GEIS-30

STATISTICAL ANALYSIS PLAN

No EudraCT: 2012-002745-38

VERSION: V2.1 from November 29th, 2018

GEIS
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS

TITLE: Pazopanib phase II clinical trial to evaluate activity and tolerability in patients with advanced and / or metastatic liposarcoma who have relapsed to standard therapy or in those in whom there is no standard therapy.

SPONSOR
GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS, GEIS

[redacted]

COORDINATORS OF THE STUDY

COORDINATOR INVESTIGATOR GENERAL OF THE STUDY:

[redacted]

COORDINATOR INVESTIGATOR OF THE STUDY IN GERMANY:

[redacted]

COORDINATOR OF THE TRANSLATIONAL STUDY:

[redacted]

GEIS TECHNICAL SECRETARY:

[redacted]

INDEX

1. SUMMARY

1.1. SPONSOR OF THE STUDY OF THE

GRUPO ESPAÑOL DE INVESTIGACIÓN EN SARCOMAS, GEIS

[redacted]

GEIS

[redacted]

1.2. TITLE OF THE STUDY

Pazopanib phase II clinical trial to evaluate activity and tolerability in patients with advanced and / or metastatic liposarcoma who have relapsed to standard therapy or in those in whom there is no standard therapy.

1.3. CODE OF THE PROTOCOL

GEIS-30

NºEudraCT: 2012-002745-38

1.4. COORDINATING INVESTIGATORS

1.4.1. Research General Coordinator of the study:

[redacted]

1.4.2. Coordinator of the study in Germany:

[redacted]

1.4.3. Coordinator of the Translational Study

[redacted]

1.5. ETHICAL COMMITTEE OF CLINICAL INVESTIGATION THAT HAS APPROVED THE STUDY

[redacted]

1.6. MONITOR RESPONSIBLE

[redacted]

1.7. STUDY TREATMENT

Single arm of treatment with Pazopanib 800 mg (2x400mg or 4x200 mg) administered as single agent once a day.

1.8. PHASE OF THE STUDY

Phase II study of two cohorts, open, non-randomized and multicenter with 11 participating centers in Spain and 5 in Germany. Patients will receive oral Pazopanib at a dose of 800mg once daily until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient, or decision of the investigator.

1.9. MAIN OBJECTIVE OF THE STUDY

The primary objective of this study is to evaluate the activity of Pazopanib in patients with advanced and / or metastatic liposarcoma through progression-free survival (PFS) determined at 12 weeks after the start of treatment (according to RECIST criteria 1.1 and central radiological review).

1.10. DESIGN

Phase II study of two cohorts, open, non-randomized and multicenter with 11 participating centers in Spain and 5 in Germany. To evaluate the activity and tolerability of pazopanib in patients with advanced and / or metastatic liposarcoma who have relapsed after standard treatment or for whom there is no established treatment.
The drug will be investigated separately in the following liposarcoma subtypes (cohorts):

- Well-differentiated liposarcoma / dedifferentiated liposarcoma (ALT-WD)
- Myxoid liposarcoma / round cell liposarcoma.

1.11. DISEASE IN STUDY

Advanced and / or metastatic liposarcoma.

1.12. MAIN ASSESSMENT VARIABLE

The primary efficacy endpoint for this study is progression-free survival (PFS) determined 12 weeks after the start of treatment (according to RECIST 1.1 criteria and central radiological review).

1.13. STUDY POPULATION. NUMBER. TOTAL PATIENTS

Patients with advanced or metastatic liposarcoma who have recurred after standard treatments or for whom there is no established treatment will be included.

1.13.1. Sample size

Estimation of 74 patients (Maximum of 37 patients in 2 different cohorts).

1.14. DURATION OF TREATMENT

Treatment will continue until disease progression, development of unacceptable toxicity, non-compliance, withdrawal of consent by the patient or decision of the investigator.

1.15. ESTIMATED CALENDAR OF THE STUDY

Start date: Third quarter of 2012.
First visit of the first patient (PVPP): Fourth quarter of 2012.
Total duration of the recruitment period: 30 months.
First visit of the last patient (PVUP): Second quarter of 2015.
Follow-up period: 12 months.
End of study date: March 2, 2018**.**

1.16. OBJECTIVES OF THE STUDY

1.16.1. Primary objective

The objective of this study is to evaluate the activity of Pazopanib in patients with advanced and / or metastatic liposarcoma by means of progression-free survival (PFS) determined after 12 weeks of treatment (according to the RECIST criteria v1.1 and central radiological revision).

1.16.2. Secondary objectives:

- Median progression-free survival (median PFS).
- Objective tumor response [Complete confirmed response (CR) and partial response (PR) defined by RECIST 1.1].
- Time to start of response.
- Duration of response.
- Overall survival (OS).
- Clinical benefit rate (CBR).
- Growth modulation index (GMI).
- Security profile (according to CTCAE, version 4.0).

1.16.3. Translational objectives

PRIMARY OBJECTIVES:

- To assess the influence of the tumor's angiogenic state on the response to Pazopanib.
- To assess the profile of serum cytokines as an indicator of response to Pazopanib.

SECONDARY OBJECTIVES:

- To assess the density of microvessels (DMV) and the pathways of p53, MDM2, PTEN, and VEGF / PDGF by immunohistochemistry, their correlation with prognosis, and their role as predictors of treatment with Pazopanib (response, PFS, and OS).
- Assess serum levels of various angiogenic factors / cytokines using Luminex XMAP Technology at baseline, after the first 3 weeks of treatment, at the time of maximum response and in tumor progression and its predictive value for survival and response to treatment: VEGF-A , PlGF-1, SDF-1 alpha (CXCL12), TNF alpha, IL-8, IL-6, PDGF-beta, HGF, E-Selectin, ICAM1, MMP-9 and FGFb.
- Analyze the presence of mutations in PIK3CA to demonstrate whether those liposarcomas with mutations in PIK3CA define a subgroup of patients with a different response to Pazopanib.

1.16.4. Populations

Population for efficacy.

- Analysis by Intention to Treat (**ITT**): Efficacy analyzes will be calculated on the population by intention to treat. All patients participating in the study will be included in the efficacy analysis.
- Analysis by Protocol **(PP**): Efficacy analyzes will be calculated on the per protocol population. All patients participating in the study and who have received at least 3 weeks of treatment with Pazopanib (without major protocol deviations) will be included in the efficacy analysis.

Population for security.

- Any patient included in the study who has received at least a single dose of study medication will be evaluable for toxicity analyzes.

1.17. GENERAL INCLUSION CRITERIA

A subject will be considered eligible for inclusion in this study if they meet each and every one of the following criteria:

1. Subjects must give their informed consent before performing any of the study evaluations or procedures and must be willing to comply with the treatment and established monitoring.

2. Age ≥ 18 years.

3. Histological diagnosis of liposarcoma of intermediate or high grade of malignancy with metastatic or locally advanced disease. A paraffin-fixed tumor block and / or lamellae with representative sections stained with H / E (hematoxylin / eosin) must be available for its central pathological review and classification of tumors into 2 eligible subtypes:
   - Well-differentiated liposarcoma / Undifferentiated liposarcoma (ALT- WD)
   - Myxoid liposarcoma / Round cell liposarcoma.

4. Patients must present documented disease progression within 6 months prior to the patient's entry into the study.

5. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

6. Measurable disease by RECIST criteria v1.1. There must be at least one measurable lesion located outside of a previously irradiated area. If the only measurable lesion is in a previously irradiated area, there should be documented progression after radiation therapy within 6 months prior to the patient's entry into the study.

7. The patient should not be considered a candidate for surgery or to receive radical radiotherapy. Eg Patients in whom surgery / radiotherapy cannot have a curative intention due to the extension of the disease. In the case of radiotherapy, it may be limited by previous irradiation on the same area.

8. The patient must have been considered a non-candidate for systemic chemotherapy or must have received at least one line of chemotherapy for metastatic or refractory disease. Up to a maximum of 3 previous lines are allowed for advanced / metastatic disease.
   Eg patients not candidates for chemotherapy treatment:
   - By age, concomitant pathology or negative of the patient.
   - Patients who received anthracyclines in the adjuvant setting are generally not eligible to receive this drug as the first line for advanced disease.
   - Monorenal patients or> 60 years are usually not good candidates for treatment with standard doses of ifosfamide.

9. Tumor tissue from all subjects is required for biomarker study before / during treatment with the study drug.

10. The patient must be able to swallow and retain the study medication.

11. Adequate organ and system function, as defined in Table 1.

Table 1. Definitions of adequate organic function.

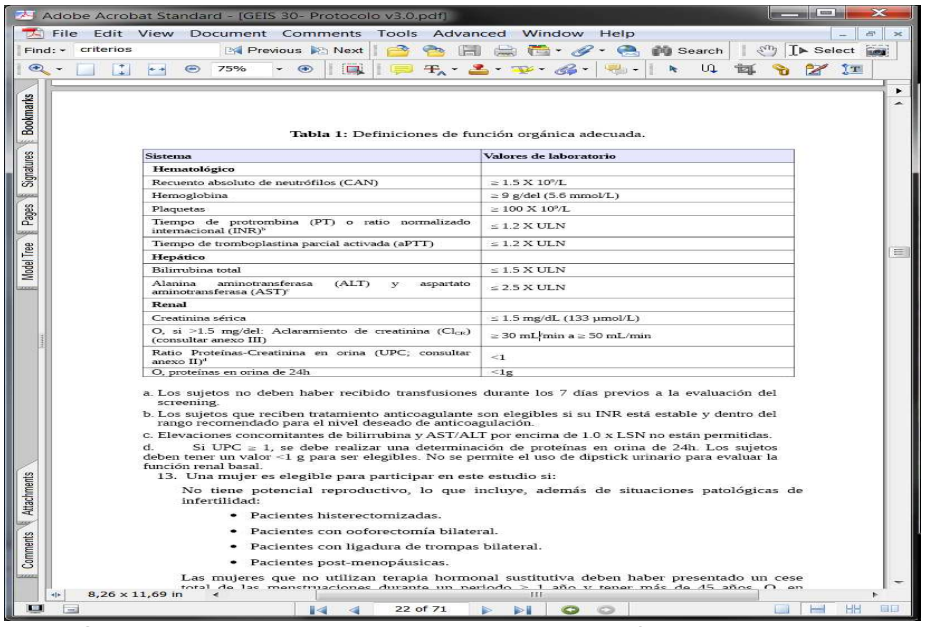

Tabla 1: Definiciones de función orgánica adecuada.

Sistema	Valores de laboratorio
Hematológico	
Recuento absoluto de neutrófilos (CAN)	≥ 1.5 X 10^9/L
Hemoglobina	≥ 9 g/del (5.6 mmol/L)
Plaquetas	≥ 100 X 10^9/L
Tiempo de protrombina (PT) o ratio normalizado internacional (INR)[b]	≤ 1.2 X ULN
Tiempo de tromboplastina parcial activada (aPTT)	≤ 1.2 X ULN
Hepático	
Bilirrubina total	≤ 1.5 X ULN
Alanina aminotransferasa (ALT) y aspartato aminotransferasa (AST)	≤ 2.5 X ULN
Renal	
Creatinina sérica	≤ 1.5 mg/dL (133 µmol/L)
O, si >1.5 mg/del: Aclaramiento de creatinina (Cl_{cr}) (consultar anexo III)	≥ 30 mL/min a ≥ 50 mL/min
Ratio Proteínas-Creatinina en orina (UPC; consultar anexo II)[c]	<1
O, proteínas en orina de 24h	<1g

a. Los sujetos no deben haber recibido transfusiones durante los 7 días previos a la evaluación del screening.
b. Los sujetos que reciben tratamiento anticoagulante son elegibles si su INR está estable y dentro del rango recomendado para el nivel deseado de anticoagulación.
c. Elevaciones concomitantes de bilirrubina y AST/ALT por encima de 1.0 x LSN no están permitidas.
d. Si UPC ≥ 1, se debe realizar una determinación de proteínas en orina de 24h. Los sujetos deben tener un valor <1 g para ser elegibles. No se permite el uso de dipstick urinario para evaluar la función renal basal.

13. Una mujer es elegible para participar en este estudio si:

    No tiene potencial reproductivo, lo que incluye, además de situaciones patológicas de infertilidad:

    - Pacientes histerectomizadas.
    - Pacientes con ooforectomía bilateral.
    - Pacientes con ligadura de trompas bilateral.
    - Pacientes post-menopáusicas.

    Las mujeres que no utilizan terapia hormonal sustitutiva deben haber presentado un cese total de las menstruaciones durante un periodo ≥ 1 año y tener más de 45 años O, en

- Subjects should not have received transfusions within 7 days prior to screening evaluation.
- Subjects receiving anticoagulant therapy are eligible if their INR is stable and within the recommended range for the desired level of anticoagulation.
- Concomitant elevations of bilirubin and AST / ALT above 1.0 x ULN are not allowed.
- If UPC ≥ 1, a 24-hour urine protein determination should be performed. Subjects must have a value <1 g to be eligible. The use of urinary dipstick is not allowed to assess basal kidney function.

12. A woman is eligible to participate in this study if: She has no reproductive potential, which includes, in addition to pathological situations of infertility:
    - Hysterectomized patients.
    - Patients with bilateral oophorectomy.
    - Patients with bilateral tubal ligation.
    - Post-menopausal patients.

Women who do not use hormone replacement therapy must have had a complete cessation of menstruation for a period ≥ 1 year and be over 45 years old, OR, in some cases, have FHS levels> 40 mIU / mL and estradiol levels < 40pg / mL (<140 pmol / L).
Women using hormone replacement therapy must have experienced a complete cessation of menstruation for a period of ≥ 1 year and be older than 45 years OR have documented evidence of menopause due to hormonal values of FSH and estradiol prior to initiation of hormonal treatment.
In the case of fertile women, those patients who have a negative result of a serum pregnancy test during the 2 weeks prior to the first dose of the study drug (preferably as close to the first dose of the drug as possible) are eligible if they agree to use appropriate contraceptive measures. The appropriate methods (when used continuously and according to the instructions of the doctor and the product) are the following:

- Complete sexual abstinence that will begin during the 14 days prior to the first exposure to the study drug, will be continued throughout treatment within the clinical trial and will continue until at least 21 days after the last dose of the drug.
- Oral contraceptives, both progestins as monotherapy and in combination with other agents.
- Injectable progesterone.

- Levonorgestrel implants.
- Vaginal ring with estrogens.
- Percutaneous contraceptive patches.
- Intrauterine device (IUD) or intrauterine system (IUS) with a documented failure rate of less than 1% per year.
- Sterilized male partner (vasectomy with documented azoospermia) prior to the entry of their partner into the study (provided they are a monogamous partner).
- Double barrier method: Male condom and cervical diaphragm / cap with vaginal spermicidal agent (foam / gel / film / cream / suppository).
- Breastfeeding women should discontinue the natural feeding of the baby before receiving the first dose of the study drug until 14 days after the last dose of treatment.

13. Left ventricular ejection fraction (LVEF) above the lower limit of normal for the institution, either by echocardiogram or MUGA.

2. EXPECTED RESULT ANALYSIS

These table summarize the expected results analysis of the clinical trial using ITT (Intent to Treat), PP (Per Protocol) populations for efficacy analysis, and those patients evaluable for toxicity for safety analyzes. This report will include complete patient follow up through the end of the estudy.

Table 2. Patients evaluable for the study according to cohort

	Cohort A	Cohort B	Total
Hospital	**N (%)**	**N (%)**	**N (%)**
Total			

2.1. BASAL CHARACTERISTICS Baseline

Characteristics will be presented for all evaluable patients, globally and according to each cohort

2.1.1. SOCIODEMOGRAPHIC CHARACTERISTICS

The proportion of men / women.

Table 3. Sex

	Cohort A	Cohort B	Total	p-value
Sex	**N (%)**	**N (%)**	**N (%)**	
Male				
Female				
Total				

1: Chi-square test

Mean age.

Table 4. Age

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Age										

1: Test Mann-Whitney U

2.1.2. VITAL SIGNS

Table 5. Vital Signs

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Height										
Weight										
BP Systolic										
BP Diastolic										
Body temperature										

1: Mann-Whitney U test

2.1.3. HAEMATOLOGICAL PROFILE

Table 6. Haematological profile

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Hemoglobin										
Platelets										
Neutrophils										
Lymphocytes										

1: Mann-Whitney U test

2.1.4. COAGULATION PROFILE

Table 7. Coagulation profile

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Prothrombin										
INR										
PTT										

1: Mann-Whitney U Test

2.1.5. BIOCHEMICAL PROFILE

Table 8. Biochemical profile

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Medi ana (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Protein										
Albumin										
BUN										
Creatinine										
Clearance										
SGOT / AST										
SGTP / ALT										
Alkaline Phosphatase										
Bilirubin										

Phosphorus									
Sodium									
Potassium									
Calcium									
Chloride									
Magnesium									
Amylase									
Lipase									
Lactate dehydrogenase									

1: Mann-Whitney U test

2.1.6. THYROID FUNCTION

Table 9. Thyroid function

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
TSH										
T4										

1: Mann-Whitney U test

2.1.7. URIANALYSIS

Table 10. Urinalysis

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Dipstick Protein	Normal				
	Abnormal				
	Not applicable				
	Total				
Microscopic analysis	Normal				
	Abnormal				
	Not applicable				
	Total				
24-Hour proteinuria	Normal				
	Abnormal				
	Not applicable				
	Total				

1: Chi-square; 2: Fisher's exact test

Table 11. Urinalysis results

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Result Dipstick Protein	Normal / No result				
	(+)				
	0.25				
	1+				
	13				
	14				
	25 mg / dl				
	negative				
	traces				
	Total				
Abnormal microscopic analysis	Normal / No result				
	Erythrocytes				
	Total				

1: Chi-square; 2: Fisher's exact test

Table 12. 24-hour proteinuria

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
24-Hour Result proteinuria										

1: Mann-Whitney U Test

2.1.8. PREGNANCY TEST

Table 13. Pregnancy test

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Pregnancy test)	Negative				
	Total				
Type of Test	Serum				
	Total				

1: Chi-square test

Table 14. Test details of pregnancy

Patient	Cohort	Sex	Age	Pregnancy test	Type of pregnancy test	Reason test not performed

2.1.9. FUNCTIONAL STATUS: ECOG

Table 15. ECOG at baseline

ECOG at baseline	Cohort A			Cohort B			Total			
	N (%)			N (%)			N (%)			p-value[1]
0										
1										
Total										
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	p-value[3]
Baseline ECOG										

1: Chi-square; 2: Fisher's exact test; 3: Test Mann-Whitney

2.1.10. TUMOR CHARACTERISTICS AND PRETREATMENT LIPOSARCOMA

2.1.10.1. Initial diagnosis

Table 16. Location of the tumor

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Location of the tumor	pelvic girdle				
	Upper Limbs				
	Lower extremities				
	Retro-peritoneum				
	Others				
	Total				

1: Chi-square; 2: Fisherexact test

Other locations:

Table 17. Other tumor locations

Patient	Cohort	Other locations

Table 18. Histological type (local review)

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Histological type	Well-differentiated Liposarcoma				
	Undifferentiated				
	Pleomorphic				
	Myxoid				
	Total				

1: Chi-square; 2: Fisher's exact test

Histological diagnosis was also analyzed centrally.

Table 19. Histological type (centralized review)

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Histological type (centralized)	Liposarcoma distinct				
	well differentiated liposarcoma / dedifferentiated				
	liposarcoma undifferentiated				
	liposarcoma myxoid				
	Total				

1: Chi -square; 2: Test Fisherexact

comparison:

Table 20. GradeFNCLCC

GradeFNCLCC	Cohort A	Cohort B	Total	
	N (%)	N (%)	N (%)	p-value[3]
1				
2				
3				
Total				

	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	p-value[3]
Degree FNCLCC										

1: Chi-square; 2: Fisher's exact test; 3: Mann-Whitney U test

Previous treatments:

Table 21. Initial treatment

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Radiotherapy for primary tumor	Yes				
	No				
	Total				
Initial treatment	Yes				
	No				
	Total				
Type of initial treatment	Radical surgery				
	Wide				
	Marginal positive resection				
	Only biopsy				
	Others				
	Total				

1: Chi-square; 2: Fisher's exact test

Other initial treatments:

Table 22. Other initial treatments

Patient	Cohort	Other types

Elapsed time between initial treatment and Pazopanib treatment:

Table 23. Time from initial treatment to start of Pazopanib (years)

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Time from initial tt to Pazopanib										

1: Mann U-test Whitney

2.1.10.2. RADIOTHERAPY

Table 24. Radiotherapy

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Radiotherapy	Yes				
	No				
	Total				

1: Chi-square; 2: Fisher's exact test

Elapsed time between initial treatment and Pazopanib treatment:

Table 25. Duration of radiotherapy (months)

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	medium (Min-Max)	N	Mean (SD)	median (min-max)	
Duration of radiotherapy (months)										

1: Test Mann-Whitney

2.1.10.2.1. RELAPSE and type of treatment

Table 26. Relapses and type of treatment

		Cohort a	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
relapse	No				
	Yes				
	Total				
Metastasis	No				
	Yes				
	Total				
Local relapse	No				
	Yes				
	Total				
Other relapse	No				
	Yes				
	Total				
radical surgery	No				
	Yes				
	Total				
wide Resection	No				
	Yes				
	Total				
Positive marginal resection	No				
	Yes				
	Total				
Only biopsy	No				

	Yes				
	Total				
Other treatments	No				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test

2.1.10.3. PREVIOUS CHEMOTHERAPY

Table 27. Previous chemotherapy

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Previous chemotherapy	No				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test

The following table will include all the chemotherapy lines prior to Pazopanib. Patients could have received more than one line of chemotherapy.

Table 28. Prior Chemotherapy:List of treatments

Prior Chemotherapy	Cohort A	Cohort B	Total
	N (%)	N (%)	N (%)
Adriamicine-Ifosfamide / 21 days			
Adriamicine			
Adriamicine / Ifosfamide / D actinomycin			
CCGM Phase I			
Cisplatin / Doxorubicin			
Dacarbazine			
Dacarbazine /Gemcitabin			
Docetaxel			
Docetaxel/ Gemcitabin			
Doxorubicin			
Epirubicin			
Eribulin			
Gemcitabin			
Gemcitabin / Taxotere			
Ifosfamide			
Mesna Ifosfamide +			
Ifosfamide / ADRIBLASTIN + G-CSF			
Ixoten			
Nilotinib			
p53-HDM2inhibitor interaction			
Tegafur			
TH-302			
Trabectedin			

Best initial response to chemotherapy:

prior chemotherapy Table 29.

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Best previous response	CR				
	PR				
	SD				
	PD				
	WITHOUT ASSESSMENT				
	Total				
Relapse in last previous chemotherapy	No				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test

Global number of cycles and duration of initial chemotherapy:

Table 30. Number of cycles and duration of previous chemotherapy

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Total number of chemotherapy cycles										
Duration of previous chemotherapy, until relapse (prior to Pazopanib) (days)										
Time from previous relapse to start with Pazopanib (days)PREVIOUS										

1: Mann-Whitney U test

2.1.11. PATHOLOGY

Table 31. Previous pathologies

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Previous pathologies	No				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test

The following table will include all pathologies prior to the start of treatment with Pazopanib. The patients could have presented more than one pathology.

Table 32. List of previous pathologies Previous

pathologies	Cohort A	Cohort B	Total
	N (%)	N (%)	N (%)

2.1.12. PHYSICAL EXAMINATION

Table 33. Physical exam

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Cardiovascular	Normal				
	Total				
Respiratory	Normal				
	Abnormal				
	Total				
CNS	Normal				
	Not performed				
	Not applicable				
	Total				
Gastrointestinal	Normal				
	Abnormal				
	Total				
Musculoskeletal	Normal				
	Abnormal				
	Not performed				
	Total				
Dermatological	Normal				
	Abnormal				
	Not performed				
	Total				

1: Chi-square; 2: Fisher's exact test

The list of patients with abnormal results on the physical examination will be presented in the following table:

Table 34. Patients with abnormal results

Patient	Cohort	Examination	Result	Specify

2.2. COMPLIANCE WITH TREATMENT VISITS

The status of completion of visits at the time of database lock:

Table 35. Completion of treatment visits

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
Baseline visit completed	**Yes**				
	Total				
Visit day 1 completed	**No**				
	Yes				
	Total				
Visit week 1 completed	**No**				
	Yes				
	Total				
Visit week 3 completed	**No**				
	Yes				
	Total				
Visit week 5 completed	**No**				
	Yes				
	Total				
Visit week 7 completed	**Yes**				
	Total				
Visit week 9 completed	**No**				
	Yes				
	Total				
Visit week 12 completed	**No**				
	Yes				
	Total				
Complete completion (from baseline to week 12)	**No**				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test

2.3. ITT and PP POPULATIONS

To determine ITT and PP populations, the definitions specified in the protocol will be followed:

- Analysis by Intention to Treat (**ITT**): Efficacy analyses will be calculated on the population by intention to treat. All patients participating in the study will be included in the efficacy analysis.
- Analysis by Protocol **(PP**): Efficacy analyzes will be calculated on the protocol population. All patients participating in the study and who have received at least 3 weeks of treatment with Pazopanib (without major protocol deviations) will be included in the efficacy analysis.

Table 36. ITT and PP Populations

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
ITT population	Yes				
	Total				
Duration tt Pazopanib (weeks)	<3 weeks				
	≥3 weeks				
	Ongoing (no end date of tt)				
	Total				
Population PP	No				
	Yes				
	Total				

1: Chi-square; 2: Test Fisherexact

Pacientes with less than 3 week of pazopanib treatment:

Table 37. Patients with duration of pazopanib <3 weeks

Study Subject ID	Cohort	PP population	Reason excluded from PP population	Tx Pazopanib duration (days)

2.4. Duration of pazopanib

Table 38. Duration of Pazopanib treatment (days)

	Cohort A		Cohort B		Total		p-value[1]
	N Mean (SD)	Median (Min-Max)	N Mean (SD)	Median (Min-Max)	N Mean (SD)	Median (Min -Max)	
Duration of treatment with Pazopanib[2]							

1: Mann-Whitney U test; *2: For a patient that the end date of treatment with Pazopanib was not available, the date of PD / Exitus was taken as the end date of treatment.*

2.5. GLOBAL FOLLOW-UP

Table 39. Global follow-up (weeks) ITT and PP

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)-	
Global follow-up ITT										
Global follow-up PP										

1: Test Mann-Whitney

2.6. EFFICACY: MAIN ENDPOINT

Following the instructions of the protocol primary efficacy endpoints in populations ITT and PP will be calculated following the criteria:
Patients who are alive and without evidence of progression at this time will be considered successes, and those who have progressed or died at this time will be considered treatment failures. Patients in whom progression is unknown or not available will also be considered failures. Diagnosis of progression should be based on measurements of tumor lesions, according to the RECIST 1.1 criteria.

2.6.1. EFFICACY BASED ON LOCAL ASSESSMENTS. ITT

The tables below will analyze the **response at 6 and 12 weeks,** based on ***local assessments*** TAC.

Table 40. Response to treatment: Local assessments at 6 and 12 weeks ITT

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks	SD				
	PD				
	Total				
Response to 12 weeks	SD				
	PD				
	Total				

1: Chi-square; 2: Test exacto de Fisher

Responses will be recoded according to **clinical benefit (CR, RP or EE)** and in the ITT population, both at 6 and 12 weeks.

Table 41. Clinical benefit, response to treatment: Local assessments at 6 and 12 weeks ITT

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				
Response at 12 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				

1: Chi-square; 2: Fisher's exact test

2.6.2. EFFICACY BASED ON LOCAL ASSESSMENTS. PP

In the PP population, both at 6 and 12 weeks.

Table 42. Response to treatment: Local assessments at 6 and 12 weeks PP

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks	SD				
	PD				
	Total				
Response to 12 weeks	SD				
	PD				
	Total				

1: Chi-square; 2: Fisher's exact test

The responses will be recoded according to the **clinical benefit (CR, RP or EE)** and in the PP population, both at 6 and 12 weeks.

Table 43. Clinical benefit, response to treatment: Local evaluations at 6 and 12 weeks PP

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				
Response at 12 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				

1: Chi-square; 2: Fisher's exact test

2.6.3. BASED ON CENTRALIZED ASSESSMENTS. ITT

The tables below will record the **response at 6 and 12 weeks,** based on ***centralized assessments*** TAC. As for the local evaluations. The centralized evaluations will be reviewed following the criteria specified in the protocol for the evaluation of the main endpoint:
"Patients who are alive and without evidence of progression at this time will be considered as successes, and those who have progressed or died at this time will be considered as treatment failures. Patients in whom it is unknown whether or not there is progression will also be considered as failures. "

In the **ITT population**, both 6 and 12 weeks.

Table 44. Response to treatment: Value. Centralized at 6 and 12 weeks ITT

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks	PD				
	SD				
	PR				
	Total				
Response at 12 weeks	PD				
	SD				
	PR				
	Total				

1: Chi-square; 2: Fisher's exact test

Responses will be recoded according to **clinical benefit (CR, RP or EE)** and in the ITT population.

Table 45. Clinical benefit, response to treatment: Value. centralized at 6 and 12 weeks ITT

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				
Response at 12 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				

1: Chi-square; 2: Fisher's exact test

2.6.4. EFFICACY BASED ON CENTRALIZED ASSESSMENTS. PP

Table 46. Response to treatment: Centralized evaluations at 6 and 12 weeks PP

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks	PD				
	SD				
	PR				
	Total				
Response at 12 weeks	PD				
	SD				
	PR				
	Total				

1: Chi-square; 2: Fisher's exact test

Responses will be recoded according to **clinical benefit (CR, RP or EE)** and in the PP population.

Table 47. Clinical benefit, response to treatment: Centralized evaluations at 6 and 12 weeks PP

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Response at 6 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				
Response at 12 weeks CLINICAL BENEFIT	Yes				
	No (PD)				
	Total				

1: Chi-square; 2: Fisher's exact test

2.7. EFFICACY: SECONDARY ENDPOINT PROGRESSION FREE SURVIVAL (PFS)

2.7.1. PFS. LOCAL ASSESSMENT. ITT

Table 48. Progression-free survival at 12 and 24 weeks according to cohorts (local assessment. ITT)

Progression-free survival		N events	N patients at risk	% Estimated cumulative survival ratio	95% CI	
at 12 weeks	Cohort A					
	Cohort B					
at 24 weeks	Cohort A					
	Cohort B					

	Strategy	N (%) events	Median (weeks)	Min-Max	Standard error	95% CI	p-value[1]
Progression-free survival	A						
	B						
	Total						

1: Log-rank test

Figure 1. Progression-free survival according to cohorts (Local assessment ITT). Kaplan-Meier curve.

Table 49. Progression during follow-up (local assessment. ITT)

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Progression-free survival	PD				
	Alive: Free of progression				
	Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 50. Types of progressions / censorship during follow-up (local assessment. ITT)

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (% , 95% CI)	
Progression-free survival	Progression-Disease progression Clinical progression				
	Alive without PD at the end of follow-up				
	Alive without PD: censored by surgery				
	Alive without PD: abandonment due to patient decision				
	Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 51. Time to PD (weeks) (Local assessment. ITT)

	Cohort A			Cohort B			Total			
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min- Max)	N	Mean (SD)	Median (Min-Max)	p-value[1]
Time to PD (weeks)										

1: Mann-Whitney U test

2.7.2. PFS. LOCAL ASSESSMENT. PP

Table 52. Progression-free survival at 12 and 24 weeks according to cohorts (local assessment. PP)

Progression-free survival		N events	N patients at risk	% Estimated cumulative survival ratio	95% CI
at 12 weeks	Cohort A				
	Cohort B				
at 24 weeks	Cohort A				
	Cohort B				

	Strategy	N (%) events	Median (weeks)	Min-Max	Standard error	95% CI	p-value[1]
Progression-free survival	A						
	B						
	Total						

1: Log-rank test

Figure 2. Progression-free survival according to cohorts (Local assessment PP). Kaplan-Meier curve.

Table 53. Progression during follow-up (local. PP)

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Progression-free survival	PD				
	Alive: Free of progression				
	Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 54. Types of progressions / censorship during follow-up (local. PP)

		Cohort A	Cohort B	Total	
		N (%, 95% CI)	N (%, 95% CI)	N (% , 95% CI)	p-value
Progression-free survival	Progression-Disease				
	progression Clinical progression				
	Alive without PD at the end of follow-up				
	Alive without PD: censored by surgery				
	Alive without PD: abandonment due to patient decision				

	Total									

1: Pearson Chi-square; 2: Fisher's exact test

Table 55. Time to PD (weeks) (Local. PP)

	Cohort A			**Cohort B**			**Total**			
	N	**Mean (SD)**	**Median (Min-Max)**	**N**	**Mean (SD)**	**Median (Min- Max)**	**N**	**Mean (SD)**	**Median (Min-Max)**	**p-value[1]**
Time to PD (weeks)										

1: Mann-Whitney U test

2.7.3 PFS. CENTRAL ASSESSMENT. ITT

To describe the event in PFS, the protocol will be followed:
"Overall progression-free survival will be calculated from the date of initiation of treatment to the first date of documented progression or date of death, whatever the cause. Live patients with no evidence of progression at the time of analysis will be censored on the date of the last follow-up. "

Table 56. Progression-free survival at 12 and 24 weeks according to cohorts (Central assessment. ITT)

Progression-free survival		**N events**	**N patients at risk**	**% Estimated cumulative survival ratio**	**95% CI**	
at 12 weeks	**Cohort A**					
	Cohort B					
at 24 weeks	**Cohort A**					
	Cohort B					

	Strategy	**N (%) events**	**Median (weeks)**	**Min-Max**	**Standard error**	**95% CI**	**p-value[1]**
Progression-free survival	**A**						
	B						
	Total						

1: Log-rank test

Figure 3. Progression-free survival according to cohorts (Central assessment ITT). Kaplan-Meier curve.

Table 57. Progression during follow-up (Central assessment. ITT)

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Progression-free survival	PD				
	Alive: Free of progression				
	Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 58. Time to PD (weeks) (Central assessment. ITT)

	Cohort A			Cohort B			Total		
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min- Max)	N	Mean (SD)	Median (Min-Max)	p-value[1]
Time to PD (weeks)										

1: Mann-Whitney U test

Table 59. Follow-up time (weeks) (Central assessment. ITT)

	Cohort A			Cohort B			Total		
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	p-value[1]
Follow-up time (weeks)										

1: Mann-WhitneyU test

2.7.4. PFS. CENTRAL ASSESSMENT. PP

Table 60. Progression-free survival at 12 and 24 weeks according to cohorts (Central assessment. PP)

Progression-free survival		N events	N patients at risk	% Estimated cumulative survival ratio	95% CI	
at 12 weeks	Cohort A					
	Cohort B					
at 24 weeks	Cohort A					
	Cohort B					

	Strategy	N (%) events	Median (weeks)	Min-Max	Standard error	95% CI	p-value[1]
Progression-free survival	A						
	B						
	Total						

1: Log-rank test

Figure 4. Progression-free survival according to cohorts (Central assessment. PP). Kaplan-Meier curve.

Table 61. Progression during follow-up (Central assessment. PP)

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Progression-free survival	PD				
	Alive: Free of progression				
	Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 62. Time to PD (weeks) (Central assessment. PP)

	Cohort A			Cohort B			Total		p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min- Max)	N	Mean (SD)	Median (Min-Max)	
Time to PD (weeks)										

1: Mann-Whitney U test

2.8. EFFICACY:ENDPOINT SECONDARY GLOBAL SURVIVAL (OS)

2.8.1. OS. ITT

Table 63. Overall survival at 12 and 24 weeks according to cohorts (ITT)

Overall survival		N events	N patients at risk	% Estimated cumulative survival ratio	95% CI
at 12 weeks	Cohort A				
	Cohort B				
at 24 weeks	Cohort A				
	Cohort B				

	Strategy	N (%) events	Median (weeks)	Min-Max	Standard error	95% CI	p-value[1]
Overall survival	A						
	B						
	Total						

1: Log-rank test

Figure 5. Overall survival according to cohorts (ITT). Kaplan-Meier curve.

Table 64. Exitus during follow-up and at 12 weeks (ITT)

		Cohort A	Cohort B	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Overall survival	Exitus				
	Live				
	Loss Follow-up				
	Total				
Reason Exitus	No				
	Disease progression				
	Kidney failure				
	Clinical deterioration				
	Post-surgical complications				
	Unknown				
	Total Overall				
survival at 12 weeks	Exitus				
	Live				
	Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 65. Time to exit (weeks) (ITT)

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	

Exit time (weeks)								

1: Mann-Whitney U test

2.8.2. OS. PP

Table 66. Overall survival at 12 and 24 weeks according to cohorts (PP)

Overall survival		N events	N patients at risk	% Estimated cumulative survival ratio	95% CI
at 12 weeks	Cohort A				
	Cohort B				
at 24 weeks	Cohort A				
	Cohort B				

	Strategy	N (%) events	Median (weeks)	Min-Max	Standard error	95% CI	p-value[1]
Overall survival	A						
	B						
	Total						

1: Log-rank test

Figure 6. Overall survival according to cohorts (PP). Kaplan-Meier curve.

Table 67. Exitus during follow-up and at 12 weeks (PP)

			Cohort A	Cohort B	Total	p-value
			N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
	Overall survival	Exitus				
		Live				
		Loss Follow-up				
		Total				
	Reason Exitus	No				
		Disease progression				
		Kidney failure				
		Clinical deterioration				
		Post-surgical complications				
		Unknown				
		Total Overall				
	survival at 12 weeks	Exitus				
		Live				
		Total				

1: Pearson Chi-square; 2: Fisher's exact test

Table 68. Time to exit (weeks) (PP)

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Exit time (weeks)										
1:					Mann-Whitney					U-test

2.9. GMI: GROWTH MODULATION INDEX

Following the definition in the protocol, the GMI will be calculated as *"the ratio between time to progression with pazopanib (TTPp) divided by time to progression with the previous line of treatment (TTPp-1)*".

The time to PD with pazopanib is presented in the section EFFICIENCY: MAIN ENDPOINT and the duration of the previous chemotherapy until relapse is presented in Table 30. Number of cycles and duration of the previous chemotherapy.

Table 69. Growth modulation index (GMI) (ITT)

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Growth modulation index (GMI)										

1: Mann-Whitney U test

Table 70. Categorized GMI (ITT)

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
GMI categorized	**<1**				
	1-1.33				
	> 1.33				
	Total				

1: Chi-square; 2: Fisher's exact test

Table 71. Growth modulation index (GMI) (PP)

	Cohort A			Cohort B			Total			p-value[1]
	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	N	Mean (SD)	Median (Min-Max)	
Growth modulation index (GMI)										

1: Mann-Whitney U test

Table 72. Categorized GMI (PP)

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
GMI categorized	**<1**				
	1-1.33				
	> 1.33				
	Total				

1: Chi-square; 2: Fisher's exact test

2.10. ECOG EVOLUTION

Table 73. ECOG evolution during treatment (ITT)

		Cohort A	Cohort B	Total	
		N (%)	N (%)	N (%)	p-value[1]
Performance Status ECOG (baseline)	0				
	1				
	Total				
Performance ECOG Status Day 1	0				
	1				
	Total				
Performance Status ECOG Week 1	0				
	1				
	2				
	Total				
Performance Status ECOG Week 3	0				
	1				
	Total				
Performance Status ECOG Week 5	0				
	1				
	2				
	Total				
Performance Status ECOG Week 7	0				
	1				
	2				
	Total				
Performance Status ECOG Week 9	0				
	1				
	2				
	Total				
Performance Status ECOG Week 12	0				
	1				
	Total				
p-value[3]	Basal vs. day 1				
	Basal vs. week 1				
	Basal vs. week 3				
	Basal vs. week 5				
	Basal vs. week 7				
	Basal vs. week 9				
	Basal vs. week 12				

1: Pearson's Chi-square; 2: Fisher's exact test; 3: Marginal homogeneity test

2.11. SAFETY: SAEs AND TOXICITIES

Following the criteria established in the protocol, "Any patient included in the study and who has received at least a single dose of study medication will be evaluable for toxicity analyzes."

AES and Toxicities Table 74. All monitoring

		CohortA	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
AE	Yes				
	Total				
toxicity (related)	No				
	Yes				
	Total				
≥3 AE grade	No				
	Yes				
	Total				
toxicity grade ≥3 (related)	No				
	Yes				
	Total				
SAE (at least one per patient)[3]	No				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test; 3: patients could present more than one SAE

Table 75. AEs and Toxicities with start date prior to treatment

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
AE	No				
	Yes				
	Total				
AE grade ≥ 3	No				
	Total				

1: Chi-square; 2: Fisher's exact test

Table 76. AEs and Toxicities during treatment

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
AE	Yes				
	Total				
Toxicity (related)	No				
	Yes				
	Total				
AE grade ≥3	No				
	Yes				
	Total				
Toxicity grade ≥3 (related)	No				
	Yes				
	Total				

1: Chi-square; 2: Fisher's exact test

Table 77. ESA and Toxicities after treatment

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
AE	No				
	Yes				
	Total				

Toxicity (related)	No				
	Yes				
	Total				
AE grade ≥3	No				
	Yes				
	Total				
Toxicity grade ≥3 (related)	No				
	Total				

1: Chi-square; 2: Fisher's exact test

Table 78. AE and Toxicities with no known date

		Cohort A	Cohort B	Total	p-value
		N (%)	N (%)	N (%)	
AE	No				
	Yes				
	Total				
Toxicity (related)	No				
	Yes				
	Total				
AE grade ≥3	No				
	Yes				
	Total				
Toxicity grade ≥3 (related)	No				
	Total				

1: Chi-square; 2: Fisher's exact test

The frequencies of all toxicities with grade ≥3 are presented below.

Table 79. Frequencies of AEs grade ≥ 3

	Cohort A	Cohort B	Total
	N (%)	N (%)	N (%)
Abscess of tumor mass - Grade 3			
ALT increased - Grade 3			
Anemia - Grade 3			
Ascites - Grade 3			
AST increased - Grade 3			
Asthenia - Grade 3			
Back pain - Grade 3			
Bilirubin increased - Grade 3			
Cardiac dysrhythmia / chest pain - Grade 3			
Diarrhea - Grade 3			
Fatigue - Grade 3			
Femur fracture - Grade 3			
Gastrointestinal bleeding - Grade 5			
General Status deterioration - Grade 5			
Ggt increased worsening - Grade 3			
Hypertension - Grade 3			
Hyporexia - Grade 3			
Muscle weakness - Grade 3			
Myocardial infarction - Grade 3			
Nausea - Grade 3			
Neutropenia - Grade 3			

Pain - Grade 3			
Toothache - Grade 3			
Vomiting - Grade 3			

The frequencies of all (related) treatment toxicities with grade ≥3.

Table 80. Frequencies of (related) toxicities grade ≥ 3

	Cohort A	Cohort B	Total
	N (%)	N (%)	N (%)
ALT increased - Grade 3			
AST increased - Grade 3			
Asthenia - Grade 3			
Bilirubin increased - Grade 3			
Diarrhea - Grade 3			
Hypertension - Grade 3			
Muscle weakness - Grade 3			
Myocardial infarction - Grade 3			
Nausea - Grade 3			
Neutropenia - Grade 3			
Vomiting - Grade 3			

All reported SAEs are listed below, by cohort.

Table 81. List of all SAEs reported

Cohort	ID	Hospital	Sex	Toxicity	. Paz o.	When the AE is presented	StartTX	dateStartAE	dateEnd date AE	Result	Continued	SAE	SAE solution

In APPENDIX II: LISTED ALL TOXICITIES RELATED

3. APPENDIX I: EFFICACY ACCORDING TO GMI

3.1. ENDPOINT MAIN ACCORDING TO GMI

In the sections presented below , the possible relationship between the main efficacy variables and the categorized GIM variables is analyzed: <1, 1-1.33 and> 3 (see Table 69. Growth modulation index (GMI) (ITT) *and* Table 71. Modulation index Growth (GMI) (PP).

3.1.1. RESPONSE LOCAL ASSESSMENTS AND ACCORDING TO GMI. ITT

The tables below show the response to treatment at 6 and 12 weeks, based on *local assessments* of the TACs based on the categorized GMI variable: <1, 1-1.33 and> 3.

Table 82. Response to treatment according to GMI: Local assessment at 6 and 12 weeks ITT

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Clinical benefit at week 6 (CR, PR or SD) local	No (PD)					
	Yes					
	Total					
Clinical benefit at week 12 (CR, PR or SD) local	No (PD)					
	Yes					
	Total					

1: Chi-square; 2: Fisher's exact test

3.1.2. RESPONSE LOCAL ASSESSMENTS AND ACCORDING TO GMI. PP

Table 83. Response to treatment according to GMI: Local evaluations at 6 and 12 weeks PP

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (% , 95% CI)	N (%, 95% CI)	
Clinical benefit at week 6 (CR, PR or SD) local	No (PE)					
	Yes					
	Total					
Clinical benefit at week 12 (CR, PR or SD) local	No (PE)					
	Yes					
	Total					

1: Chi-square; 2: Fisher's exact test

3.1.3. RESPONSE LOCAL ASSESSMENTS AND ACCORDING TO GMI. ITT. IN EACH COHORT

The tables shown below show the **response to treatment at 6 and 12 weeks,** in the **ITT population,** based on ***local assessments*** of TACs based on the categorized GMI variable: <1, 1-1.33 and> 3, separated according to each cohort.

Table 84. Response to treatment according to GMI: local assessments at 6 and 12 weeks ITT. Cohort A

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Clinical benefit at week 6 (CR, PR or SD) local	No (PD)					
	Yes					
	Total					
Clinical benefit at week 12 (CR, PR or SD) local	No (PD)					
	Yes					
	Total					

1: Chi-square; 2: Fisher's exact test

Table 85. Response to treatment according to GMI: Local assessments at 6 and 12 weeks ITT. Cohort B

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Clinical benefit at week 6 (CR, PR or SD) local	No (PD)					
	Yes					
	Total					
Clinical benefit at week 12 (CR, PR or SD) local	No (PD)					
	Yes					
	Total					

1: Chi-square; 2: Fisher's exact test

3.1.4. RESPONSE LOCAL ASSESSMENTS AND ACCORDING TO GMI. PP. IN EACH COHORT

The tables shown below show the **response to treatment at 6 and 12 weeks,** in the **PP population,** based on ***local assessments*** of TACs based on the categorized GMI variable: <1, 1-1.33 and> 3, separated according to each cohort.

Table 86. Response to treatment according to GMI: Local evaluations at 6 and 12 weeks PP. Cohort A

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Clinical benefit a week 6 (CR, PR or	No (PD)					

SD) local	**Yes**					
	Total					
Clinical benefit at week 12 (CR, PR or SD) local	**No (PD)**					
	Yes					
	Total					

1: Chi-square; 2: Fisher's exact test

Table 87. Response to treatment according to GMI: Local assessments at 6 and 12 weeks PP. Cohort B

		GMI categorized				
		<1	**1-1.33**	**> 1.33**	**Total**	**p-value**
		N (%, 95% CI)	**N (%, 95% CI)**	**N (%, 95% CI)**	**N (%, 95% CI)**	
Clinical benefit a week 6 (CR, PR or SD) local	**No (PD)**					
	Yes					
	Total					
Clinical benefit at week 12 (CR, PR or SD) local	**No (PD)**					
	Yes					
	Total					

1: Chi-square; 2: Fisher exact

3.2. SECONDARY ENDPOINT PFS ACCORDING TO GMI

3.2.1. PFS ACCORDING TO GMI. LOCAL ASSESSMENT

Figure 7. PFS according to GMI (Local Assessment. ITT). Kaplan-Meier curve.

Table 88. PFS according to GMI (Local assessment. ITT)

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
PFS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log-rank test

Figure 8. PFS according to GMI (Local Assessment. PP). Kaplan-Meier curve.

Table 89. PFS according to GMI (Local assessment. PP)

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
PFS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log-rank test

3.2.2. PFS ACCORDING TO GMI . LOCAL ASSESSMENT. IN COHORT A

Figure 9. PFS according to GMI (local assessment. ITT). Kaplan-Meier curve. Cohort A

Table 90. PFS according to GMI (local assessment. ITT) Cohort A

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
PFS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Test of Log- rank

Figure 10. PFS according to GMI (Local assessment. PP). Kaplan-Meier curve. Cohort A

Table 91. PFS according to GMI (local assessment. PP) Cohort A

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
PFS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log Test- rank

3.2.3. PFS ACCORDING TO GMI. LOCAL ASSESSMENT. IN COHORT B

Figure 11. PFS according to GMI (local assessment. ITT). Kaplan-Meier curve. Cohort B

Table 92. PFS according to GMI (local assessment. ITT) Cohort B

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
PFS	<1					
	1-1.33					
	Overall					

1: Log-rank test

Figure 12. PFS according to GMI (Local assessment. PP). Kaplan-Meier curve. Cohort B

Table 93. PFS according to GMI (local assessment. PP) Cohort B

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
PFS	<1					
	1-1.33					
	Overall					

1: Log-rank test

3.3. SECONDARY ENDPOINT OS ACCORDING TO GMI

3.3.1. OS ACCORDING TO GM.

Figure 13. OS according to GMI (ITT). Kaplan-Meier curve.

Table 94. OS according to GMI (ITT)

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
OS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log-rank test

Figure 14. OS according to GMI (PP). Kaplan-Meier curve.

Table 95. OS according to GMI (PP)

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
OS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log-rank test

3.3.2. OS ACCORDING TO GMI. IN COHORT A

Figure 15. OS according to GMI (ITT). Kaplan-Meier curve. Cohort A

Table 96. OS according to GMI (ITT) Cohort A

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
OS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log-rank test

Figure 16 OS according to GMI (PP). Kaplan-Meier curve. Cohort A

Table 97. OS according to GMI (PP) Cohort A

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
OS	<1					
	1-1.33					
	> 1.33					
	Overall					

1: Log-rank test

3.3.3. OS ACCORDING GMI. IN COHORT B

Figure 17. OS according to GMI (ITT). Kaplan-Meier curve. Cohort B

Table 98. OS according to GMI (ITT) Cohort B

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
OS	<1					
	> 1.33					
	Overall					

1: Log-rank test

Figure 18. OS according GMI (PP). Kaplan-Meier curve. Cohort B

Table 99. OS according to GMI (PP) Cohort B

	GMI	N (%) events	Median (weeks)	Standard error	95% CI	p-value[1]
OS	<1					
	> 1.33					
	Overall					

1: Log-rank

3.4. ECOG test (BASAL) ACCORDING GMI

3.4.1. ECOG BASAL ACCORDING TO GMI. ITT

The following tables analyze the possible relationship between the variables ECOG baseline and categorized GMI: <1, 1-1.33 and> 3.

Table 100. Baseline ECOG according to GMI (ITT)

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (% , 95% CI)	
Performance status	0					
	1					
	Total					

1: Chi-square; 2: Fisher exact test

3.4.2. ECOG BASAL ACCORDING TO GMI. PP

Table 101. Baseline ECOG according to GMI (PP)

		Categorized GMI				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
Performance status	0					
	1					
	Total					

1: Chi-square; 2: Fisher's exact test

3.5. GRADE FNCLCC (BASAL) ACCORDING TO GMI

3.5.1. GRADE FNCLCC BASAL ACCORDING TO GMI. ITT

The following tables analyze the possible relationship between the variables grade FNCLCC baseline and categorized GMI: <1, 1-1.33 and> 3.

Table 102. GRADE FNCLCC baseline according to GMI (ITT)

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
GRADE FNCLCC	1					
	2					*0.017*[2]
	3					
	Total					

1: Chi-square; 2: Fisher's exact test

3.5.2. GRADE FNCLCC BASAL ACCORDING TO GMI. PP

Table 103. GRADE FNCLCC baseline according to GMI (PP)

		GMI categorized				
		<1	1-1.33	> 1.33	Total	p-value
		N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	N (%, 95% CI)	
GRADE FNCLCC	1					
	2					
	3					
	Total					

1: Chi-square; 2: Fisher's exact test

4. ANNEX II: LISTING OF ALL RELATED

TOXICITIES All the related toxicities collected in the database are listed below, by cohort.

Table 104. List of all related toxicities

Cohort	ID	Hospital	Sex	Toxicity	Relative. Pazo.	When the AE is presented	StartTX	date Start	date AE End	Result	Continuous	SAE	SAE solution