Clinical trial title: "Multicenter, prospective, non-randomized, phase I-II trial to evaluate the efficacy and safety of the combination of oral quizartinib and the FLAG-IDA chemotherapy regimen in patients with relapsed/refractory acute myeloid leukemia in first relapse."

Protocol code: FLAG-QUIDA

EudraCT number: 2019-001976-12

Final report – 29/june/2026

Study drug: Quizartinib (AC220)
Study phase: I-II
Sponsor:

PETHEMA Foundation
Tax ID: G-81245706
Representative: Dr. Juan José Lahuerta
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Trial coordinator in Spain: ***Dr. Pau Montesinos Fernández***

Dr. Teresa Bernal del Castillo

Date of authorization: July 11, 2019
Completion date: December 5, 2023

This clinical trial has been conducted in accordance with the Declaration of Helsinki on ethical principles for research involving human subjects and with good clinical practice in the conduct of clinical trials with medicinal products.

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LIST OF ABBREVIATIONS

alloSTC	Allogeneic hematopoietic stem cell transplant
AML	Acute Myeloid Leukemia
CI	Confidence Interval
CREC	Clinical Research Ethics Committee
CR/CRi	Complete remission/complete remission with incomplete haematological recovery
DLT	Dose Limiting Toxicity
ECG	Electrocardiograms
ECOG	Eastern Cooperative Oncology Group
EFS	Events-free Survival
ELN22	European Leukemia Net 2022
EORTC	European Organization for Research and Treatment of Cancer
FLAG-IDA	Fludarabine, Cytarabine, and Idarubicin
FLT3-ITD	FMS-LIKE TYROSINE KINASE 3-INTERNAL TANDEM DUPLICATION
G-CSF	Granulocyte Colony Stimulating Factor
HiDAC	High Dose Cytarabine Cycle
HR	Hazard Ratio
HRQoL	Health-related Quality of Life
HIV	Human Immunodeficiency Virus
IMGW	International Myeloma Working Group
ITT	Intention-to-treat population
MTD	Maximum Tolerated Dose
MPFC	Multi-Parametric Flow Cytometry
MRD	Minimal Residual Disease

NGS	Next Generation Sequencing
OS	Overall Survival
PCR	Polymerase Chain Reaction
PFS	Progression-free Survival
PR	Partial Response
QLQ C30	Quality-of-Life Questionnaire Core 30
RP2D	Recommended Phase II Dose
RR	Relapse/Refractory
SAE	Serious Adverse Event
SGOT	Aspartate Transaminase
TKI	Tyrosine Kinase Inhibitor
VAF	Variant Allelic Frequency

1. Ethical considerations

1.1. Clinical research ethics committees

The study has been evaluated by the Clinical Research Ethics Committees (CRECs) corresponding to the participating centers or regional CRECs, with the CREC of the Ethics Committee of the Hospital Universitario Politécnico La Fé acting as the reference CEIC for the single approval decision.

1.2. Conduct of the clinical trial

The clinical trial has been conducted in accordance with current legislation, Royal Decree 223/2004 of February 6, the 2013 Declaration of Helsinki, and Good Clinical Practice Standards.

1.3. Patient information sheet and informed consent

Patients were invited to participate during the visit to assess the inclusion criteria. Participation in the trial was completely voluntary, and patients could decide whether or not to participate and change their decision and withdraw their consent at any time during the trial, without this affecting their relationship with their doctor in any way or causing any harm to their treatment.

2. Identification of the sponsor, investigators, and administrative infrastructure

2.1. Sponsor details

Name: Spanish Hematology Treatment Program Foundation (PETHEMA).

Address: C/ Santa Balbina, 2, Offices 3-4-5
28023 ARAVACA (Madrid)

Fax: +34 91 6266232

Person authorized by the developer to sign the protocol:

Name: Dr. Juan José Lahuerta

2.2. Researchers and centers

Coordinating researchers in Spain:

Name: Dr. Pau Montesinos Fernández
La Fe University and Polytechnic Hospital, Valencia
Dr. Teresa Bernal del Castillo
Asturias Central University Hospital, Asturias.

Researchers and centers participating in the study:

The list of centers participating in the clinical trial is attached in the corresponding Annex (Annex 1).

2.3. dentification CRO

Name: OPTIMAPHARM

Address: Calle Núñez de Balboa, 120, 28006, Madrid (Spain)

Phone +34 930 160 126

3. Scientific report

This clinical trial was a multicenter, prospective, non-randomized, phase I-II study to evaluate the efficacy and safety of the combination of oral quizartinib and the FLAG-IDA chemotherapy regimen in patients with R/R AML in first relapse. It was designed to include between 6 and 24 patients in the first phase and 68 patients (34 positive for the FMS-LIKE TYROSINE KINASE 3-INTERNAL TANDEM DUPLICATION [FLT3-ITD] mutation and 34 patients without this mutation) from approximately 20 centers of the PETHEMA Foundation who received the FLAG-QUIDA regimen. Those who achieved complete remission/complete remission with incomplete hematologic recovery (CR/CRi) received an allogeneic hematopoietic stem cell transplant (alloSCT) followed by up to 3 optional cycles of consolidation with high-dose cytarabine (HiDAC). All patients in CR/CRi received maintenance therapy.

3.1. Rationale for the study

Most patients diagnosed with AML will show refractoriness or relapse after first-line treatment. The prognosis for patients with AML who relapse or are refractory after induction therapy is poor, and there is no established standard rescue therapy to achieve a new complete remission (CR). The ideal pre-relapse therapy should achieve the highest possible CR rate prior to alloSCT, which is considered the best opportunity to cure these patients. The combination of fludarabine, cytarabine, and idarubicin (FLAG-IDA) is considered one of the most active therapies in this context, with a second CR/CRi rate of 51% in patients with primary refractory disease or first relapse (data published by the PETHEMA Foundation from 259 patients in the Spanish epidemiological registry). The FLAG-IDA regimen appears to be relatively safe, with 10% mortality due to toxicity (mainly due to infections), and is one of the preferred regimens for rescue treatment in patients with AML in good physical condition.

There is considerable interest in the role of quizartinib monotherapy in patients with the FLT3-ITD mutation, which induces approximately 45-50% CR/CRi (mostly CRi) in patients with

refractory AML who have received previous intensive treatments. The Quantum-R trial analyzed the results of AC220 monotherapy versus a standard salvage regimen chosen by the investigator (including MEC, FLAG-IDA, and LoDOAC. AC220 monotherapy was associated with a higher CR/CRi rate, lower toxicity, and superior overall survival (OS) in patients with relapsed FLT3-ITD AML, who are a very difficult population to treat. However, the OS benefit was not remarkable (20-week) in the control group versus 27 weeks in the quizartinib monotherapy group), and the improvement in DFS (which involves the duration of remission) was not even statistically significant. In fact, survival outcomes depended not only on the CR/CRi rate and tolerability achieved after treatment with AC220 versus standard rescue regimen groups, but also on the quality of response, allo-HSCT rate, and medium- and long-term outcomes of allo-HSCT for patients who achieved CR/CRi. Although it was assumed that the CR/CRi rate achieved with AC220 monotherapy might be surprisingly high for a single tyrosine kinase inhibitor (TKI) regimen, it was also recognized that this predicted CR/CRi rate of 40-50% was not exceptional compared to classic chemotherapy regimens such as FLAG-IDA. For this reason, at the time of the FLAG-QUIDA trial design, it was considered that a clinical trial exploring the safety and efficacy of AC220 in combination with a well-known, "optimal" chemotherapy regimen, such as FLAG-IDA, would provide valuable information and the possibility of establishing a new chemotherapy regimen with outstanding CR/mCRi results. An improved rescue regimen would allow for more allo-HSCTs to be performed once CR/CRi has been achieved in this population (and ideally with lower minimal residual disease (MRD)). However, the potentially greater antileukemic efficacy of this new combination (FLAG-QUIDA) had to be accompanied by an acceptable increase in toxicity that would allow for a higher allo-HSCT rate (with CR/CRi or not) after rescue therapy.

It is worth mentioning that there is considerable evidence supporting the potential use of this drug in AML patients who do not carry the FLT3-ITD mutation. *FLT3* expression is closely related to leukemic blasts, providing a survival advantage, perhaps independently of the presence of an activating mutation such as ITD or TKD. Therefore, a potent type II FLT3 inhibitor could play a role as an adjuvant therapy to eradicate AML blasts in conjunction with classic chemotherapeutic agents, even in patients without the FLT3-ITD mutation. In fact, previous phase II studies, although conducted in a relatively small number of patients, showed an CR/CRi rate of up to 30% with quizartinib monotherapy in patients with R/R AML without the FLT3-ITD mutation. Since oral monotherapy did not achieve similar results in this challenging patient group, it was necessary to develop new strategies using this innovative treatment for those without FLT3-ITD mutations. Likewise, at the time of designing this trial, the hypothesis was considered that a FLAG-QUIDA regimen could offer advantages in patients with R/R AML who

do not carry the FLT3-ITD mutation. A phase I/II study could provide valuable information on the efficacy and safety of a new regimen, FLAG-QUIDA, in patients with R/R AML (both carriers and non-carriers of the FLT3-ITD mutation). This is why this phase II trial was designed, which would allow for a future confirmatory randomized phase III trial if the FLAG-QUIDA regimen resulted in outstanding CR/CRi rates. This study could be the first comprehensive step toward a pivotal trial for the first-line indication of quizartinib in FLT3-ITD AML.

3.2. Clinical trial objectives

3.2.1. Primary objective

The primary objective of the first phase of this trial was to determine the recommended phase II dose (RP2D). The primary objective of the second phase was to evaluate the CR/CRi rate after one cycle of FLAG-QUIDA.

3.2.2. Secondary objectives

The secondary objectives were:

- To evaluate the efficacy of treatment in terms of overall response rate, according to IMWG criteria, including different response categories and negative MRD rate.
- To compare the CR/CRi rate achieved in the phase II cohort with a matched historical control (among more than 460 patients treated with FLAG-IDA in the PETHEMA Foundation registry).
- To evaluate OS at 1 and 2 years.
- Evaluate the safety and tolerability of the program.
- Evaluate progression-free survival (PFS) (time to events, death in CR or relapse, whichever occurs first), event-free survival (EFS) (resistance, death in CR or relapse, whichever occurs first), iCR, and non-relapse mortality.
- Evaluate long-term follow-up (i.e., 3 years).
- Evaluate the negative EMR rate prior to allo-STC.
- Evaluate the feasibility of a maintenance program in the context of allo-STC and without allo-STC.
- Subanalyze different populations (FLT3-ITD, secondary AML, NPM1, IDH-positive, and by relapse type).
- Evaluate the impact of potential baseline factors for response (e.g., FLT3 mutations, FLT3 overexpression, KIT mutations, or other signaling pathways).

- Assess early mortality (30 and 60 days).
- Assess overall hematologic and non-hematologic toxicity.
- Assess the impact on the use of medical resources during the induction phase (i.e., antibiotics, transfusions, length of hospitalization, need for central venous access).
- Evaluate post-remission programs to which patients are assigned, including the rate of allogeneic stem cell transplantation, allogeneic stem cell transplantation in CR/CRi, or subsequent rescue therapies.
- Biological procedures to obtain information on the mechanism of action of quizartinib in patients with R/R AML.
- Evaluate clinical benefits, safety, tolerability, and health-related quality of life (HRQoL).
- Mean trajectories and changes over time in the following HRQoL parameters: fatigue, physical function, social function, and role function from the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire-Core 30 (QLQ C30).
- Safety parameters, including changes in clinical laboratory measures (clinical chemistry, hematology, coagulation, urinalysis), vital signs, electrocardiograms (ECG), incidence and severity of adverse events (AEs), and incidence of serious adverse events (SAEs) and deaths.

3.3. Inclusion and exclusion criteria

Inclusion criteria

Patients had to meet all of the following inclusion criteria to participate in this study:

1. Written informed consent in accordance with national, local, and institutional guidelines. The patient had to give informed consent before the first screening procedure. The informed consent form had to be signed by the patient and the investigator.

2. Patients aged ≥ 18 years and ≤ 70 years at the time of screening.

3. First R/R AML defined as:

• First relapse after intensive first-line chemotherapy (with or without prior allogeneic stem cell transplantation), regardless of the duration of the first CR. Patients previously treated with an FLT3 inhibitor other than quizartinib may be included.

• First refractory disease (defined as patients who did not achieve at least a partial response (PR) after the first induction cycle and/or did not achieve CR/CRi after the first two cycles). Patients previously treated with an FLT3 inhibitor other than quizartinib may be included.

4. AML without a diagnosis of acute promyelocytic leukemia.

5. Patient eligible for an intensive approach at the investigator's discretion.

6. ECOG 0-2.

7. No contraindications for quizartinib.

8. No contraindications for intensive chemotherapy.

9. No severe abnormalities in organ function.

10. No relevant active graft-versus-host disease.

11. For phase II, patients with FLT3-ITD accounted for 50% of the study cohort (FLT3-TKD were not excluded but included in the FLT3-ITD-WT group).

12. Female patients of childbearing potential had to test negative for pregnancy at screening and agree to use reliable contraception at the time of enrollment, during the treatment period, and for 6 months after the last dose of the investigational drug or cytarabine, whichever occurred last.

13. Male patients were required to use reliable contraception (if sexually active with a woman of childbearing potential) at the time of recruitment, during the treatment period, and for 6 months after the last dose of the investigational drug or cytarabine, whichever occurred last.

Exclusion criteria

Patients who met any of the following exclusion criteria were not included in the clinical trial:

1. Patients with a genetic diagnosis of acute promyelocytic leukemia.

2. Blastic phase of chronic myeloid leukemia bcr/abl.

3. Patients with another neoplastic disease, for whom the investigator suspected active disease at the time of recruitment. Note: Patients with early-stage squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or adequately treated cervical intraepithelial neoplasia were considered eligible for this study. Hormonal or adjuvant therapies for breast or prostate cancer were permitted if a stable dose had been administered for at least 2 weeks prior to the first dose.

4. Presence of any serious psychiatric illness or physical condition/comorbidity that, in the physician's judgment, contraindicated the patient's inclusion in the clinical trial.

5. Serum creatinine ≥ 250 µmol/L (≥ 2.5 mg/dL) (unless attributable to AML activity).

6. Bilirubin, alkaline phosphatase, or aspartate transaminase (SGOT) >3 times the upper normal limit (unless attributable to AML activity).

7. Uncontrolled or significant cardiovascular disease, including any of the following:

− Symptomatic bradycardia of less than 50 beats per minute, unless the subject had a pacemaker.

− QTcF >450 ms at screening. Note: QTcF will be obtained from the mean of three readings.

− Diagnosis or suspicion of long QT syndrome (including family history of long QT syndrome).

− History of clinically relevant ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation, or torsades de pointes).

− History of second-degree (Mobitz II) or third-degree heart block (subjects with pacemakers were eligible if they had no history of syncope or clinically relevant arrhythmias while using the pacemaker).

− History of uncontrolled angina pectoris or myocardial infarction within 6 months prior to selection.

− History of New York Heart Association class 3 or 4 heart failure.

− Complete left bundle branch block.

− Right bundle branch block and left anterior hemiblock (bifascicular block).

− Systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg.

− Previously known left ventricular ejection fraction < 45%.

8. Uncontrolled (i.e., clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals in the week prior to the first dose; however, prophylactic use of these agents, even if parenteral, was acceptable.

9. Active hepatitis B or hepatitis C infection.

10. Previously known and documented human immunodeficiency virus (HIV) infection (HIV testing is not required as part of this study).

11. Active acute or chronic graft-versus-host disease requiring prednisone >10 mg or an equivalent corticosteroid per day.

12. Any patient with known significant impairment of gastrointestinal function or gastrointestinal disease that could significantly alter the absorption of quizartinib.

13. History of hypersensitivity to any excipient in quizartinib tablets.

14. Pregnant or lactating women.

15. Isolated extramedullary R/R AML.

16. Only applicable to patients selected after the first cohort of 34 patients in phase II had been reached (e.g., FLT3-ITD negative): patients must have had confirmation of FLT3-ITD status at relapse, and this must correspond to the unmet cohort (e.g., FLT3-ITD positive).

3.4. Relevant amendments

Amendment No. 1 of March 3, 2020

The study sponsor is preparing this Significant Amendment No. 1 in order to modify the Patient Information and Informed Consent Form dated October 14, 2019, as well as the second version of the protocol dated February 27, 2020. The sponsor requests that Dr. Juan Martínez López be replaced by Dr. Pilar Martíney Sánchez as the principal investigator at the 12 de Octubre University Hospital. The following centers are also included in the study with their corresponding principal investigators:

-Dr. Negrín University Hospital Complex of Gran Canaria: Dr. Carlos Rodríguez Medina.

-University Hospital of Jerez de la Frontera: Dr. Eusebio Martín Chacón.

-Insular-Materno Infantil University Hospital Complex: Dr. Laura Torres Miñana.

-Virgen de la Victoria University Hospital: Dr. Alfonso Fernández Fernández.

-Catalan Institute of Oncology-Germans Trias i Pujol Hospital: Dr. Susana Vives Polo.

- Catalan Institute of Oncology-Duran i Reynals Hospital: Dr. Montserrat Arnan Sangerman.

-Puerta del Mar University Hospital: Dr. Inmaculada Marchante Cepillo.

All these changes are reflected in version 2.1 of the protocol, dated March 17, 2022.

3.5. Trial characteristics

This clinical trial was a **multicenter**, **prospective**, **non-randomized**, **phase I-II study** to evaluate **the efficacy and safety** of the **combination of oral quizartinib and the FLAG-IDA chemotherapy regimen** in patients with **R/R AML in first relapse**. It was designed to include between 6 and 24 patients in the first phase and 68 patients (34 FLT3-ITD mutation-positive and 34 patients without this mutation) from approximately 20 centers of the PETHEMA Foundation.

A **first phase (phase I-dose escalation)** was conducted with 40 mg x 14 days of quizartinib in the **first three patients**, and it was planned that, if no dose-limiting toxicity (DLT) was observed in this cohort, the next cohort of patients would receive 60 mg x 14 days. The possibility of dose reduction cohorts to 60 mg x 7 days and 40 mg x 7 days was also considered.

Patients participating in phase I received the assigned dose level and, therefore, should not have received potent CYP3A4 inhibitors concomitantly with quizartinib.

Phase II included **68 patients** treated with the RP2D (34 FLT3-ITD-positive patients and 34 patients without the FLT3-ITD mutation). A **one-year maintenance schedule** was implemented, starting at 30 mg and increasing to 60 mg/day on day 15 if the mean QTcF interval from triplicate ECGs was ≤ 450 ms continuously. Twelve 4-week cycles were recommended after completion of chemotherapy or allogeneic stem cell transplantation. Appropriate dose adjustment was required at each dose level in the event of concomitant CYP3A4 inhibition.

Molecular diagnosis and monitoring of MRD was performed through the centralized platform of the PETHEMA Foundation (central laboratory with harmonized tests). The molecular profile of each patient at the time of diagnosis was performed by next-generation sequencing (NGS), and MRE was evaluated by standardized multiparametric flow cytometry in bone marrow samples.

Patients were **followed** up for **a minimum of 1 year** from the first visit of the last patient included.

Treatment regimen

Phase I (dose escalation):

Patients participating in phase I received the assigned dose level and, therefore, should not have received potent CYP3A4 inhibitors while taking quizartinib during the DLT observation period. If started earlier, the potent CYP3A4 inhibitor had to be discontinued at least 24 hours before starting treatment with quizartinib. Following DLT assessment, if the patient required a CYP3A4 inhibitor, the appropriate dose adjustment was made, as in phase II of the trial.

The maximum tolerated dose (MTD) was defined as the highest dose of quizartinib associated with the occurrence of a DLT in less than 33% of subjects in a cohort and was estimated to be the dose level at which ≤1 in 6 subjects experienced a DLT and below the lowest dose level at which ≥2 in 6 subjects experienced a DLT.

DLT was assessed during induction treatment and was defined as any grade 4 related extrahematologic toxicity or grade 4 neutropenia with a duration of ≥57 days unrelated to leukemia (for more information, see section 5.3.1.3 of the protocol).

Level 1: FLAG-IDA: fludarabine, 30 mg/m^{2}intravenously on days 1 to 4, cytarabine 2 g/m^{2}intravenously on days 1 to 4 (1 g/m^{2}in patients over 59 years of age), idarubicin 10 mg/m^2 intravenously on days 1 to 3, and non-pegylated G-CSF at a daily dose of 300 mcg/m^{2}from day -1 to day 5) plus quizartinib (AC220) 40 mg/d from day 5 for 14 days for the first 3 patients.

If no DLT was observed in the first three patients, the next cohort would be increased to AC220 60 mg x 14 days (level 2).

If 1 DLT was observed among 3 patients, the other 3 patients would receive 40 mg x 14 days (level 1); if ≥2 DLTs were observed, the medication for the next cohort would be reduced to 60 mg x 7 days (level -1). There was also the possibility of reducing the medication to 40 mg x 7 days (level -2) depending on the DLT observed.

Level 2: FLAG-IDA: fludarabine, 30mg/m²intravenously on days 1 to 4, cytarabine 2 g/m²intravenously on days 1 to 4 (1 g/m² in patients over 59 years of age), idarubicin 10 mg/m² intravenously on days 1 to 3, and non-pegylated G-CSF at a daily dose intravenously on days 1 to 3, and non-pegylated G-CSF at a daily dose of 300 mcg/m² from day -1 to day 5) plus quizartinib (AC220) 60 mg/d from day 5 for 14 days.

Level -1: FLAG-IDA: fludarabine, 30 mg/m² intravenously on days 1 to 4, cytarabine 2 g/m²intravenously on days 1 to 4 (1 g/m²in patients over 59 years of age), idarubicin 10 mg/m² intravenously on days 1 to 3, and non-pegylated G-CSF at a daily dose of 300 mcg/m², from day -1 to day 5) plus quizartinib (AC220) 60 mg/day, from day 5 for 7 days.

Level -2: FLAG-IDA: fludarabine, 30mg/m² intravenously on days 1 to 4, cytarabine 2 g/m²intravenously on days 1 to 4 (1 g/m²in patients over 59 years of age), idarubicin 10 mg/m²intravenously on days 1 to 3, and non-pegylated G-CSF at a daily dose of 300 mcg/m²from day -1 to day 5) plus quizartinib (AC220) 40 mg/d from day 5 for 7 days.

It was planned **to include between 6 and 24 patients in phase I** of the trial, as follows (Figure 1):

The 40 mg x 14 days dose of level 1 would be administered in a first cohort of 3 patients:

- If no DLT was observed in any of the first 3 patients, the next cohort would proceed to level 2. If no DLT or 1 DLT was observed in the next level 2 cohort of 3 patients, 3 additional patients would also receive 60 mg/day x 14 days (level 2), establishing this dose as the RP2D if only 0-1 DLT is observed in 6 patients.

- If 1 out of 3 patients experienced a drug-related DLT, then 3 additional patients would receive that level 1 dose.

- If ≤ 1 out of 6 patients experienced a drug-related DLT, the next scheduled dose level would be available. If, at a given dose level, ≥ 2 out of tes experienced a drug-related DLT, the MTD would have been exceeded, enrollment of additional patients within that cohort would be stopped, and dose escalation would be halted.

- If a dose level was found to be intolerable (either ≥ 2 out of 6 patients for a full dose level or

≥ 2 out of 3 for the first cohort level experienced a DLT), patient enrollment would continue at a lower dose level.

Patients in phase I would continue to receive quizartinib during consolidation and maintenance, unless they had experienced a DLT with the assigned dose and/or the investigator decided that the patient had unacceptable toxicity.

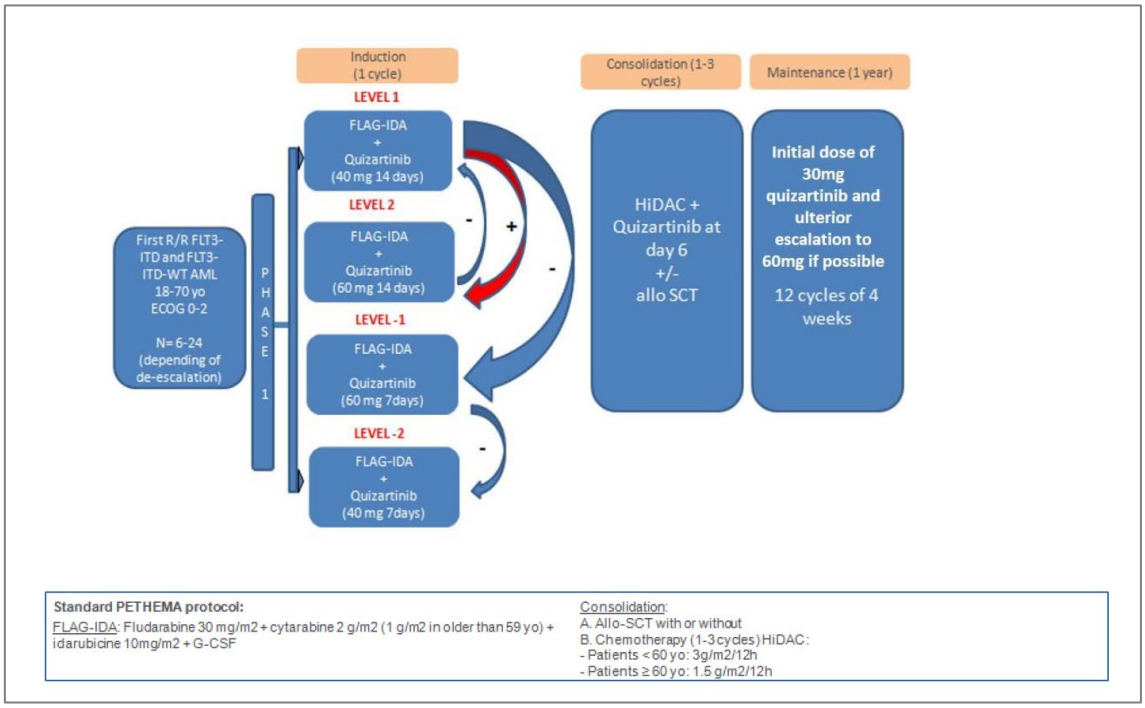


Figure 1. Schematic representation of dose escalation in the first phase of the study.

Phase II (expansion cohort)

Phase II included up to 68 patients treated with FLAG-QUIDA induction using the RP2D schedule (34 FLT3-ITD positive and 34 FLT3-ITD negative) (Figure 2).

AlloSCT was considered at second CR/CRi if possible, followed by maintenance therapy with quizartinib (30 mg followed by 60 mg continuously, starting maintenance between days 60 and 180 after alloSCT infusion) if there were no contraindications.

Optional consolidation regimen with HiDAC (2 cycles at 3 g/m²/12 hours x 3 days in patients younger than 60 years; 1.5 g/m^2 /12 hours x 3 days in patients ≥ 60 years) using quizartinib from day 6 (at RP2D) for 14 days, followed by maintenance with quizartinib if allo-STC was not feasible (same maintenance dose) between days 30 and 60.

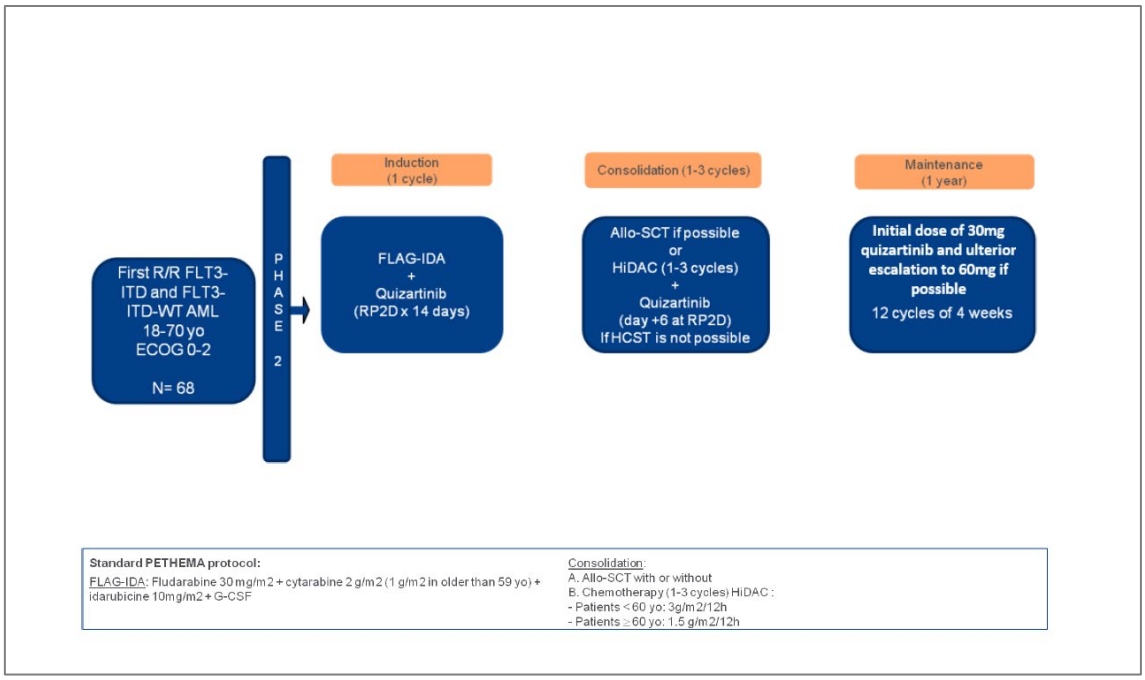


Figure 2. Schematic representation of the treatment carried out in the second phase of the study.

Molecular biomarker plan

Biomarkers played a key role in this trial, as they provided information on the potential role of quizartinib in AML and identified the subgroups of patients who benefited most from this therapeutic approach. The plan that was carried out is detailed below:

1. Biobank for subsequent studies, at baseline and for each centralized sample.

2. Initial polymerase chain reaction (PCR) (FLT3-ITD, FLT3-TKD, NPM1, CBF rearrangements, CEBPA).

3. Mandatory NGS at baseline (including a panel of 26 relevant mutations such as FLT3-TKD, CEBPA, NPM1, KIT, IDH1, IDH2, DNMT3A, P53, TET2, RAS, RUNX1, ASXL1). The variant allele frequency (VAF) was determined for each mutation.

4. Multiparametric flow cytometry (MPFC) in bone marrow at the time of selection.

5. MRD by high-throughput MPFC after the first induction cycle in the bone marrow.

6. MRD by high-throughput MPFC in bone marrow prior to allogeneic stem cell transplantation.

7. In addition,

MRD by RT-qPCR for patients with NPM1 and CBF.

8. *FLT3* expression levels in all patients at the start of the study.

Tests were performed at a reference center, details of which are included in the protocol.

3.6. Methods for statistical analysis

The population size was estimated using Fleming's one-stage procedure, taking into account that a CR/CRi rate of 50% would be insufficient to continue with the development of the combination of treatments, and that a CR/CRi rate of 65% would be an exceptional result that would warrant a phase III study. The objective was to recruit between 6 and 24 patients (phase I) plus 68 patients (phase II).

To achieve a statistical power of approximately 90% and be able to reject the null hypothesis with a one-sided alpha level of 0.05, it was estimated that 52 patients would need to be included in the second phase of the study. Considering that the response rate would be evaluated on an intention-to-treat basis and estimating a dropout rate of 10%, it was decided to include 5 more patients in the trial, estimating **the final sample size** at **57 patients**.

α	Power	p0	pn	SSiz
0.05	0.8	0.50	0.65	67

α = Probability of Type I Error
Power = power (1 - β)
p0 = lower proportion for rejection of Treatment
pn = higher proportion for acceptance of Treatment
SSiz = sample size required

Figure 3. Calculation of the size of the population included in the study to reject the null hypothesis.

The **analysis of the primary variable** of this study, i.e., **efficacy**, measured in terms of CR, CRi , was performed in **the intention-to-treat (ITT) population**, which was defined as all patients who were included in the trial and whose response to treatment had been evaluated, regardless of patient compliance with protocol procedures after enrollment. CR, CRi, and PR were reported as percentages of patients using descriptive statistics. **DLT** was analyzed in all patients who completed the induction cycle in phase I or who had to discontinue treatment during this period due to DLT. The Kaplan-Meier stratification method was used **to analyze secondary variables** such as PFS, defined as the time from the first documentation of remission to the documentation of disease recurrence or death, and OS, defined as the number of days from randomization to death from any cause. Comparisons of OS between treatment regimen groups were performed using the stratified log-rank test based on the ITT analysis set. The median OS was calculated based on Kaplan-Meier estimates, and the corresponding 95% confidence interval (CI) was calculated using the Brookmeyer and Crowley method. In addition, hazard ratios (HR) were estimated in the ITT population using the Cox proportional hazards regression model.

A propensity score analysis was planned to compare the CR/CRi rate achieved in the phase II cohort with a matched historical control (more than 460 patients treated with FLAG-IDA in the PETHEMA Foundation registry).

3.7. Analysis of results

3.7.1. Patients and treatment

This study was conducted between December 2019 and January 2023 and included a total of 61 patients across two phases (**Figure 4**). Overall, 77 patients were screened, of whom 14 were excluded prior to enrolment in phase 2 due to screening failures. In addition, one patient withdrew from the trial without receiving quizartinib due to a pericardial effusion, and another was withdrawn from the study due to discordant *FLT3*-ITD mutational results. Due to slow recruitment of *FLT3*-ITD-positive patients, phase 2 was closed prematurely. A total of 61 patients from 18 different centres were included in the trial, of whom 9 were included in the phase 1 portion and 52 in the phase 2 portion.

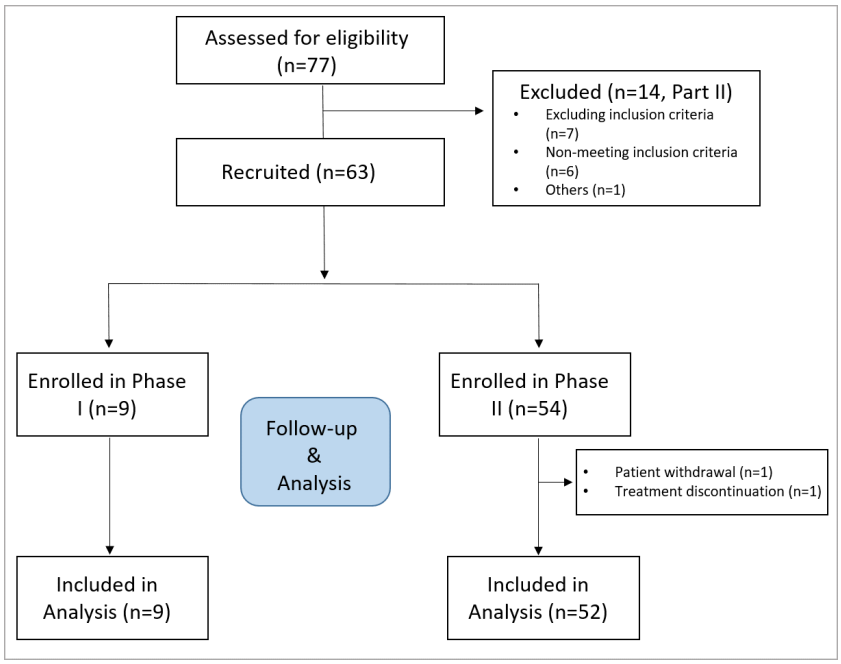


Figure 4. Inclusion of patients in the two phases of the study.

The median age of the patients included in the trial was 50 years (range 44-57) (**Table 1**), of whom 49% were female (n=30). First-line treatment consisted of idarubicin plus cytarabine (3+7) in 65% of patients (n=40), 3+7 plus midostaurin in 27% (n=15), CPX-351 in 6% (n=4), venetoclax plus azacitidine in 1% (n=1), and FLAG in 1% (n=1). Response to first line treatment was CR in 62% of patients (n=38) and resistant disease in 38% (n=23). Forty-one percent of patients (n=25) had AML with recurrent genetic abnormalities at diagnosis according to the 2016 World Health Organization classification, while 38% (n=23) had AML with myelodysplasia-related changes and 21% (n=13) had unspecified AML. Most patients (75% [n=46]) had a score of 0 on the ECOG performance scale, while 21% (n=13) and 3% (n=2) had a score of 1 and 2, respectively, at the time of diagnosis. Genetic risk according to the European Leukemia Net

2022 classification (ELN22) was favourable in 13 patients (21%), intermediate in 21 (34%), adverse in 26 (43%), and not available in 1 (1%). Almost one-third of patients (30%, [n=18]) were positive for the FLT3-ITD mutation. Among them, 8 patients were also positive for NPM1 mutation.

Table 1 shows the baseline characteristics of the patients included in the trial.

Characteristics **n (%)**	**All patients** **n=61**	**Phase 1** **n=9**	**Phase 2** **n=52**
Age (years)	50 (44-57)	50 (46-52)	55 (48-63)
Sex (male)	31 (51)	4 (44)	27 (52)
ECOG performance status **0** **1** **2**	 46 (76) 13 (21) 2 (3)	 8 (89) 0 1 (11)	 38 (73) 13 (25) 1 (2)
Hemoglobin	9.8 (9.1-11.6)	9.6 (9.5-11.2)	9.8 (9-12)
WBC **(x10^9 cells/L)**	3.7 (1.7-6.8)	4.6 (1.3-6.9)	3.6 (1.8-10)
ANC **(x10^9 cells/L)**	0.87 (0.4-2.1)	1.4 (0.8-2.6)	0.8 (0.4-2)
Platelet count **(x10^9 cells/L)**	61 (27-120)	77 (31-186)	61 (27-111)
Bone marrow blasts **%**	35 (22-77)	77 (55-84)	33 (20-65)
Cytogenetic category **Favorable** **Intermediate** **Adverse** **NA**	 7 (12) 33 (54) 16 (26) 5 (8)	 1 (11) 5 (56) 3 (33) 0	 6 (11) 28 (54) 13 (25) 5 (10)
ELN 2022 genetic category **Favorable** **Intermediate** **Adverse** **NA**	 13 (21) 21 (34) 26 (43) 1 (1)	 1 (11) 3 (33) 5 (56) 0	 12 (23) 18 (35) 21 (40) 1 (2)
WHO classification **Recurrent genetic abnormalities** **MDS-related** **NOS**	 25 (41) 23 (38) 13 (21)	 5 (56) 2 (22) 2 (22)	 20 (39) 21 (40) 11 (21)
FLT3 ITD mutation (%) **Allelic ratio**	18 (29.5) 0.7 (0.12-0.96)	2 (22) 0.83 (0.73-0.93)	16 (31) 0.7 (0.11-0.94)

NPM1 mutation	13 (21)	2 (22)	11 (21)
Secondary AML (%)	7 (11)	2 (22)	5 (10)

ECOG: Eastern Cooperative Oncology Group performance status. WBC: White Blood Cell Count; ANC: Absolute Neutrophil Count. ELN22: European leukemia Net 2022; AML: Acute Myeloid Leukemia. WHO: World Health Organization; MDS: myelodysplastic syndrome; NOS: Not otherwise specified.

3.7.2. Recommended dose and efficacy

In the phase 1 portion of the study (dose escalation), 3 patients received quizartinib at dose level 1 (40 mg/day for a period of 14 days) and, as no toxicity was observed, another 3 patients received dose level 2 (60 mg/day for a period of 14 days). One patient experienced treatment-unrelated grade 4 hyperbilirubinemia. No dose-limiting toxicity (DLT) was observed in 6 consecutive patients at 60 mg/day. Therefore, the recommended phase 2 dose (RP2D) for the phase 2 portion of the trial was set at 60 mg/day for a period of 14 days. In accordance with the protocol guidelines for quizartinib dosing, during the phase 2 portion, 26 patients (19 *FLT3*-ITD-negative and 7 *FLT3*-ITD-positive) initiated quizartinib treatment on day 5 of induction with a dose of 30 mg/day due to concomitant administration of a strong CYP3A4 inhibitor (n=25) for an equivalent exposure of 60 mg/day, or due to a prolonged baseline QT interval (n=1). The remaining 24 patients initiated quizartinib with a dose of 60 mg/day.

The aggregate CR/CRi rate for the phase 1 and 2 cohorts was 56% (n=34), with a CR rate of 15% (n=9) and a CRi rate of 41% (n=25). Six additional patients (10%) achieved a morphologically leukemia-free state (CR+CRi+MLFS rate: 66%). Among patients in CR/CRi, the MRD-negativity rate was 38% (n=13). **Table 2** details the responses grouped by study phase. CR/CRi rates were comparable among patients with mutations in *FLT3*-ITD (61%, 11 patients), *FLT3*-TKD (75%, 3 patients), *NPM1* (62%, 8 patients), *DNMT3A* (65%, 15 patients), *IDH1* (56%, 5 patients), *IDH2* (100%, 3 patients), and *c-KIT* (60%, 3 patients). A CR/CRi was reported in 1 of 5 patients with *TP53* mutations (20%). Median duration of response (DoR) in patients achieving CR/CRi was 16.5 months (95% confidence interval [CI]: 7.7-54.5).

Table 2. Response assessment.

Response	All patients (n=61) (%)	Phase 1 (n=9) (%)	Phase 2 (n=52) (%)
ORR (CR+CRi+MLFS)	40 (66)	5 (55)	35 (67)
CR/CRi	34 (56)	5 (55)	29 (56)
CR			
MRD(-)	1 (2)	0	1 (2)
MRD(+)	7 (11)	2 (22)	5 (10)
MRD NA	1 (2)	0	1 (2)
CRi			
MRD(-)	12 (20)	3 (33)	9 (17)
MRD(+)	13 (21)	0	13 (25)
MLFS	6 (10)	0	6 (11)
PR	2 (3)	1 (11)	1 (2)

Resistance	15 (24)	3 (33)	12 (23)
Death in aplasia	4 (6)	0	4 (8)

ORR: Overall Response (CR+CRi+MLFS); CR: Complete Remission; MRD: Minimal Residual Disease; NA: Not available; CRi: Complete Remission with incomplete hematological recovery; MLFS: Morphological Leukemia Free Status; PR: Partial Remission. Percentage of patients with negative minimal residual disease.

Four patients with *FLT3*-ITD mutations were refractory to FLAG-IDA. Two of them received gilteritinib, achieved MLFS, but later relapsed; one was treated with high-dose cytarabine without response, and one received palliative care. None of the *FLT3*-ITD-positive patients who relapsed received gilteritinib. None of the *FLT3*-ITD-negative patients received gilteritinib after refractoriness to FLAG-QUIDA.

Fifty-one percent of patients (n=31) in the entire cohort were bridged to allogeneic stem cell transplantation (allo-SCT) after FLAG-QUIDA, including 3 after MLFS and 28 after CR/CRi (82% of the patients who achieved CR/CRi). Evaluation of pre-transplant response was consistent with CR/CRi with negative MRD in 32% of patients (n=10), CR/CRi with positive MRD in 55% of patients (n=17), MLFS in 3% (n=1), and resistance in 6% of patients (n=2). Minimal residual disease data were not available in one patient (3%). The allo-SCT rate was 55% (n=10) in *FLT3*-ITD-positive patients and 48% (n=21) in *FLT3*-ITD-negative patients. Conditioning was myeloablative in 61% of patients (n=19), while 39% (n=12) received reduced-intensity conditioning. The donor was a sibling in 48% of patients (n=15), unrelated in 26% (n=8), and another family member in the remaining 8 patients. HLA-identical, haploidentical, and non-compatible transplants were performed in 58% (n=18), 36% (n=11), and 6% (n=2) of patients, respectively.

Maintenance treatment with quizartinib was initiated in 14 patients, 12 of whom had received allo-SCT. Among the 10 patients with *FLT3*-ITD mutation who received allo-SCT, maintenance was initiated in 5. The median time between infusion and initiation of maintenance was 99 days (75-119). The median number of maintenance cycles received was 8 (3-12). Seven out of 14 patients did not complete the 12-cycle schedule due to relapse (n=4), viral infection (n=1), and pancytopenia (n=2). Among the 2 patients who proceeded to maintenance without prior allo-SCT, one is alive in remission at 52 months.

With a median follow-up of 15.8 months (5-50), the median overall survival (OS) was 15.8 months (95% CI, 10.6-24.2), with 44 deaths reported at the time of data cut-off. OS at 1 and 2 years was 60% (95% CI, 49-74) and 36% (95% CI, 26-50), respectively. Non-relapse mortality (NRM) at 1 and 2 years was 6% (95% CI, 2-24) and 13% (95% CI, 5-32), respectively. In responding patients, median OS was 33.3 months (95% CI, 21-NR).

In *FLT3*-WT patients, median OS was 8 months longer than in *FLT3*-ITD patients: 20 months (95% CI, 14–NR) versus 11.5 months (95% CI, 5–41.2), respectively. However, this difference was not statistically significant (P=0.12), probably due to the small number of patients. By contrast, analyses in patients with *NPM1* mutations suggested that *NPM1* status was not associated with improved OS: median OS was 15.8 months (95% CI, 12.6–32.2) in *NPM1*-negative patients, compared with 16.5 months (95% CI, 4.3–NR) in *NPM1*-positive patients. **Table 3**.

Table 3. Overall survival by mutation status.

	Wild type	**Mutated**	**P value**
FLT3-ITD	20 (14-NR)	11.5 (5-41.3)	0.12
NPM1	15.8 (12.6-32.3)	16.5 (4.3-NR)	0.91
IDH1	16.5 (13-24.2)	10.6 (3.5-NR)	0.62
IDH2	15.8 (10.6-22.8)	NR (16.5-NR)	0.2
KIT	16.5 (12.6-24.2)	15 (5-NR)	0.78

DNMT3A	15.8 (10-62.7)	20.9 (10.4-NR)	0.48
TP53	16.5 (12.6-32.2)	15 (6.57-NR)	0.22

Data are presented in months and 95% confidence interval. NR: not reached.

Median OS in non-transplanted patients was 5 months (95% CI, 3.1-12.9), as compared to 34 months (95% CI, 21-NR) in transplanted patients (**Figure 2D**). Among the latter, *FLT3*-ITD mutational status did not correlate with differences in OS: patients carrying the *FLT3*-ITD mutation: 21.1 months (95% CI, 10.4-NR); non-carriers: NR (95% CI, 22.8-NR), P=0.16. Similar survival was observed between patients who received maintenance therapy after transplantation (median OS of 28.6 months, [95% CI, 19.3-NR]) and those who did not (median OS 41 months, [95% CI, 21.3-NR], P=0.85).

Figure 5. A) Overall Survival (OS) in patients receiving allogeneic stem cell transplant (SCT); B) OS according to transplant; C) OS in transplanted patients according to *FLT3* ITD mutation status; D)) OS in transplanted patients according to receiving maintenance with quizartinib.

The CR/CRi rate was compared between the FLAG-QUIDA cohort and a historical cohort composed of 1,079 patients treated with FLAG-IDA and reported to the PETHEMA registry. For this comparison, patients were matched by the SALFLAGE score with a 1:2 ratio. **Table 4** shows the baseline characteristics and standard mean differences (SMDs) of the selected covariates before and after matching. After matching, CR/CRi was achieved in 64 of the 122 matched patients treated with FLAG-IDA (52%) (P=0.67 for the comparison with the CR/CRi rate observed in patients treated with the FLAG-QUIDA regimen). Among *FLT3*-ITD-positive patients, CR/CRi rates were 46% (13/28) in patients treated with FLAG-IDA and 61% (11/18) in those treated with FLAG-QUIDA (P=0.33).

Table 4. Baseline characteristics of the historical cohort before and after matching.

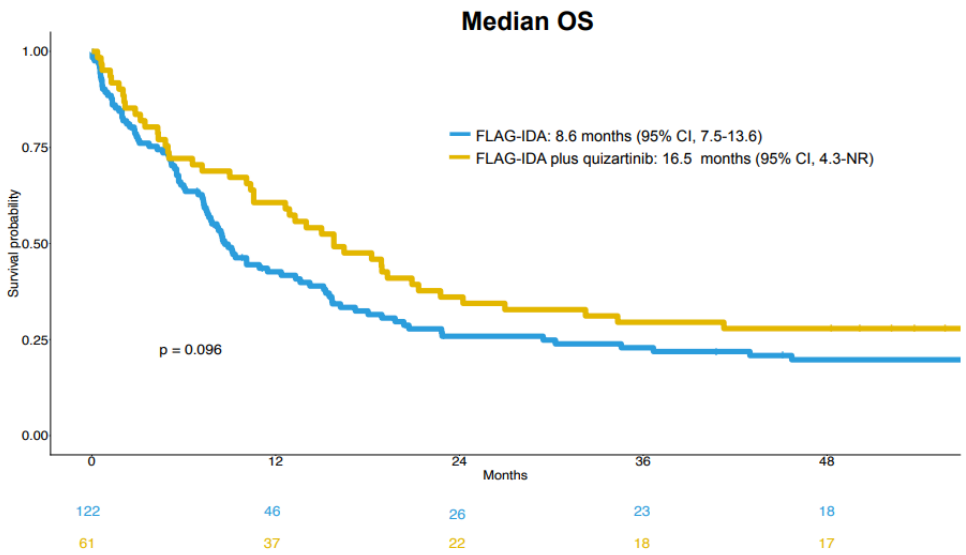
The proportion of patients bridged to allo-SCT in the matched cohort treated with FLAG-IDA was 35% (n=43) compared with 51% (n=31) in patients treated with FLAG-QUIDA (P=0.06). Median OS of patients treated with FLAG-IDA was 8.6 months (95% CI, 7.5-13.6), P=0.09 for the comparison with patients treated with FLAG-QUIDA (**Figure 6 A 6B)**. Median relapse-free survival (RFS), defined as time from CR/CRi until relapse or death, was 17 months (95% CI, 12.7-NA) in the FLAG-QUIDA cohort and 7.6 months (95% CI, 6.1-15.1) in the FLAG-IDA cohort (P=0.028). Median duration of response, defined as time from CR/CRi until relapse with patients dying in remission being censored, was 7.5 months (95% CI: 4-21) in the historical FLAG-IDA cohort, and 16.5 months in the FLAG-QUIDA cohort (P=0.057).

Characteristics n (%)	**All patients in the historical cohort n=1079**	**Historical cohort after matching n=122**	**FLAG-QUIDA cohort (n=61)**
Age (years)	53 (40-62)	55 (42-64)	50 (44-57)
Sex (male)	664 (55)	71 (58)	31 (52)
FLT3 ITD mutation (%)	172 (16)	28 (23)	18 (29)
SALFLAGE category			
Good	211 (20)	40 (33)	20 (33)
Intermediate	222 (20)	40 (33)	20 (33)
High	378 (35)	42 (34)	21 (34)
Not available	268 (25)	-	-
Secondary AML (%)	165 (16)	14 (11)	7 (11)

In the overall population, the cumulative incidence of relapse at 1 and 2 years was 21% (95% CI, 13-34) and 34% (95% CI, 23-47), respectively (**Figure 8**. The probability of relapse in *FLT3*-ITD-negative patients was 19% (95% CI, 10-35) and 28% (95% CI, 17-45) at 1 and 2 years, compared with 28% (95% CI, 13-58) and 44% (95% CI, 26-75) in patients with *FLT3*-ITD mutation at 1 and 2 years, respectively.

Figure. 6 A and B overall survival OS and median relapse-free survival RFS

A



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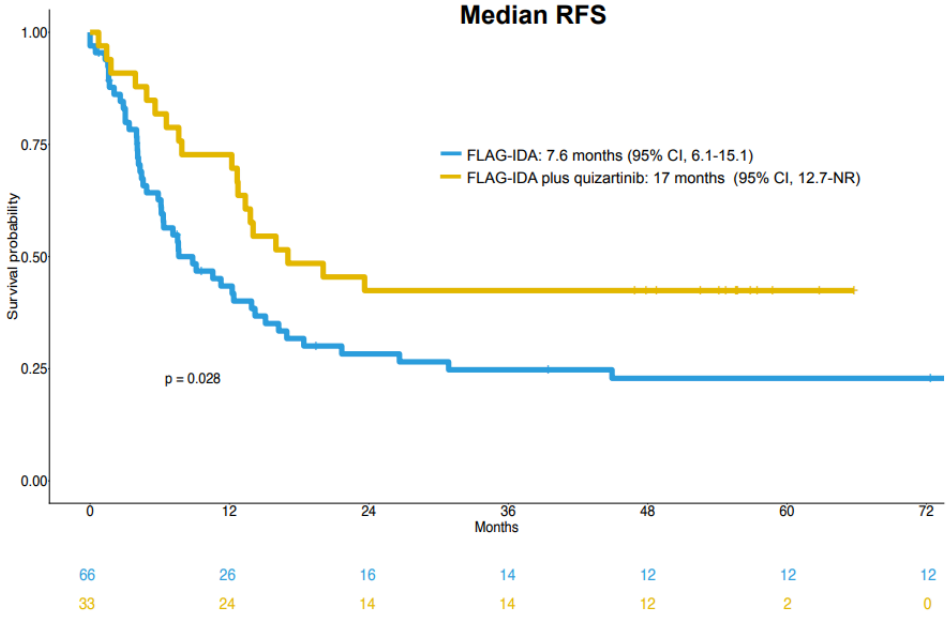

3.7.3. Safety

All 61 patients experienced at least one treatment-related adverse event (AE) (total events, n=148). Haematological AEs were frequent, with 23 (38%), 29 (47%), and 39 (64%)

episodes of anaemia, decreased absolute neutrophil count, or decreased platelet counts in the entire cohort. None of these adverse events were grade 5. Bone marrow suppression was transient in patients who achieved CR. In these patients, the median time to absolute recovery with a neutrophil count >0.5 × 10^9/L was 35 days (range, 34–43). The median time to recovery with a platelet count >100 × 10^9/L was 39 days (range, 35–45).

The most common non-hematologic AEs were fever (n=42, 68%), bacteraemia (n=33, 53%), febrile neutropenia (n=28, 46%), nausea (n=25, 40%), diarrhoea (n=24, 39%), infection (n=23, 37%), rash (n=22, 35%), oral mucositis (n=17, 27%), and vomiting (n=16, 26%). Grade 3 and grade 4 events were observed in 46 (75%) and 32 (52%) patients, respectively. The most frequently reported grade 3-4 non-hematologic AEs were febrile neutropenia (n=14, 23%), bacteraemia (n=11, 17%), pulmonary infection (n=10, 16%), and sepsis (n=9, 14%).

Ten patients experienced grade 5 AEs. All of these patients were included in the phase 2 portion of the trial. These AEs were: sepsis in 4 pancytopenic patients resulting in death at days 17, 20, 40, and 64 after the first day of induction; one lung infection in the context of progressive disease; invasive aspergillosis in 2 patients who achieved MLFS without hematopoietic recovery; one thrombotic event in a patient with persistent bacteraemia and resistant disease; and a septic event in a patient with resistant disease. None of these deaths were attributed to quizartinib. The cumulative incidence of mortality at 30 and 60 days was 6% (n=3) and 9% (n=6), respectively.

Ten patients in the phase 2 cohort developed a prolonged QT interval during the induction cycle (n=6), first consolidation (n=2), or maintenance (n=2). Of these AEs, 7 were considered quizartinib-related, with 8 events classified as grade 1-2 and 2 events as grade 3. Seven AEs ceased with dose reduction or discontinuation, while 3 resolved spontaneously. Other AEs considered related to quizartinib by investigator assessment were infrequent and mostly single occurrences. These included hepatic events (grade 1 transaminitis [n=1] and grade 2 liver function test abnormalities [n=2]); dermatologic events (grade 1 toxicodermia [n=1] and grade 3 skin rash [n=1]); cardiac and gastrointestinal events (grade 1 sinus bradycardia [n=1] and grade 1 abdominal bloating [n=1]); ocular toxicity (grade 3 dry eye [n=1]); and hematologic events, including grade 4 neutropenia (n=1), grade 4 pancytopenia (n=1), grade 3 thrombocytopenia (n=1), grade 3 anaemia (n=1), and grade 3 febrile neutropenia (n=1). All events resolved with quizartinib dose omission (n=3), dose reduction (n=1), or spontaneously (n=9).

Of the 31 patients who received allo-SCT, 16% (n=5) developed graft-versus-host disease (GVHD). None of the episodes were attributed to quizartinib. Four of these patients completed the planned 12 cycles of maintenance therapy; one patient was unable to initiate quizartinib maintenance. All haematological AEs, frequent non-haematological AEs, and grade 3-5 AEs are shown in **Table 5** and **Table 6**.

Table 5. Haematological and non-haematological most frequent adverse events

Treatment-emergent adverse events	N of events in phase 1 and 2 (n=61)				N of events in phase 1 (n=9)				N of events in phase 2 (n=52)			
	G1-2	G3	G4	G5	G1-2	G3	G4	G5	G1-2	G3	G4	G5

Hematologic												
-Anemia	16 (26)	4 (6)	3 (5)	0	2 (22)	1 (11)	1 (11)	0	14 (27)	3 (5)	2 (4)	0
-Decreased neutrophil counts	9 (15)	5 (8)	15 (24)	0	6 (66)	0	1 (11)	0	3 (5)	5 (9)	14 (27)	0
-Decreased platelet counts	10 (16)	11 (18)	18 (29)	0	2 (22)	0	4 (44)	0	8 (15)	11 (21)	14 (27)	0
Non-hematologic												
-Fever	38 (62)	3 (5)	0	1 (1)	6 (66)	3 (33)	0	0	32 (61)	0	0	1 (2)
-Bacteremia	22 (36)	10 (16)	1 (1)	0	1 (1)	0	1 (1)	0	21 (41)	9 (17)	1 (2)	0
-Febrile neutropenia	14 (23)	9 (15)	5 (8)	0	3 (33)	0	1 (12)	0	11 (21)	9 (17)	4 (7)	0
-Nausea	24 (39)	0	0	0	8 (89)	0	0	0	16 (31)	0	0	0
-Diarrhea	20 (33)	1 (1)	0	0	5 (55)	0	0	0	19 (36)	1 (2)	0	0
-Infection	24 (39)	2 (3)	1 (1)	0	0	0	0	0	20 (38)	1 (2)	0	0
-Rash	21 (34)	1 (1)	0	0	3 (33)	1 (11)	0	0	18 (34)	1 (2)	0	0
-Oral mucositis	14 (23)	2 (2)	0	0	2 (22)	1 (11)	0	0	12 (23)	1 (2)	0	0
-Vomiting	16 (26)	0	0	0	5 (55)	0	0	0	11 (21)	2 (4)	0	0
-Pulmonary infection	6 (9)	0	0	3 (5)	0	1 (11)	0	0	6 (11)	0	0	3 (5)
-Sepsis	1 (1)	10 (16)	5 (8)	5 (8)	3 (33)	1 (11)	0	0	8 (17)	9 (17)	5 (9)	5 (9)
-QT prolongation	8 (15)	4 (6)	0	0	0	0	0	0	1 (2)	3 (5)	0	0
		2 (2)			0				8 (17)	2 (4)		

G: Grade.

Table 6. Main Treatment Emergent Adverse Events during treatment. N(%).

Treatment-emergent adverse event	**Overall (n=61)**				**Phase 1 (n=9)**				**Phase 2 (n=52)**			
	G1-2	**G3**	**G4**	**G5**	**G1-2**	**G3**	**G4**	**G5**	**G1-2**	**G3**	**G4**	**G5**
Any	61 (100)	46 (75)	32 (52)	9 (15)	9 (100)	7 (78)	5 (55)	0	48 (92)	39 (75)	27 (52)	9 (17)
Fever	38 (62)	3 (5)	0	1 (1)	6 (66)	3 (33)	0	0	32 (61)	0	0	1 (2)
Platelet count decreased	10 (16)	11 (18)	18 (29)	0	2 (22)	0	4 (44)	0	8 (15)	11 (21)	14 (27)	0
Bacteremia	22 (36)	10 (16)	1 (1)	0	1 (1)	0	1 (11)	0	21 (40)	9 (17)	1 (2)	0

Neutropenia	9 (15)	5 (8)	15 (24)	0	6 (66)	0	1 (11)	0	3 (5)	5 (9)	14 (27)	0
Febrile neutropenia	14 (23)	9 (15)	5 (8)	0	3 (33)	0	1 (12)	0	11 (21)	9 (17)	4 (7)	0
Nausea	24 (39)	1 (1)	0	0	8 (89)	0	0	0	16 (31)	1 (2)	0	0
Diarrhea	24 (39)	0	0	0	5 (55)	0	0	0	19 (36)	0	0	0
Non specified infection	20 (33)	2 (3)	1 (1)	0	0	1 (11)	0	0	20 (38)	1 (2)	1 (2)	0
Rash maculopapular	21 (34)	1 (1)	0	0	3 (33)	0	0	0	18 (34)	1 (2)	0	0
Anemia	16 (26)	4 (6)	3 (5)	0	2 (22)	1 (11)	1 (11)	0	14 (27)	3 (5)	2 (4)	0
Lung infection	6 (9)	10 (16)	0	3 (5)	0	1 (11)	0	0	6 (11)	9 (17)	0	3 (5)
Oral mucositis	14 (23)	2 (3)	1 (1)	0	2 (22)	0	0	0	12 (23)	2 (4)	1 (2)	0
Vomiting	16 (26)	0	0	0	5 (55)	0	0	0	11 (21)	0	0	0
Leukopenia	5 (8)	4 (6)	9 (15)	0	0	0	1 (11)	0	5 (10)	4 (7)	8 (15)	0
Sepsis	1 (1)	4 (6)	5 (8)	5 (8)	0	1 (11)	0	0	1 (2)	3 (5)	5 (9)	5 (9)
Epistaxis	10 (16)	0	0	0	3 (33)	0	0	0	7 (13)	0	0	0
Constipation	10 (16)	0	0	0	2 (22)	0	0	0	8 (15)	0	0	0
QT prolongation	8 (15)	2 (2)	0	0	0	0	0	0	8 (17)	2 (4)	0	0
Hemorrhoids	7 (11)	1 (1)	0	0	0	0	0	0	7 (13)	1 (2)	0	0
Fatigue	6 (9)	1 (1)	0	0	1 (11)	1 (11)	0	0	5 (10)	0	0	0
Headache	5 (8)	0	0	0	0	0	0	0	5 (10)	0	0	0
Herpes simplex reactivation	8 (13)	0	0	0	1 (11)	0	0	0	7 (13)	0	0	0
Hypotension	7 (11)	1 (1)	0	0	1 (11)	0	0	0	6 (11)	1 (2)	0	0
Localized edema	8 (13)	0	0	0	1 (1)	0	0	0	7 (13)	0	0	0
Oral hemorrhage	8 (13)	0	0	0	4 (44)	0	0	0	4 (7)	0	0	0
Erythema	7 (11)	0	0	0	3 (33)	0	0	0	4 (7)	0	0	0
Blood bilirubin increased	3 (5)	3 (5)	1 (1)	0	0	0	1 (11)	0	3 (5)	3 (5)	0	0
Pruritus	7 (11)	0	0	0	2 (22)	0	0	0	5 (9)	0	0	0

Hypertransaminemia	4 (6)	1 (1)	0	0	1 (11)	0	0	0	3 (5)	1 (2)	0	0
Hypertension	3 (4)	2 (3)	0	0	0	0	0	0	3 (5)	2 (4)	0	0
Pancytopenia	2 (3)	1 (1)	2 (3)	0	0	1 (11)	1 (11)		2 (4)	0	1 (2)	0
Thrombosis	4 (6)	0	0	1 (1)	0	0	0	0	4 (7)	0	0	1 (2)
Anorexia	3 (5)	1 (1)	0	0	2 (22)	0	0	0	1 (2)	1 (2)	0	0
Hepatotoxicity	2 (3)	2 (3)	0	0	0	0	0	0	2 (4)	2 (4)	0	0
Hypotension	7 (11)	1 (1)	0	0	1 (11)	0	0	0	6 (11)	1 (1)	0	0
Pain in extremity	3 (5)	1 (1)	0	0	0	1 (11)	0	0	3 (5)	0	0	0
Dermatitis	3 (5)	0	1 (1)	0	0	0	0	0	3 (5)	0	1 (2)	0
Colitis	1 (1)	2 (3)	0	0	0	0	0	0	1 (2)	2 (4)	0	0
Lower intestinal hemorrhage	2 (3)	0	1(1)	0	0	0	0	0	2 (4)	0	1 (2)	0
Lump appearance	2 (3)	1 (1)	0	0	2 (22)	0	0	0	0	1 (2)	0	0
Pleural effusion	2 (3	1 (1)	0	0	2 (11)	0	0	0	0	1 (2)	0	0
Respiratory failure	0	2 (3)	1 (1)	0	0	0	0	0	2 (4)	0	1 (2)	0
Small intestinal mucositis	2 (3)	0	1 (1)	0	1 (11)	0	0	0	1 (2)	0	1 (2)	0
Atrial fibrilation	1 (1)	1 (1)	0	0	1 (1)	1 (1)	0	0	0	0	0	0
Catheter related infection	0	2 (3)	0	0	0	0	0	0	0	2 (4)	0	0
Cholecystitits	0	2 (3)	0	0	0	0	0	0	0	2 (4)	0	0
Colitis	1 (1)	2 (3)	0	0	0	0	0	0	1 (1)	2 (4)	0	0
Encephalopathy	0	1 (1)	1 (1)	0	0	0	0	0	0	1 (2)	1(2)	0
Gastroesophageal reflux disease	1 (1)	1 (1)	0	0	0	0	0	0	1 (2)	1 (2)	0	0
Lymphangitis	1 (1)	1 (1)	0	0	0	0	0	0	1 (2)	1 (2)	0	0
GGT increased	1 (1)	1 (1)	0	0	0	0	0	0	1 (2)	1 (2)	0	0
Heart failure	1 (1)	0	1 (1)	0	0	0	0	0	1 (2)	0	1 (2)	0
Infusion related reaction	1 (1)	0	1 (1)	0	0	0	0	0	1 (2)	0	1 (2)	0
Allergic reaction	1 (1)	0	0	0	0	0	0	0	1 (1)	0	0	0
Appendicitis	0	1 (1)	0	0	0	0	0	0	0	1 (2)		

Arthritis	0	1 (1)	0	0	0	0	0	0	0	1 (2)	0	0
Creatinine increased	0	1 (1)	0	0	0	0	0	0	0	1 (2)	0	0
Dry eye	0	1 (1)	0	0	0	1 (1)	0	0	0	0	0	0
Enterocolitis infectious	0	1 (1)	0	0	0	0	0	0	0	1 (2)	0	0
Folliculitis	0	1	0	0	0	0	0	0	0	1 (2)	0	0
Gallbladder pain	0	1	0	0	0	0	0	0	0	1 (2)	0	0
Glossomegaly	0	1 (1)	0	0	0	0	0	0	0	1 (2)	0	0
Pancreatitis	0	1 (1)	0	0	0	1 (1)			0	0	0	0
Typhlitis	0	1	0	0	0	0	0	0	0	1 (2)	0	0

3.8. Conclusions

This study demonstrated that the FLAG-QUIDA regimen followed by maintenance with quizartinib is a promising regimen, equally effective for patients with *FLT3-ITD* mutation and patients without this mutation. However, longer follow-up is needed to establish its long-term efficacy.

Signed:

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Dr. Pau Montesinos Fernández ***Dr. Teresa Bernal del Castillo***

Trial Coordinator *Trial coordinator*

Appendix 1: List of participating centers

CENTER	PRINCIPAL INVESTIGATOR	PATIENT CANDIDATES
La Fe Hospital	Dr. Rebeca Rodriguez Veiga	24
Asturias Central University Hospital	Dr. Teresa Bernal del Castillo	7
Virgen del Rocío University Hospital	Dr. Eduardo Rodriguez Arbolf	7
San Pedro Alcántara Hospital	Dr. Juan Miguel Bergua	5
German Trias i Pujol Hospital	Dr. Susana Vives Polo.	5
ICO L'Hospitalet	Dr. Montserrat Arnan Sangerman.	5
Doce de Octubre University Hospital	Dr. Pilar Martínez Sanchez	3
Ramón y Cajal University Hospital	Dr. Pilar Herrera Puente	3
Reina Sofía University Hospital	Dr. Josefina Serrano López	3
Jerez de la Frontera Hospital	Dr. Vicente Rubio	3
Puerta del Mar Hospital	Dr. Inmaculada Marchante Cepillo	3
Joan XXIII Hospital	Dr. Marta Cervera Calvo	2
Son Espasses Hospital	Dr. Andrés Novo García	2
Insular Maternal and Child Hospital	Dr. Rosa del Carmen Fernandez Martin	1
Alicante General Hospital	Dr. Cristina Gil Cortés	2
Negrín Hospital, Gran Canaria	Dr. Carlos Rodríguez Medina	1
University Hospital Complex, A Coruña	Dr. Víctor Noriega Concepción	1
University Clinic of Navarra	Dr. Ana Alfonso Piérola	1

Appendix 2: Serious Adverse Events

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
La Fe University and Polytechnic Hospital	1137-12	Sepsis	02/28/2021	03/02/2021	Life-threatening illness or injury	resolved	Not related
	1137-4	Cholecystitis	08/24/2020	08/26/2020	Significant medical event	Resolved	not related
	1137-1	Sepsis	January 16, 2020	01/17/2020	Life-threatening illness or injury , Significant medical event	resolved	unrelated
	1137-2	Hyperbilirubinemia	04.05.2021	06/03/2021	Requires hospitalization or prolongs hospital stay	Resolved with sequelae	Not related
		Pancreatitis	04/23/2021	04/26/2021	Requires hospitalization or prolonged hospital stay	Resolved	Not related
	1137-11	Sepsis	10/04/2021	10/04/2021	Requires hospitalization or prolongs hospital stay, Significant medical event	Resolved	unrelated
		Febrile neutropenia	10/29/2021	11/23/2021	Requires hospitalization or prolonged hospital stay	Resolved	Not related

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
	1137-16	Gastrointestinal bleeding	11/06/2021	09.11.2021	Life-threatening illness or injury , Requires hospitalization or prolongs hospital stay	Unresolved	Not related
	1137-16	Pneumonia	09/29/2021	10/04/2021	Requires hospitalization or prolongs hospital stay, Significant medical event	Resolved	Not related
	1137-13	Sepsis	05/24/2021	May 26, 2021	Significant medical event	Resolved	unrelated
	1137-10	Pneumonia	01/15/2021	Jan. 19, 2021	Significant medical event	resolved	NA
	1137-5	Sepsis	08/20/2020	08/24/2020	Significant medical event	Resolved	unrelated
		Sepsis	10/12/2020	10/14/2020	Death, Requires hospitalization or prolongs hospital stay	Death	Unrelated
	1137-6	Sepsis	10/14/2020	10/15/2020	Death, Life-threatening illness or injury, Significant medical event	death	unrelated
Asturias Central	1147-3	Prolonged QT electrocardiogram	July 12, 2021	July 13, 2021	Significant medical event	Resolved	unrelated

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
University Hospital		The patient has a grade 3 lump in the left cervical area of the neck.	08/01/2020	08/12/2020	Requires hospitalization or prolonged hospital stay	Resolved	Not related
Virgen del Rocío University Hospital	1152-5	Acute respiratory failure	02/26/2021	03.03.2021	Life-threatening illness or injury, Requires hospitalization or prolonged hospital stay	Resolved	Not related
	1152-6	Appendicitis	11.03.2021	03/12/2021	Requires hospitalization or prolongs hospital stay	Resolved	Not related
	1152-7	Septic shock	06/14/2021	06/16/2021	Death	Death	unrelated
	1152-2	Septic shock	July 20, 2020	07/28/2020	Death	Death	unrelated
	1152-1	Bronchopulmonary aspergillosis	January 21, 2020	01/23/2020	Significant medical event	Resolved	unrelated
		Septic shock	12/27/2019	01/07/2020	Significant medical event	Resolved	NA
San Pedro Alcántara Hospital to	1151-5	Bronchopulmonary aspergillosis	08/18/2021	08/25/2021	Death, requires hospitalization, or prolongs hospital stay	Death	unrelated

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
	1151-2	Pneumonia	03/25/2021	03/30/2021	Life-threatening illness or injury requiring hospitalization or prolonged hospital stay	Resolved	not related
		Colitis	03/04/2021	03/16/2021	Requires hospitalization or prolonged hospital stay	resolved	unrelated
		Reactivation of cytomegalovirus infection	02/09/2021	02/17/2021	Requires hospitalization or prolongs hospital stay, significant medical event	Resolved	unrelated
	1151-2	Escherichia coli bacteremia	02/15/2021	03/04/2021	Requires hospitalization or prolongs hospital stay	Resolved	Not related
		Hypertensive crisis	03/13/2021	03/17/2021	Requires hospitalization or prolongs hospital stay, significant medical event	Resolved	unrelated
	1151-1	Infectious enterocolitis	02/16/2021	02/19/2021	Requires hospitalization or prolongs hospital	Resolved	unrelated

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
					stay, significant medical event		
		Electrocardiogram with prolonged QT interval	02/18/2021	02/18/2021	Requires hospitalization or prolonged hospital stay	Resolved	possible link to medication under investigation
		Septic shock	02/15/2021	02/17/2021	Life-threatening illness or injury requiring hospitalization or prolonging hospital stay	Resolved	unrelated
German Trias i Pujol Hospital	1140-4	Fungal pneumonia	01/17/2021	January 25, 2021	Death, requires hospitalization, or prolongs hospital stay	Death	unrelated
	1140-2	Aspergillus infection	10/28/2020	10/05/2020	Death, serious medical event	Death	unrelated
	1140-1	Device-related infection	06/24/2020	06/29/2020	Persistent/significant disability/incapacity	Resolved	Not related
		Bacterial enterocolitis	06/25/2020	06/30/2020	Significant medical event	resolved	unrelated
ICO L'Hospitalet	1155-4	Sepsis	12/06/2020	07.12.2020	Life-threatening illness or injury,	death	unrelated
	1155-3	Sepsis	11/17/2020	11/18/2020	Death, requires hospitalization, or prolongs hospital stay	Resolved	not related

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
	1155-2	Metabolic encephalopathy	08/27/2020	08/31/2020	Life-threatening illness or injury,	resolved	unrelated
		Post-metabolic encephalopathy syndrome	09/01/2020	09/17/2020	Life-threatening illness or injury,	resolved	unrelated
12 de Octubre University Hospital	1145-3	Febrile neutropenia	04/23/2021	04/28/2021	Requires hospitalization or prolongs hospital stay	Resolved	Possible link to medication under investigation
		Klebsiella bacteremia	02/28/2021	03/02/2021	Requires hospitalization or prolonged hospital stay	Resolved	Possible link to medication under investigation
		Febrile neutropenia	02/20/2021	03/02/2021	Requires hospitalization or prolonged hospital stay	Resolved	Not related
Jerez de la Frontera Hospital	1146-1	Mucormycosis	10/25/2020	10/28/2020	Significant medical event	resolved	unrelated
Jerez de la Frontera Hospital	1146-1	Removal of damaged mucosa from the septum and motor side (nostril).	11/04/2020	11/05/2020	Significant medical event	resolved	unrelated
		Pseudomonas bacteremia	12/27/2020	01/21/2021	Requires hospitalization or	Resolved	Not related

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
					prolongs hospital stay		
		Increased temperature	12/11/2020	12/18/2020	Significant medical event	resolved	unrelated
		Electrocardiogram with prolonged QT interval	12/18/2020	12/24/2020	Significant medical event	Resolved	possible link to medication under investigation
		Febrile neutropenia	10/12/2020	10/13/2020	Requires hospitalization or prolonged hospital stay	Resolved	Not related
		Increased blood creatinine	11/16/2020	11/18/2020	Requires hospitalization or prolonged hospital stay	Resolved	Not related
Puerta del Mar Hospital	1150-2	The patient presented with an episode of hypoxemic respiratory failure with hypoxemia and urticarial reaction following a grade 4 platelet transfusion.	06/04/2021	06/08/2021	Life-threatening illness or injury,	resolved	unrelated
		Pneumonia	09/18/2021	09/23/2021	Requires hospitalization or	Resolved	Not related

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
					prolongs hospital stay		
		Escherichia sepsis	09/18/2021	09/23/2021	Requires hospitalization or prolongs hospital stay	Resolved	not related
	1150-3	Cardiac tamponade	07/08/2021	07/09/2021	Life-threatening illness or injury,	resolved	NA
Son Espasses Hospital	1148-2	COVID-19 pneumonia	07/04/2022	6435	Requires hospitalization or prolongs hospital stay	Resolved	not related
		Pneumonia	September 16, 2022	6438	Requires hospitalization or prolongs hospital stay	Resolved	Not related
Son Espasses Hospital	1148-2	Medication-induced renal failure	08/31/2021	6393	Requires hospitalization or prolongs hospital stay, significant medical event	Resolved	NA
	1148-1	Fungal pneumonia	04/30/2021	6376	Death, requires hospitalization or prolongs hospital stay	Death	unrelated
	1148-1	Sepsis	04/17/2021	6371	Life-threatening illness or injury requiring	resolved	unrelated

CENTER	PATIENT CODE	SAE DESCRIPTION	SAE START DATE	SAE NOTIFICATION DATE	SEVERITY CRITERION	OUTCOME	CAUSALITY RELATED TO TREATMENT
					hospitalization or prolonged hospital stay		
Alicante General Hospital	1138-3	Sinusitis	12/15/2020	02/22/2022	Requires hospitalization or prolonged hospital stay	Resolved	Not related
	1138-2	Blurred vision	11/17/2020	11/18/2020	Requires hospitalization or prolongs hospital stay	Resolved	Not related
Insular Maternal and Child Hospital	1142-1	Sepsis	12/26/2020	01/19/2021	Death	death	unrelated

Appendix 3: Major deviations

CENTER	NUMBER OF DEVIATION	DATE	CATEGORY	DESCRIPTION	ACTION TAKEN
La Fe University and Polytechnic Hospital	46406	2022-04-01	Patient treatment adherence 1137-10_IND01-D05_IP	During the last visit, the CRA confirmed the increase in the quizartinib dose. Compliance was not as expected (the subject returned one less pill than expected) and should be documented in the medical report (along with the reason, if known). June 28, 2022: issue not reviewed due to lack of time. January 11, 2023: issue pending; during MV11, only the CRF was reviewed due to lack of time and because only the data entry clerk responded and attended to the CRA.	Treatment compliance must be documented in the medical records.
	46405	2022-04-01	Patient treatment adherence	During the MV conducted on March 23, 2022, the CRA confirmed that the subject reduced the quizartinib dose to 30 mg on October 23, 2020, due to QTcF prolongation (treatment started on October 21, 2020). Accordingly, 20 tablets were expected to be returned, but the subject only returned 14. Site staff are awaiting confirmation of whether the dose was increased again for any reason or if they know the reason why the subject took more tablets than expected. This is not documented in the medical records. June 28, 2022: issue not reviewed due to lack of time. January 11, 2023: issue	The center staff must document in the medical records the subject's compliance at this visit and the reason why compliance is not as expected (if they know the reason).

				pending; during MV11, only the CRF was reviewed due to lack of time and because only the CRA responsible for data entry responded and attended.	
	46404	2022-04-01	Patient treatment adherence	March 31, 2022: Following a routine review, the CRA detected that subject 1137-3's compliance was lower than expected at induction. The subject was expected to have returned 2 tablets (60 mg dose - 14 days), but the subject returned 3 tablets. June 28, 2022: issue not reviewed due to lack of time. January 11, 2023: issue pending; during MV11, only the CRF was reviewed due to lack of time and because only the data entry clerk responded and attended to the CRA. May 18, 2023: issue not reviewed due to lack of time.	Compliance must be documented in medical records.
La Fe University and Polytechnic Hospital	46361	2022-03-24	Patient 1137-3_Maintenance was not performed.	March 23, 2022: There are no maintenance visits in the medical records. Only the EOT. It is indicated that maintenance was not performed during the permitted period and that is why the EOT visit was made. The reason why maintenance was not performed must be documented in the medical records. June 28, 2022: reason still pending documentation. January 11, 2023: pending issue, reason why maintenance was not performed pending documentation. May 18, 2023: reason still pending documentation.	NA

	45212	2022-01-11	Patient 1137-2_Non-compliance with treatment	Jan 11, 2022 - Subjects were found to be non-compliant with treatment. - MTO-02, 6 tablets returned (more than expected); MTO-04, no tablets returned (less than expected); MTO-06, 8 tablets returned (more than expected). At the next MV, it remains to be reviewed whether these treatment deviations have been documented in the medical records. March 23, 2022 - The CRA was unable to review this aspect during the visit. June 28, 2022: issue not reviewed due to lack of time. October 5, 2022: issue pending communication in medical records. January 11, 2023: issue pending; during MV11, only the CRF was reviewed due to lack of time, and only the person in charge of data entry responded and attended to the CRA. May 18, 2023: Issue not reviewed due to lack of time	NA
	45123	2022-01-13	Patient 1137-2_Kits 85389 and 85390 not returned (MTO-09)	Jan. 13, 2022 - The accountability log provided by the Pharmacy Department indicates that kits 85389 and 85390 were administered on Mar. 30, 2021 (MTO-09). However, these kits were not available at the Pharmacy Service and their destruction is not documented on the previous IP destruction form (Jun 7, 2021). The center staff is waiting to confirm whether these kits were not returned. If the kits were not returned,	NA

				the CRA will verify at the next MV whether it is documented in this subject's medical records that these kits were not returned and why. March 23, 2022: The CRA was unable to verify whether the medical records document that kits 85389 and 85390 were not returned. June 28, 2022: The Pharmacy Service could not be visited because it was unavailable. This issue will be reviewed at the next MV. October 5, 2022: Medical records indicate that two MTO-07 kits were returned, pending verification that they are the MTO-08 kits. Pending documentation that the kits were not returned and the reason why. May 18, 2023: Issue not reviewed due to lack of time.	
La Fe University and Polytechnic Hospital	45118	2022-01-11	Patient 1137-11_Kit IP 85396 MTO-03 non-compliance	JAN/11/2022: Subject 1137-11 returned 22 tablets from kit 85396. The kit was administered on September 30, 2021, and returned on October 21, 2021. Center staff are awaiting confirmation of whether administration was interrupted during this time period due to the SAE "grade 3 sepsis" reported on October 21, 2021. According to the data, the SAE occurred between October 4 and October 18, 2021. In addition, this SAE indicates that the dose administered was 60 mg, but the dispensing record indicates 30 mg. The SAE report also indicates that no changes were made to	The center staff must document in the medical records the compliance and the reason why the subject did not follow it or if the dose was not modified.

				the administration of the IMP. These issues are pending resolution. March 23, 2022: From October 4 to October 8, 2021, the dose administered was increased to 60 mg. Treatment was discontinued on October 9, 2021, according to the original documents. However, 22 tablets were returned. Based on the specified dose, only 16 tablets were expected to be returned. Center staff are awaiting confirmation of whether the dose was increased or discontinued earlier, if they are aware of this. June 28, 2022: Issue not reviewed due to lack of time.	
	45109	2022-01-11	Patient 1137-11_ Kit 85393 not returned	JAN/11/2022: During the visit, it was reported that kit 85393 was dispensed to subject 1137-11 but was not returned (the kit is missing and there is no IP return document). Center staff are waiting to confirm whether this kit was not returned or whether it was stored elsewhere. If the subject did not return the kit, an addendum should be added to the subject's medical record indicating that the product was not returned and, if it was, the explanation for this, e.g., if the subject lost the vial or threw it away. March 23, 2022: An addendum to the medical record indicating that kit 85393 was not returned is pending.	NA

	45050	2021-12-23	Patient 1137-11_No serious adverse events have been reported.	Subject 1137-11 was hospitalized from July 6 to July 12, 2021, due to fever. According to the original documents, the fever began on July 5, 2021. The fever was determined to be related to CMV reactivation. The SAE should be reported and indicated in the original documents that it was considered an SAE.	NA
La Fe University and Polytechnic Hospital	45030	2021-12-23	Patient 1137-12_Maintenance visit not indicated in the medical record.	DEC/23/2021 - The CRA noted that maintenance visits are not included in the medical records. They are also not indicated in the eCRF. According to the medical records, the alloSCT was performed on June 1, 2021. The deadline for starting maintenance was November 28, 2021 (maintenance must be started between 60 and 180 days after allogeneic stem cell transplantation). The site is awaiting confirmation as to why maintenance has not been started. March 23, 2022: The SC confirmed that the maintenance period had not been performed. The reason is not documented, and the EOT has not been added. June 28, 2022:	The reason why maintenance was not performed must be indicated in the medical records. In addition, the EOT must be indicated.
	45026	2021-12-23	Patient 1137-12_IND01-D15 Blood count	12/22/2021: White blood cell counts were not evaluated in IND01-D15, probably due to severe leukopenia. The CRA has asked the site staff why the differential counts of white blood cell populations were not evaluated in IND01-D15. The cause must be indicated in the original documents.	NA

	45014	2021-12-23	Patient 1137-9: maintenance in medical records.	DEC/23/2021: The CRA reported that, according to medical records, no maintenance visits have been performed since the allogeneic hematopoietic stem cell transplant (alloSCT). According to the data, the alloSCT was performed on April 16, 2021. MT01 (between 60 and 180 days after allogeneic stem cell transplantation) was to be performed. March 23, 2022: The study coordinator confirmed that maintenance was not performed. This must be confirmed by the investigator and the reason must be documented in the medical records. The EOT must be documented.	NA
	44754	2021-12-03	Patient 1137-3_central laboratory samples prior to allogeneic hematopoietic stem cell transplantation (alloSCT)	Pre-alloSCT was performed on July 8, 2020, according to eCRF data, and samples for the central laboratory were collected on July 1, 2020. There is no set time period for pre-alloSCT procedures, so these procedures were performed outside of that period. The date of the visit remains to be confirmed during the MV. In addition, the qPCR MRD results are not available (the subject tested positive in the screening test). It remains to be confirmed whether the central laboratory received the samples. 12/22/2021: The central laboratory has not responded. This issue could not be discussed with the site staff during the MV, as they were unavailable. March 23, 2022: The Central Laboratory has yet to	NA

				confirm whether the samples were received and whether they were valid. The center staff has yet to confirm the date of the pre-alloSCT. If the visit took place on July 8, 2021, as indicated in the CRF, this visit was conducted by Aitana Balaguer, who is not a delegate in the study. May 18, 2023: The samples were sent on July 1, 2020, and the visit took place on July 8, 2020, so no samples were sent during the pre-allo-STC visit. The visit was conducted by Aitana Balaguer, who is not delegated to the study, so her CV, GCP, delegation, and training record are pending.	
La Fe University and Polytechnic Hospital	43705	2021-09-24	Patient 1137-12_IND01-D05 Blood count	24/SEP/2021 - Leukocyte values were not evaluated in IND01-D05, probably due to severe leukopenia. Not indicated in SD. It remains to be confirmed whether this should be considered a PD. Dec 22, 2021 - The CRA has reminded the center staff that it remains to be confirmed why the differential values of the white blood cell populations were not evaluated in IND01-D05.	Site staff should document the reason why this information was not assessed in the medical records.
	40195	2021-06-07	Patient 1137-6_PI not returned by patient	Vial 85035 dispensed on 10/06/2020 to patient 1137-6 was found to be missing and compliance could not be verified. DEC 22, 2021 - During the monitoring visit, the CRA did not have time to check whether this information had been included in the medical records. JAN 13, 2022 - During the accountability review	This must be documented in the medical records. CRA will review this during the next MV.

				following the MV conducted on January 11, 2022. It was detected that kit 85035 was not administered to subject 1137-6, but to subject 1137-2. The kit dispensed on 06-OCT-2020 was 85025 (probably a typographical error). The kits administered were 85025 and 85028. According to the pharmacy accountability log, 85023 was returned (23 tablets) and 85028 was not returned, but kit 85028 is indicated as having been destroyed on June 7, 2021, while kit 85025 was not. Neither kit was available during the MV performed on January 11, 2022. The email sent by the previous CRA indicated that the kit to be destroyed was 85028 (23 tablets). Pharmacists are waiting to confirm which of the two kits was returned and to modify the information in the IP dispensing record where necessary. If kit 85025 was destroyed, an NTF must be completed indicating that the IP destruction form stated that kit 85028 (dispensed on October 16, 2020) was destroyed instead of 85025 and that kit 85028 was not returned. During the next on-site MV, the CRA will check whether the original documents show that the kit was not returned. Jan. 14, 2022: The pharmacist reported that the kit that was not returned was 85025; the subject lost this kit. This should be noted in the	

				medical records. This will be reviewed during the next on-site MV. March 23, 2022: The medical records still need to document that kit 85025 was lost and that kit 85028 was dispensed on October 16, 2020. This kit was not returned.	
La Fe University and Polytechnic Hospital	40194	2021-06-07	Patient 1137-2_IP has not been returned by patient 85022.	It was detected that bottle 85022 dispensed on 08/17/2020 to patient 1137-2 was not returned by the patient and compliance could not be verified. 12/22/2021: During the visit, the CRA did not have time to check whether this information was documented in the medical records. This will be reviewed at the next MV. March 23, 2022: The CRA was unable to review whether the appendix indicated that the kit had not been returned.	It must be documented in the medical records. The CRA will review it at the next medical visit.
	50843	2023-06-09	1137-19_Height prior to allogeneic hematopoietic stem cell transplantation not performed	June 9, 2023: The center did not measure the patient's height at the visit prior to allogeneic hematopoietic stem cell transplantation.	
	50842	2023-06-09	1137-13_EoT QLQC30 not performed	June 9, 2023: The center did not perform the QLQC30 at the EoT visit.	

	48006	2022-10-05	1137-19_IND01-D22_Total proteins	October 5, 2022: Total proteins not evaluated in the chemical analyses performed during IND01-D22.	
	48005	October 5, 2022	1137-19_IND01-D05_Complete blood count not performed.	October 5, 2022: On December 13, 2021, patient 1137-19 attended IND01-D05 to begin treatment with quizartinib, but the patient started treatment without having the blood count required by the protocol, which put the subject's health at possible risk. January 11, 2023: On October 6, 2022, the sponsor was informed by email by the CRA. On October 10, 2022, the sponsor responded that it did not consider this to be a serious violation and that it was not necessary to report it, so no further action was taken. The email was recorded in the center's correspondence.	
La Fe University and Polytechnic Hospital	48004	2022-10-05	1137-19_IND01-D01_Laboratory tests not performed	October 5, 2022: On December 7, 2021, patient 1137-19 attended his screening visit. As described in the medical record, neither the hemostasis nor the biochemistry tests, which were requested urgently, could be performed on that day, although the results were not available until December 8, 2021. The patient began chemotherapy on December 7, 2021, without the results of those tests, which may compromise the subject's health. January 11, 2023: On October 6, 2022, the CRA informed	NA

				the sponsor by email. On October 10, 2022, the sponsor responded that it did not consider this to be a serious violation and that it was not necessary to report it, so no further action was taken. The email is recorded in the site's correspondence.	
	48003	2022-10-05	1137-19_IND01-D01_ECOG	October 5, 2022: ECOG in IND01-D01 not performed.	NA
	48002	2022-10-05	1137-19_Chemical screening incomplete	October 5, 2022: Missing values in screening chemistry: BUN, CO2, urate, alkaline phosphatase, albumin, magnesium, phosphate, and calcium.	NA
	47105	2022-06-28	1137-5_IND01-D05 late visit	Patient 1137-5 IND01-D05 visit outside the time limit by 1 day	NA
	46388	2022-03-23	Patient 1137-7_IND01-D05_ECG	March 23, 2022: CRA reported that the time between ECGs in IND01-D05 was less than 2 minutes.	NA
	46380	2022-03-23	Patient 1137-6_ECGs	March 3, 2022: During the visit, the CRA noted that only two ECGs were performed in IND01-D15. According to the protocol, three ECGs should be performed per visit.	NA
	46371	2022-03-23	Patient 1137-4_ECGs	March 23, 2022: During the visit, the CRA observed that the time between ECGs was less than 2 minutes in IND01-D05, IND01-D15, and IND01-D22.	NA
	46365	2022	Patient 1137-3_IND01-D22_ECG	March 23, 2022: The time between ECGs was less than 2 minutes in IND01-D22.	

La Fe University and Polytechnic Hospital	46364	March 23, 2022	Patient 1137-3_prealloSCT_QLQC30	March 23, 2022: QLQC30 has not been filed in the patient's folder. Center staff is waiting to confirm whether this questionnaire has been provided and completed.	NA
	46363	2022-03-24	Patient 1137-3_SAE #bloody diarrhea	March 23, 2022: During the visit, the CRA noted that the subject was hospitalized from November 19, 2020, to November 24, 2020. Initially diagnosed as grade 4 intestinal GVHD, but this was ruled out based on colon biopsy results. Center staff are awaiting confirmation of the name of this AGE, characterized by bloody diarrhea. June 28, 2022: Center staff confirm that GVHD was suspected, so it is directly related to the transplant and is not considered an AAE.	NA
	46360	2022-03-23	Patient 1137-2_ECGs	2323Mar2022 - The CRA noted that the time between ECGs at visits IND01-D05, IND01-D15, IND01-D22, MTO-01, MT01-D15, MTO-02, MTO03, MTO-04, and MTO-05 was less than 2 minutes. According to the protocol, the time between ECGs must be at least 2 minutes.	NA
	45250	2022-01-24	Patient 1137-7_QTcF interval prolongation	JAN/24/2022: Site staff are awaiting confirmation of whether the subject has a QTcF greater than 480. The eCRF indicates a QTcF prolongation as an adverse event on October 23, 2020, and a reduction in quizartinib. In addition,	NA

				the ECG indicates a value of 484 on October 23, 2020. In this case, it should be reported as an AESI and this issue should be classified as PD. The CRA has sent an email to the site staff to resolve this issue. March 23, 2022: During the MV, the CRA confirmed that the QTcF prolongation was reported and that on October 23, 2020 (484 ms, ECG only), the quizartinib dose was reduced to 30 mg for that reason. The QTcF normalized on October 28, 2021, but the dose was maintained because the subject started treatment with posoconazole.	
	45216	2022-01-24	Patient 1137-6_QLQ30 - IND01-D05	JAN/24/2022 - The eCRF indicates that some QLQ30 data is missing. The CRA is waiting to confirm this at the next medical visit. If this is correct, this action should be considered a protocol deviation.	NA
	45054	2022-06-28	Patient 1137-11_pre-alloSCT - vital signs	Vital signs measured on April 19, 2021, outside the range described by the protocol	NA
La Fe University and Polytechnic Hospital	45038	2021-12-22	Patient 1137-9_IND01-D01 - Pregnancy test	23/DEC/2021 - Pregnancy test not performed in IND01-D01 (screening test indicated in eCRF for this visit).	NA
	44782	2021-12	Patient 1137-13_EOT - Laboratory tests	The bone marrow samples were not sent at the EOT visit (July 26, 2021). It remains to be confirmed whether the peripheral blood samples were sent.	

				According to the sample inventory form, these samples were sent, but the date of confirmation of receipt at PLATAFO-LMA is not indicated.	
	44781	2021-12-09	Patient 1137-12_IND01-D22 out of window	According to the data in the eCRF, IND01-D22 was done outside the window. Visit IND01-D15 was done on 16-Mar-2021. The visit IND01-D22 was planned on 25-Mar-2021 (+/- 2 days), but the visit was done on 22-Mar-2021. 22/DEC/2021 - During the visit it was notified that in the medical records it is not indicated that visit as IND01-D22 (it is indicated day 26).	The center is reminded of the procedures to be carried out according to the protocol.
	44775	2021-12-04	Patient 1137-10_EOT - Laboratory tests	The samples were not sent to the central laboratory at the EOT (visit made on March 11, 2021).	The center is reminded of the procedures to be carried out according to protocol.
	44774	2021-12-04	Patient 1137-9_IND01-22 out of range	According to eCRF data, IND01-D22 was performed on January 25, 2021. According to the protocol, this visit should have been performed on January 29, 2021 (+/- 2 days).	The site is reminded of the procedures to be performed according to the protocol.
	44773	2021-12-03	Patient 1137-7_EOT visit	On November 24, 2020, the site sent the IND01-D35 samples (visit performed on November 24, 2020) in accordance with the eCRF. The EOT samples were not sent. It remains to be confirmed whether the EOT visit was performed (it was indicated that this visit was performed on the same day as IND01-D35).	The site is reminded of the procedures to be carried out according to the protocol

	44767	2021-12-03	Patient1137-5_Screening - cytogenetics	According to the eCRF data, cytogenetics were not evaluated during screening.	The center is reminded of the procedures to be carried out according to the protocol.
	44756	2021-12-03	Patient 1137-3_EOT Laboratory tests	The samples to be sent to the central laboratory were not collected at the EOT.	The center is reminded of the procedures to be carried out according to protocol.
	44755	2021-12-03	Patient 1137-3_EOT visit	The eCRF indicates that the EOT visit took place on June 2, 2021, while the alloSCT (the last visit recorded in the eCRF took place in August 2020).	NA
	44750	2021-12-02	Patient 1137-7_EOT visit	Discontinuation of EOT is planned 30 days before the last dose of quizartinib if CR/CRi has not been achieved. In this case, the EOT visit was scheduled for April 29, 2021 (+/-7 days) because the last dose was taken on March 30, 2021. However, the visit was conducted on May 28, 2021.	NA
La Fe University and Polytechnic Hospital	44749	2021-12-02	Patient 1137-2_MT07 visit after hours	The MTO-07 was performed after the deadline. This visit was scheduled for February 4, 2021 (the previous cycle began on January 7, 2021), but was performed on February 2, 2021. For this reason, the MTO6 cycle lasted 26 days and the patient received treatment for 26 days with MTO6.	The center is reminded of the procedures to be carried out according to protocol
	44748	2021-12-02	Patient 1137-2_MT05 visit after hours	MTO-05 was performed after the deadline. This visit was scheduled for December 8, 2020 (the previous cycle began on November 10, 2020), but was performed on December 10, 2020. For	NA

				this reason, MTO4 was 2 days longer and the patient took quizartinib for 30 days.	
	43709	2021-09-24	Patient 1137-16_Hemostasis was not measured on IND01-D01.	24/SEP/2021 - Hemostasis values were not assessed during IND01-D01.	The center is reminded of the procedures to be carried out according to protocol.
	50871	2023-06-23	1137-12_EOT not performed	June 3, 2023: EoT was not completed because the center team staff forgot to restart treatment after AlloSCT.	NA
	50870	2023-06-23	137-2_Additional response assessment #6_Vital signs not taken.	June 3, 2023: Additional response assessment #6_Vital signs not taken.	NA
	50738	May 18, 2023	1137-7_IND01-D15_Laboratory tests performed prior to visit	May 18, 2020: At visit IND01-D15, the chemistry panel should have been performed along with the rest of the assessments on October 30, 2020, but it was performed on October 29, 2020, not complying with the protocol assessment schedule.	The center is reminded of the procedures to be carried out according to protocol
	50737	2023-05-18	1137-7_IND01-D05_Off schedule	May 18, 2023: The IND01-D05 visit should have been conducted on October 20, 2020, according to the protocol, but it was conducted on October 22, 2020, two days outside the established timeframe.	The center is reminded of the procedures to be carried out according to protocol.
	50736	2023-05-18	1137-5_EoT visit not performed	May 18, 2023: The EoT visit was not performed because the patient was hospitalized at another center before	NA

				passing away, without being able to comply with the protocol's evaluation schedule.	
	50735	May 18	1137-4_Additional response assessment #2_incomplete assessments	May 18, 2023: At the additional response assessment visit #2, the following assessments were not performed: vital signs, chemistry (urate, total bilirubin, alkaline phosphatase, albumin, phosphate, magnesium), peripheral blood biobank.	NA
La Fe University and Polytechnic Hospital	50734	May 18, 2023	1137-4_Additional response assessment no. 1_incomplete assessments	May 18, 2023: During the additional response assessment visit no. 1, the following assessments were not performed: complete blood count (blasts), chemical analysis (BUN, urate, total bilirubin, alkaline phosphatase, albumin, phosphate, magnesium, calcium).	NA
	50732	2023-05-18	1137-3_EoT visit not performed	May 18, 2023: The end-of-treatment visit was not performed because the center forgot to restart the patient's treatment after allogeneic hematopoietic stem cell transplantation and forgot to perform the end-of-treatment visit, failing to comply with the protocol evaluation schedule.	The center is reminded of the procedures to be carried out according to the protocol.
	50731	2023-05-18	1137-2_Additional response assessment #5_Incomple	May 8, 2023: At the additional response evaluation visit #5, the following evaluations were not performed: ECOG, complete blood count, chemistry (AST, BUN).	NA

			te assessment		
	50730	May 18	1137-2_EoT_Incomplete assessments	May 18, 2023: The following assessments were not performed at the EoT visit: MRD by flow cytometry and RT QPCR, BM and PB biobank, BM assessment, chemistry (phosphate, calcium, magnesium), QLQC30, and ECOG.	The center is reminded of the procedures to be carried out according to the protocol.
	48577	2023-01-11	1137-19: Local and central bone marrow evaluation was not performed prior to allogeneic hematopoietic stem cell transplantation (pre-alloHSCT).	January 11, 2023: During pre-alloHSCT, the center did not take the local bone marrow evaluation sample or send the samples to the central laboratory.	The center is reminded of the procedures to be carried out according to protocol
	48576	2023-01-11	1137-16 EoT evaluations not performed	January 11, 2023: During EoT, the center did not perform any evaluations because the patient was urgently hospitalized for chemotherapy due to disease progression.	NA
	48575	2023-01-11	1137-11 Additional response assessment	January 11, 2023: During response assessment #1, the site did not perform the physical exam.	The center is reminded of the procedures to be carried out according to the protocol.

			#1: Physical examination not performed.		
La Fe University and Polytechnic Hospital	48574	2023-01-11	1137-11 EoT: multiple assessments have not been performed.	January 11, 2023: during the EoT, the center did not perform the ECOG, the QLQ30, the local BM assessment, or the centralized shipment of samples.	The center is reminded of the procedures to be carried out according to the protocol.
	48573	2023-01-11	1137-10 EoT QLQ30 not performed	January 11, 2023: During EoT, the site did not perform the QLQ30.	The center is reminded of the procedures to be carried out according to the protocol.
	48572	2023-01-11	1137-9: Multiple pre-allogeneic hematopoietic stem cell transplantation (pre-alloHSCT) assessments were not performed.	January 11, 2023: During allogeneic pre-HSCT, the center did not take vital signs, did not send samples to the central laboratory, and did not perform calcium assessment in the QLQ30 and chemical analysis.	The center is reminded of the procedures to be carried out according to protocol
	48571	2023-01-11	1137-7-EoT QLQ30 not performed	January 11, 2023: During EoT, the site did not perform QLQ30.	The center is reminded of the procedures to be carried out according to the protocol.
	48570	2023-01-11	1137-2 ECOG response assessment #2 not performed	January 11, 2023: ECOG did not perform response assessment #2.	The center is reminded of the procedures to be carried out according to the protocol.

	47106	2022-06-28	1137-6_IND01-D15_ECG missing	June 28, 2022: Patient 1137-6 IND01-D15, only two ECGs were performed out of the three required by the protocol. January 11, 2023 - Pending issue, during MV11 only the CRF was reviewed due to lack of time and because only the person in charge of data entry responded and attended the CRA.	The center is reminded of the procedures to be carried out according to the protocol.
	45215	2022-01-24	Patient 1137-4_Cytogenetics - Screening	JAN/24/2022 - The eCRF indicates that cytogenetics were evaluated on a date prior to the signing of the ICF. This is pending confirmation during the next MV. If confirmed, it should be reported as a PD. March 23, 2022: It is confirmed that the cytogenetic analyses were evaluated previously and were not repeated. It is permissible not to repeat them if they were performed according to clinical practice.	NA
	45056	2021-12-23	Patient 1137-11_MTO02_ECG	In MTO02, the time between ECGs was less than 2 minutes. According to the protocol, the difference between ECGs must be at least 2 minutes.	The center is reminded of the procedures to be carried out according to protocol.
	45043	December 22, 2021	Patient 1137-11_IND01-D35 – Physical examination	The physical examination was not performed during the IND01-D35 visit.	The center is reminded of the procedures to be carried out according to protocol
	45043	2021-12-22	Patient 1137-11_IND01-D15 - ECG	The time between ECGs was less than 2 minutes. According to the protocol, the difference between ECGs must be at least 2 minutes. The center is waiting to	NA

				confirm why this problem is recurring in several patients and visits (whether it was because the center staff was unaware of it or because they perform the ECG according to clinical practice following another standard).	
La Fe University and Polytechnic Hospital	45042	2021-12-22	Patient 1137-11_IND01-D15 - Chemical values not evaluated	In the analysis performed on IND01-D15, the following values were not evaluated: urate, alkaline phosphatase, albumin, magnesium, phosphatase, and calcium.	NA
	45027	2021-12-23	Patient 1137-12_IND01-D15 ECG	12/23/2021 - The time between ECGs was less than 2 minutes. According to the protocol, at least 2 minutes are required between ECGs. The center has not yet indicated why the time between ECGs was not as specified in the protocol.	NA
	45024	2021	Patient 1137-12_IND01-D15 BQ parameters	12/22/2021 - Urate, alkaline phosphatase, albumin, magnesium, and phosphatase values were not measured in IND01-D15.	NA
	45023	2021-12-23	Patient 1137-12_IP Treatment	DEC 23, 2021 - Medical records indicate that subject 1137-12 took the medication for longer than indicated in the protocol. The end of treatment should have been March 21, 2021, however, the subject took the medication until March 29, 2021. The physician made a note in the medical	NA

				records indicating that this did not compromise patient safety.	
	45020	2021-12-23	Patient 1137-9-IND01-D22 - ECG	12/23/2021 - The time between ECGs in IND01-D22 was less than 2 minutes. According to protocol, the time between ECGs must be at least 2 minutes.	The center is reminded of the procedures to be carried out according to protocol.
	2021-12-22	2021-12-22	Patient 1137-19_Inclusion in the study	12/22/2021: During MV, the CRA detected that subject 1137-19 had been included in the study without central laboratory results. The site locally assessed the FLT3 cohort (indicated as FLT3-ITD in the results of December 2, 2021). The patient has started treatment with quizartinib. The central laboratory results are still pending. February 2, 2022: There is a discrepancy in the results between the local and central laboratories, but the local coordinators confirmed that the subject can continue in the study. In the central laboratory, the results indicated that the subject was FLT3-ITD positive, but with a low burden.	NA
	44780	2021-12-09	Patient 1137-11_MTO2 off schedule	According to eCRF data, MTO02 was performed on September 2, 2021. The visit date is to be confirmed at the next MV. If the visit date is correct, the visit was performed outside the established timeframe. According to the protocol, each maintenance cycle of is performed every 28 days. The previous cycle began on July 22, 2021, so MTO02 should have	NA

				been performed on August 19, 2021 (24 days before the date indicated in the eCRF). Dec 23, 2021 - Medical records indicate that the visit was delayed due to QTcF prolongation (observed on August 19, 2021).	
La Fe University and Polytechnic Hospital	44779	Dec 9, 2021	Patient 1137-12_pre-alloSCT - QLQ30	According to the eCRF data, the QLQ30 was not assessed during the visit prior to allogeneic stem cell transplantation. It remains to be confirmed whether this procedure was assessed during the following MV. 12/22/2021: during the MV, it was confirmed that this document was missing. The assessment was not performed.	NA
	44778	2021-12-09	Patient 1137-11_Screening_MPFC central laboratory samples	According to PLATAFO-LMA data, the samples to be evaluated by IMIBIC (MPFC sample evaluation) were not sent for screening (neither in the shipment of January 18, 2021, nor in that of January 21, 2021). The CRA has sent an email to the central laboratory to confirm this. DEC/22/2021: the central laboratory is awaiting confirmation. MAR/23/2022: the central laboratory is still awaiting confirmation on this matter. The CRA has reminded them. 5/18/2023: Samples sent by the center on January 18 and 21, 2021, but the central laboratory has not generated any reports.	NA
	44777	2021-12-09	Patient 1137-11_pre-	According to the eCRF data, the QLQ30 was not assessed in the pre-alloSCT. This	NA

			alloSCT - QLQ30	is pending confirmation in the next MV. 12/22/2021 - The site confirmed that the QLQ30 was not assessed in the pre-alloSCT. It is pending confirmation whether the pre-alloSCT was performed. This is not indicated in the original documents.	
	43728	2021-09-24	Patient 1137-13_EOT samples	PB and BM samples were not collected at EOT.	NA
	44765	2021-12-03	Patient 1137-4_IND01-D35 - Central laboratory samples	The sample inventory form indicates that only blood samples were sent on September 2, 2020. However, the sample inventory form dated September 3, 2020, indicates that all IND01-D35 samples were shipped. This point remains to be clarified. Whether the sample inventory form dated September 2, 2020, was completed in error. If the IND01-D35 samples were collected and sent to the central laboratory on September 3, 2020, the samples will be sent between the time period (the visit was made on August 28, 2020, according to the eCRF data) and additional response assessment #1 can be deleted. Dec. 22, 2021 - This issue could not be reviewed during the MV due to lack of time. It will be reviewed at the next MV. May 18, 2023. At visit IND01-D35, blood	NA

				and bone marrow samples were not sent to the central laboratory, so the following assessments (MRD assessment by flow cytometry and RT QPCR and BM and PB biobank) were not performed, but were performed as an additional response assessment #1.	
La Fe University and Polytechnic Hospital	44581	2021-11-22	Patient 1137-11_SAE Febrile neutropenia October 29, 2021_	Nov. 22, 2021: The center sent the final SAE report for "febrile neutropenia" with a start date of Oct. 29, 2021. The center has not sent the initial report for this SAE. Some fields in the report have not been completed correctly. The version used is not the latest (v6.0 instead of the current version v7.0). Nov 23, 2021: The center reported that it sent the initial SAE to another email address. The email address was incorrect and the message was never received (message sent on October 29, 2021). The center sent the completed initial and final reports on November 23, 2021.	NA
	43727	2021-09-23	Patient samples 1137-1_EOT	The samples that were sent to the central laboratory were not collected at the treatment discontinuation visit.	NA
	43704	2021-09-24	Patient 1137-12_IND01-D05 BQ parameters	24/SEP/2021 - Several values are not evaluated in the IND01-D05 biochemistry. 22/DEC/2021 - Urate, alkaline phosphatase, albumin, magnesium, and phosphatase values were not measured in IND01-D05.	NA

	43703	2021-09-24	Patient 1137-12: Cytogenetic testing was not performed.	No cytogenetic tests were performed.	NA
	43702	2021-09-24	Patient 1137-13_QLQ30 EOT not evaluated	QLQ30 EOT not evaluated. Document missing.	NA
La Fe University and Polytechnic Hospital	43701	2021-09-24	Patient 1137-13_EOT vital signs	Vital signs were not assessed in the EOT.	The center is reminded of the procedures to be carried out according to protocol.
	43699	2021-09-24	All patients_Did not report when quizartinib was administered.	24/SEP/2021 - During the MV, the CRA observed that, in several cases, the date on which quizartinib was administered was not provided in SD, so it was not possible to verify whether the ECG was performed before or after the dose. A note indicating the time of quizartinib administration should be included. Dec 22, 2021: The time at which quizartinib was taken cannot be provided retrospectively. When the time of quizartinib administration is not indicated, the "time" field on the ECG form should be left blank. This has been communicated to site staff via email.	NA
	43695	2021-09-24	Patient 1137-13_SAE No. 6379_Sepsis	24/SEP/2021 - The FU report for the SAE due to sepsis was not reported on time; the event ended on 18/JUN/2021 and the FUP report was sent to safety on	NA

				24/SEP/2021, when the CRA detected during the MV that the FUP had not been sent. Furthermore, the SD does not indicate that this event was considered an SAE. The next MV will review whether the SAE has been correctly reported in the SD. 22/DEC/2021 - During the MV, it was not possible to check whether this had been documented in the original documents due to lack of time. 23/MAR/2022 - It remains to be documented that the event was considered an SAE. This is summarized in another issue.	
	43672	2021-09-23	Patient 1137-01_QLQ30 IND01-D05 and EOT missing	24/SEP/2021 - During the visit, it was reported that the QLQ30 IND01-D05 and EOT documents were missing. The site has not yet confirmed whether the subject did not complete this document. 22/DEC/2021 - The documents were not provided.	NA
	40201	2021-06-07	Patient 1137-12_SAE No. 6352_Sepsis_ Final form submitted after deadline - 06/07/2021 - FLAG-QUIDA - 1137	06/07/2021: SAE#6352_Sepsis1137-12: During the MV, the CRA detected that the sepsis SAE was considered completed on 03/17/2021 and the final SAE form was not reported until 03/31/2021.	NA

	40200	2021	Patient 1137-10_SAE No. 6341_Pneumonia_Delay in reporting SAE	1137-10: SAE No. 6341_Pneumonia_Lung infection. The SAE was considered closed on February 9, 2021, and the final SAE form was not reported until March 9, 2021.	NA
La Fe University and Polytechnic Hospital	38604	2021-02-23	Patient 1137-11_Cytogenetics performed outside the schedule	Cytogenetics performed outside schedule	No corrective measures required.
	37814	2021-01-18	Patient 1137-10_Delay in starting treatment with quizartinib	Delay in starting treatment with quizartinib due to lack of stock at the center. Treatment begins on day 8: -On January 12, 2021, the pharmacy service informed the CRA that they only had one bottle of quizartinib 30 mg available. -On January 13, 2021, the PM sent the request to the warehouse, which reported that, with the shipment leaving on January 14, 2021, the drug would arrive on Monday, January 18, 2021. According to the conversation between the CRA and the pharmacy service, no dispensing was expected. To avoid the IMP being in transit over the weekend, the PM decided that it was best for the drug to be shipped on Monday, January 18. This way, the drug would arrive on Wednesday, January 20. -On January 18,	PM contacted the warehouse to obtain information about alternatives for urgent shipping. PM was informed that, in order to meet the requirements for shipping with a certified company, the cost would exceed €1,000. PM contacted the site to confirm whether it was okay for the patient to start treatment on Wednesday, the 20th (day 8 of the IND). The investigator confirmed that it was okay. Therefore, express shipping was not necessary, and the patient started treatment with quizartinib on day 8 of induction.

				2021, SC David Pellicer reported that patient 1137-10 had to start induction treatment with quizartinib 30 mg (day 6 of IND). There is no stock of this medication at the center. JAN/19/2021: Discussed with the pharmacy service to report IP stock in advance. In addition, CRA will keep the IP tracking updated in the control table.	
	37804	2020-12-02	Patient 1137-1_No blood count or chemistry tests were performed in the additional respiratory evaluation.	1137-2: Blood count and chemistry were not evaluated in an additional response evaluation performed on 04/22/2020. All other tests necessary to perform the response assessment were performed, and blood counts and chemistry were assessed on 04/17/2020. 01/15/2021: CRA has sent an email to site staff reminding them that all tests must be performed at the additional response assessment.	NA
	37169	2020-12-02	Patient 1137-4_SAE No. 6293_Cholecystitis_Delay in reporting SAE	1137-4 Cholecystitis: center staff became aware of the event on August 24, 2020, but it was not reported until August 28, 2020, outside the permitted time frame. Javier Anuncibay (January 15, 2021): It was confirmed that this SAE was actually reported on August 25. This complies with the notification requirements of in terms of deadlines. Therefore, this is not a deviation.	NA
La Fe University and Polytechnic Hospital	37163	2020-12-02	Patient 1137-7_Cytogeneti	Screening cytogenetics performed on 08/21/2020, more than 21 days before	NA

			cs more than 21 days before treatment	IND01-01 (10/16/2020). It was clarified that cytogenetics was performed according to standard practice at the center. Jan. 15, 2021: The CRA has sent the training email to the PI regarding the timeframes allowed for the pre-ICF signature procedure. In addition, it has been confirmed that the results of this cytogenetic analysis have been recorded in the CRF.	
	31816	2020-08-25	Patient 1137-2_New ICF consent v2.0	All patients (ongoing and WD) must re-consent to participate in the study by signing the new ICF during their next visit to the center. The CRA will check this at the next MV. 08/25/2020: Patient 1137-2 has not signed the ICF v2.0. 12/02/2020: Patient 1137-2 has still not signed the ICF v2.0. The CRA has requested it again from the SC. In addition, researchers will be reminded again to sign it as soon as possible. 02/FEB/2021: It is confirmed that the patient signed the ICF v2.0 on 02/FEB/2021. The CRA has documented the new training on the ICF procedure in the site training log. It is pending signature by the PI. 07/JUN/2021: The site training log was not provided to the CRA during the VM because it was pending update, so this issue could not be reviewed. The CRA has requested that site staff email a copy as soon as possible. 12/22/2021: The site training	Patients must sign the ICF v2.0 as soon as possible.

				log does not document this new training conducted on January 15, 2021. This sheet is missing. This issue is summarized in issue #45,029.	
	31688	2020-09-08	Patient 1137-01_Monitoring error	During an on-site monitoring visit on August 25, 2020, the CRA identifies a potential SAE that appears to have occurred within the reporting timeframe. This potential SAE had not been reported to the sponsor. The CRA managed the deviation. However, it was not escalated until September 8, 2020, during the MV report generation process (documenting the deviation in ODOO). This is considered a monitoring error, as significant deviations should be escalated as soon as possible, given their potential impact on the study. NOTE: It was ultimately confirmed that the event did not meet the criteria for reporting to the sponsor.	NA
La Fe University and Polytechnic Hospital	31211	2020-08-25	Patient 1137-3_Cytogenetics - Screening - Procedure prior to signing the ICF	1137-1: Cytogenetic analysis was not performed for selection. Cytogenetic results from July 1, 2019, were used, and the patient signed the ICF on May 11, 2020. December 2, 2020: Training could not be performed during MV3 due to limited availability of center staff. The CRA will send a training email to the center staff. This will be documented in the training log during the next MV. Jan. 15, 2021: The CRA has sent a training email. It will be documented in the	NA

				training log during the next MV. Feb. 23, 2021: The CRA has documented the training in the center's training log. It is pending signature by the principal investigator. 07/JUN/2021: The site training log was not provided to the CRA during the MV because it was pending update, so this issue could not be reviewed. The CRA has requested that site staff email a copy as soon as possible. 22/DEC/2021: The site has trained	
	30617	2020-04-23	Patient 1137-1_ICF v2.0 post-reconsent	All patients (ongoing and WD) must re-consent to participate in the study by signing the new ICF during their next site visit. The CRA will check this at the next MV. 08/25/2020: Patient 1137-1 has not signed the ICF v2.0. 10/05/2020: After review, the PM considers that this is not a major deviation, as the patient's safety and willingness to continue in the study have not been affected. The patient has already left the study due to not achieving a complete response after the induction cycle. DEC 2, 2020: It was detected that the patient died on NOV 19, 2020, without having signed the ICF v2.0. No corrective measures are being taken in this case. Jan. 15, 2021: The CRA sent an email to site staff reminding them of the importance of signing new versions of the ICF as soon as they are approved.	Patients should sign the ICF v2.0 as soon as possible, if possible.

	25585	2020-02-21	Patient 1137-1_Cytogenetics performed before signing the informed consent form ( ).	The cytogenetic test was performed on November 28, 2019, and the ICf was signed on January 2, 2020, meaning that the test was performed more than 21 days before the ICF was signed. August 25, 2020: Due to time constraints and the availability of center staff during the MV2 , these training sessions could not be held. The CRA will conduct them at the next MV. October 5, 2020: Upon review, the PM considers the correct classification of this deviation to be "minor." Patient safety or data integrity were not compromised, and patient eligibility did not depend on this test. December 1, 2020: Due to site availability, the on-site training could not be conducted. The CRA will provide training to site staff via email. It will be documented in the training log during the next MV. January 15, 2021: The CRA has sent the training email. February 23, 2021: The CRA has documented the training in the site training log. It is pending signature by the principal investigator. June 7, 2021: The site training log was not provided to the CRA during the MV because it was pending update, so this issue could not be reviewed. The CRA has requested that site staff email a copy as soon as possible.	No corrective measures apply.

La Fe University and Polytechnic Hospital	25584	2020-02-21	Patient 1137-1_G-CSF IND01 incorrect dose	G-CSF was administered from January 6, 2020 (day -1) to January 12, 2020 (day 5). The dose administered was 526 mcg/day. According to the protocol, the dose should be 300 mcg/m2/day, so patient 1137-1 should receive 480 mcg/day. 08/25/2020: Due to lack of time and the availability of center staff during MV2, these trainings could not be carried out. The CRA will conduct them during the next MV. DEC 1, 2020: The on-site training could not be conducted. The CRA will send a training email and it will be documented in the training log during the next MV. JAN/15/2021: The CRA has sent the training email. FEB/23/2021: The CRA has documented the training in the center's training log. It is pending signature by the IP. 07/JUN/2021: The center's training log was not provided to the CRA during the MV because it was pending update, so this matter could not be reviewed. The CRA has asked the center's staff to send a copy by email as soon as possible. DEC 22, 2021: The new training is still pending documentation in the center's training log. This matter is documented in case no. 45,029.	NA
Central University Hospital of Asturias	53371	2023-10-24	1147-7_EOT chemical elements not evaluated.	In the chemical analysis of the EOT for patient 1147-7, some parameters required by the protocol were not	No corrective actions can be taken, as the window period has ended. The missing evaluations can be clearly

				evaluated: chloride, magnesium, and total proteins.	identified in the original documents.
	53370	2023-10-24	1147-7_IND01-D01 Chemical elements not evaluated.	In the IND01-D01 chemistry for patient 1147-7, some parameters required by the protocol were not evaluated: chloride and albumin.	No corrective action can be taken, as the window period has passed. The missing assessments can be clearly identified in the original documents.
	53369	2023-10-24	1147-6_physical examination in relapse-progression resistance.	During the progression-relapse-resistance visit for patient 1147-6, the physical examination was not performed. May 8, 2025: Since the sponsor blocked the database and the eCRF was closed unilaterally, it is not possible to modify the case report form data during the COV. Therefore, this issue is closed without resolution.	No corrective actions can be taken as the window period has expired. However, the CRA will request an addendum to record this deviation in the medical records.
	53367	2023-10-24	1147-6_Chemical elements EOT not evaluated.	In the chemical analysis of the EOT for patient 1147-6, some parameters required by the protocol were not evaluated: chloride and total protein.	No corrective actions can be taken, as the window period has already ended. In addition, the missing evaluations can be clearly identified in the original documents.
	53363	2023-10-24	1147-2_EOT QLQ-c30 not performed	In the EOT, patient 1147-2 did not complete the QLQ-c30.08. May 2025: Since the sponsor performed the database lock and the eCRF was closed unilaterally, it is not possible to modify the case report form data during the COV. Therefore, this issue is now considered closed without resolution.	No corrective action can be taken as the deadline has already passed. However, the CRA will request the principal investigator to report this in an appendix.

	53360	2023-10-24	1147-2_EOT rt-qPCR samples not sent to the central laboratory	In the case of patient 1147-2, during the EOT, bone marrow and peripheral blood samples for rt-qPCR were not sent to the central laboratory. Corrective action cannot be taken, as the window period has ended. New training on study procedures was previously conducted, and this deviation occurred before the new training, so no further preventive measures are necessary.	No corrective action can be taken, as the window period has ended.
	53359	2023-10-24	1147-2_EOT chemical elements not evaluated.	In the chemical analysis of the EOT for patient 1147-2, some parameters required by the protocol were not evaluated: chloride and total protein.	No corrective action can be taken, as the window period has already ended. In addition, the missing evaluations can be clearly identified in the original documents.
Central University Hospital of Asturias	53357	2023-10-24	1147-1_Lead sample from the biobank not sent.	October 24, 2023: The CRA detected that the peripheral blood sample for the biobank was not sent in IND01-D35. For patient 1147-1.08 May 2025: Since the sponsor blocked the database and the eCRF was closed unilaterally, it is not possible to modify the case report form data during the COV. Therefore, this matter is considered closed without resolution.	No corrective action can be taken, as the window period has ended. However, the CRA will ask the principal investigator to record in an appendix that this sample was not sent to the central laboratory.
	50869	2023-06-16	1147-7 MTO12 vital signs	In the case of patient 1147-7 from MTO12, heart rate and blood pressure were not assessed. The original documents show that these values were not recorded during the vital signs assessment.	No corrective action can be taken, as the window period has already ended. In addition, the missing assessments can be clearly identified in the original documents.

	50862		1147-4 Visit for progressive relapse resistance	June 9, 2023: At the progression visit, relapse resistance, the physical exam was not performed.	
	50861	2023-06-09	1147-4 Chemistry: pending evaluations	June 9, 2023: In the EOT discontinuation chemistry, creatinine, chloride, total bilirubin, alkaline phosphatase, AST, ALT, LDH, magnesium, phosphate, and total protein were not evaluated for patient 1147-4.	No corrective action can be taken, as the window period has already ended. In addition, the missing assessments can be clearly identified in the original documents.
	50851	2023-06-02	1147-2 Procedures not performed	In IND01-D01 and IND01-D05 chemistry, chloride, magnesium, or protein were not evaluated.	Corrective action cannot be taken, as the window period has already ended.
	50769		1147-7 Procedures not performed	- Temperature not evaluated in visits MTO1 and MTO8. - Chloride and total proteins not evaluated in chemical analyses of MTO2.	NA
	50768	2023-06-02	1147-6 procedures not performed	Reticulocytes not evaluated in the blood count at the progression-relapse-resistance visit. - Chloride and total protein not evaluated in the chemistry at the progression-relapse-resistance visit.	Corrective actions cannot be taken, as the deadline for performing these evaluations has already passed. The missing values can be clearly identified in the blood tests.
	50767		1147-5 procedures not performed	The Bm sample for evaluation at MTO12 is past due, as it is performed one month after the end of the cycle, coinciding with the EOT visit. Blasts are not evaluated in the EOT blood count. Chloride and total protein are not evaluated in the EOT chemistry.	NA

	50766	2023-05-18	1147-2 evaluations not performed	Reticulocytes and blasts were not evaluated in the IND01-D05, IND01-D15, IND01-D22 blood count. ECOG was not evaluated in IND01-D22. BM and PB samples were not sent to the central laboratory in IND01-D35.	No corrective action can be taken, as this patient has already completed the study and this assessment must be performed during the end-of-treatment visit. The principal investigator will prepare an appendix to document that this procedure has not been performed.
	50765	2023-05-29	1147-2 assessments not performed	EOT also coincided with Prog-rel-res visit. - Physical assessment - Vital signs - ECOG - Send BM samples for flow cytometry, rt-q-PCR, biobank - Send peripheral blood for rt-qPCR and biobank June 2, 2023 - The principal investigator reviewed the data with the CRA and reported that the actual EOT date was February 17, 2020, as the patient progressed on that date; however, it was not indicated in the medical records which visit corresponded to the EOT. The principal investigator made an addendum to clarify that the patient relapsed on that date, and all eCRF data related to EOT and the progression-relapse-resistance form were updated with the data from that day. Therefore, the only procedures that were not performed were: - Sending a BM and PB sample to the central laboratory for rt-qPCR and a PB sample to the biobank. - Performing the	No corrective action can be taken, as this patient has already completed the study and this assessment must be performed during the end-of-treatment visit. The principal investigator will prepare an appendix to document that this procedure has not been performed.

				Qlq-C30.09 June 2023: not reviewed due to lack of time. June 16, 2023: not reviewed due to lack of time. October 24, 2023: not reviewed due to lack of time.	
Central University Hospital of Asturias	50764	May 18, 2023	1147-5 Qlq C30 EOT not performed	02Jun2023 - This issue was not reviewed due to lack of time.	No corrective action can be taken, as this patient has already completed the study and this assessment must be performed during the end-of-treatment visit. The principal investigator will prepare an appendix to document that this procedure has not been performed.
	50752	May 19, 2023	MTO01-D15 ECG is off schedule	The MTO01-D15 ECG form is out of schedule, as it was performed on day +17.	No corrective action can be taken, as this patient has already completed the study and this assessment must be performed during the end-of-treatment visit. The principal investigator will make an appendix to document that this procedure has not been performed.
	48798	2023-02-14	Patient 1147-6_Procedures not performed	Screening: the patient's race is not listed in the medical record. EOT: physical examination was not performed. Temperature was not recorded. ECOG and Qlq C30 tests were not performed.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	48797	2023-02-14	Patient 1147-5_Procedure	Screening: chloride, CO2, and direct bilirubin not evaluated in chemical	The CRA requested that the PI add an appendix to the medical

			s not performed	analysis. Blastocytes not evaluated in complete blood count. IND01-D01: chloride not evaluated in chemical analysis. IND01-D35: ECOG not evaluated. Reticulocytes and blasts not evaluated in complete blood count. MTO1: chloride and total protein not evaluated in the chemical analysis . MTO5: blasts not evaluated in the blood count. MTO8: ECOG not performed.	record to document this deviation.
Central University Hospital of Asturias	48796	2023-02-14	Patient 1147-5_Procedures not performed	Screening tests: CO2 and direct bilirubin levels were not evaluated in the chemical analyses. Only an electrocardiogram was performed.	The CRA asked the PI to add an appendix to the medical record to document this deviation.
	48794	2023-02-14	Patient 1147-5_Procedures not performed	Screening: The following parameters are not evaluated in the chemical analysis: chloride, CO2, direct bilirubin, Mg, and total protein. Only an ECG was performed. IND01-D01: Chloride was not evaluated in the chemical analysis. ECOG was not performed. IND01-D05: ECOG was not evaluated. IND01-D15: ECOG was not evaluated. No ECG was performed. IND01-D22: The following parameters are not evaluated in the chemical analysis: chloride, urate, total bilirubin, alkaline phosphatase, ALT, AST, LDH, albumin, Mg, phosphate, total protein, and calcium. In addition, it remains to be indicated in the medical	The CRA requested that the PI add an appendix to the medical record to document this deviation.

				record that visit Ind01-D35 and EOT were performed at the same time.	
	48251	2022-10-06	Patient 1147-5_Procedures not performed	Screening: An addendum to the medical record is pending to document that BUN, chloride, CO2, magnesium, and total protein were not evaluated because they were forgotten. IND01-D1: An addendum is pending to document in the medical record that GCSF was administered for 5 days instead of 6 days.	CRA requested that the principal investigator make additions to the medical record to document all protocol deviations and demonstrate that they were aware of them.
	48249	2022-10-06	Patient 1147-5_IND1-D22_Post-dose ECG	ND1-D22: An addition to the medical record is pending to document that an ECG was performed after taking the medication. According to protocol V2.0, the ECG should be performed before the dose at this visit. The CRA reminded the PI that this issue should be resolved as soon as possible. February 14, 2023. The PI made the addition to the medical record.	The CRA requested that the PI make an appendix to the medical record to document this deviation.
	48248	2022-10-06	Patient 1147-4_Screening, IND, EOT_Procedures not performed	Screening: An addendum to the medical record is pending to clarify that the ECOG at screening was documented one day before screening. However, it was not documented at the screening visit, even though it remained the same. Selection: The center did not assess temperature because it was forgotten. An addition to the medical record is pending to document this deviation.	The CRA requested that the PI add an appendix to the medical record to document this deviation.

				IND01-D1: It is pending to document in the medical record that the patient started chemotherapy on the same day as the selection ( ) due to the urgency of starting treatment as soon as possible. IND01-D1: It remains to be documented in the medical record that the center did not evaluate blasts, reticulocytes, and BUN by mistake. IND01-D1: It remains to be specified in the medical record IN01-D35: It remains to be documented in the medical record that the physical examination, ECOG, and vital signs were not collected. In addition, it remains to be documented that the center did not evaluate BUN, creatinine, chloride, total bilirubin, alkaline phosphatase, AST, ALT, LSH, magnesium, phosphate, and total protein.	
Central University Hospital of Asturias	48246	2022-10-06	Patient 1147-3_MTO6_Incorrect dispensing of quizartinib 20 mg	Oct 6, 2022 The CRA detected that this was a pharmacy error. The kit prescribed by the investigator is 30 mg, and the pharmacist dispensed a 20 mg kit. The pharmacist wrote a note on the dispensing documenting that this was a pharmacy error. An addendum to the medical record is pending to document that this patient took a lower dose than he should have. February 14, 2023. An	NA

				addendum to the medical record is still pending to document this deviation.	
	47263	2022-06-30	Patient 1147-3_MTO6_QTc prolongation and quizartinib discontinuation.	Jun 0, 2022 CRA detected the following significant deviations from the protocol: -MTO6: The cycle was delayed due to a prolonged QTc. An addendum is pending to document that this cycle was delayed due to a prolonged QTc rather than a QTcF by mistake. This is a major protocol deviation. 7/21/2022 This deviation is repeated in Odoo, so it was closed, considering the incident valid.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	47262	2022-06-30	Patient 1147-5_MTO1-D15 and MTO5_discontinuation of quizartinib and missing ECG	June 30, 2022 CRA detected the following significant deviations from the protocol: -MTO1-D15: ECGs were performed, but the original document is not available due to an error. The QTc values are 454, 462, and 465, but the QTcF is not available for that date. For this reason, treatment with quizartinib was interrupted for 3 days. On 09/30/2021, another ECG was performed with QTcF values of 429, 430, and 422, so it was decided to increase the dose to 60 mg/day. This is a significant deviation from the protocol. -MTO 5: It remains to be documented that the original ECG was not available because the center had lost it. The medical record only documented the three QTc values. This is a significant deviation from the protocol. Oct 6, 2022	The CRA asked the PI to make an appendix to the medical record to document this deviation.

				This addendum to the medical record has yet to be made. Feb 14, 2023 The principal investigator made the addendum.	
Central University Hospital of Asturias	47261	2022-06-30	Patient 1147-5_IND01, Pre-AlloSCT, MTO1-MTO11	Jun 30, 2022 The CRA detected that an appendix is pending to document the following minor deviations: -IN01-D1: The patient started IND01-D1 on the same day as the selection visit due to the urgency of starting chemotherapy. An appendix is pending to document this deviation from the protocol. -IND01-D15: The center did not evaluate the ECOG and an ECG was not performed every 2 minutes due to an error. -IND01-D35: An appendix is pending to document that this visit corresponds to the visit performed on March 15, 2021. Subsequently, on March 23, 2021, the center performed the bone marrow evaluation. -PreAlloSCT: An appendix is pending to document that this visit corresponds to the visit made on April 28, 2021. -MTO2: By mistake, the temperature was not taken. An appendix is pending to document this deviation from the protocol. In addition, an appendix is pending to document that chloride and total protein were not evaluated. -MTO 3: An appendix is pending to document that chloride and total protein were not evaluated. -MTO 4: An appendix is pending to document	The CRA asked the PI to add an appendix to the medical record to document this deviation.

				that ECOG, temperature, chloride, and total protein were not recorded. -MTO 6: An appendix is pending to document that ECOG, temperature, chloride, and total protein were not recorded. In addition, ECGs were not performed every 2 minutes and the MRD was negative. Documentation that this visit corresponds to the visit performed on February 4, 2022, is pending. -MTO 7: An addendum is pending to document that ECOG, temperature, chloride, and total protein were not recorded. In addition, ECGs were not performed every 2 minutes. -MTO 8: An addendum is pending to document that vital signs, chloride, and total protein were not recorded. In addition, ECGs were not performed every 2 minutes. -MTO 9: An addendum is pending to document that vital signs, ECOG, chloride, and total protein were not recorded. In addition, it is pending to specify that the MRD was negative. -MTO 10: An appendix is pending to document that temperature, ECOG, and chloride were not recorded. -MTO 11: An appendix is pending to document that temperature, ECOG, chloride, and total protein were not recorded. In addition, ECGs were not performed every 2 minutes. -AE: An appendix is pending to document the grade of all AEs. Oct 6, 2022: This	

				appendix is still pending in the medical record. Feb 14, 2023: Only the following appendices are pending: MTO11: ECGs were not performed every 2 minutes. AE: Document the severity of all AEs.	
Central University Hospital of Asturias	47260	June 29, 2022	Patient 1147-3_Delay in MTO6 due to QTc prolongation	Jun 29, 2022 The CRA detected that there was a one-week delay in MTO6 because the center considered a prolonged QTc instead of a QTcF. The cycle should not have been delayed because the QTcF was normal. The CRA requested that the principal investigator make an addendum to document this protocol deviation. The CRA reiterated the importance of considering the QTcF. Oct 6, 2022 This addendum to the medical record is still pending.	The CRA requested that the PI make an addendum to the medical record to document this deviation.
	46777	Apr 18, 2022	Patient 1147-5_IND01, preAlloSCT, MTO1, MTO2, and MTO3 _Procedures not performed	Apr 18, 2022 The CRA detected that the following additions were pending: - Make an addition to document that ECOG is not performed in the selection. - Make an addition to document that ECOG is not performed in IND01-D1. - Make an addition to document that ECOG is not performed in IND01-D5. - Make an addendum to document that the dose in IND01-D5 is 30 mg/day because posaconazole is being taken. - Make an addendum to document that in IND01-D5, an ECG is not performed every 2 minutes due to an error. - Make an appendix to document that the time of quizartinib administration was not	The CRA asked the PI to make an appendix in the medical record to document this deviation.

				recorded in IND01-D5 and, therefore, it is not possible to know how many hours later the ECG was performed.	
	46776	2022-04-18	Patient 1147-3_AE grade pending documentation in the medical record.	Apr 18, 2022 The CRA detected that the grade of all AEs was pending documentation in the medical record. The CRA reminded the PI of the importance of documenting the grade of all AEs in a timely manner.	The CRA asked the principal investigator to create an appendix to document the severity of adverse events in the medical record.
Central University Hospital of Asturias	46775	Apr 18, 2022	Patient 1147-3_MTO5, MTO6, MTO7, MTO8, MTO9, MTO10, MTO11, MTO12, and EOT	Apr 18, 2022 MTO5: The center did not evaluate chloride, LDH, and total protein. MTO6: The center did not evaluate chloride and total protein. MTO7: The center did not evaluate vital signs, chloride, and total protein. MTO8: The center did not assess vital signs, chloride, or total protein. In addition, ECGs were performed every minute. MTO9: The center did not assess vital signs, chloride, or total protein. MTO10: The center did not assess chloride or total protein. In addition, only one ECG was performed. MTO11: The center did not assess chloride or total protein. MTO12: The center did not assess chloride or total protein. EOT: The center did not assess chloride or total protein.	

	46775	2022-04-18	Patient 1147-3_MTO3	The site did not evaluate chloride and total protein at the MTO3 visit.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	46775	2022-04-18	Patient 1147-3_MTO1	The CRA detected that chloride, urate, and total protein were not assessed in chemistry during the MTO1 visit.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	46775	2022-04-18	Patient 1147-3_IND01-D15_Procedures not performed	April 8, 2022 The CRA detected that ECOG, urate, LDH, albumin, total protein, and the 3 ECGs were not performed in IND01-D15.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	46775	2022-04-18	Patient 1147-3_IND01-D15_Procedures n	Apr 18, 2022 The CRA detected that the ECOG and Electrocardiogram were not performed on IND01-D5. An addendum is pending to document this protocol deviation.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	46775	2022-04-18	Patient 1147-3_IND01-D1_Complete blood count performed outside of schedule.	Apr 18, 2022 The CRA detected that the complete blood count, chemistry panel, and hemostasis are out of range in IND01-D1. These procedures are the same as in the screening visit. An addendum is pending to document this protocol deviation.	The CRA requested that the PI add an appendix to the medical record to document this deviation.
	39281	Apr 20, 2021	Patient 1147-3_SAE No. 6289_Cervical bultoma_Delay in reporting SAE	1147-3: lump in the left cervical area ended on 08/17/2020, but the final report was submitted on 04/20/2021.	NA

	39281	20	Patient 1147-4_Complete chemistry to be confirmed	The chemistry reported in the CRF for IND01-D15 (Sep 9, 2020) has many parameters unavailable. Site staff should check if there is another more complete chemistry panel performed within the visit window and update the CRF if applicable. Jan 20, 2022 The CRA verified that SC changed the data in the CRF. It entered another more comprehensive chemical analysis dated 09/07/2020 (within the window period). The values for chloride, LDH, glucose, and urate are missing. This deviation from the protocol is pending documentation in the medical record.	The CRA asked the PI to add an appendix to the medical record to document this deviation.
Central University Hospital of Asturias	39281	2021-04-20	Patient 1147-3_Date of bone marrow extraction to be confirmed.	According to medical records and the CRF, the IND01-D35 bone marrow samples were obtained on September 1, 2020, but Platafo-LMA documents that the samples are from September 9, 2020. Center staff should confirm the date of extraction and correct as appropriate. On January 20, 2022, the CRA detected that the site sent the sample outside the IND01-D35 window period to the central laboratory. The sample collected on September 1, 2020, was evaluated by the local laboratory, and the sample collected on September 9, 2020, was evaluated by the central laboratory. The CRA retrained the PI and SC, who signed a training log.	NA

	39281	2021-04-20	Patient 1147-3_Date of vital signs to be confirmed	In IND01-D35, the CRF reports that vital signs were not assessed. Site staff should check whether there is a vital signs assessment within the visit interval and update the CRF if appropriate. 01/20/2022 The CRA verified that the site collected vital signs outside the interval in IND01-D35 by mistake. The CRA explained this protocol deviation and retrained the staff on protocol procedures.	The CRA requested that the PI make an appendix in the medical record to document this deviation.
	39281	2021-04-20	Patient 1147-3_IND01-D22_ECG to be updated in the CRF	In IND01-D22, the CRF reports the ECG from 7/28/2020, but there is only 1 ECG. SC should update the CRF with the triplicate ECGs performed on 7/27/2020. 1/20/2022.	The CRA asked the PI to add an appendix to the medical record to document this deviation.
	39281	2021-04-20	Patient 1147-2_Complete chemistry to be confirmed	The chemistry reported in the IND01-D35 CRF (04/07/2020) has many parameters unavailable. Site staff should check if there is another more complete chemistry panel performed within the visit period and update the CRF if appropriate. 01/20/2022 The SC changed the chemistry panel dated 04/07/2020 to another chemistry panel dated 04/07/2020 because it was more complete. However, chloride, urate, and LDH were not evaluated. An appendix is pending to document this issue. 04/18/2022 This appendix is still pending in the medical record.	The CRA requested that the PI add an appendix to the medical record to document this deviation.

Central University Hospital of Asturias	39281	Apr 20, 2021	Patient 1147-1_Medical history pending update	IND01-D35: vital signs, physical examination, and ECOG not documented in medical records. The investigator must modify the information on the tests performed during the visit on 7/15/2021: IND01-D35. The physical examination was documented in the medical records. Vital signs were not available, and the ECOG value was not documented in the medical records.	The CRA retrained the PI and SC on protocol procedures, and they signed a training log. This issue was closed.
	39281	2021-04-20	Patient 1147-5_GCS-F not administered	GCS-F was not administered on IND01 D-1. The medical record indicated that it was not advisable, as white blood cell counts were >25,000.	NA
	39281	2021	Patient 1147-1_Incorrect dose dispensed	The patient received 20 mg/day for 14 days instead of 40 mg/day for 14 days during induction treatment. He did not take any medication that would justify the dose reduction, nor did he have any complications during treatment. 04/21/2022: The CRA has informed the PM to clarify with the sponsor whether this could be considered a serious violation. The sponsor has confirmed that this is not a serious violation, as it did not affect the safety of the patient or subsequent patients, since patients in the 60 mg group did not experience DLT.	The principal investigator has documented this deviation in the medical records.
	39281	2021-04-20	Patient 1147-3_QLQ C30 not available	1147-3: QLQ c30 was not performed on IND01-D5. 20/JAN/20221147-3 did not complete the questionnaire on IND01-	The main cause should be documented in the medical records.

				D5 and preAlloSCT because the center forgot this procedure.	
	38371	2021-01-22	Patient 1147-2_ICF v2.0 still unsigned	The ICF v2.0 was approved on April 23, 2020, and the patient has not yet signed it. Due to the high number of deviations detected in the ICF, the principal investigator has been trained on how to complete the ICF and the ICF procedure during the next medical visit.	The principal investigator must provide it to the patient during the next visit, and the patient must sign it to continue in the study.
	38371	2021-01-22	Patient 1147-4_ECOG not assessed in IND01-D1	Patient 1147-4_ECOG not assessed in IND01-D1	NA
	38371	2021	Patient 1147-4_Saliva sample not sent with ORAGENE kit	The saliva sample was sent to the central laboratory in a urine tube instead of in the ORAGENE kit. The central laboratory confirmed that it was storing the sample for the biobank, but did not guarantee that it could be evaluated.	NA
	38371	2021-01-22	Patient 1147-1_ blood count not performed in IND01-D05	Patient 1147-1_No complete blood count performed in IND01-D05	NA
Asturias Central University Hospital	37933	2021-01-22	Patient 1147-3_Maintenance not yet started -	Maintenance should begin 60 days after allogeneic hematopoietic stem cell transplantation (10/16/2020), so it should start on 12/14/2020. The principal investigator has reported that it has not yet started because the patient has not fully recovered. The principal investigator has reported that	The main cause should be documented in the medical records.

				maintenance is scheduled to start on 01/26/2021.	
	37932	2021-01-22	Patient 1147-2_Vital signs checks have not been performed.	Selection: It has been detected that vital signs were not assessed according to the CRF and were not assessed after signing the ICF according to medical records. The CRA has asked the center staff to check if there is any previous analysis performed by standard clinical practice that has been used for selection. If available, it should be added to the CRF. If not, it will be noted as a protocol deviation.	NA
	37930	2021-01-22	Patient 1147-2_Hemostasis not assessed, confirmation	Selection: it has been detected that hemostasis was not assessed according to the CRF nor was it assessed after signing the ICF according to medical records.	The CRA has asked the center staff to check whether there is any previous analysis performed through routine clinical practice that has been used for selection. If available, it should be added to the CRF. Otherwise, it will be noted as a protocol deviation.
	37930	2021-01-22	Patient 1147-1_ICF v2.0 without new consent	1147-1: It was detected that the patient died before signing the ICF v2.0.	Due to the high number of deviations and problems detected in the ICF, the principal investigator has received training on how to complete the ICF and the ICF procedure during the next MV.
	37926	2021-01-22	Patient 1147-3_ICF not	The ICF v1.0 signed by the patient on 07/JUL/2020 was not signed by the investigator. The principal investigator	The CRA has asked the investigator to sign and add a note to the ICF filed in the ISF.

			signed by the investigator	has confirmed that the copy provided to the patient was duly signed by both parties.	The CRA will review it at the next MV. Due to the high number of deviations and issues detected in the ICF, the PI has received training on how to complete the ICF and the ICF procedure during the next MV.
	31753	2020-09-16	Patient 1147-3_D35 Sample lost	15/SEP/2020: The central laboratory H. PI reported that the bone marrow and peripheral blood samples (D35) from patient 1147-3 were not delivered for analysis. The sample is from day 35, the last day of induction. It is not essential to determine the cohort, as the patient is already in the study. 16/SEP/2020: The center is asked about the shipment of the samples. They commented that they made the shipment and did not receive any notification about the samples until today, when we asked them about it. If there have been customs issues with the shipment of the samples, the transport company (MRW) has not reported anything.	The study director has reviewed this deviation in which he has been involved, as has the CRA. The incident will be handled with the courier company, as it had been agreed that should notify the study team of all incidents. This did not happen in this case. Jan 22, 2021: Reviewed and discussed with the courier company to prevent this from happening again.
Central University Hospital of Asturias	28140	June 25, 2020	Patient inclusion in relation to the eligibility form	The trial coordinator states that investigators do not need to wait for feedback on the eligibility form, which they must send to the trial coordinators for review, before including the patient in the study. Patient inclusion in the study is at the investigator's discretion. This will only be necessary once one of the two phase II cohorts has been	The principal investigator comments to the trial coordinator that this contravenes point 9.4 of the protocol. The principal investigator comments that the protocol description should be amended, as otherwise there would be a deviation

				completed. This contravenes point 9.4 of the protocol, which states that "All patients will be selected and assigned to treatment after review of the site eligibility form by the trial coordinator." According to the trial coordinator's criteria, this will only apply once one of the cohort groups has been completed. This is considered a minor deviation that will take place in the study until the protocol is amended. The notification to the investigators is attached as requested by the trial coordinator.	from the protocol. It is agreed to accept the deviation at this point and review the protocol to confirm whether it needs to be modified. The investigators are informed as requested by the trial coordinators.
Virgen del Rocio University Hospital	39299	2021-04-29	Patient 1152-6_ICF v2.0: not completed correctly by the patient and the investigator.	29/APR/2021: ICF v2.0 signed by patient 1152-6. Patient 1152-6 did not write the investigator's name (it is blank) and did not check the consent boxes for the samples. The PI also did not sign or date the ICF. The CRA will send an email to the PI explaining that the patient must check, sign, and date them, and that the PI must sign and date the ICF. Aug 4, 2021: Patient 1152-6 signed the current approved version of the ICF version 2.0 Oct 14, 2019 on Feb 18, 2021, but the date recorded in the clinical records is Feb 19, 2021. The investigator's name appears to be written in a different handwriting. The name, service, address, and phone number of the contact person on the ICF are blank (page 11).	The blank boxes must be completed. The ICF must be signed and dated by the investigator.

	50864	2023-06-19	Patient 1152-5_COND01-D35_ r bone marrow aspiration was not performed.	June 23, 2023: The CRA detected that the bone marrow aspiration had not been performed at visit COND01-D35. The CRA will ask the principal investigator for the reason for this deviation and clarify it in the medical records. October 3, 2023: The principal investigator wrote an appendix explaining that the bone marrow aspiration had not been performed due to an error.	The CRA will ask the principal investigator for the reason for this deviation and clarify it in the medical records.
Virgen del Rocio University Hospital	50863	June 20, 2023	Patient 1152-5_FU visits 2, 3, 5, and 6_Non-delegated staff	June 23, 2023: Follow-up visits #2, 3, 5, and 6 were performed by a non-delegated physician. The CRA will ask the PI if the physician worked under his supervision. If so, the PI would clarify this in the medical records. The CRA will send an email to the center staff in the coming days to obtain an answer to this question. October 3, 2023: The principal investigator documented in the medical records that the follow-up visits on June 23, 2022, September 28, 2022, February 1, 2023, and May 10, 2023, were conducted under the supervision of the principal investigator.	The CRA will ask the PI whether the physician worked under his supervision. If so, the PI would clarify this in the medical records.
	50794	2023-05-25	Patient 1152-7_IND01-D01_Height and weight measurement		The principal investigator will add an appendix to the medical record if this procedure was not performed as it was performed at the screening visit or was simply not performed by mistake.

	50793	2023-05-25	Patient 1152-7_IND01-D01 and IND01-D05_Physical examination and ECOG	May 25, 2023: The principal investigator did not assess the ECOG or perform the physical examination at visits IND01-D01 and IND01-D05. June 19, 2023: The principal investigator made an addendum documenting that these procedures had not been performed.	The principal investigator will make an addendum to the medical records.
	49149	2023-03-16	Patient 1152-6_Pre-AlloSCT_QLQ-C30 not performed	March 17, 2022: At the visit prior to allogeneic stem cell transplantation (PreAlloSCT), the QLQ-C30 was not performed.	May 25, 2023: The principal investigator (PI) made an addendum explaining that the procedure had not been performed.
	49148	2023-03-16	Patient 1152-6_Pre-AlloSCT_Blood test	March 17, 2022: Pre-AlloSCT: In the blood test, the hemostasis parameters, phosphate, albumin, LDH, alkaline phosphatase, urate, and chloride were mistakenly not measured. The principal investigator will add an addendum to the medical record.	The principal investigator will make an addendum to the medical records.
	49147	2023-03-16	Patient 1152-6_Screening_ Cytogenetics and chest X-ray	March 17, 2022: At the screening visit, X-ray chest and cytogenetic tests were not performed.	The principal investigator will make an addendum to the medical records.
	49146	2023-03-16	Patient 1152-5_Pre-transplant visit for allogeneic stem cell t not performed.	March 17, 2022: Pre-AlloSCT: The visit was not performed due to an error. The CRA will inform the principal investigator about the major deviation. The principal investigator will make an appendix and explain the reason for this deviation from the protocol. October 3, 2023: The principal investigator made an appendix	The CRA will inform the principal investigator of the significant deviation. The principal investigator will prepare an appendix to the protocol ( ) and explain the reason for this deviation from the protocol.

				explaining that the PreAlloSCT visit was not performed due to an error.	
Virgen del Rocío University Hospital	49145	2023-03-16	Patient 1152-5_CON01-D06_ECGs	March 17, 2022: Electrocardiograms were performed on COND01-D06 after quizartinib administration.	NA
	49144	2023-03-16	Patient 1152-5_IND01-D35_Blood Test	March 17, 2022: In the blood assessment for visit IND01-D35, phosphate, magnesium, albumin, LDH, alkaline phosphatase, urate, and chloride levels were mistakenly not measured.	The CRA reminded site staff that the above parameters were not tested in MV#13.
	49143	2023-03-16	Patient 1152-5_Non-delegated site staff_Physical examination	March 17, 2022: Dr. José Antonio Farah Gamarra participated in the study under the supervision of Dr. José González Campos when he performed the physical examination during visit IND01-D35. Dr. Manuela Aguilar Guisado participated in the study under the supervision of Dr. José González Campos when she performed the physical examination during visit CON01-D35. We are waiting for the principal investigator to sign the NTF to confirm that Dr. González Campos supervised both physicians. May 25, 2023: The principal investigator signed the NTF, confirming that both physicians were supervised by Dr. José González Campos.	The principal investigator must sign an NTF to confirm that Dr. González Campos supervised both physicians.
	48476	2022-12-15	Patient 1152-6_EOT visit	December 15, 2022: The disappearance of patient 1152-6's medical records was previously reported. At the last MV, the principal investigator mentioned that	NA

				this patient was included in another trial after allogeneic hematopoietic stem cell transplantation (AlloSCT). The missing medical records were provided to the CRA, and it can be confirmed that no EOT visit was performed. The date of death is still pending. December 22, 2022: Correction of the issue: EOT was not performed because the patient died.	
	48474	2022-12-15	Patient 1152-5_IND01-D5_QLQ C30	December 16, 2022 - IND01-D5: QLQ C30 was not performed.	The principal investigator will make an addendum to the medical records.
	48473	2022-12-15	Patient 1152-2_Screening_ Cytogenetics	December 16, 2022: Screening: Cytogenetic tests were not performed. The principal investigator must clarify why they were not performed. March 17, 2023: The principal investigator made an addendum explaining that the procedure had not been performed due to an error.	The principal investigator must clarify why it was not performed.
Virgen del Rocio University Hospital	48472	2022-12-15	Patient 1152-1_Blood tests IND01-D35 and EOT	December 15, 2022: In IND01-D35: chloride, phosphate, urate, alkaline phosphatase, AST, LDH, albumin, and magnesium were not measured in the blood test. EOT: Chloride, albumin, alkaline phosphatase, magnesium, and phosphate were not measured in the blood test. The principal investigator must indicate this in the medical records and clarify whether the lack of results for these parameters posed a risk to the patient. March 17, 2023: The principal	The principal investigator must indicate this in the medical records and clarify whether not having the results of these parameters posed a risk to the patient.

				investigator made an addendum to the medical records explaining that this was not done by mistake in IND01-D35. The EOT parameters that were not measured are missing.	
	47742	2022-09-15	Patient 1152-5_EOT not performed	September 16, 2022: Subject 1152-5 was enrolled in another study after allogeneic hematopoietic stem cell transplantation (AlloSCT). The principal investigator confirmed that this had not been documented in the medical records. Furthermore, at the meeting with the clinical investigator, the principal investigator decided not to perform the EOT at this time.	The principal investigator must document this deviation in the medical record.
	47741	2022-09-15	Patient 1152-5_IND01-D15_Physical examination	September 15, 2022: The CRA detected that the physical examination had not been performed in IND01-D15. The principal investigator confirmed this.	NA
	47734	September 15, 2022	Patient 1152-1_Follow-up visit not performed	September 15, 2022: Site staff confirmed that the follow-up visit was not performed because the patient entered another study and they forgot to perform the follow-up visits.	NA
	47732	2022-09-15	Patient 1152-1_Blood tests: screening, IND01-D5, COND01-D6, MTO01-D1, and MTO02	September 15, 2022: Blood tests for screenings IND01-D5, COND01-D6, MTO01-D1, and MTO02 have not been evaluated, signed, or dated on the original document. However, the principal investigator has stated that the test values listed in the medical records	CRA will perform a NTF to clarify values written in the medical records are considered CS

			not evaluated.	are considered CS. The CRA will perform an NTF to clarify the situation.	
	47073	2022-06-09	Patient 1152-6_Screening, IND01-D1 and IND01-D5 Hematology and ECG	Screening, and ECG IND01-D1 IND01-D5 Hematology	The CRA will remind the principal investigator to evaluate these results, sign them, and date them.
	47064	June 9, 2022	Patient 1152-1_IND01-D1 Pregnancy test	June 9, 2022: IND01-D1: No pregnancy test was performed. There is one from the previous day (screening).	The procedure still needs to be explained in the medical records.
Virgen del Rocio University Hospital	47063	2022-06-09	Patient 1152-1_IND01-D5 ECG	June 9, 2022: Electrocardiograms were performed prior to quizartinib administration.	This is indicated in the original document, but the procedure has yet to be explained in the medical records.
	47060	2022-06-09	All patients_ICF	June 9, 2022: In the ICFs for patients 1152-1, 1152-2, 1152-4, 1152-5, 1152-6, and 1152-7, the center contact information is blank. The CRA will provide additional training on ICF procedures and remind the principal investigator to document in the medical records why this information was not included in the ICF for these patients.	The principal investigator must document in the medical records the reason why this information was not included in the ICF for these patients.
	47033	2022-06-09	Patient 1152-4 and 1152-5_ECG	09Jun2022 - Patient 1152-4: Screening ECGs are not photocopied, evaluated, signed, and dated. CRA will remind SC in a FU email to send the ECGs to PI for further evaluation. Also, the results have to be included in the CRF. Patient 1152-5	CRA will remind SC to send the ECGs to PI for further evaluation.

				All of the ECGs are not photocopied, evaluated, signed, and dated. CRA will remind SC in a FU email to send the ECGs to PI for further evaluation. 08Mar2023Patient 1152-4: It is not necessary to include additional data as it is SF.19Jun2023The ECGs are photocopied, evaluated, signed, and dated by PI.	
	47022	2022-06-09	Patient 1152-1_COND01-D6 ECGs	June 9, 2022: COND01-D6: Two ECGs were performed in triplicate (around 12:00 and 15:00). Only pre-dose ECGs are required. However, since the time of quizartinib administration is not documented in the medical record or original documents, it is not possible to know if a pre-dose ECG was performed. Both the triplicate ECGs and the administration were performed on the same day. In addition, one of the first ECGs (the one at 12:00 noon) was not available at the site. The medical record indicates that all three ECGs were performed at 12:00 p.m. The CRA will ask the SC to locate this missing ECG and add a second ECG form to include the results of the 3:00 p.m. ECG. In addition, the CRA will contact the former PI to try to find a source document indicating the time of quizartinib administration.	The CRA will ask the SC to find this missing ECG and add a second ECG form to include the results of the 3:00 p.m. ECG. In addition, the CRA will contact the former principal investigator to try to find a source document indicating the time of quizartinib administration.
	46217	2022-03-17	Patient 1152-5_COND01-D01_Laborat	Mar 17, 2022 - The CRA noticed that the following parameters were not assessed in COND01-D01: chloride, albumin,	NA

			ory assessment has not been performed.	magnesium, calcium, and alkaline phosphatase.	
Virgen del Rocio University Hospital	46215	2022-03-17	Patient 1152-5_IND01-D5_ECOG	March 17, 2022: ECOG was not assessed in IND01-D05.	NA
	46214	2022-03-17	Patient 1152-5_IND01-D5_QLQC30 not performed	March 17, 2022: QLQC30 is not present in the original documents. The medical records do not indicate that this questionnaire was provided to the subject. Site staff is awaiting confirmation of whether the subject completed this questionnaire and whether it was provided to them.	NA
	46213	2022-03-17	Patient 1152-5_IND01-D35_ ECOG	March 2022: ECOG value is missing from IND01-D35 medical records.	NA
	46211	2022-03-17	Patient 1152-5_IND01-D01 ECOG	March 17, 2022: ECOG value could not be used in IND01-D01 because 0 is indicated and then 1.	NA
	46201	2022	ISF_New member Francisco Martín	March 17, 2022: During the visit, the CRA detected that the ICF v2.0 (February 19, 2021) for subject 1152-5 was signed by Francisco Martín (without delegation in the study). In addition, this physician made several visits to subject 1152-5 in this study. The principal investigator must confirm whether Francisco Martín is a member of the center's staff for this study and, if so, the physician must be included in the center's authorization	The principal investigator noted the reason why Francisco Martín (SI) was not listed in the training log and the delegation log.

				and delegation log and in the training log. In addition, a copy of his CV and GCP certificate are pending submission, and the originals must be filed with the ISF. September 15, 2022: The CRA met with the PI, who confirmed that the physician had received training and had been delegated to the study. However, he forgot to include him. The PI noted the reason why Francisco Martín (SI) was not listed in the training log and delegation log. The CRA trained the PI in GCP procedures to avoid such deviations.	
	46195	2022-03-17	Patient 1152-2_G-CSF time of administration	March 17, 2022: The start date for G-CSF is indicated as the same day as chemotherapy (day 0). According to the protocol, G-CSF treatment should begin one day earlier (day -1). Site staff are awaiting confirmation as to why G-CSF treatment began later than planned.	NA
	46115	2022-03-10	Patient 1152-6 _IND01-D35_Central Laboratory Samples	March 10, 2022: The required samples were not sent to the central laboratory in IND01-D35 (March 26, 2021). Site staff are awaiting confirmation as to why these samples were not sent in this visit. March 17, 2022: Site staff have not yet indicated the reason, if they know it.	NA
Virgen del Rocio University Hospital	46114	2022-03-10	Patient 1152-6 _IND01-D35_saliva sample screening	March 10, 2022: The saliva sample was not sent on February 18, 2021, or February 20, 2021.	

	46113	2022-03-10	Patient 1152-6 _BM and PB screening samples	March 10, 2022: Samples from the PB selection period were not sent to the central laboratory. In addition, BM samples were not sent to Dr. Negrín. The samples were sent after the deadline (February 20, 2021, IND01-D01). The center staff is waiting to confirm why the samples were not sent by the deadline.	NA
	46107	2022-03-08	Patient 1152-5 _Screening_saliva samples	March 8, 2022: According to the sample inventory form, this sample was not collected during the screening visit. This PD will be confirmed during the next MV. March 17, 2022: Medical records indicate that these samples were sent on February 11, 2021, with PB samples, but this is not indicated on the sample inventory form. The central laboratory is awaiting confirmation of whether it received this sample. September 15, 2022: Saliva samples were not obtained due to an error.	The principal investigator made an addendum explaining that it was not performed.
	46093	2022-03-06	Patient 1152-5 _IND01-D22 Visit	March 6, 2022: According to the eCRF, visit IND01-D22 was not performed. The CRA is waiting to review this at the next MV. If this is confirmed, this issue should be considered a PD. March 17, 2022: Site staff are waiting to confirm whether this visit took place. It is not documented in the medical records. September 15, 2022: The principal investigator confirmed that the visit did not take	NA

				place because the patient was hospitalized in the ICU.	
	46092	2022-03-06	Patient 1152-7 _kit not returned 85080	March 5, 2022: According to the accountability log, this kit was not returned. The subject died before the end of the induction period. March 17, 2022: A note should be included in the medical record indicating that the medication was not returned. September 15, 2022: The principal investigator adds to the medical record that kit 85080 was not returned by the patient (deceased). The CRA notified the pharmacy.	NA
Virgen del Rocio University Hospital	46091	2022-03-06	Patient 1152-5 _COND01-D06_Treatment compliance	March 5, 2022: According to the accountability log, the subject returned three tablets in COND01-D06. If the dose administered was 60 mg, two tablets would normally be returned. The CRA will check at the next MV whether a note has been made in the medical records about this or whether the center staff remembers anything about why the subject did not take the treatment correctly. December 15, 2022: The principal investigator documented that quizartinib administration (April 16, 2021) was postponed until April 18, 2021, because the patient had non-neutropenic fever. It was also noted in the medical records that kit 85097 was not returned.	NA

	46090	2022-03-06	Patient 1152-5_IP not returned 85097	10/29/2021 - During the visit, the CRA verified the returned medications. The number of tablets returned from kit 85097 is not indicated. The pharmacist confirmed by email that this kit was not returned. MARCH 17, 2022 - The information is pending documentation in the medical records. SEPTEMBER 15, 2022 - The principal investigator adds in the medical records that kit 85097 was not returned by the patient.	The principal investigator adds in the medical records that kit 85097 was not returned by the patient.
	46089	2022-03-06	Patient 1152-1_MT02_IP Medication	March 5, 2022: According to the accountability log, the subject returned 10 tablets in MTO02. According to the medical record data observed in the previous MV, the subject received a dose of 60 mg. In this case, 4 tablets are expected to be returned, as the subject received 2 kits (85090 and 85096). Site staff are awaiting confirmation as to whether they are aware of this non-compliance or whether the treatment was interrupted for any reason. March 22, 2022: This issue is still pending clarification by the site staff. September 15, 2022: The CRA reminded the principal investigator to clarify this, but no addendum has been made yet. December 15, 2022: The principal investigator indicated that treatment was interrupted for 3 days.	

	46087	2022-03-05	Patient 1152-1_COND01-D06_IP Medication	March 5, 2022: The accountability log indicates that the subject returned 4 tablets instead of 2 if the dose administered was 40 mg. No interruption was reported in the medical records in the previous MV. Site staff are waiting to clarify, if they remember, why the subject took fewer tablets than prescribed. Not documented in the medical records in the previous MV. March 17, 2022: Not documented. The center staff is waiting to confirm the reason, if they know it. September 15, 2022: The CRA reminded the principal investigator to clarify this, but no addendum has been made yet. December 15, 2022: The principal investigator documented that the patient returned 2 more tablets by mistake.	NA
Virgen del Rocio University Hospital	44316	10/29/2021	Patient 1152-1_COND01-D35 teleconsultation	OCT/29/2021 - It is reported that the visit was conducted by telephone. The procedures for the visit were performed two days earlier (April 27, 2020), but this visit does not appear in the medical records. There is a 7-day deadline for performing the procedures for this visit.	NA
	44312	2021-10-29	Patient 1152-1_COND01-D15 - ECG_not performed	OCT/29/2021 - In COND01-D15, the ECGs were not performed.	NA

	44311	2021	Patient 1152-1_COND01-D15 - Blood sample analysis	OCT 29, 2021 - In COND01-D15, the following values were not evaluated in blood samples: neutrophils, monocytes, eosinophils, basophils, blasts, reticulocytes, chloride, urate, potassium, BUN, phosphate, magnesium, AST, alkaline phosphatase, LDH, and albumin. The test was performed one day before the visit, but in this case, it is not considered a deviation, as there is a two-day margin for this visit.	NA
	44310	2021-10-29	Patient 1152-1 - COND01-D15 - ECOG not performed	COND01-D15 - ECOG not performed	NA
	44309	2021-10-29	Patient 1152-1_COND01-D15 - Vital signs	OCT 29, 2021 - Vital signs were not assessed in COND01-D15.	NA
	44308	2021-10-29	Patient 1152-1_COND01-D06_Blood samples	OCT 29, 2021 - The following values were not evaluated in blood samples in COND01-D06: blasts and BUN.	NA
	44307	2021-10-29	Patient 1152-1_COND01-D01_Biochemistry	10/29/2021 - The AST value was not evaluated in COND01-D01.	NA
	44306	2021-10-29	Patient 1152-1_COND01-D01_Hemostasis	10/29/2021 - Hemostasis was not evaluated in COND01-D01.	NA

	44305	2021	Follow-up visits for patient 1152-1 were not performed.	OCT 6, 2021 - The CRA reported that FU visits are not included in the eCRF. The SC confirmed that these visits were not performed. No information is available in the medical records since the EOT discontinuation visit (only information available through September 2020). The visits were not performed.	NA
Virgen del Rocio University Hospital	44303	2021-10-29	Patient 1152-5_SAE FU	In the FU provided on March 8, 2021, for the SAE "acute respiratory failure" (subject 1152-5), it was reported that the event is ongoing. The center must send a follow-up with an update on this SAE. 2/25/2022: The CRA reminded the center staff that the follow-up on this SAE is pending submission. 3/22/2022: During the visit, the CRA explained to the SC how to complete this form and that the follow-up should be sent as soon as possible. This form has not yet been submitted. Site staff are waiting to confirm the start date of this SAE, as according to medical records, the lung injury with pulmonary aspergillosis began on February 22, 2021 (in the SAE report, the start date of this SAE is indicated as February 26, 2021). In addition, the medical records should indicate that it was considered an SAE.	The site should provide the final outcome of this SAE. At the last FU, it was reported that the event was ongoing.
	44301	2021-10-20	Patient 1152-6 - SAE FU pending	10/20/2021 - The safety department notified the center that it has not received a FU for SAE 1152-6 "appendicitis" reported on March 12,	The site has to provide the FU report of the SAE "appendicitis" reported on 12-Mar-2021

				2021. The initial SAE report indicates that this SAE had not been finalized at that time (event start date: March 11, 2021). FEB/25/2022: The CRA has reminded center staff that the FU for this SAE is pending submission. MARCH 22, 2022: The CRA explained to the SC how to complete the SAE report during the MV. The FU is still pending submission. The SAE was probably completed on March 16, 2021, according to the source documents. June 9, 2022: The SC informed the CRA that it had not yet submitted the FU form. The CRA will remind it and follow up until it is submitted. August 8, 2022: The SAE was resolved by the Security department and the SC.	
	44300	2021-10-29	Patient 1152-5_SAE - investigator's signature	The SAE report dated March 2, 2021, was signed in the "investigator" field by Lucía Mezquita. She does not appear in the center's authorization and delegation registry. Center staff are waiting to confirm whether this physician is involved in the study. If the physician is involved in the study, she must be listed in the SAD registry and the training registry, and provide her CV and GCP certificate. If the physician is not involved in the study, this document must be signed by another person responsible for this task in the study. March 17, 2022: Center staff are	The personnel who signed the document must be included in the delegation log, or the document must be signed by another person.

				awaiting confirmation of whether Lucía Mezquita is a member of the center's staff. May 25, 2023: The principal investigator indicated that Lucía Mezquita was under the supervision of the principal investigator in an NTF. During MV9 (September 15-16, 2022), the CRA reminded the PI that only delegated personnel should sign SAE reports.	
Virgen del Rocío University Hospital	44295	2021-10-29	Patient 1152-1_Time of quizartinib administration	OCT 29, 2021 - The time at which quizartinib was administered is not reported in medical records. It is not possible to know if the ECGs of IND01-D05 and COND01-D06 were done pre-dose or post-dose. The CRA has asked the site staff if the time at which the IP was taken was indicated in any source documents.	NA
	43548	08/04/2021	Patient 1152-6_Eligibility for selection	Patient 1152-6. Exclusion criterion 6: Alkaline phosphatase >3 times the upper normal limit. However, this value was not recorded in the original documents. The site must include this information in the medical records. Oct 29, 2021: This issue could not be reviewed during the visit because the medical records for this subject were not available. March 17, 2022: The value does not appear in the original documents. The investigator must indicate why he considers this subject eligible without this value. A note indicating this should be included in	The principal investigator must document and justify the deviation in the medical record (based on patient safety).

				the medical records. June 9, 2022: There was no note in the medical records. The CRA did not find the eligibility form or any note indicating whether the principal investigator considered the patient to meet the criteria. Alkaline phosphatase was also not assessed in IND01-D01. September 15, 2022: The CRA received training on protocol procedures because the medical records did not document the principal investigator assessing alkaline phosphatase at eligibility. However, he recently made an addendum explaining that AP was assessed at the February 15, 2021, evaluation. It was elevated due to his underlying disease. The subject did not meet the exclusion criteria, so he was able to participate in the trial without compromising patient safety. The value was elevated but did not exceed three times the upper limit of the range. 214 U/L (40-129).	
Virgen del Rocio University Hospital	43545	2021-08-04	Patient 1152-6_IND01-D05. Hemogram and ECOG	Patient 1152-6: IND01-D05. No blood count (blasts) or ECOG was performed.	NA
	43543	2021-08-04	Patient 1152-6_IND01-D05. Biochemistry	Patient 1152-6: IND01-D01. No chemical analyses (chloride, alkaline phosphatase, LDH, albumin, and magnesium) were performed.	NA

	43534	2021-08-04	Patient 1152-7_ICF V2.0 not completed properly	Patient 1152-7 signed the current approved version of the ICF version 2.0 14/OCT/2019 on June 4. The name, service, address, and phone number of the contact person are blank (page 11). 10/29/2021 - It was not possible to verify whether this issue had been resolved during MV6 because the patient's folder was not available. March 17, 2022 - This page is still pending completion. July 25, 2023 - The patient died in June 2021 and the ICF is still missing the above information. The patient was hospitalized since signing the ICF.	The data not completed must be completed as soon as possible.
	39372	2021-04-29	The date of signature of the ICF form for patient 1152-5 is different from that recorded in the medical record.	29/APR/2021: 1152-5 signed and dated the ICF on 04/FEB/2021, but the medical records show it as 11/FEB/2021. The investigator must confirm the date on which the ICF was signed and modify it, if necessary, in the medical records.	The investigator must provide an explanation indicating that the data is correct and make an addendum or correction if required.
	38158	2021-01-26	ECOG performance not evaluated on IND01-D15	ECOG performance was not evaluated on IND01-D15. 08/FEB/2021: CRA has provided new training to PI and SC via email. It will be documented in the site training log during the next MV. 04/29/2021: ECOG performance in IND01-D15 training will be documented in the training log at the next MV	NA

				(because CRA was unable to print the training log template at the site) and an NTF will explain that CRA, who performed ECOG performance in IND01-D15, ended collaboration on the study prior to MV4.	
	38156	2021-04-29	Patient 1152-4_ICF V2.0	The ICF signed by the patient was not available during MV3. CRA has asked SC to locate it and file it in ISF so that it can be reviewed during the next MV. 03/FEB/2021: SC has confirmed to CRA that ICF v2.0 is now available in ISF and CRA can review it during the next MV. 29/APR/2021: The signed and dated version of the ICF available was v1.0. This is a protocol deviation. This issue has been escalated to Protocol Deviation. The CRA has requested that the SC locate the signed v 2.0 and will send an email to the PI explaining that if the ICF v2.0 is not signed and dated, the patient should do so as soon as possible. 10/29/2021: This issue could not be verified during MV6. The patient records were not available. MARCH 17, 2022: In the patient's folder, the signed ICF v1.0 and v2.0 versions were available during the visit. The CRA reported that both ICFs were signed on the same day (SEP 30, 2020). The medical records document that the ICF was signed on September 30, 2020, but do not indicate the signed version. Site staff should	The subject must sign the applicable version.

				make an addendum indicating why ICF v1.0 and v2.0 were signed (v1.0 is not applicable to this subject because v2.0 was already approved during the screening visit). June 9, 2022: The CRA reminded the principal investigator prior to the visit to make the addendum explaining why ICF v1.0 was signed. The CRA confirmed during the visit that the addendum had not been made. In addition, the investigator's contact information had not been written on either ICF (page 11). September 15, 2022: The principal investigator completed an addendum explaining why ICF v1.0 was signed and also completed the investigator contact box.	
Virgen del Rocio University Hospital	38153	January 26, 2021	No triplicate ECG was performed.	Only 1 post-dose ECG performed in IND01-05, not triplicated. 08/FEB/2021: New training was provided to the principal investigator by email. It will be documented in the center's training log during the next medical visit.	
	36043	2020-11-19	ISF_Celia Cifuentes did not sign the consent form for the processing of personal data.	Celia Cifuentes did not sign the consent form for the processing of researchers' personal data, as she had not previously requested it from the center staff. 01/26/2021: An NTF relating to Celia Cifuentes (ex-SC) who left the center without signing the consent form for the processing of researchers' personal data was not submitted to ISF due to an	The CRA will issue an NTF to clarify this deviation. This will be submitted to the ISF during the next MV.

				oversight by the CRA. It will be submitted to the ISF during the next MV.	
	35137	2020-10-16	Patient 1152-2_Biochemistry not performed at visit IND 01-D01	Chemistry not evaluated in IND01-D01. 01/26/2021: Recap could not be performed due to limited availability of site staff. 02/08/2021: The CRA has performed a recap to the PI and EC via email. It will be documented in the site training log during the next MV.	
	35136	2020-10-16	Patient 1152-2_Hemostasis not assessed and blood count not performed at IND01-D01	Hemostasis was not assessed in IND01-D01. 01/26/2021: Retraining could not be carried out due to limited availability of center staff. 02/08/2021: The CRA has provided retraining to the PI and SC by email. This will be documented in the center's training log during the next MV.	
Virgen del Rocio University Hospital	35134	2020-10-16	Patient 1152-2_ECOG not assessed in IND01-D01	ECOG not evaluated in IND01-D01	NA
	35133	2020-10-16	Patient 1152-2_Screening samples have not been received at the central laboratory.	The screening samples sent to the central laboratory of the Dr. Negrín University Hospital in the Canary Islands did not reach the laboratory. The center sent the screening samples to the central laboratories, but according to customs, the package did not have the necessary documentation to go to the Canary Islands, and according to the center, it did have the necessary documentation, because otherwise the	NA

				courier service would not have accepted it... The fact is that this happened on June 20, and we did not find out until September-October, when the laboratory said it had not received the sample. MRW never notified us of anything.	
	35131	2020-10-16	Patient 1152-2_No chest X-ray was performed during the screening exam.	CRA has provided new training to PI and SC via email. It will be documented in the site training log during the next MV.	NA
	35122	2020-10-16	Patient 1152-1_Pregnancy test not performed on IND01-	Pregnancy test not performed on IND01-D01 (12/27/2019). 02/08/2021: Retraining on study procedures performed to PI and SC by email. It will be documented on Site Training log during next MV	A pregnancy test should be performed on the patient as soon as possible.
	32173	2020-10-16	Patient 1152-1_ICF v2.0 not completed correctly by the patient.	All patients (ongoing and WD) must reconsent their participation in the study by signing the new ICF during the next visit on site. CRA will check on next MV	The subject must sign the document.
	32158	2020-03-02	Patient 1152-1_SAE No. 6344_Delay in reporting a serious	Patient 1152-1: SAE 2 Aspergillosis: initially reported on 01/22/2020, but no follow-up has been provided, even though, according to new conversations with the principal investigator, the patient has recovered. SC/PI will send	SC/PI will send the SAE follow-up report to the security department as acknowledgment of receipt of the FUP.

			adverse event	the SAE follow-up report to the safety department. 10/16/2020: Reminder sent that SAE follow-up has not been reported. CRA has resubmitted request to SC. 10/30/2020: CRA has resubmitted request to SC and PI via email. The PI confirmed that it will be sent as soon as possible. NOV 6, 2020: The SAE report was communicated to the security department.	
Virgen del Rocio University Hospital	32157	03/02/2020	Patient 1152-1_SAE _Delay in reporting a serious adverse event	Patient 1152-1 SAE 1 Shock: initially reported on 12/30/2019, but no follow-up has been provided, even though, as discussed with the principal investigator, it has been resolved prior to the SAE2 start date (01/22/2020). The SC/IP will send the SAE follow-up report to the safety department. The SC will update the EDC as appropriate and the CRA will check it at the next MV. Site staff will receive new training on safety management and reporting procedures, and the training will be recorded in the site training log. March 9, 2020: follow-up. Not resolved. March 25, 2020: Follow-up. Not resolved. April 27, 2020: The security department has again requested follow-up from center staff. October 16, 2020: A reminder has been sent that the SAE follow-up has not been reported. The CRA has requested it again from the SC. October 30, 2020: The CRA has requested it again from the SC and	

				the PI by email. The PI has confirmed that it will be sent as soon as possible. November 6, 2020: The SC has sent the final updated SAE form to the security department.	
	25583	2020-03-02	Patient 1152-1_IND-D01: Hemostasis test not performed.	Patient 1152-1 Induction phase D01: Hemostasis test not performed 10/16/2020: Could not be performed due to limited availability of site staff during the MV. The CRA will remind them of the procedures by email, and the new training will be recorded in the site training log during the next MV.	NA
	25582	2020-03-02	Patient 1152-1_G-CSF IND01 incorrect administration	Patient 1152-1 G-CSF C1D1: According to the original documents, the patient has not taken G-CSF due to a white blood cell count >25,000 uL. According to the protocol, G-CSF should be administered from day -1 to day 5, and if the patient has a white blood cell count >25,000 uL on day 1 (C1D1), they should not take G-CSF. Patient 1152-1 has a white blood cell count >25,000 uL, so they should not take G-CSF from day 1 to day 5, but they did not take G-CSF on day -1. OCT 16, 2020: Training could not be conducted due to limited availability of center staff during the MV. The CRA will remind them of the procedures by email and the new training will be recorded in the site training log during the next MV. JAN 26, 2021: Training could not be performed due to limited site availability. FEB 8,	The site has been informed that this practice is not permitted under the protocol and that no corrective action will be taken.

				2021: The CRA has provided the new training to the PI and CE by email. It will be documented in the site training log during the next MV. 04/29/2021: Training on G-CSF C1D1 will be documented in the training log at the next MV (because the CRA was unable to print the training log template at the site) and an NTF will explain that the CRA who conducted the training on G-CSF C1D1 ended their collaboration on the study before MV4. 08/04/2021: Training on procedures was documented in the training log. The PI did not sign it. The note for the file will be filed with the ISF at the next MV.	
San Pedro De Alcántara Hospital	51907	May 16, 2023	1151-1 The program's relapse resistance follow-up visit was not performed.	1151-1 The program's relapse resistance check-up was not performed and the prolapse was detected at another hospital.	NA
	51010	2023-06-30	1151-5 EOT procedures	September 25, 2023: The CRA discussed the deviations with the center staff, who reported that they would make the additions. September 27, 2023: The SC reported that the additions had been made and filed in the patient's folder.	An addendum will be made documenting all procedures that were not performed.
	51009	2023-06-30	1151-3 Prog-rel-resistance procedures	September 5, 2023: The CRA retrained the SC on study procedures.	No corrective actions can be taken, as the patient has already completed the study.

					The items not evaluated can be identified in the chemistry.
	51008	2023-06-30	1151-1 Pre-transplant procedures	Some assessments applicable to the preallo were not performed for patient 1151-1. The Qlq-C30 was not performed, and in chemistry, chloride, urate, alkaline phosphatase, magnesium, phosphate, and calcium were not evaluated; in addition, samples were not sent to the central laboratory. June 30, 2023: new training pending. September 25, 2023: The CRA discussed the deviations with the site staff, who reported that they would make the additions. September 27, 2023: The SC reported that the additions to th s had been made and filed in the patient's folder.	The site will create an appendix to document the procedures that were not performed.
San Pedro De Alcántara Hospital	50858	2023-06-06	1151-2 Mpcf Lead sample for central laboratory IND01-D35	In the case of patient 1151-2, during the IND01-D35 period, a lead sample for the evaluation of Mpcf disease was not sent to the central laboratory. June 30, 2023 -New training pending.	No corrective actions can be taken, as the patient has already completed the study. In addition, these minor deviations can be clearly identified in the original documents. The center will also produce an appendix.
	50857	2023-06-06	1151-2 Biochemistry IND01-D01	Uric acid, alkaline phosphatase, and phosphate were not evaluated.	No corrective action can be taken, as the patient has already completed the study. Furthermore, this deviation can be clearly identified in the source document.

	50855	2023-06-06	1151-2 PCR Pb sample for central laboratory. Screening.	In the case of patient 1151-2, a sample for PCR biomarkers was not sent to the central laboratory during screening.	NA
	50854	2023-06-06	1151-3 Pregnancy test	Pregnancy test	No corrective action can be taken, as the test has already been performed. In addition, the center added an appendix to indicate that the test was a urine test, and the result was also included in that appendix.
	50727	2023-05-16	1151-1 CON1-D06 triplicate ECGs not done 2min apart		NA
	48878	2023-02-17	1151-5 ECG Ind01-D05	February 17, 2023 Only one post-dose ECG was performed on IND01-D05.	This issue was discussed with site staff. An appendix was created to document this deviation.
	47286	2022-07-15	Patient 1151-2_Incorrect Procedures	Jul 15, 2022 CRA detected the following issues: Screening: The site mistakenly did not assess CO2 and total bilirubin. In addition, the chest X-ray was performed on IND01-D1 instead of at the screening visit. An addendum to the medical record is pending to document this protocol deviation. IND01-D1: The center failed to evaluate urate, alkaline phosphatase, and phosphate. In	CRA requested PI to perform addenda in the medical chart to document these protocol deviations and the reason for them.

				addition, GCSF was administered for 5 days instead of 6 days, as indicated in the protocol. An addendum to the medical record is pending to document this deviation from the protocol. A training log was signed. Nov. 4, 2022: These additions are still pending. Feb. 17, 2023: These additions are still pending.	
San Pedro De Alcántara Hospital	47284	July 15, 2022	Patient 1151-1_Incorrect procedures_ Protocol deviations	IND01-D15: The center only performed one ECG by mistake.	Addendum
	46606	2022-04-11	Patient 1151-3_EOT_Parameters not evaluated and bone marrow sample not sent.	The center did not evaluate the following parameters: EOT: urate, alkaline phosphatase, and phosphate. An addendum is pending to document this deviation.	NA
	45211	2022-01-17	Patient 1151-5_IND01-D01, IND01-D5, IND01-D35_Parameters not evaluated	Patient 1151-5_IND01-D01, IND01-D5, IND01-D35_Parameters not evaluated	NA
	45211	2022	Patient 1151-3_IND01-D35_Paramet	Chemistry: Uric acid, phosphate, and alkaline phosphatase were not evaluated in biochemistry. An	Addendum

			ers not evaluated	addendum is pending to document this issue.	
	43750	2021-09-30	Patient 1151-5_Screening ECG, IND01-D5, D15, and D22	30/SEP/2021: Patient 1151-5: Screening electrocardiograms were performed with a 1-minute interval between the second and third electrocardiograms. They should be copied.	NA
	40528	2021-06-30	Patient 1151-3_Laboratory procedures (IND01-D01)	Hemostasis: The coagulation laboratory test was not performed in IND01-D01. The principal investigator must explain why it was not performed in the clinical records.	Addendum
	40517	2021-06-30	Patient 1151-3_Screening: central laboratory samples	No bone marrow extraction was performed for local analysis during screening.	The CRA has reiterated the importance of following study procedures.
	38976	2021-03-24	Patient 1151-1_Parameters not evaluated	IND01D22: Reticulocytes and blast percentage were not evaluated in the blood count. BUN, urate, and alkaline phosphatase were not evaluated in biochemistry. CON01D01: Reticulocytes and blast percentage were not evaluated in the blood count. BUN, urate, and alkaline phosphatase were not evaluated in the biochemistry. CON01D06: Reticulocytes and blast percentage were not evaluated in the blood count. BUN, urate, phosphate, and alkaline phosphatase were not evaluated in the biochemical analysis. CON01D15: The percentage of blasts in	NA

				the blood count was not evaluated. BUN was not evaluated in the biochemical analysis. CON01D35: Reticulocytes and the percentage of blasts in the blood count were not evaluated. BUN, urate, phosphate, magnesium, calcium, and alkaline phosphatase were not evaluated in biochemistry. 1/17/2022 Urate, alkaline phosphatase, phosphate, magnesium, and calcium were not evaluated in biochemistry. These parameters are mandatory in biochemistry. The percentage of blasts and reticulocytes are not mandatory in the complete blood count. The CRA explained all mandatory parameters in chemistry and complete blood count to the staff. The CRA reminded the staff of this deviation from the protocol and retrained them in the protocol procedures. The PI and SC signed a training log on the protocol procedures. This matter was closed.	
San Pedro De Alcántara Hospital	38975	2021-03-24	Patient 1151-2_Parameters not evaluated	IND01D22: Reticulocytes and blast percentage were not evaluated in the blood count. BUN, urate, and alkaline phosphatase were not evaluated in the biochemistry. CON01D01: Reticulocytes and blast percentage were not evaluated in the blood count. BUN, urate, and alkaline phosphatase were not evaluated in the biochemistry. CON01D06: Reticulocytes and blast	NA

				percentage were not evaluated in the blood count. BUN, urate, phosphate, and alkaline phosphatase were not evaluated in the biochemical analysis. CON01D15: The percentage of blasts in the blood count was not evaluated. BUN was not evaluated in the biochemical analysis. CON01D35: Reticulocytes and the percentage of blasts in the blood count were not evaluated. BUN, urate, phosphate, magnesium, calcium, and alkaline phosphatase were not evaluated in biochemistry. 1/17/2022 Urate, alkaline phosphatase, phosphate, magnesium, and calcium were not evaluated in biochemistry. These parameters are mandatory in biochemistry. The percentage of blasts and reticulocytes are not mandatory in the complete blood count. The CRA explained all mandatory parameters in chemistry and complete blood count to the staff. The CRA reminded the staff of this deviation from the protocol and retrained them in the protocol procedures. The PI and SC signed a training log on the protocol procedures. This matter was closed.	
	28140	2020-06-25	Patient enrollment in relation to the eligibility form	The trial coordinator states that investigators do not need to wait for feedback on the eligibility form, which must be sent to the trial coordinators for review before including the patient in	The principal investigator tells the trial coordinator that this violates section 9.4 of the protocol. The principal investigator says that the

				the study. The inclusion of patients in the study is at the investigator's discretion. This will only be necessary once one of the two phase II cohorts has been completed.	protocol description must be modified, otherwise there will be a deviation from the protocol. It is agreed to accept the deviation on this point and to review the protocol to confirm whether it needs to be modified. The investigators are informed as requested by the trial coordinators.
Catalan Institute of Oncology - Germans Trias i Pujol Hospital	48546	2023-01-02	ISF_NTF_Olga Fernández_Training record	ISF_NTF_Olga Fernández_Training record	The CRA sent the principal investigator an NTF clarifying this issue, which is pending signature.
	46947	2022-06-01	Patient 1140-2_IND01-D22_ECGs	Patient 1140-2_IND01-D22_ECGs	The principal investigator or delegated site staff must complete an appendix to document the reason why only one ECG is being evaluated.
	45897	2022-03-02	Patient 1140-5_IND01-D01 - GCSF	March 2, 2022: The CRA confirmed that filgastrim was administered at a dose different from that indicated in the protocol (300 ug/m2 instead of 300 mg/m2). The CRA noted that there are discrepancies in the G-CSF dose to be administered in protocol v2.0, synopsis v2.0, and the eCRF. Throughout the protocol and eCRF, a dose of 300 mg/m2 is indicated. However, the synopsis indicates 300 ug/m2.	The principal investigator or delegated site staff should create an appendix to document the reason why only one ECG is evaluated.
	45896	2022-03-02	Patient 1140-4_ IND01-	Patient 1140-4_ IND01-D35 - BQ Evaluation	NA

			D35 - BQ assessment		
	45894	2022-03-02	Patient 1140-4_ Differential white blood cell count	Patient 1140-4_ Differential white blood cell count	NA
	45893	2022-03-02	Patient 1140-4_IND01-D01 - GCSF	March 2, 2022: The CRA confirmed that filgastrim was administered at a dose different from that specified in the protocol	The principal investigator or delegated site staff must complete an appendix to document the cause
	45892	March 2, 2022	Patient 1140-3_IND01-D01 - GCSF	March 2, 2022: The CRA confirmed that filgastrim was administered at a dose different from that indicated in the protocol	The principal investigator or designated staff at the center must complete an appendix to document the cause.
	45895	2022-03-02	Patient 1140-4_ IND01-D22 - BQ assessment	Patient 1140-4_ IND01-D22 - BQ Evaluation	
Catalan Institute of Oncology - Germans Trias i Pujol Hospital	45894	2022-03-02	Patient 1140-4_ Differential white blood cell count	March 2, 2022: In cases IND01-D15, IND01-D22, and IND01-D35, the differential white blood cell count could not be evaluated due to severe leukopenia.	NA
	45893	March 2	Patient 1140-4_IND01-D01 - GCSF	The dose administered was 300ug instead of 300mg/m2. The dose is not the dose indicated according to the protocol. The CRA observed that there are discrepancies in the dose to be administered of G-CSF in the protocol v2.0, synopsis v2.0 and eCRF.	NA

	45892	2022-03-02	Patient 1140-3_IND01-D01 - GCSF	The dose administered was 300ug instead of 300mg/m2. The dose is not the dose indicated according to the protocol. The CRA observed that there are discrepancies in the dose to be administered of G-CSF in the protocol v2.0, synopsis v2.0, and eCRF.	NA
	45891	2022-03-02	Patient 1140-2_IND01-D01 - GCSF	The dose administered was 300ug instead of 300mg/m2. The dose is not the dose indicated according to the protocol. The CRA observed that there are discrepancies in the dose to be administered of G-CSF in the protocol v2.0, synopsis v2.0, and eCRF.	NA
	44866	2021-12-13	Patient 1140-2_IND01-D35 not performed	IND01-D35 not performed	NA
	44864	2021-12-13	Patient 1140-3_EOT QLQ30	Patient 1140-3_EOT QLQ30	NA
	44863	2021-12-13	Patient 1140-3_IND01-D35 - White blood cell count assessment	IND01-D35 - White blood cell count assessment	NA
	44859	2021-12-13	Patient 1140-1_EOT_Central laboratory samples	EOT_Central laboratory samples	NA
	44723	2021-12-01	Patient 1140-5_EOT_Samp	EOT_Samples from the central laboratory	NA

			les from the central laboratory		
	44715	2021-11-30	Patient 1140-4_Additional response assessment	Additional response assessment	NA
	44714	2021-11-30	Patient 1140-3_EOT visit	EOT visit	NA
Catalan Institute of Oncology - Germans Trias i Pujol Hospital	44713	November 30, 2021	Patient 1140-3_EOT_Samples from the central laboratory	Patient 1140-3_EOT_Samples from the central laboratory	NA
	44710	2021-11-30	Patient 1140-1_EOT-treatment discontinuation visit	Patient 1140-1_EOT-treatment discontinuation visit	NA
	43629	2021-09-13	Patient 1140-1_COND01-D35_Laboratory samples	COND01-D35_Laboratory samples	NA
	43611	2021-09-13	Patient 1140-1_COND01-D06_ECG discrepancy	COND01-D06_ECG discrepancy	NA
	39726	2021-06-02	Patient 1140-1_IND01-D15 - White blood cells not evaluable	IND01-D15 - Leukocytes not evaluable	NA

	39724	2021-06-02	Patient 1140-4_Quizartinib bottle not returned	Quizartinib bottle not returned	NA
	39722	June 2, 2021	Patient 1440-5_The IND01-D35 samples for MRD assessment were not sent to the central laboratory.	The IND01-D35 samples for MRD assessment were not sent to the central laboratory.	The CRA has requested the SC to include the local results in the CRF.
	38640	2021-03-03	Patient 1140-1_Height not measured in IND01-D01	Height not measured in IND01-D01. Screening measurement was used.	NA
	36436	2020	Patient 1140-1_Quizartinib treatment was started late.	Treatment with quizartinib was started late.	NA
	30723	2020-08-17	Patient 1140-1_SAE No. 6276_Bacterial enterocolitis_ Delay in reporting SAE	The initial report of severe Clostridium difficile enterocolitis was notified on June 30, 2020, and center staff became aware of the case on June 25, 2020.	NA
Catalan Institute of Oncology - Germans Trias i Pujol Hospital	30722	2020-08-17	Patient 1140-1_SAE No. 6275_-	The initial report of the SAE catheter-related infection was notified on 29/JUN/2020, and the center's staff had	NA

			QUIDA_SAE_ Pat 1140-01_Catheter-related infection_Delay in reporting the SAE	been aware of the event since 24/JUN/2020.	
	30717	2020-08-17	Patient 1140-1_IND01-D35 samples for MRD assessment were not sent to the central laboratory.	Patient 1140-1: IND01-D35 samples for MRD assessment by flow cytometry were not sent to IMIBIC.	The CRA has requested the SC to include the local results in the CRF.
	30716	2020-08-17	Patient 1140-1_Glycosylated G-CSF was not administered.	Glycosylated G-CSF was not administered to patient 1140-1 on day -1.	The principal investigator has documented in the medical record that the patient has >25,000/µL leukocytes and, based on his criteria, there was no benefit and there was a risk in administering G-CSF in this case.
	27635	2020-06-08	The pharmacy service does not retain IP addresses returned by patients.	PH has reported that, for the safety of its staff, it does not retain IPs returned by patients. IPs are reviewed and tablets are counted by two members of the pharmacy staff, and then destroyed as described in the standard operating procedure for destruction. This is not	There is a standard operating procedure (SOP) that explains this procedure (SOP for the destruction of used/returned investigational drugs). PH sent it to the CRA for review and approval by the sponsor, and it

				permitted under the protocol and IP management plan.	was approved on June 11, 2020.
Catalan Institute of Oncology - Bellvitge Hospital	46322	2022-01-18	Patient 1155-1_EOT not performed	EOT not performed	This must be documented in the medical records.
	50733	2023-05-15	Patient 1155-3_Bone marrow evaluation not performed in MTO-12	Bone marrow evaluation not performed in MTO-12	The principal investigator must clarify this in the medical records, explaining the reason.
	49548	2023-03-21	Patient 1155-5_Pre-logeneic hematopoietic stem cell transplant visit_Blood test not performed.	Pre-transplant visit for allogeneic hematopoietic stem cell transplantation_Blood test not performed.	The principal investigator will add an appendix to the medical record.
Catalan Institute of Oncology - Bellvitge Hospital	49447	2023-03-21	Patient 1155-2_Date of EOT visit	Date of unscheduled EOT visit	The principal investigator conducted the visit once she observed that the patient had progressed.
	48486	2022-12-21	Patient 1155-3_PreAlloSCT_QLQ C30	PreAlloSCT_QLQ C30	The principal investigator should clarify this in the medical records, explaining the reason.
	48484	2022-12-21	Patient 1155-2_IND01-D35_ECOG	IND01-D35_ECOG not performed	The principal investigator must add an appendix indicating

					that this procedure was not performed due to an error.
	46340	2022-03-21	Patient 1155-5_IND01-D35 - Central lab samples	March 21, 2022: Samples that were to be sent to the central lab were not collected within the established time frame. They were collected more than 7 days after the visit.	NA
	46336		Patient 1155-4_ECGs missing	The ECGs for IND01-D15 (Dec. 9, 2020) and IND01-D22 (Dec. 16, 2020) are not filed in the patient's folder. The center's staff is waiting to confirm whether these ECGs were performed.	NA
	46334	2022-03-21	Patient 1155-3_BM evaluation not performed in MTO-06 and MTO-09.	Bone marrow evaluation not performed in MTO-06 and MTO-09. Performed later.	NA
	46333	2022	Patient 1155-3_IND01-D01_ECOG	IND01-D01_ECOG not performed	NA
	46325	2022-03-21	Patient 1155-2_IND01-D01_ECOG	IND01-D01_ECOG not performed	NA
	46321	2022-03-21	Patient 1155-1_ follow-up visits	On January 18, 2022, the SC asked if follow-up visits could be performed even if they did not start on time. The sponsor agreed. However, there are no follow-up visits indicated in the medical records.	The CRA asked the sponsor if the subject could start the follow-up visit later than planned, and the sponsor agreed. Follow-up visits must be reported every three

					months starting in February 2022.
	46124	2022-03-11	Patient administration 1155-5_IP	Based on the information obtained in the previous MV (MV6), a dose of 30 mg was prescribed to this subject due to treatment with posaconazole during induction. However, the subject only returned 6 tablets (number of tablets expected to be returned with a 30 mg treatment: 14). The subject took more tablets than prescribed. The CRA will check the medical records to see if the investigator explained this fact. The CRA will discuss this with the investigator during the visit.	The principal investigator must document the reason for the non-compliance in the medical records.
Catalan Institute of Oncology - Bellvitge Hospital	45100	2022-01-07	Patient compliance 1155-3_MTO-09_IP	The site staff explained to the CRA that the subject took an incorrect dose of the IP during MTO-09 due to a misunderstanding on the part of the subject. March 22, 2022: In MTO-09, the subject returned 35 tablets instead of 4. The subject took an incorrect dose of quizartinib by mistake.	NA
	45064	2021-12-20	Patient 1155-3_pre-alloSCT - evaluation not performed	Vital signs, ECOG, and QLQ30 were not assessed at the visit on January 8, 2021. Pending confirmation whether this visit was prior to allogeneic stem cell transplantation (alloSCT) on June 16, 2022: the CRA reminded the principal investigator to make an addendum to clarify this point.	The CRA reminded the principal investigator to add an appendix to clarify this point.

	45058	2021-12-20	Patient 1155-3_IND01-D15 - Complete blood count - Differential white blood cell count	Leukocyte population values were not evaluated in IND01-D15, probably due to low leukocyte levels. The site is awaiting confirmation and should make a note in the medical records indicating why these values could not be evaluated. The same deviation was observed in IND01-D22.	NA
	44743	2021-12-02	Patient 1155-5_pre-alloSCT-Central laboratory samples	Central laboratory samples not collected.	NA
	44742	2021-12-02	Patient 1155-5_IND01-D35 Visit and vital signs	The IND01-D35 for subject 1155-5 was performed outside the scheduled time frame. The visit was estimated for May 19, 2021 (+/-7 days) according to the protocol and was performed on May 31, 2021. The center is pending explanation of the main reason why this visit was conducted outside the scheduled timeframe. Some procedures were performed on May 19, 2021 (measurement of vital signs, collection of blood samples, and bone marrow aspiration).	NA
	44738	2021-12-01	Patient 1155-2_EOT_Central laboratory samples	Central laboratory samples not collected.	NA
	44737	2021-12-01	Patient 1155-2_EOT visit	The EOT discontinuation visit was performed outside the planned	The reason for the visit outside of normal hours must be

				timeframe. This visit is scheduled for 30 days (+/-7 days) after the last dose of quizartinib. Quizartinib treatment began on 08/11/ 2020 and lasted for 14 days. The EOT discontinuation was due on September 24, 2020 (+/-7 days) and was performed on October 20, 2020.	documented in the medical records.
Catalan Institute of Oncology - Bellvitge Hospital	44735	2021-12-01	Patient 1155-1_pre-alloSCT Central laboratory samples	The CRA reported that the samples prior to allogeneic stem cell transplantation were collected outside the established time frame. The visit took place on August 21, 2020, and the samples were collected on August 17, 2021. The procedures for this visit must be performed on the same day as the visit.	NA
	43655	2021-09-17	Patient 1155-5_No QLQ30 IND01-D05 available and pre-alloSCT	No QLQ30 IND01-D05 available and pre-alloSCT	The CRA reminded the principal investigator to make an appendix to clarify this point.
	40261	2021-06-09	Patient 1155-4_Vital signs IND01-D22 not measured	Vital signs IND01-D22 not measured	The CRA reminded the principal investigator to add an appendix to clarify this point.
	40260	2021-06-09	Patient 1155-4_QLQ-C30 IND01-D05 not performed	QLQ-C30 IND01-D05 not performed	The CRA reminded the principal investigator to add an appendix to clarify this point.

	38659	2021-03-09	Patient 1155-1_Start maintenance to clarify	The patient underwent allogeneic hematopoietic stem cell transplantation (allo-SCT) on September 10, 2020. According to the protocol, maintenance treatment can be started between 60 and 180 days after allogeneic hematopoietic stem cell transplantation, so the patient should have already started the maintenance phase. The SC has reported that it has not yet been possible to start. The medical record should be reviewed and clarified as to why it was not started on time and whether it will be carried out. It will be reported as PD if applicable.	The CRA reminded the principal investigator to add an appendix to clarify this point.
	38658	2021-03-09	Patient 115-4_QLQ-C30 IND01-D05 not performed	QLQ-C30 IND01-D05 not performed	The CRA reminded the principal investigator to add an appendix to clarify this point.
	38657	2021-03-09	Patient 1155-1_QLQ-C30 preAlloSCT not performed	QLQ-C30 preAlloSCT not performed	CRA reminded the principal investigator to add an appendix to clarify this point.
	38655	2021-03-09	Patient 1155-4_IND01-D01: vital signs, physical examination,	Vital signs, physical examination, and ECOG out of range.	NA

			and ECOG out of range.		
Catalan Institute of Oncology - Bellvitge Hospital	38654	2021-03-09	Patient 1155-4_Additional evaluation of response after deadline	Additional assessment of response after the deadline	The investigator must clarify why the assessment was not repeated within 7 days of IND01-D35.
	38654	2021-03-09	Patient 1155-3_Additional assessment of response after the deadline	Additional assessment of response outside the deadline	The investigator should clarify why the assessment was not repeated within 7 days after IND01-D35.
	38654	2021-03-09	Patient 1155-2_Additional assessment of response after the deadline	Additional assessment of response outside the deadline	The investigator should clarify why the assessment was not repeated within 7 days after IND01-D35.
	38651	2021-03-09	Patient 1155-2_Height and weight not measured at screening	Height and weight not measured at screening	These were measured at IND01-D01.
	38648	2021-03-09	Patient 1155-4_IP is not available at the pharmacy.	IP is not available at the pharmacy.	This must be documented in the medical records.
	37176	2020-12-03	Patient 1155-4_Cytogeneti	Cytogenetics more than 21 days before IND-D01	Screening cytogenetics performed on 03/SEP/2020,

			cs more than 21 days ago IND-D01		more than 21 days before IND01-01 (26/NOV/2020). It was clarified that cytogenetics was performed according to standard practice at the center and would not be repeated, as it was normal.
	37174	2020-12-03	Patient 1155-4_ICF not completed correctly	ICF not completed correctly	NA
	37173	2020-12-03	Patient 1155-3_IP is not available at the pharmacy.	PH detected and confirmed that the bottle (No. 85186) returned by patient 1155-3 had not been returned to the pharmacy department. It would be returned around November 16, 2020. CRA discussed this with SC, who replied that it would be in the nursing department office and that she would confirm this with SN as soon as possible. March 9, 2021: The vial had still not been returned to PH. CRA has again asked SC to follow up with the nurses. The patient was hospitalized during treatment, so the vial did not leave the hospital.	The CRA reminded the principal investigator to make an appendix to clarify this point.
Catalan Institute of Oncology - Bellvitge Hospital	37173	December 3, 2020	Patient 1155-2_IP is not available at the pharmacy.	PH detected and confirmed that the bottle (no. 85186) returned by patient 1155-3 had not been returned to the pharmacy service. It would be returned around November 16, 2020. CRA discussed this with SC, who replied that	The CRA reminded the principal investigator to make an appendix to clarify this point.

				it would be in the nursing department office and that she would confirm this with SN as soon as possible. March 9, 2021: The vial had still not been returned to PH. CRA has again asked SC to follow up with the nurses. The patient was hospitalized during treatment, so the vial did not leave the hospital.	
	31026	2020-08-18	Patient 1155-1_Screening samples have not been received at the Canary central laboratory.	Screening samples have not been received at the Canary central laboratory.	NA
12 De Octubre University Hospital	64056	May 14, 2025	Patient 1145-1 signed the ICF v1.0.	Patient 1145-1 signed the ICF v1.0	
	45673	2022-01-31	Patient 1145-3_AEs_Grade pending documentation in the medical record.	AEs_Grade pending documentation in the medical record.	The CRA requested that the principal investigator prepare an appendix documenting the ratings of all adverse events in the medical record.
	45671	2022-01-31	Patient 1145-3_EoT_Laboratory parameters not performed	Laboratory parameters not performed. Urea, urate, and phosphate levels were not assessed at the EoT visit because they were forgotten. The CRA explained to SC the importance of assessing all	The CRA requested that the PI and SC add an appendix to the medical record to document this deviation.

				chemical parameters and will send a reminder in the follow-up letter.	
	45669	2022-01-31	Patient 1145-3_Additional late response	Additional late response	The CRA requested that the PI and SC add an appendix to the medical record to document this deviation.
	44121	2021-10-07	Patient 1145-1_Quizartinib 85137 30 mg kit - Not returned	The 30 mg quizartinib 85137 kit was not returned after the cycle. An addendum needs to be added to the medical record explaining that the vial was not returned due to an error. November 18, 2021: SC confirmed to CRA by email that the addendum has been added to the medical record. Pending verification on site. January 31, 2022: CRA verified that this addendum had been included in the medical record. This issue was closed.	The principal investigator and study coordinator signed a protocol procedures training log.
12 De Octubre University Hospital	40473	June 28, 2021	Patient 1145-3_ECG	JUN/28/2021: Screening. ECG with less than 2 minutes between them.	CRA has reminded the SC that the time between ECGs is 2 minutes or more.
	29014	2020-03-16	Patient 1145-1_G-CFS Dose	MAR/16/2020: CRA reviewed the status of patient 1145-1 with SC. The dose of GCSF IND01-001 was 300 mg/day. It should be 300 mcg/m2/day, as indicated in the protocol. Pending verification on site. JUL/17/2020: This patient has received a dose of 300 µg/day. Since their m2 value is 1.65, they should be administered 495 µg/day. This PD is pending discussion with the PI, who will	NA

				be asked to try to comply with the protocol. (PD: 29,014)	
Ramon y Cajal University Hospital	48604	2023-01-11	Patient 1139-1_MTO 12_Undocumented returned pills	Jan. 11, 2023 CRA detected that the returned pills from kits 85057 and 85059 from MTO12 are pending documentation.	The CRA requests that the principal investigator make an addendum to document the returned pills.
	47684	2022-09-12	Patient 1139-1_MTO5 and MTO9	Sep 12 The CRA detected that the center must document that the patient returned 4 tablets from kit 85042 (MTO5) and did not return kit 85563 (MTO9).	The CRA requests that the principal investigator make an addendum to document the returned pills.
	47683	2022-09-12	Patient 1139-1_Blood tests, ECOG, and vital signs_PreAllo, MTO1, MTO2, MTO3, MTO4, MTO5, MTO6, MTO7, MTO8, MTO9, MTO10, MTO11, MTO12	Blood tests, ECOG and vital signs_PreAllo, MTO1, MTO2, MTO3, MTO4, MTO5, MTO6, MTO7, MTO8, MTO9, MTO10, MTO11, MTO12	The CRA requests that the principal investigator make an addendum
	47006	2022-03-23	Patient 1139-1_Modified dose of GCSF	Mar 23, 2022 During the inspection of this study, the inspectors found that the principal investigator only administered	The CRA requests that the principal investigator make an addendum.

				GCSF for one day. However, she did not document the reason. The protocol specifies that the duration of treatment is 6 days. Therefore, it is necessary to document the reason for this deviation. The finding was as follows: 1. The medical record for the screening visit shows that Neupogen (Gcsf) is administered according to the protocol (D-1).	
	46126	2022-03-08	Patient 1139-2_Start of treatment with FLAG-QUIDA befor s of confirming the central laboratory results.	08/MAR/2022 CRA discussed this issue with PI and SC, who reported that the patient should receive FLAG-IDA chemotherapy as soon as possible because his life was in danger. Therefore, this is not a major deviation from the protocol. However, the v2.0 tes the following: "Once patients meet all eligibility criteria, they will begin treatment immediately." Each treatment cycle will begin with the administration of FLAG-IDA (fludarabine, 30 mg/m2 IV on days 1 to 4, cytarabine 2 g/m2 IV in patients aged 18 to 59 or cytarabine 1 g/m2 IV in patients aged 60 to 70 on days 1 to 4, idarubicin 10 mg/m2 IV on days 1 to 3, and non-pegylated G-CSF at a daily dose of 300 mcg/m2, from day -1 to day 5) plus quizartinib (AC220) from day 5 for 14 days.	
Ramon y Cajal University Hospital	46086	2022-03-04	EDC_not updated before visits	Mar 4, 2022 CRA detected that SC had not updated patient visits in the CRF	CRA reminded SC of this task before the visit by email. This

				prior to the monitoring visit (Mar 8, 2022).	email was archived in Sharepoint.
	45544	2022-02-19	Patient 1139-1_Missing ECG documents from MTO3 visit	Missing ECG documents from visit MTO3	NA
	45543	2021-11-24	Patient 1139-1_IMP_No dose increase at MTO-D15	No dose increase at MTO-D15	When SC reported this via email, CRA consulted with the sponsor about the possibility of increasing the dose at MTO3. The sponsor confirmed that this was possible, and the site increased the dose to 60 mg. In addition, the principal investigator must complete an appendix to document this error.
	45542	2022-01-19	Patient 1139-1_triplicate electrocardiogram not performed at MTO1-D1	Triplicate electrocardiogram not performed in MTO1-D1	CRA requests the principal investigator to make an addendum
	45541	2022-01-19	Patient 1139-1: incorrect time between ECGs in IND01-D22, MTO1-D1,	Incorrect time between ECGs in IND01-D22, MTO1-D1, MTO1-D15, MTO2, and MTO4.	CRA requests the principal investigator to perform an addendum.

			MTO1-D15, MTO2, and MTO4.		
	45540	2021-06-16	Patient 1139-1: bone marrow sample in screening not available for local evaluation.	Screening bone marrow sample not available for local evaluation.	NA
Ramon y Cajal University Hospital	45539	2022-01-19	1139-1_ICF incorrect date of signature	ICF incorrect signature date	The principal investigator documented in the ICF that the principal investigator and the patient wrote an incorrect date and that the correct date was 06-02-2021. The patient will have to go to the center to change their date.
	45537	2022	Patient 1139-1_ECOG missing in IND01-D5, IND01-D15, IND01-D22, IND01-D35, and visits prior to allogeneic hematopoietic stem cell transplantati	ECOG missing in IND01-D5, IND01-D15, IND01-D22, IND01-D35, and visits prior to allogeneic hematopoietic stem cell transplantation (preAlloSCT).	CRA requests the principal investigator to make an addendum

			on (preAlloSCT).		
	45213	2022-01-19	Patient 1139-1_IMP incorrect returned	19/JAN/2022 CRA explained the problem to PI and SC. Patient 1139-1 returned the following kits: - Quizartinib 30 mg - Lot 11-311967-1 - kit 85054: 1 tablet (patient 1139-1, IND01) - Quizartinib 30 mg - Lot 11-3119667-1 - kit 85040 16 tablets (patient -Quizartinib 30 mg – Lot 11-311967-1 – kit 85043: 3 tablets (Patient 1139-1, MTO-02) Confirmation is pending from SC as to why the patient returned an incorrect number of tablets. In addition, there were kits that were not returned, so the CRA was unable to perform IP accountability. The kits will remain at the site until the next monitoring visit. nte 1139-1, MTO-01) The patient had returned the following kits in total: - Quizartinib 30 mg - Batch 11-311967-1 - kit 85054: 1 tablet (Patient 1139-1, IND01) - Quizartinib 30 mg – Batch 11-3119667-1 – Kit 85040: 16 tablets (Patient 1139-1, MTO-01) - Quizartinib 30 mg – Lot 11-311967-1 – Kit 85043: 3 tablets (Patient 1139-1, MTO-02) - Quizartinib 30 mg - Batch 11-311967-1 - Kit 85056: 10 tablets (Patient 1139-1, MTO-03) - Quizartinib 30 mg -	The CRA reminded the PI of the importance of documenting all kits dispensed and returned. Jan 11, 2023 The PI created an appendix to document this deviation. This issue was closed.

				Batch 11-311967-1 - kit 85046: 8 tablets (Patient 1139-1, MTO-04) The patient has lost the following kits: -Quizartinib 30 mg - Batch 11- t 311967-1 - kit 85058 (MTO-01) -Quizartinib 30 mg - Batch 11-311967-1 - kit 85051 (MTO-02) - Quizartinib 30 mg – Lot 11-311967-1 – kit 85045 (MTO-03)-Quizartinib 30 mg – Lot 11-311967-1 – kit 85041 (MTO-05) Therefore, these kits were not returned to the center, and the principal investigator made an appendix to document this issue. The principal investigator retrained the patient and his sister on the management of the investigational drug and the importance of returning used kits. The drug will be destroyed when the patient returns the outstanding kits. May 30, 2022 The CRA did not review the new tablets returned due to lack of time. The CRA will check this issue during the next monitoring visit. Sep 12, 2022 The CRA reviewed all kits returned by the patient. The CRA found that the following kits had not been returned: -Quizartinib 30 mg – Batch 11-311967-1 – kit 85563 (MTO-09) An addendum is pending to specify that this kit was not returned by the patient.	
Ramon y Cajal University Hospital	44815	2021-12-29	Patient 1139-3_Start of treatment with FLAG-	Start of treatment with FLAG-QUIDA before confirming the results from the central laboratory.	NA

			QUIDA before confirming the results from the central laboratory.		
	43754	2021-09-30	Patient 1139-1_QlQ-C30 not performed on IND1-D5	QlQ-C30 not performed in IND1-D5	CRA requests the principal investigator to perform an addendum
	40284	June 2, 2021	Patient 1139-1_Bone marrow sample in the selection	Bone marrow sample in the selection	NA
	40283	2021-06-16	Patient 1139-1_Parameters not evaluated in the blood test.	Parameters not evaluated in the blood test	CRA requests that the principal investigator perform an addendum
Reina Sofía University Hospital	48676	2023-01-26	Patient 1143-3_PreAlloSCT_Heart rate and temperature	PreAlloSCT_Heartbeat and temperature	CRA requests the principal investigator to make an addendum
Reina Sofía General Hospital	48671	2023-01-27	Patient 1143-3_PreAlloSCT_Dr. Luque not	Dr. Luque not delegated or trained	Dr. Luque is no longer at the center. The principal investigator will write an appendix explaining that the

			delegated or trained		visit was supervised by Dr. Martín.
	47813	2022-09-21	The samples from patient 1143-3_PreAllo_Samples did not arrive at Dr. Negrin's laboratory.	The samples did not arrive at the laboratory for analysis.	CRA requests that the principal investigator make an addendum.
	47812	2022-09-21	Patient 1143-3_IND01-D15_ECG	IND01-D15_ECG	CRA requests the principal investigator to make an addendum
	47811	2022-09-21	Patient 1143-1_Bone marrow extraction_End of treatment	Bone marrow extraction_End of treatment	NA
	47810	2022-09-15	Patient 1143-1_Blood test in the program's relapse assessment.	Blood test in the program's relapse assessment.	CRA requests the principal investigator to perform an addendum.
	40618	2021-07-21	Patient 1143-1_Quizartinib kit 85202 returned due to lack of stock.	Quizartinib kit 85202 returned due to lack of stock.	The CRA asked the principal investigator to make an addendum to document that the patient did not return the quizartinib kit.

	40617	2021	Patient 1143-3_Quizartinib kit 85200 returned due to lack of stock.	Quizartinib kit 85202 returned due to lack of stock.	The CRA requested that the principal investigator prepare an appendix to document that the patient did not return the quizartinib kit.
	35319	2020-09-21	Patient 1143-3 - Sample bank D35	Problems with samples for sample bank D35	
	35318	2020-09-21	Patient 1143-3: incomplete induction cycle.	21/SEP/2020: The site reported that patient 1143-3 has not completed the induction cycle and has received an allo-HSCT because they could not wait until the end of the cycle.	NA
	32193	2020-09-21	Patient 1143-3 - D35 MRD	SEP 21, 2020: The center reported that patient 1143-3 has not completed the induction cycle and has undergone alloSTC because he could not wait until the end of the cycle. Due to a lack of knowledge about the procedures and samples to be evaluated, and poor communication between the research team, only bone marrow was extracted for local MRD evaluation.	NA
Hospital General Del H.U. Reina Sofía	27888	2020-06-04	Patient 1143-1_G-CSF dose	Patient 1143-1_G-CSF dose	
	27886	2020-06-04	Patient 1143-1_V4: Missing laboratory test	Laboratory test missing. Complete blood count: Reticulocytes, Blasts	NA

	27885	2020-06-04	Patient 1143-1_V3: Missing laboratory test	Laboratory test missing. Complete blood count: Reticulocytes, Blasts	NA
	27884	2020-06-04	Patient 1143-1_V2: Missing laboratory test	Laboratory test missing. Complete blood count: Reticulocytes, Blasts	NA
	27884	2020-06-04	Patient 1143-1_V1: Missing laboratory test	Laboratory test missing. Complete blood count: Reticulocytes, Blasts	NA
	27884	2020-06-04	Patient 1143-1_Screening: Missing laboratory test	Laboratory test missing. Complete blood count: Reticulocytes, Blasts	NA
University Hospital of Jerez de la Frontera	48698	02/07/2023	Patient 1146-1_ECG not evaluated in the SD	ECGs not evaluated in the SD	The Quality Department has not yet communicated the corrective measures to be taken to the CRA.
	48364	2022-11-08	Patient 1150-2_EOT visit	November 8, 2022. Subject 1150-2 was scheduled to start maintenance, but is taking Letermovir, a prohibited concomitant medication, as it is a	The CRA asked the sponsor to decide whether it is worthwhile to conduct an EOT visit outside the established

				CYP3A4 inhibitor. Once the subject finished this medication, the disease progressed to the point that the research team decided not to start maintenance cycles. MTO should have been initiated in July at the latest. Therefore, the site decided to withdraw the patient without performing the EOT, as the visit would have already exceeded the deadline.	deadline. Further action will be taken after receiving their response.
University Hospital of Jerez de la Frontera	48360	2022-11-08	Patient 1146-1_IND01-D15 and IND01-D22_Not evaluated	Patient 1146-1_IND01-D15 and IND01-D22_Not evaluated	The CRA asked the principal investigator and secondary investigators to evaluate the ECGs.
	48357	2022-11-08	Patient 1150-1_EOT_Blood evaluation	Blood test	PI will add an appendix indicating the reason why it was not performed.
	48356	2022-11-08	Patient 1150-1_MTO01_ECG not tripled	ECG not tripled	PI will prepare an appendix indicating the reason why it was not performed.
	46916	2022-05-05	Patient 1150-1_EOT_Bone marrow and peripheral blood samples	Bone marrow and peripheral blood samples are missing	PI will prepare an appendix indicating the reason why it was not carried out.
	46782	2022-05-11	Patient 1150-1_EOT past due	EOT past due	CRA called SC to explain this deviation from the protocol and remind them that the principal investigator must add a note to the medical record

					indicating that this visit was scheduled outside the deadline by mistake.
	45783	2022-02-10	Patient 1150-1_Parameters not evaluated	-MTO8: urea-MTO9: chloride and urea-MTO10: urea-MTO11: chloride and urea-	PI will add an appendix indicating the reason why it was not performed.
	39214	2021-04-14	Patient 1146-1_Parameters not evaluated in the PreAlloSCT blood test.	Some parameters were not evaluated: - Complete blood count: % reticulocytes and blasts - Biochemistry: BUN, urea, chloride	PI will prepare an appendix indicating the reason why it was not performed.
	38378	2021	Patient 1146-1_CON01-D15: Analytical values were not evaluated.	Neither the complete blood count nor the reticulocytes were evaluated	PI will add an appendix indicating the reason why it was not carried out.
	38375	2021	Patient 1146-1_IND01-D35: Analytical values were not evaluated.	Neither the complete blood count nor the reticulocytes were evaluated.	PI will add an appendix indicating the reason why it was not carried out.
	36413	2020-10-21	PH_Temperature deviation	A temperature of 25.6 °C has been reached. PH must report	PH must report the temperature deviation by completing the temperature deviation report form. Since

				the temperature excursion by completing the temperature excursion report form.	the temperature of 25.6 °C was not reached for a period exceeding 6 days, the IMP is not considered to be in quarantine.
	35164	2020-10-21	Patient 1146-1_Chemistry not evaluated in IND01-D01	Chemistry not evaluated in IND01-D01	PI will add an appendix indicating the reason why it was not performed
University Hospital of Jerez de la Frontera	35162	2020-10-21	Patient 1146-1_Chest X-ray and cytogenetics performed before signing the ICF.	Chest X-ray performed before signing the ICF.	NA
	35160	2020-10-21	Patient 1146-1_Triplicate ECG performed every hour.	Triplicate ECG performed every hour.	The principal investigator must clarify in the medical records due to a misunderstanding.
Insular Maternal and Child Hospital	50532	May 10, 2023	1142_1IND01-D15_only one ECG was performed	only an ECG was performed	NA
	50531	2023-05-10	1142-1IND01-D05_QLQC30 partially completed	QLQC30 partially completed	NA

	50530	2023-05-10	1142-1_IND01-D05_Quizartinib vial not returned	Due to the patient's critical condition and subsequent death, the quizartinib bottle could not be returned to the center and proper accountability could not be carried out, making it impossible to determine how many pills were taken during induction (according to the protocol, 28 at a dose of 60 mg per day), thus breaching the protocol.	NA
	38475	2021-02-11	Patient 1142-1_End of study: values not evaluated.	Complete blood count: Reticulocyte and blast percentages were not evaluated. Biochemistry: BUN, urate, phosphate, total protein, and calcium were not evaluated.	NA
	38473	2021-02-11	Values for patient 1142-1_IND01-D5 not evaluated.	Complete blood count: Reticulocyte and blast percentages were not evaluated. Biochemistry: BUN, urate, phosphate, total protein, and calcium were not evaluated.	NA
	38471	2021-02-11	Patient 1142-1_Screening: values not evaluated	Screening: values not evaluated	NA
Puerta del Mar Hospital	51955	2023-09-19	1150-3 - Parameters not evaluated in screening chemistry	Parameters not evaluated in screening chemistry	NA
Puerta del Mar Hospital	51951	2023-09-19	1150-3 - Parameters not	For patient 1150-3, during EOT, blasts, neutrophils, lymphocytes, eosinophils,	NA

			evaluated in the hemogram of EOT	basophils, and monocytes were not evaluated in the blood count.	
	51949	2023-09-19	1150-3 - QLQ-C30 not performed during EOT	An appendix was added to clarify the reason why the procedures were not performed during EOT.	PI will add an appendix indicating the reason
	51948	2023-09-19	1150-3 – Bone marrow for response assessment not extracted during EOT	bone marrow for response assessment not extracted during EOT	PI will add an appendix indicating the reason why it was not performed
	50792	2023-05-22	IND01-D35 samples for the central laboratory are missing	Samples for the central laboratory are missing	Corrective action cannot be taken, as the patient is no longer participating in the study; furthermore, the sample should have been collected during the IND01-D35 interval.
	48584	2023-01-10	Patient 1150-2_COND03-D01_QLQ C30	June 20, 2023: This procedure was not performed during the visit due to an error. An addendum was made to clarify this PD.	No corrective action can be taken, as the deadline for the procedure has passed. However, the website drafted an addendum to clarify this deviation.
	48583	2023-01-10	Patient 1150-2_COND01-D01_Blood test parameters	COND01-D01_Blood test parameters not measured	PI will write an appendix indicating the reason why it was not performed.

			not measured		
	45567	2022-01-25	Patient 1150-2_Serious adverse events pending notification	Serious adverse events pending notification	The CRA requested that PI and SC report on this as soon as possible.
	45561	2022-01-25	Patient 1150-2_ECOG not performed in IND01-D15	ECOG not performed in IND01-D15	PI will add an appendix indicating the reason why it was not performed.
	45559	2022	Patient 1150-2_Chemistry_Parameters not evaluated	IND01-D1: Potassium, chloride, urate, total bilirubin, alkaline phosphatase, ALT, AST, LDG, magnesium, albumin, phosphate, total proteins, calcium.IND01-D15: urateIND01-D22: urateCON01-D1: chloride, urate, alkaline phosphatase, albuminCON01-D6: urate, alkaline phosphatase, albuminCON01-D15: chlorideCON2-D1: phosphateIt is a minor deviation	The CRA retrained the staff on the protocol procedures, and the principal investigator and safety officer signed a training log. This issue has been resolved.
Puerta del Mar Hospital	45558	2022-01-25	Patient 1150-2_General ICF-CI signed in error	General ICF-CI signed in error	The PI wrote a note in the general ICF to document that it was signed in error. In addition, the PI will need to document that the patient signed the general ICF-CI in error.
	39454	2021-05-05	Patient 1150-01_Values not	IND01D15 Reticulocyte and blast values were not available in the blood count. The BUN value was not available in the	

			evaluated in sample test results	biochemistry. IND01D22 Reticulocyte and blast values were not available in the blood count.	
	36558	2020-11-25	Patient 1150-01_Quizartinib started late	Quizartinib was not started on day 5 (09/NOV/2020). It was started on 10/NOV/2020. The investigators explained that it was delayed due to a misunderstanding with the pharmacy staff.	NA
	36557	2020	Patient 1150-01_GCS-F not administered on day D-1.	The investigators reported that GCS-F was not administered on day D-1 due to hyperleukocytosis (> 25,000).	NA
	36556	2020-11-25	Patient 1150-01_Only an ECF was performed at screening.	Screening: An ECG was requested in triplicate, but only 1 ECG was performed on 05/NOV/2020 due to an error.	The CRA explained that, according to the protocol, it is necessary to perform 3 ECGs every two minutes each.
Joan XXIII University Hospital of Tarragona	52573	2023-06-28	1154-2 IND01-D15 ECG	The CRA detected that the original ECG document was not available and did not appear in the electronic medical records.	NA
	52572	2023-06-08	1154-2 MTO6 Sample evaluation and responses.	An evaluation of the response was performed, but no bone marrow extraction was performed.	PI will add an appendix indicating the reason why it was not performed.
	50722	2023-05-05	MTO visits after the deadline	MTO visits after the deadline	PI will prepare an appendix indicating the reason why it was not carried out.
	48599	2022-09-01	Patient 1154-2 - EOT - Central	Central Laboratory samples sent back	NA

			Laboratory Samples		
	47258	2022-07-19	MT0-03 IMP dispensed after expiration date	On 05/APR/2022, batch 85292 is dispensed and an empty bottle is returned, but this dispensing does not coincide with the MTO-04 visit; rather, it is an additional MTO dispensing.	An appendix must be added to the medical record indicating the dispensing of bottle 85292 as an additional bottle for MTO-03 and justifying the reason.
	46439	2022-04-05	Patient 1154-2_MTO-03_Laboratory evaluation	April 5, 2022: Creatinine, sodium, potassium, chloride, glucose, magnesium, phosphatase, and calcium values were not evaluated in MTO-03.	NA
Joan XXIII University Hospital of Tarragona	46438	2022-04-05	Patient 1154-2_MTO-04, 05, and 07_past due	Visits MTO-04, 05 and 07_past due	PI will add an appendix indicating the reason
	46437	2022-04-05	Patient 1154-2_MTO-02_kits 85295 and 85276	April 5, 2022: CRA observed that the subject returned kits 85295 and 85276 empty. According to site staff, the reason was that the subject took the remaining medication during MTO-03.	PI will add an appendix indicating the reason.
	45198	2022-01-19	Values for patient 1154-2_MTO-02_BQ not assessed.	T19/JAN/2022 -It was noticed that magnesium and phosphate were not assessed in the blood samples collected on 27-Dec-2021 (MTO-02).	NA
	45197	2022-01-19	Patient 1154-2_MTO-01_ECG	T19/JAN/2022 -In MTO-01, the time between ECGs was less than 2 minutes.	NA
	45186	2022	Patient 1154-1: kits not returned.	Subject 1154-1 has not returned the following kits: 85296, 85299, 85283, and probably 85287 (not indicated as	NA

				administered on July 8, 2021, but it is the only one that is unavailable and has not been assigned to another subject).	
	45181	2022-01-19	1154-2_IP Prescription MTO-02	The MTO-02 IP prescription form indicates "30 mg dose for 15 days, then increase to 60 mg." The medical records do not indicate the dose administered at this visit. According to the protocol, if the dose was increased to 60 mg in MTO-01D15, the dose to be administered during MTO-02 will be 60 mg.	NA
	45179	2022-01-19	1154-2_MTO1-D15 not performed	MTO1-D15 not performed	The CRA detected that the IP prescription for IND01-D05 was missing. However, the internal IP accountability report indicated that kit 85274 was administered to this subject on June 10, 2021, and that the kit was returned.
	44262	2021-10-27	1154-2 - Blood samples prior to allogeneic hematopoietic stem cell transplantation (pre-alloSCT)	No blood samples were collected prior to allogeneic hematopoietic stem cell transplantation	NA
	44259	2021-10-27	1154-2 - IND01-D15 - ECG	The medical records report that the ECG was performed, but the results are not available.	NA

	44250	2021-10-27	Patient 1154-1 - MT03 - Laboratory evaluation	The following data from the blood samples tests were not analyzed: Blasts, BUN, chloride, urate, bilirubin, alkaline phosphatase, LDH, albumin, magnesium, phosphate, total protein, calcium	NA
Joan XXIII University Hospital of Tarragona	44248	2021-10-27	Patient 1154-1 - EOT - Vital signs	Temperature not taken	NA
	44244	2021-10-27	Patient 1154-1 - EOT - Central Laboratory Samples	Samples not collected	NA
	44242	2021-10-27	Patient 1154-1 - MT03 - Visit	MT03 – Late visit	NA
	43383	2021	Patient 1154-1 - MTO01-D15 - Visits	MTO01-D15 – Late visits	NA
	39282	2021-04-23	Patient 1154-1_No cytogenetic analyses were performed.	No cytogenetic analyses were performed.	NA
	38468	2021-02-12	Patient 1154-1: administration of an incorrect	Administration of an incorrect dose of cytarabine.	NA

			dose of cytarabine.		
	38181	2021-01-29	Patient 1154-1_G-CSF not administered in IND01 D-1	G-CSF not administered in IND01 D-1	NA
Son Espases University Hospital	44513	2021-11-11	ISF_DoA_Physicians not included	These physicians were not included in the training registry and their CVs and BPC certificates must be provided.	These doctors must be designated in the study, included in the training registry, and their CVs and BPC certificates must be provided.
	50748	2023-05-22	1148-2_EoT assessments not completed	EoT assessments not completed	
	50746	2023-05-22	1148-2_EoT assessments completed after the deadline prior to the visit	EoT assessments completed after the deadline prior to the visit	NA
	50739	2023-05-22	1148-2_MTO-07_IMP non-compliance	May 23, 2023: In MTO-07, the patient returned a total of 56 tablets from two bottles (60 in total) after taking only 4 tablets of quizartinib at 60 mg/day. According to the patient's medical history, from December 19, 2022, to December 29, 2022, he had to take quizartinib until it was discontinued on December 29, 2022, due to influenza B and the patient's clinical deterioration.	Appendix

				Therefore, if he had complied every day until the date of discontinuation, he should have returned 40 tablets, but he returned 56, thereby failing to comply with the treatment protocol.	
Son Espases University Hospital	48598	2023-01-12	1148-2_MTO-01 to MT0-07_Evaluations not performed	Assessments not performed due to possible discontinuation of treatment by the patient	NA
	48595	2023	1148-2_MTO-06_Past due	Visit MTO-06_Past due	NA
	48594	2023-01-12	1148-2_MTO-05_Non-compliance with drug treatment	Non-compliance with drug treatment	The center must explain in an appendix why the patient did not comply with the medication established by the protocol and took fewer days than they should have.
	48593	2023-01-12	1148-2_MTO-05_Late visit	Late visit	The medical record reflects the problem and its justification.
	48591	2023-01-12	1148-2_MTO-04_Incorrect compliance with IMP	January 12, 2023: Quizartinib 30 mg from September 9, 2022, to September 16, 2022, 8 days, return of 18 tablets, should return 22 due to reported community-acquired pneumonia.	Sponsor approves resumption at 30 mg/day on October 26, 2022.
	48590	2023-01-12	1148-2_MTO-04_	Non-delegated staff and late visit	An annex must be drafted indicating the reason for the visit outside the established deadline, and Sandra Pérez

					must be delegated, trained in the study, and her CV and GCP obtained.
	48589	2023-01-12	1148_2_MTO-03_Non-compliance with treatment	Non-compliance with treatment	The center must indicate in an annex why the patient did not comply with the medication established by the protocol.
	48586	2023-01-12	Patient 1148-2 - MTO1-D15 past due	January 12, 2023: The site conducted the visit on day +13 due to human error.	NA
	47650	September 7, 2022	Patient 1148-2: MTO-01 and MTO-02 ECOG not performed.	ECOG not performed.	An appendix will be drafted indicating that the ECOG has not been evaluated and the reasons why.
Son Espases University Hospital	47649	September 7, 2022	Patient 1148-2 - MTO-02 returned incorrect pills.	During MTO-02, patient 1148-2 received 1 bottle of quizartinib 30 mg, kit, 85157, at a reduced dose of 30 mg/day due to febrile neutropenia. The patient takes the medication from June 20, 2022, to July 4, 2022, and discontinues it due to COVID pneumonia. In total, the patient returned 0 tablets. January 12, 2023: from 06/20/21 to 07/04/21, quizartinib 30 mg, 15 tablets, interruption due to COVID pneumonia, resumption on 08/02/21 until 08/16/21, 15 tablets.	The center must explain in an appendix why the patient did not comply with the medication established by the protocol.
	47002	2022-09-07	Patient 1148-2_pre-alloSCT, MTO-01 and	10/JUN/2022 - The following laboratory parameters were not evaluated in the pre-allo-HSCT: BUN, magnesium, chloride, and urea. 07/SEP/2022 - The	Center staff have been reminded of the importance of complying with all protocol assessments and, if this is not

			MTO-02 evaluations not performed.	following laboratory parameters were not evaluated in the pre-allo-HSCT, MTO-01, and MTO-02: BUN, magnesium, chloride, and urea.	done, to correctly note this in the patient's medical record.
	45834	2022-02-23	Patient 1148-2_IND01-D22_Laboratory parameters	23/FEB/2022 - "Urea, chloride, and magnesium values were not evaluated in IND01-D22."	NA
	45816	02/02/2022	Patient 1148-2_IP Administration	23/FEB/2022 - Subject 1138-2 returned 0 tablets; if the dose administered was 60 mg and the subject took the medication for 14 days, they should return 2 tablets. The Pharmacy Service is waiting to confirm whether the bottle was provided to the subject or whether they received the prescribed number of tablets each day.	The center must explain in an appendix why the patient did not comply with the medication established by the protocol.
	44535	2021-11-11	Patient 1148-2_G-CSF not taken	G-CSF not taken	The center must explain in an appendix why the patient did not comply with the medication established by the protocol.
	44516	2021-11-11	Patient 1148-2_ICF not completed correctly	ICF not completed correctly	The subject (or responsible family member) must cross out the part of the ICF indicated for "consent before a witness" and date and sign this correction. The correction in the "withdraw consent" section must also be signed and dated.

	43559	2021-08-11	Patient 1148-1_SAE FU Death_delay in notification	Death_delay in notification	NA
	43558	2021-08-11	Patient 1148-1_IND01-D15, IND01-D22_ECOG	ECOG not performed correctly	The center's staff has been reminded of the importance of complying with all protocol evaluations and, in case of failure to do so,
Son Espases University Hospital	43556	2021-08-11	Patient 1148-1_IND01-D22_Chemistry	The following values were not evaluated in the blood tests: urate, LDH, and magnesium.	NA
	43554	2021-08-11	Patient 1148-1_IND01-D15_ECG	ECG not performed correctly	NA
	39453	2021-05-12	Patient 1148-1_IMP administration interrupted	MAY 12, 2021: Quizartinib was suspended on APR 17, 2021, and quizartinib was administered on APR 18, 2021, to complete 14 days from the first day (from D5 to D19).	The CRA reminded that the protocol must always be followed.
	39449	2021-05-12	Patient 1148-1_Medication-IND01-D01-	May 12, 2021: IND01-D01. Total idaburicin administered (mg) x day, 10 mg/m² (2.43 m² due to weight). Should be 24 mg, but was 23 mg; induction with cytarabine. 2 or 1 g/m². Should be 4800 mg, but was 4600 mg; fludarabine. 30 mg/m². Should be 72 mg, but was 69 mg. The CRA will be reminded to always	The CRA reminded them that the protocol must always be followed.

				follow the protocol by email to the principal investigator.	
	39447	May 12, 2021	Patient 1148-1_Samples sent to the wrong laboratory	MAY 12, 2021: Bone marrow, peripheral blood, serum, and saliva samples (Dr. Negrín's laboratory) were sent to La Fe Hospital. Bone marrow and peripheral blood samples (IMIBIC laboratory) were sent to La Fe Hospital. The CRA will send an email reminding the correct laboratory to send the samples.	NA
Alicante General Hospital	53205	2023-10-30	1138-6 Follow-up not performed	Follow-up visit not performed	NA
	48427	December 14, 2022	1138-6_EoT_Incomplete Biochemistry	Incomplete Biochemistry	NA
	47820	2022-09-29	1138-6_IND01-D05_Laboratory values not evaluated	IND01-D35: The following parameters were not evaluated in biochemistry: BUN, total bilirubin, alkaline phosphatase, LDH, albumin, magnesium, phosphate, and calcium.	NA
	47112	2022-06-29	1138-3 IND01-D05 Physical examination not evaluated	physical examination not performed	Attachment indicating the reason why the evaluation was not performed.
	45752	2022-02-02	Patient 1138-5_IND01-	Laboratory test evaluation	NA

			D01_Laboratory test evaluation		
Alicante General Hospital	45747	February 16, 2022	Patient 1138-5_Administration of G-CSF	15/FEB/2022 - Medical records document that a double dose of G-CSF was taken.	NA
	45745	2022	Patient 1138-4_IND01-D01_ECOG	ECOG not performed	NA
	45744	2022-02-16	Patient 1138-2_IND01-D35_	ECOG and physical examination not performed.	NA
	45737	2022-02-16	Patient 1138-3_IND01-D05_Missing values	Phosphatase and magnesium were not evaluated in IND01-D05.	The CRA reminded that the protocol must always be followed.
	45735	2022-02-16	Patient 1138-3_IND01-D01_Hemostasis	Hemostasis needs to be performed	NA
	45730	2022-02-16	Patient 1138-3_ECG	ECG not performed	NA
	45536	2020-11-23	Patient 1138-2_Cytogenetics not performed.	Cytogenetics not performed.	NA
	45137	2022-01-14	Patient 1138-3_IMP administration	14/JAN/2022: After reviewing the IP dispensing record provided on November 23, 2021, the CRA reported that the IMP was not dispensed according to protocol, the quizartinib dose was reduced during the induction	Jan. 14, 2022: After reviewing the IP dispensing log provided on Nov. 23, 2021, the CRA reported that the IMP was not dispensed according to protocol, the quizartinib dose

				period on December 12, 2020, and was increased again on December 16, 2020.	was reduced during the induction period on Dec. 12, 2020, and was increased again on Dec. 16, 2020. The CRA discussed this issue with the PI. The medical records indicate that the subject reduced the quizartinib dose to 40 mg due to voriconazole; however, the prescription sheet indicates 20 mg. According to the returned pills, the subject took a 40 mg dose. On the other hand, the site was aware of this and reduced the dose to 30 mg. The case should be noted in the medical records. However, according to the returned pills, the subject took a 60 mg dose while taking voriconazole. This is not permitted by the protocol. 2/22/2022 - The deviation was reported to the sponsor. Regarding the discrepancy in the dose on the prescription sheet and the medical records, a note should be made on the pharmacy prescription sheet indicating the correct dose.
Alicante General Hospital	44648	2021-11-23	Patient 1138-2_SAE Impaired	The final SAE report on the "vision impairment in the left eye" was not provided.	The final SAE report must be provided.

			vision in the left eye		
	44642	2021-11-23	Patient 1138-2_Laboratory values	Laboratory values and ECG not performed correctly	NA
	44634	2021-11-23	Patient 1138-2_IND01-D15_ECOG	ECOG	The CRA reminded that the protocol must always be followed.
	44329	2021-11-23	Patient 1138-7_COND01-D06 past due	The COND01-D06 visit took place on October 11, 2021. The COND01-D01 visit took place on October 4, 2021 (the date scheduled for the COND01-D06 visit according to the protocol was October 9, 2021).	NA
	44327	2021-11-23	Patient 1138-5_Screening - Central laboratory samples	Central laboratory samples	NA
	44324	2021-11-23	Patient 1138-3_Additional response assessment #2	According to the protocol, aspiration should be repeated every 7 days (if possible) if the sample is not evaluated. In IND01-D35, the sample was not evaluated according to PLATAFO-LMA data. Additional evaluation #1 was performed on January 14, but the second additional evaluation was performed on February 18, 2021.	NA
	43565	2021-08-19	Patient 1138-6_Eligibility criteria	19/AUG/2021 (MM): Patient 1138-6 did not meet inclusion criterion 11 (for phase II, FLT3-ITD will represent 50% of the study cohort) and met exclusion	NA

				criterion 16 (belongs to the FLT3-ITD-WT cohort subjects that has been reached). 11/23/2021: The site reported that the subject was included because the FLT3-WT cohort was open on the date of inclusion (July 5, 2021), and the local coordinator confirmed that the subject could be included without confirmation of FLT3-ITD results (correspondence added to this PD).	
	39655	2021-05-18	Patient 1138-5: cytogenetic screening	Cytogenetic screening not performed during screening	NA
Alicante General Hospital	39463	May 18, 2021	Patient 1138-5_ICF not completed correctly	ICF not completed correctly	CRA will ask La Fe CRA (where the patient is located) to have the patient write a note explaining the situation.
	39462	May 18	Patient 1138-4_ICF not completed correctly	ICF not completed correctly. The witness did not write the name of the researcher (it is blank).	The subject must write the name of the researcher who provides the ICF.
	29880	2020-07-23	Patient 1138-1_IMP administration	The patient starts quizartinib on May 15, 2020, with a dose of 60 mg/day of IMP. He interrupts the dose after the first IMP intake (May 16, 2020). He resumes taking IMP on May 20, 2020. Due to reported discomfort, the patient decides not to take IMP on May 24 and 25, 2020. On May 26, 2020, he resumes taking IMP at a lower dose (40 mg/day) until the end of treatment (May 28, 2020).	NA

	29862	2020-07-23	Patient 1138-1: hemostasis test not performed, visit IND01-D01.	Hemostasis test not performed, visit IND01-D01	NA
	29861	2020-07-23	Patient 1138-1_IMP Administration	The patient started quizartinib on May 15, 2020, with a dose of 60 mg/day of IMP. He discontinued the dose after the first IMP intake (May 16, 2020). He resumed taking IMP on May 20, 2020. Due to reported discomfort, the patient decides not to take the IMP on May 24 and 25, 2020. On May 26, 2020, he resumes taking the IMP at a lower dose (40 mg/day) until the end of treatment (May 28, 2020).	NA
	29860	2020-07-23	Patient 1138-1_G-CSF dose	According to the protocol, G-CSF should be administered from day -1 to day 5 at a dose of 300 µg/m2/day if the patient has a white blood cell count >25,000 µL on day 1. This patient has received a dose of 300 µg/day; however, since his m2 value is 2.18, he should be administered 654 µg/day.	In relation to this patient, the principal investigator believes that the dose administered caused him severe bone pain (a side effect that we see quite frequently), so he probably would not have tolerated higher doses either.
Dr. Negrín University Hospital of Gran Canaria	50539	May 11, 2023	1141-1_Progressive relapse resistance assessments not performed	Progression-relapse-resistance: physical examination, vital signs, ECOG, chemistry (magnesium and albumin), QLQC30, and central laboratory samples not evaluated due to error, protocol noncompliance.	

Dr. Negrín University Hospital of Gran Canaria	50538	2023-05-11	1141_1_End of treatment_assessments not performed	evaluations not performed	NA
	50537	2023-05-11	1141-1_Additional response evaluation_evaluations not performed	assessments not performed	NA
	50536	2023-05-11	1141-1_IND01-D35_	assessments not performed	NA
	50535	2023-05-11	1141_1_IND01-D15_ECG partially performed	In IND01-D15, the center staff performed only two ECGs instead of three, as required by the protocol, by mistake, without complying with the protocol assessments.	NA
	50534	May 11, 2023	1141_1IND01-D01_Partially evaluated blood count	Complete blood count (reticulocytes and blasts) not evaluated by mistake, failing to comply with protocol evaluations.	NA
	50533	2023-05-11	1141_1_Partial evaluation of clinical chemistry and blood count	Chemical analyses (direct bilirubin and BUN) and complete blood count (reticulocytes and blasts) were not evaluated due to an error, in breach of protocol evaluations.	NA

Clinica Universidad De Navarra	50983	2023-06-27	Patient 1338-1_COND01-D35	June 27, 2023 CRA detected that the physical examination of COND01-D35 was not performed or documented in the medical records.	June 27, 2023 The CRA detected that the physical examination of COND01-D35 was not performed or documented in the medical records.
	48405	2022-12-05	Patient 1338-1_COND01-D1_QLQ-C30	QLQ-C30 not performed	Attach to medical record to document reason why this procedure was not performed.
	48404	2022-12-05	Patient 1338-1_PreAllo_Bone marrow aspiration	Bone marrow aspiration not performed	Addendum to the medical record to document the reason why this procedure was not performed.
	48403	2022-12-05	Patient 1338-1_MTO02 past due	MTO02 past due	Addendum to medical record to document reason
	47673	2022-09-13	Results of patient sample 1338-1_EOT_BP	Sep 12, 2022 PB tests from the EOT visit, urate, phosphate, and albumin were not measured. In addition, the results were not evaluated, signed, or dated.	The CRA will remind the principal investigator to evaluate the results and draft an appendix describing the reasons why these results were not measured.
Clinica Universidad De Navarra	47671	2022-09-13	Patient 1338-1_PreAllo_QLQ-C30 not performed	QLQ-C30 not performed	Attach to medical record to document reason why this procedure was not performed.
	47670	2022-09-13	Patient 1338-1_IND01-D35 and PreAllo_ECOG not performed	ECOG not performed	Addendum to the medical record to document the reason why this procedure was not performed.

	47667	2022-09-12	Patient 1338-1_EOT: pending procedures	Sep 12, 2022 The CRA detected that the following procedures were not performed during the EOT visit: - Physical examination - ECOG - QLC-C30 - PB and BM samples were not sent to the central laboratory Feb 28, 2023 PB and BM samples were not sent to the central laboratory.	Addendum to the medical record to document the reason why this procedure was not performed
	47088	2022-06-13	Patient 1338-1_PreAlloSCT Blood samples	PreAlloSCT Blood samples not performed	CRA will remind the principal investigator to review, sign, and date the report.
	47078	2022-06-13	Non-delegated site staff	Dr. Villar Fernández performed the PreAlloSCT and MTO01-D1 visits, and Dr. Ramos performed COND01-D15 without having been delegated. June 13, 2022 CRA trained the principal investigator on how to control who performs study visits. The training record is pending signature. September 12, 2022: The principal investigator confirms that Dr. Villar Fernández was delegated prior to the PreAlloSCT visit (delegation date: January 17, 2022). In addition, Dr. Artaiz did not evaluate any ECGs, as he has not been delegated. Therefore, the principal investigator has to evaluate them all. December 5, 2022: The principal investigator confirmed that he reevaluated the ECGs. He signed and dated the ECGs.	NA

	46416	2022-03-11	Patient 1338-1_CON01-D35_ECOG not performed	ECOG not performed	Attachment to the medical record to document the reason why this procedure was not performed
	46415	2022-03-11	Patient 1338-1_CON01-D1_QlQ-C30 not performed	QlQ-C30 not performed	Addendum to the medical record to document the reason why this procedure was not performed.
	46403	2022-03-11	Patient 1338-1_Concomitant medication_ Quizartinib dose not reduced.	The patient had been taking posaconazole since November 25, 2021, and the quizartinib dose was not reduced because the PI forgot.	I am attaching this to the medical record to document the reason why this procedure was not performed.
Clinica Universidad De Navarra	46402	2022-03-11	Patient 1338-1_Dispensations IMP_Pending documentation in medical record	Kit 85486 was dispensed in error and is also documented in the medical records. The principal investigator did not have access to the returned kits, so compliance was performed by pharmacy staff.	Appendix in the medical record to document the reason why this procedure was not performed
	46401	2022-03-11	The DC_PreAlloSCT and AlloSCT pages are not complete for the second medical visit	The DC_PreAlloSCT and AlloSCT pages are not complete for the second medical visit.	NA

	46399	2022-03-11	Patient 1338-1_CON01-D6_ECG not performed	ECG not performed	Attach to medical record to document reason why this procedure was not performed
	46396	2022-03-11	Patient 1338-1_ICF pending completion and documentation.	CRA detected that page 11 of the ICF v2.0 was blank. The center's contact details are pending inclusion in the principal investigator's copy and the patient's copy. Therefore, the patient will have to return to the center to return their original ICF for completion.	The CRA verified on site that this had not been done. The CRA reminded the principal investigator by email to implement the appropriate modifications as soon as possible. Since the patient has died, this issue cannot be corrected.
	44776	2021-12-02	1338-1_IMP_incorrect dispensing	Patricia Glaria (SC) wrote an email to CRA (María Carranza) to explain that she dispensed an additional bottle of quizartinib to patient 1338-1 because she forgot the number of bottles she was supposed to dispense on the patient's first visit. Patricia also indicated that the patient had not opened the additional bottle. Dec 15, 2021 María Carranza (CRA) performed the medication accountability check during MV1. She confirmed that the patient returned two tablets from the used bottle and another full bottle with 30 tablets (dispensed in error). The CRA signed a destruction form and this medication was destroyed by the center.	The CRA explained to Patricia that she had to call the patient to explain that he would have to return the leftover bottle to the center, as it could not be used later because the temperature traceability had been lost. The CRA will then destroy this medication during the next follow-up visit.