY ASSESSMENT

The safety period runs from the date of the signature of the informed consent form until 28 days after the last dose of the study drug. Safety will be evaluated according to adverse event reports, the frequency of treatment discontinuations due to adverse events, and laboratory or ECG tests. Descriptive analysis will be used.

Adverse Events

An adverse event is defined as any unwanted or unintended symptom, sign, disease or experience (including a clinically significant laboratory result of any grade according to the common terminology criteria for adverse events [CTCAE] of the National Cancer Institute, version 4.0) that emerges or worsens during the course of the study, whether related or not to the study drug.

1.5.4. DETERMINATION OF SAMPLE SIZE

It is estimated that a total of 43 eligible patients will be enrolled in the study (having received at least one dose of treatment). The design will follow Simon's two-stage design for phase II studies, with a baseline number of 18 patients. The combination of TH-302 with sunitinib will be considered as inactive in terms of the response rate if less than 5% of patients are

responders, with a response rate threshold of 20%. These figures are based on the results shown with other drugs for the treatment of pNET.

Should a response be identified in at least 3 out of every 18 patients treated, recruitment will continue up to 43 patients in order to be able to better estimate the response rate. If the study shows a response in at least 8 patients, the treatment is likely to continue its research development.

The likelihood of terminating the study after the first part with 18 patients enrolled is 0.42 if the response rate is 10%, and 0.06 if the response rate is 25%.

The likelihood of not accepting the null hypothesis and considering the combination of TH-302 with sunitinib active with a response rate less than 5% is 5% (Type I or alpha error).

The likelihood of not rejecting the null hypothesis and considering the combination of TH-302 with sunitinib inactive with a response rate greater than 5% is 20% (Type II or beta error). The statistical power of the study will be 0.80.

1.5.5. METHODS OF STATISTICAL ANALYSES

1.5.5.1 Descriptive analysis

The descriptive analysis of patient characteristics will include demographic data, disease-specific data and prior treatments. Qualitative data will be described with absolute frequencies and corresponding percentages. Quantitative data will be studied using the mean ± standard deviation, median, minimum and maximum values. The response percentages will be estimated using confidence intervals of 95%.

In the safety analysis, adverse events will be specified according to the maximum grade described at the discretion of the investigator and defined by NCI-CTCAE, version 4.0, including adverse events described from treatment initiation until 28 days following its completion.

The following safety analysis data will be presented:

- Temporary and permanent treatment discontinuations due to an adverse event.
- Deaths.
- Adverse Events (AEs) and Serious Adverse Events (SAEs).
- Hospitalisations.
- Use of concomitant medication and growth factors.

1.5.5.2 Primary Efficacy analysis

Objective response rate (ORR).

The objective response rate corresponding to the percentage of patients in which there is confirmation of a complete response (CR) or a partial response (PR) according to RECIST criteria, in relation to the total analysis population, will include a confidence interval of 95%.

1.5.5.3 Secondary Efficacy analysis

The secondary efficacy objectives of the study are:

- Progression-free survival
- Time to tumour progression
- Duration of response
- Overall survival
- Prognostic/predictive value of biomarkers analysed in peripheral blood and in paraffin-embedded tumour tissue.

The survival analyses will be performed using the Kaplan-Meier method presented with the corresponding graph, as well as by Cox regression analysis to obtain the hazard ratios and confidence intervals for the associations. For patients without documented progression or death at the time of analysis, the PFS will be censored at the last date of tumour assessment. For patients who have not died at the time of analysis, the OS will be censored.

The association between the marker expression profiles analysed in plasma and treatment response (yes/no) will be assessed using logistic regression models and univariate and multivariate Cox regression, establishing the corresponding hazard ratio and confidence interval at 95%. The predictive value (of genetic biomarkers, in plasma and tumour tissue) of each model will be estimated using an area under the ROC curve.

All statistical tests are bilateral, two-tailed tests, and all values with $p<0.05$ will be considered significant.

1.5.5.4 Safety analysis

Safety of TH-302 treatment in combination with sunitinib

Adverse events and serious adverse events, laboratory test results, physical examination findings and vital signs, and their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

1.5.6. INTERIM ANALYSES

There are no efficacy interim analyses planned on the primary endpoint because all secondary variables and safety at the end of the treatment period and during the follow-up period will be evaluated.

1.5.7. RECORDING OF DATA

An Electronic Data Capture (EDC) System will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRF as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the GCPs.

2. RESULTS

2.1. STUDY POPULATION

2.1.1. Recruited patients (centres/investigators)

Initially **XXX patients** were recruited in XXX Spanish sites. The recruited period lasted from **xxxxxx 20xx** until **xxxxxx 20xx**. The distribution of patients by centres will be shown in the following table:

Table 1. Recruited patients by site

Centre	Investigator	Patients
		N (%)
Total		xx (100.0)

Moreover **XXX** patients were screened without being finally recruited for the study.

2.1.2. Evaluable patients

Following protocol indications it was analysed which patients could be included in the analysis:

General inclusion criteria:

- Patients over 18 years with performance status ECOG 0 or 1.
- Obtaining informed consent in writing and signed.
- Pancreatic neuroendocrine tumours (pNET) diagnosed histologically with a Ki67 ≤ 20% (well- or moderately-differentiated tumours).
- Evidence of unresectable or metastatic disease. Locally advanced disease must not be amendable to surgical resection or radiation therapy with curative intent.
- Prior systemic therapy is not permitted. Patients may be treated with somatostatin analogues prior to or during the trial. Concomitant or prior interferon (IFN) treatment is not permitted.
- Adequate hematologic, hepatic, renal and cardiac function

In the following table the number of non evaluable patients along with the reason why, will be reported.

Table 2. Non evaluable patients

No.	ID patient	Hospital	Reason

The population by sites will be described in **Table 3**:

Table 3. Patients evaluable by Site

	Total
	N (%)
Hospital 1	
Hospital 2	
…	
Total	xx (100.0)

In this report, data from **xxx patients from xx** Spanish sites will be analysed. A database cut-off was made in **xxxxxx 2017** for this 1st preliminary analysis.

Table 4. Evaluable patients

	n	%[1]
Total number of recruited patients		**100,0**
Recruited		
- *Patients over 18 years with performance status ECOG 0 or 1.*		
- *Obtaining informed consent in writing and signed.*		
- *Pancreatic neuroendocrine tumours (pNET) diagnosed histologically with a Ki67 ≤ 20% (well- or moderately-differentiated tumours).*		
- *Evidence of unresectable or metastatic disease. Locally advanced disease must not be amendable to surgical resection or radiation*		

therapy with curative intent.

- *Prior systemic therapy is not permitted. Patients may be treated with somatostatin analogues prior to or during the trial. Concomitant or prior interferon (IFN) treatment is not permitted.*
- *Adequate hematologic, hepatic, renal and cardiac function*

Total number of non recruited patients

- *Exclusion criteria*

[1] Calculated percentage from the total of patients with available data

2.2. BASELINE PATIENT CHARACTERISTICS

For the descriptive analysis of the patients, the evaluable population will be used (see section 2.1).

The mean age of the women included in the study was **XXXX** years.

Table 5. Baseline patient characteristics

Sociodemographic	N	Mean (SD)	Median (Min-Max)
Age			
			N (%)
Gender	**Male**		
	Female		
Race	**White**		
	Black		
	Hispanic		
	Asian		
	Other		
Vital signs			**N (%)**
Performance status	**0**		
	1		
	N	**Mean (SD)**	**Median (Min-Max)**
Body weight			
Height			
BMI			
Body area			
Systolic Blood pressure			
Diastolic Blood pressure			
Basal comorbidity			**N (%)**
Charlson	**0**		
	1		
	2		
	≥3		
Cerebral vascular disease	**Normal**		
	Abnormal		
Peripheral arterial disease	**Normal**		
	Abnormal		
Diabetes	**Normal**		
	Abnormal		

Heart failure/ ischemic heart disease	**Normal**	
	Abnormal	
Dementia	**Normal**	
	Abnormal	
Chronic renal failure	**Normal**	
	Abnormal	
Cancer	**Normal**	
	Abnormal	
Chronic obstructive pulmonary disease	**Normal**	
	Abnormal	
Electrocardiogram (ECG)		**N (%)**
QT interval corrected	**<450 mseg**	
	450-480 mseg	
	481-500 mseg	
	>501 mseg	
	Others	
Echocardiogram /MUGA		N (%)
LVEF	**<50%**	
	≥50%	

Table 6. Baseline analytics

Haematology	**N**	**Mean (SD)**	**Median (Min-Max)**
Haemoglobin (g/dL)			
White blood cells (x10^9/L)			
Absolute neutrophil count (x10^9/L)			
Absolute Lymphocytes count (x10^9/L)			
Platelet count (x10^9/L)			
Biochemical	**N**	**Mean (SD)**	**Median (Min-Max)**
Sodium (mmol/L)			
Potassium (mmol/L)			
Calcium(mmol/L)			
Magnesium (mmol/L)			
Glucose (mmol/L)			
Creatinine (mg/dL)			
Aspartate AST (SGOT)			
Alanine transaminase ALT (SGPT)			
AST (SGOT)/ ALT (SGPT)			
Total bilirubin (mg/dL)			
Gamma-glutamyltransferase (GGT)			
Alkaline phosphatase (AP)			
Albumin (mg/dL)			
Lactate dehydrogenase [LDH]			
Blood clotting	**N**	**Mean (SD)**	**Median (Min-Max)**
Prothrombin time (PT)			
Activated Partial Thromboplastin Time (aPTT)			
Thyroid function	**N**	**Mean (SD)**	**Median (Min-Max)**
Thyroid-Stimulating Hormone (TSH)			
T4			
Tumour markers	**N**	**Mean (SD)**	**Median (Min-Max)**

Cg A
Enolase 1

2.3. TUMOR DATA AND PRIOR TREATMENTS

Baseline tumour characteristics will be reported in this section.

Table 7. Tumour characteristics

			N (%)
Histological grade	**G1 – Well differentiated**		
	G2 – Moderately differentiated		
	Unknown		
Ki-67 Index	**≤2%**		
	>2-5%		
	>5-10%		
	>10%		
Mitosis 10 CGA	**<2**		
	2-20		
Type of tumour	**Functioning**		
	Not functioning		
Histological subtype	**Gastrinoma**		
	Glucagonoma		
	Insulinoma		
	VIPoma		
	Somatostatinoma		
	Others, multisecretor or unknown		
Surgery	**Yes**		
	No		
Stage at diagnosis	**I**		
	II		
	III		
	IV		
CT relapse	**Yes**		
	No		
Relapse location	**Hepatic**		
	Extra-hepatic		
	N	**Mean (SD)**	**Median (Min-Max)**
Time between diagnosis (anatomical pathology) and treatment initiation			
Time between diagnosis (anatomical pathology) and surgery			
Time between diagnosis (anatomical pathology) and CT relapse			
Somatostanine analoguesprior the trial	**Yes**		
	No		

2.4. CONCOMITANT MEDICATION

In this section concomitant medications will be shown.

Table 8. Concomitant medication

		N (%)
Concomitant medication	**No**	
	Yes	
Concomitant medications	**Concomitant medication 1**	
	Concomitant medication 2	
	Concomitant medication 3	
	…	

2.5. TREATMENT EXPOSURE

The TH-302 dose administered will be 340 mg/m2 by intravenous infusion over 30-60 minutes, on days 8 and 22 of each cycle. The dose should be adjusted according to body surface area. In the event of patient weight variation > 10%, the body surface area will be recalculated and the TH-302 dose readjusted.

Details of TH-302 compliance will be shown in the following table:

Table 9. TH-302 compliance

	N	Mean (SD)	Median (Min-Max)
Number of TH-302 cycles			
Length of TH-302 treatment (weeks)			
			N (%)
Total number of cycles with TH-302	**1 cycle**		
	2 cycles		
	3 cycles		
	4 cycles		
	5 cycles		
	6 cycles		
	…		
Total number of TH-302 reductions	**1 reduction**		
	2 reductions		
	3 reductions		
	4 reductions		
	…		
Reason for TH-302 reductions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Total number of TH-302 delays	**1 delay**		
	2 delays		
	3 delays		
	4 delays		
	…		
Reason for TH-302 delays	**Reason 1**		
	Reason 2		

	Reason 3		
	…		
Total number of TH-302 omissions	**1 omission**		
	2 omissions		
	3 omissions		
	4 omissions		
	…		
Reason for TH-302 omissions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
	N	**Mean (SD)**	**Median (Min-Max)**
Length of TH-302 temporary interruption (weeks)			

If any patient did not receive TH-302 it will be listed below along with her details.

Table 10. List of patients that did not receive TH-302

Patient ID code	Total number of TH-302 cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle 6
	0						

Sunitinib will be administered at a dose of 37.5 mg per day (1 capsule of 25 mg and 1 capsule of 12.5 mg) orally for 28 days on an ongoing basis. It must always be taken at the same time every day (or as close as possible) and capsules must be swallowed whole.

Details of Sunitinib compliance will be shown in the following table:

Table 11. Sunitinib compliance

	N	**Mean (SD)**	**Median (Min-Max)**
Number of Sunitinib cycles			
			N (%)
Total number of cycles with Sunitinib	**1 cycle**		
	2 cycles		
	3 cycles		
	4 cycles		
	5 cycles		
	6 cycles		
Total number of Sunitinib reductions	**1 reduction**		
	2 reductions		
	3 reductions		
	4 reductions		
	5 reductions		
	6 reductions		
Reason for Sunitinib reductions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Total number of Sunitinib delays	**1 delay**		
	2 delays		

	3 delays		
	4 delays		
	5 delays		
	6 delays		
Reason for Sunitinib delays	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
Total number of Sunitinib omissions	**1 omission**		
	2 omissions		
	3 omissions		
	4 omissions		
	5 omissions		
	6 omissions		
Reason for Sunitinib omissions	**Reason 1**		
	Reason 2		
	Reason 3		
	…		
	N	**Mean (SD)**	**Median (Min-Max)**
Length of Sunitinib temporary interruption (weeks)			

If any patient did not receive Sunitinib it will be listed below along with her details.

Table 12. List of patients that did not receive Sunitinib

Patient ID code	Total number of Sunitinib cycles	Date of cycle 1	Date of cycle 2	Date of cycle 3	Date of cycle 4	Date of cycle 5	Date of cycle 6
	0						

2.5.1. Withdrawal of patients from therapy or assessment

Treatment with TH-302 in combination with sunitinib will continue until disease progression, unacceptable toxicity, non-compliance with the protocol, the patient's withdrawal of informed consent or at the discretion of the investigator. In case of withdrawal of the study medication for toxicity, the patient will continue follow-up according to the scheduled study activities, and the investigator following the patient shall be responsible for initiating another systemic treatment option if deemed appropriate.

If any patient stopped the study treatment prematurely, it will be listed below along with her details.

Table 13. Study treatment premature interruption

		N (%)
Study treatment premature interruption	**Yes**	
	No	
Reasons for study treatment premature interruption	**Reason 1**	
	Reason 2	
	Reason 3	
	…	

If any patient did not receive Sunitinib/TH-302 during any cycle, it will be listed below along with her details.

Table 14. List of patients that did not receive Sunitinib/TH-302

Patient ID code	Reason for premature interruption

Details of the end of treatment reasons will be shown in the following table.

Table 15. Reason for end of treatment

			N (%)
Reasons for end of treatment	**Progression**		
	Unaccepted toxicity		
	Details of toxicities	**Toxicity 1**	
		Toxicity 2	
		….	
	Investigator decision		
	Details of investigator decisions	**Investigator decision 1**	
		Investigator decision 1	
		…	
	Other reasons		
	Details of other reasons	**Other reasons 1**	
		Other reasons 2	
		…	

The median of the study treatment was XXX weeks:

Table 16. Study treatment length

	N	Mean (SD)	Median (Min-Max)
Length of study treatment (weeks)			

2.6. ANALYSIS SETS

All safety and efficacy analyses will be based in the total analysis population. Any patient fulfilling all the inclusion criteria and none of the exclusion criteria will be included the total analysis population.

Table 17. Analysis sets

			N (%)
Total analysis population	**Yes**		
	No		
Reason excluded		**Reason 1**	
		Reason 2	
		….	

If any patient is excluded from the total analysis population, it will be listed below along with the reasons why:

Table 18. List of patients that are excluded total analysis population

Patient ID code	Total analysis population	Reason excluded from total analysis population

2.7. EFFICACY ANALYSIS

The total analysis population will be used to present the efficacy analysis.

2.7.1. Primary efficacy analysis

Objective response rate (ORR)

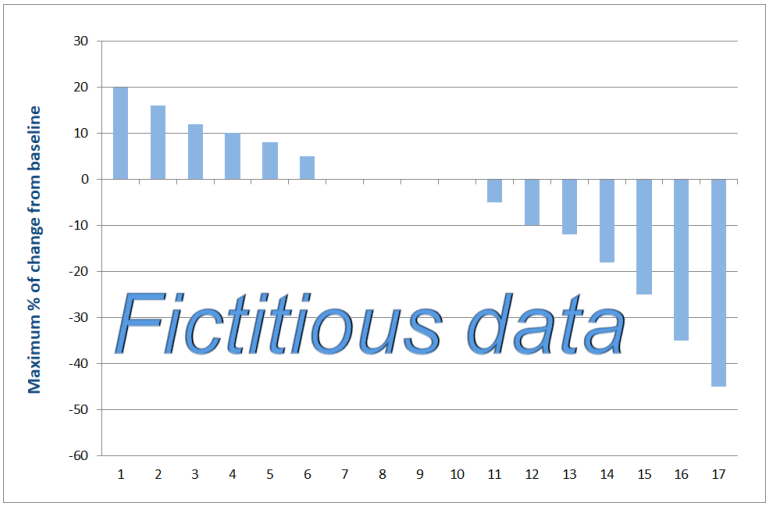
The objective response rate (ORR) will be reported with absolute and relative frequencies and using the binomial test procedure their 95% confidence interval (CI95%) will be provided. According to the protocol the ORR is defined as the percentage of patients in which there is confirmation of a complete response (CR) or a partial response (PR) according to RECIST criteria, in relation to the total analysis population.

In the total analysis population (n=XX), the objective response rate, disease control rate and CA 125 rate will be detailed below:

Table 19. Response

		N (%; IC 95%)
Response rate according to RECIST	Complete response (CR)	
	Partial response (PR)	
	Stable disease (SD)	
	Progression disease (PD)	
	Total	
Objective response rate: CR or PR according to RECIST	Yes	
	No	
	Total	
Disease–control rate: CR or PR o SD according to RECIST	Yes	
	No	
	Total	

Figure 4 Waterfall plot: Maximum % change from baseline in target tumor measurement for each patient



In those patients that responded (CR or PR according to RECIST) the "time to response" will be calculated. This is defined as the time between date of treatment initiation and the first recorded objective response (CR or PR), which is subsequently confirmed.

The median of the time to response was XXX weeks:

Table 20. Time to response

	N	Mean (SD)	Median (Min-Max)
Time to response (weeks)			

2.7.2. Secondary efficacy analysis

The progression free survival will be estimated and plotted using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals

Time to tumour progression, duration of response and overall survival will also be described using these same Kaplan-Meier methods.

Cox regression analysis will be used to obtain hazard ratios and their confidence intervals for the associations. For patients without documented progression or death at the time of analysis, the PFS will be censored at the last date of tumour assessment. For patients who have not died at the time of analysis, the OS will be censored.

The association between the marker expression profiles analysed in plasma and treatment response (yes/no) will be assessed using logistic regression models and univariate and multivariate Cox regression, establishing the corresponding hazard ratio and confidence interval at 95%. The predictive value (of genetic biomarkers, in plasma and tumour tissue) of each model will be estimated using an area under the ROC curve.

2.7.2.1 Progression Free Survival

The progression-free survival rate will be estimated and plotted using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals.

In the total analysis population (n=**XX**), at 3 months the proportion of patients that survived without PD or exitus was **XXXX** with a 95% CI **XXXX-XXXX**. The overall median of PFS was **XXX** months (95% CI **XXX-XXX**).

Table 21. Progression free survival

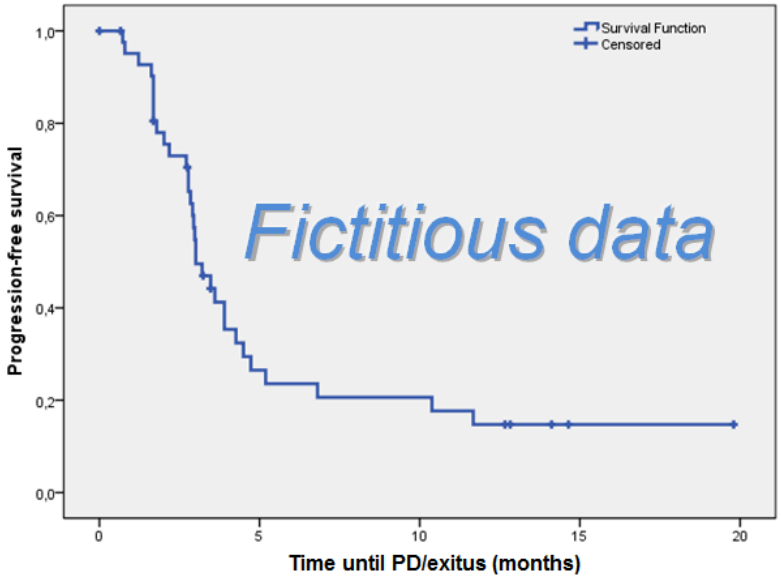
PFS	N events	Patients at risk	% estimated cumulative survival ratio[1]	95% CI	% with PD
at 3 months					
at 6 months					
at 12 months					
	N	**N (%) events**	**Median (months)**	**Standard error**	**95% CI**
Estimated PFS[1]					

1: Estimated using Kaplan-Meier product-limit method

Table 22. Progression free survival events

		N (%; IC 95%)
PFS event	**Without PD/Exitus**	
	PD	
	Exitus (without previous PD)	
	Total	

Figure 5 Kaplan Meier curve: PFS



2.7.2.2 Time to tumour progression

The time to tumour progression will be calculated in those patients with objective evidence of radiological progression. This is defined as the time between the start of study treatment to the date of first objective evidence of radiological progression.

The median of the time to tumour progression was XXX weeks:

Table 23. Time to tumour progression

	N	Mean (SD)	Median (Min-Max)
Time to tumour progression (weeks)			

2.7.2.3 Response duration

The response duration (RD) will be calculated in those patients with objective response (CR + PR). This is defined as the time between the first recorded objective response (CR or PR), which is subsequently confirmed, to the first objective evidence of radiological progression or death from any cause.

The median of the RD was XXX weeks:

Table 24. Response duration time

	N	Mean (SD)	Median (Min-Max)
Response duration time (weeks)			

2.7.2.4 Overall survival

The overall survival rate will be estimated and plotted using the Kaplan-Meier product-limit method, along with their corresponding log-log transformed 95% confidence intervals.

In the total analysis population (n=**XX**), at 3 months the proportion of patients that survived was **XXXX** with a 95% CI **XXXX-XXXX**. The overall median of OS was **XXX** months (95% CI **XXX-XXX**).

Table 25. Overall survival

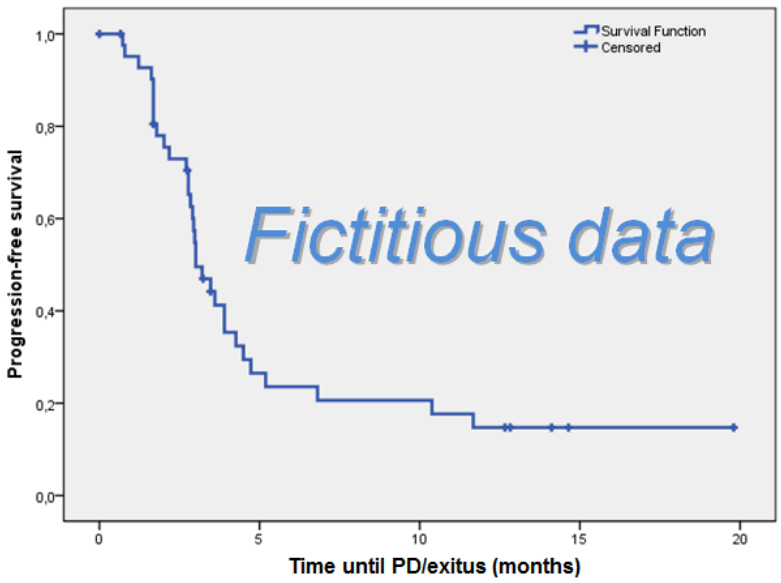
OS	N events	Patients at risk	% estimated cumulative survival ratio[1]	95% CI	% exitus
at 3 months					
at 6 months					
at 12 months					
	N	**N (%) events**	**Median (months)**	**Standard error**	**95% CI**
Estimated OS[1]					

1: Estimated using Kaplan-Meier product-limit method

Table 26. Overall survival events

		N (%; IC 95%)
OS event	**No exitus at end of follow-up**	
	Exitus	
	Total	

Figure 6 Kaplan Meier curve: OS



2.7.2.5 Biomarkers

In the total analysis population (n=**XX**), the proportion of patients with the following expression levels:

- ENO1 (enolase 1) in plasma (it will be performed locally at the same time as chromogranin at each participating site)
- SNPs (single nucleotide polymorphisms) related to the activity and metabolism of sunitinib and TH-302 VEGFR2 (rs2305948 and rs1870377), VEGFR3 (rs307826), IL8 (rs1126647), CYP3A4 (rs35599367 and rs67666821), CYP3A5 (rs776746), ABCB1 (rs1045642, rs1128503 and rs2032582), POR (rs1057868 and c.1705_1706insG). If a polymorphism of particular relevance and related to the effectiveness of sunitinib or TH-302 appears in the literature as the study progresses, its inclusion in the study could be considered.
- Hypoxia markers related to paraffin-embedded tumour tissue (HIF1- α, CYP2W1 and c-Myc).

Table 27. Biomarkers

		N (%; IC 95%)
ENO1	**Yes**	
	No	
	Total	
VEGFR2	**Yes**	
	No	
	Total	
VEGFR3	**Yes**	
	No	
	Total	
IL8	**Yes**	
	No	
	Total	
CYP3A4	**Yes**	
	No	
	Total	
ABCB1	**Yes**	
	No	
	Total	
POR	**Yes**	
	No	
	Total	
HIF1- α	**Yes**	
	No	
	Total	
CYP2W1	**Yes**	
	No	
	Total	
c-Myc	**Yes**	
	No	
	Total	

2.7.2.6 Association between ORR and Biomarkers

In the total analysis population, the association between the marker expression profiles analysed in plasma and treatment response (yes/no) will be assessed using logistic regression models (univariate and multivariate).

Table 28. Univariate logistic regression

Variables	Categories	Exp(B)	p-value	95% CI EXP(B) Inferior	95% CI EXP(B) Superior	N
ENO1	Yes					
	No					
	Total					
VEGFR2	Yes					
	No					
	Total					
VEGFR3	Yes					
	No					
	Total					
IL8	Yes					
	No					
	Total					
CYP3A4	Yes					
	No					
	Total					
ABCB1	Yes					
	No					
	Total					
POR	Yes					
	No					
	Total					
HIF1- α	Yes					
	No					
	Total					
CYP2W1	Yes					
	No					
	Total					
c-Myc	Yes					
	No					
	Total					

In the total analysis population, in the multivariate model, those variables that were found statistically significant (p<0,1), will be entered as factors in the multivariate model for treatment response (yes/no).

Table 29. Multivariate logistic regression

				95% CI EXP(B)		
Variables	**Categories**	**Exp(B)**	**p-value**	**Inferior**	**Superior**	**N**
ENO1	**Yes**					
	No					
	Total					
VEGFR2	**Yes**					
	No					
	Total					
VEGFR3	**Yes**					
	No					
	Total					
IL8	**Yes**					
	No					
	Total					
CYP3A4	**Yes**					
	No					
	Total					
ABCB1	**Yes**					
	No					
	Total					
POR	**Yes**					
	No					
	Total					
HIF1- α	**Yes**					
	No					
	Total					
CYP2W1	**Yes**					
	No					
	Total					
c-Myc	**Yes**					
	No					
	Total					

2.7.2.7 Association between PFS and Biomarkers

In the total analysis population, the association between the marker expression profiles analysed in plasma and PFS will be assessed using the Cox regression models (univariate and multivariate).

Table 30. Univariate Cox regression PFS

				95% CI HR		
Variables	**Categories**	**HR**	**p-value**	**Inferior**	**Superior**	**N**
ENO1	**Yes**					
	No					
	Total					
VEGFR2	**Yes**					
	No					
	Total					
VEGFR3	**Yes**					
	No					
	Total					
IL8	**Yes**					
	No					
	Total					
CYP3A4	**Yes**					
	No					
	Total					
ABCB1	**Yes**					
	No					
	Total					
POR	**Yes**					
	No					
	Total					
HIF1- α	**Yes**					
	No					
	Total					
CYP2W1	**Yes**					
	No					
	Total					
c-Myc	**Yes**					
	No					
	Total					

In the total analysis population, in the multivariate model, those variables that were found statistically significant (p<0,1), will be entered as factors in the multivariate model for PFS.

Table 31. Multivariate logistic regression PFS

				95% CI HR		
Variables	**Categories**	**HR**	**p-value**	**Inferior**	**Superior**	**N**
ENO1	**Yes**					
	No					
	Total					
VEGFR2	**Yes**					
	No					
	Total					
VEGFR3	**Yes**					
	No					
	Total					
IL8	**Yes**					
	No					
	Total					
CYP3A4	**Yes**					
	No					
	Total					
ABCB1	**Yes**					
	No					
	Total					
POR	**Yes**					
	No					
	Total					
HIF1- α	**Yes**					
	No					
	Total					
CYP2W1	**Yes**					
	No					
	Total					
c-Myc	**Yes**					
	No					
	Total					

2.7.2.8 Association between OS and Biomarkers

In the total analysis population, the association between the marker expression profiles analysed in plasma and OS will be assessed using the Cox regression models (univariate and multivariate).

Table 32. Univariate Cox regression OS

				95% CI HR		
Variables	**Categories**	**HR**	**p-value**	**Inferior**	**Superior**	**N**
ENO1	**Yes**					
	No					
	Total					
VEGFR2	**Yes**					
	No					
	Total					
VEGFR3	**Yes**					
	No					
	Total					
IL8	**Yes**					
	No					
	Total					
CYP3A4	**Yes**					
	No					
	Total					
ABCB1	**Yes**					
	No					
	Total					
POR	**Yes**					
	No					
	Total					
HIF1- α	**Yes**					
	No					
	Total					
CYP2W1	**Yes**					
	No					
	Total					
c-Myc	**Yes**					
	No					
	Total					

In the total analysis population, in the multivariate model, those variables that were found statistically significant (p<0,1), will be entered as factors in the multivariate model for OS.

Table 33. Multivariate logistic regression OS

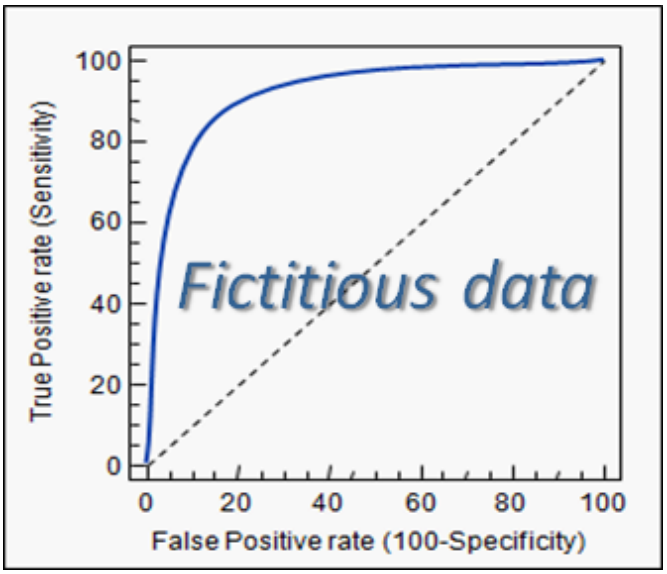
				95% CI HR		
Variables	**Categories**	**HR**	**p-value**	**Inferior**	**Superior**	**N**
ENO1	**Yes**					
	No					
	Total					
VEGFR2	**Yes**					
	No					
	Total					
VEGFR3	**Yes**					
	No					
	Total					
IL8	**Yes**					
	No					
	Total					
CYP3A4	**Yes**					
	No					
	Total					
ABCB1	**Yes**					
	No					
	Total					
POR	**Yes**					
	No					
	Total					
HIF1- α	**Yes**					
	No					
	Total					
CYP2W1	**Yes**					
	No					
	Total					
c-Myc	**Yes**					
	No					
	Total					

2.7.2.9 ROC curves: Area Under Curve, ORR vs. Biomarkers

The predictive value (of genetic biomarkers, in plasma and tumour tissue) of each model previously obtained assessing the factors (marker expression profiles analysed in plasma) of treatment response (yes/no). The accuracy will be measured by the area under the ROC curve. An area of 1 represents a perfect test and an area of 0,5 represent a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system:

- 0,90-1 = excellent (A)
- 0,80-0,90 = good (B)
- 0,70-0,80 = fair (C)
- 0,60-0,70 = poor (D)
- 0,50-0,60 = fail (F)

Figure 7 ROC curve: ORR vs. Biomarker model 1



2.8. SAFETY ANALYSIS

Adverse events and serious adverse events, laboratory test results, physical examination findings and vital signs, and their changes from baseline will be summarized using descriptive statistics. Abnormal values will be flagged.

The total analysis population will be used for the safety analysis.

Table 34. Adverse events

Adverse Events	**Grade 1 N (%)**	**Grade 2 N (%)**	**Grade 3 N (%)**	**Grade 4 N (%)**	**Total N (%)**
Hematologic					
Neutropenia					
Anaemia					
Thrombocytopenia					
Metabolic/Laboratory					
GGT (γ-Glutamyl transpeptidase)					
Alkaline phosphatase					
Lipase					
AST, SGOT (serum glutamic oxaloacetic transaminase)					
ALT, SGPT (serum glutamic pyruvic transaminase)					
Gastrointestinal					
Nausea					
Diarrhoea					
Abdominal pain					
Constipation					
Vomiting					
Heartburn/dyspepsia					
Mucositis					
Others					
Hypertension					
Fatigue (asthenia)					
Dry mouth/salivary gland (xerostomia)					
Headache					
Anorexia					
Vaginal bleeding					
Fistula					
Hypothyroidism					
Subclinical Hypotiroidism					
Neuropathy					
Hepatic toxicity					

GGT: Gamma glutamil transpeptidase; AST: Aspartate aminotransferase; ALT: Alanine transaminase.

3. CONCLUSIONS

4. ANEXES

4.1. ANEX I: DATABASE MANAGEMENT

In this section, the process of data base management and data cleaning will be described.

5. REFERENCES

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