INSTITUT DE RECHERCHES INTERNATIONALES SERVIER (I.R.I.S.)

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Document title	**STATISTICAL ANALYSIS PLAN (SAP)**
Full title	**A Phase 1/2, Safety Lead-in and Dose Expansion, Open-label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Activity of Ivosidenib in Combination with Nivolumab and Ipilimumab in Previously Treated Subjects with Nonresectable or Metastatic Cholangiocarcinoma with an IDH1 Mutation**
Short title	**Ivosidenib, Nivolumab, and Ipilimumab Combination in Previously Treated Subjects with Nonresectable or Metastatic IDH1-Mutant Cholangiocarcinoma**
Test drug code	**S95031 (formerly identified as AG-120)**
Indication	**Second- or third-line treatment of IDH1-mutant cholangiocarcinoma**
Development phase	**Phase 1/2**
Protocol code	**CL1-95031-006**
Sponsor	**Institut de Recherches Internationales Servier (I.R.I.S.)**
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Signatories

Prepared by:	Signature	Date
[redacted] Senior Biostatistician IQVIA		
Approved by:	Signature	Date
[redacted] Study Biostatistician Director Servier Pharmaceuticals		
[redacted] Senior Director Servier Pharmaceuticals		
[redacted]. Senior Medical Director Global Clinical Lead Servier Pharmaceuticals		

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Follow up of versions

Version	Release date (dd/mm/yyyy)	Key change(s) (*)	Protocol version associated	Rationale
1.0	11/12/2024	Not applicable	Version 5.0	Initial version

(*) Key changes as compared to the statistical analyses planned in the protocol for the first SAP signed version (1.0). Key changes from the previous signed version for the other SAP signed version(s). See also section 7 for the changes to protocol-planned analyses.

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List of abbreviations

Abbreviation	Definition
2-HG	2-Hydroxygluturate
5-FU	5-Fluorouracil
ADA	Anti-Drug Antibody
ADI	Actual Dose Intensity
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Concentration-vs-Time Curve
AUC_{0-t}	AUC from 0 to Time of Last Measurable Concentration
$AUC_{tau,ss}$	AUC over 1 Dosing Interval at Steady State
BMI	Body Mass Index
BOR	Best Overall Response
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
C1D1	Cycle 1 Day 1
CCA	Cholangiocarcinoma
CI	Confidence Interval
CL/F	Apparent Clearance
C_{max}	Maximum Concentration
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	Trough Concentration
DBP	Diastolic Blood Pressure
DLT	Dose Limiting Toxicity
DOR	Duration of Response
DRT	Data Review Team
ECG	Electrocardiogram
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EOT	End of Treatment
GGT	Gamma Glutamyl Transferase
I.R.I.S.	Institut de Recherches Internationales Servier
ICH	International Conference for Harmonization
IDH1	Isocitrate Dehydrogenase 1
IE	Intercurrent Event
IMAE	Immune-Mediated Adverse Event
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
LLN	Lower Limit of Normal

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NE	Non Evaluable
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Pharmacodynamic or Progressive Disease
PD-L1	Programmed Death-Ligand 1
PDI	Planned Dose Intensity
PFS	Progression-Free Survival
PK	Pharmacokinetic
PO	Orally
PR	Partial Response
PT	Preferred Term or Prothrombin Time
Q3W	Once Every 3 Weeks
Q4W	Once Every 4 Weeks
QD	Once Daily
RBC	Red Blood Cell
RCD	Recommended Combination Dose
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Stable Disease or Standard Deviation
SOC	System Organ Class
T3	Triiodothyronine
TEAE	Treatment-Emergent Adverse Event
TLG	Tables, Listings and Graphs
T_{max}	Time to Maximum Concentration
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
ULN	Upper Limit of Normal
Vd/F	Apparent Volume of Distribution
WBC	White Blood Cell
WHODD	World Health Organization Drug Dictionary

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1. INTRODUCTION

This SAP details the planned analyses to be performed, in accordance with the main characteristics of the amended study protocol CL1-95031-006 version 5.0 dated 06 May 2024. The templates for Tables, Listings and Graphs (TLG) are described in a separate document.

Enrollment was stopped during the Safety Lead-in phase and the study does not proceed to the Expansion phase. Early study termination letter was issued 21 August 2024.

1.1. Study objectives, endpoints and estimands

The study objectives and corresponding endpoints are summarized in Table (1.1) 1 and Table (1.1) 2 for the Safety Lead-in phase and Expansion phase, respectively.

Table (1.1) 1 - Study Objectives and Endpoints of the Safety Lead-in Phase

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of ivosidenib in combination with nivolumab and ipilimumab and determine the recommended combination dose (RCD) of ivosidenib, nivolumab, and ipilimumab	• Dose limiting toxicities (DLTs) associated with ivosidenib in combination with nivolumab and ipilimumab during the first 2 cycles of treatment • Adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)
Secondary	
To evaluate the pharmacokinetics (PK) of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma concentrations and PK parameters including, but not limited to, area under the concentration-vs-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), apparent volume of distribution (Vd/F), and apparent clearance (CL/F)
To evaluate the pharmacodynamic (PD) effects of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma 2-hydroxygluturate (2-HG) concentration
Exploratory	
To evaluate ivosidenib exposure in tumor tissue	Tumor tissue concentrations of ivosidenib
To evaluate the PK of nivolumab and ipilimumab when given in combination with ivosidenib	Serum concentrations of nivolumab and ipilimumab
To evaluate immunogenicity of nivolumab and ipilimumab when given in combination with ivosidenib	Measurement of anti-drug antibody (ADA) to nivolumab and ipilimumab
To evaluate the PD effects of ivosidenib in tumor tissue when given in combination with nivolumab and ipilimumab	Tumor tissue 2-HG concentration
To identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and the mechanism of action	• Associations of pre-treatment molecular and cellular markers with patient outcome • Differences in molecular and cellular markers between on-treatment and/or pre-treatment samples

Table (1.1) 2 - Study Objectives and Endpoints of the Expansion Phase

Objectives	Endpoints	Other Estimand Attributes
Primary		

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Objectives	Endpoints	Other Estimand Attributes
To assess the clinical activity of ivosidenib in combination with nivolumab and ipilimumab using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	Objective response (confirmed complete response [CR] or confirmed partial response [PR]) of anti-tumor activity (using RECIST v1.1)	The primary estimand of interest is the objective response rate (ORR). The attributes of the primary estimand are defined as follows: • Treatment: ivosidenib plus nivolumab and ipilimumab • Population: Safety Analysis Set • Summary measure: objective response (Yes, No) • Intercurrent events (IEs): 1. Early treatment discontinuation 2. Administration of further anti-cancer therapy
Secondary		
To confirm the safety and tolerability of the recommended combination dose (RCD) of ivosidenib, nivolumab and ipilimumab	Adverse events (AEs), adverse events of special interest (AESIs), and serious adverse events (SAEs)	Not applicable
To evaluate additional efficacy parameters to assess anti-tumor activity of ivosidenib in combination with nivolumab and ipilimumab	• Duration of response (DOR), progression-free survival (PFS) and disease control (CR, PR, or SD maintained for at least 5 months), time to response (TTR) according to RECIST v1.1 • Overall survival (OS)	Not applicable
To evaluate the pharmacokinetics (PK) of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma concentrations and PK parameters including, but not limited to, area under the concentration-vs-time curve (AUC) from 0 to time of last measurable concentration (AUC_{0-t}), AUC over 1 dosing interval at steady state ($AUC_{tau,ss}$), time to maximum concentration (T_{max}), maximum concentration (C_{max}), trough concentration (C_{trough}), apparent volume of distribution (Vd/F), and apparent clearance (CL/F)	Not applicable
To evaluate the pharmacodynamic (PD) effects of ivosidenib when given in combination with nivolumab and ipilimumab	Plasma 2-hydroxyglutarate (2-HG) concentration	Not applicable
Exploratory		
To evaluate ivosidenib exposure in tumor tissue	Tumor tissue concentrations of ivosidenib	Not applicable
To evaluate the PK of nivolumab and ipilimumab when given in combination with ivosidenib	Serum concentrations of nivolumab and ipilimumab	Not applicable

Objectives	Endpoints	Other Estimand Attributes
To evaluate immunogenicity of nivolumab and ipilimumab when given in combination with ivosidenib	Measurement of anti-drug antibody (ADA) to nivolumab and ipilimumab	Not applicable
To evaluate the PD effects of ivosidenib in tumor tissue when given in combination with nivolumab and ipilimumab	Tumor tissue 2-HG concentration	Not applicable
To identify molecular and cellular biomarkers that may be indicative of clinical response/resistance, PD activity, and the mechanism of action	• Associations of pre-treatment molecular and cellular markers with patient outcome • Differences in molecular and cellular markers between on-treatment and/or pre-treatment samples	Not applicable

1.2. Study design

This is a Phase 1/2, non-comparative, multicenter, open-label study of ivosidenib, an oral mutant IDH1 inhibitor, administered in combination with nivolumab and ipilimumab. Participants are required to have a histologically confirmed diagnosis of cholangiocarcinoma (CCA), a local molecular IDH1 gene-mutation CCA and not eligible for curative resection, transplantation, or ablative therapies. The study is conducted in adult participants with nonresectable or metastatic CCA. Participants must have progression of disease or treatment intolerance and have received at least 1 but not more than 2 prior treatment regimens for advanced disease (nonresectable or metastatic). All participants must have received either a gemcitabine- or a 5-fluorouracil (5-FU)–based chemotherapy regimen.

This study consists of a Safety Lead-in phase followed by an Expansion phase as shown in Figure (1.2) 1 and Figure (1.2) 2, respectively.

The Safety Lead-in phase will enroll up to approximately 6-12 DLT-evaluable participants. The first 6 participants enrolled will receive a dose of 500 mg once daily (QD) of ivosidenib in combination with nivolumab 3 mg/kg and ipilimumab 1 mg/kg concurrently once every 3 weeks (Q3W) for 4 doses followed by nivolumab 480 mg once every 4 weeks (Q4W) until progression (up to a maximum of 24 months of nivolumab). DLTs will be evaluated through Cycle 2 (i.e., during the first 42 days, 21 days/cycle). Based on the DLT evaluation of 500 mg QD by the Data Review Team (DRT), an additional 6 participants may be enrolled to test an alternative dose of 250 mg QD in order to reach the RCD after further review of the DRT before the Expansion phase.

The Expansion phase is conducted in 2 IDH1-mutated CCA subpopulations:

- Cohort 1: anti-PD-L1–naïve subpopulation: This subpopulation includes up to approximately 40 participants with nonresectable or metastatic CCA who have not received any anti-PD-L1 therapy.
- Cohort 2: anti-PD-L1 previously treated subpopulation: This subpopulation includes up to approximately 40 participants with nonresectable or metastatic CCA who have received anti-PD-L1 therapy.

Participants enrolled in this phase receive the RCD of ivosidenib in combination with nivolumab 3 mg/kg and ipilimumab 1 mg/kg concurrently Q3W for 4 doses followed by nivolumab at 480 mg every 4 weeks until progression (up to a maximum of 24 total months of nivolumab).

Figure (1.2) 1 - Safety Lead-in Phase

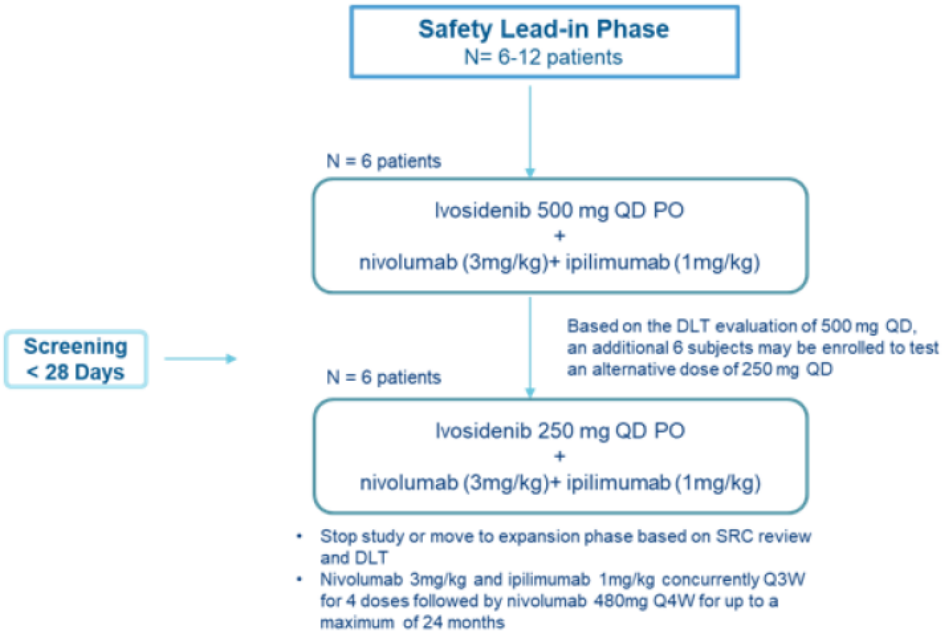
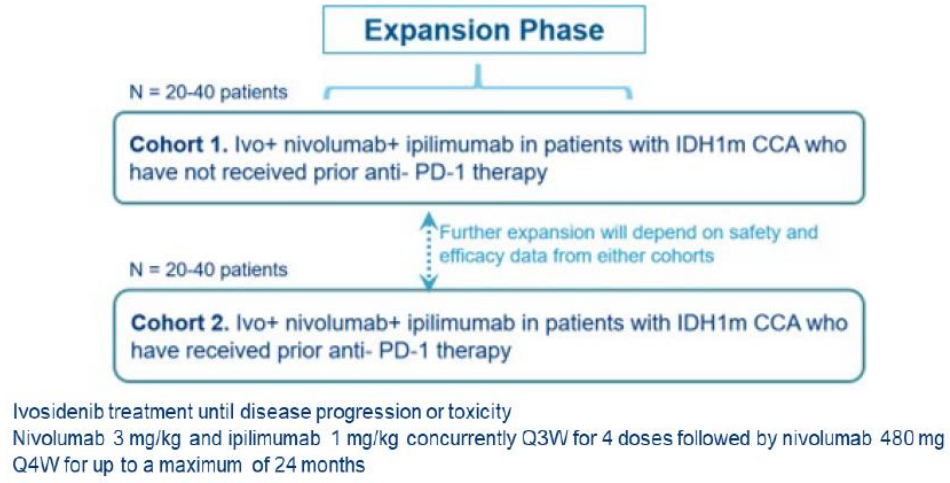


Figure (1.2) 2 - Expansion Phase



1.2.1. Study plan

The overall study plan is demonstrated in Figure (1.2) 1 and Figure (1.2) 2. Participants will continue to receive study treatment until disease progression unless discontinued due to other reasons. Following treatment discontinuation, participants will have 30 (+5) day safety follow-up visit from the last dose of all study drugs. Following discontinuation of nivolumab, participants will have 100 (+5) day safety follow-up visit from the last dose of nivolumab. Participants who discontinued treatment for reasons other than disease progression or withdrawal of consent and are alive by end of treatment (EOT) will be followed in PFS follow-up with the same schedule of assessments as before study treatment discontinuation, until documented disease progression, the initiation of new anti-cancer therapy, death, withdrawal of consent, or the end of study/study termination, whichever occurs first. OS follow-up assessments will occur approximately every 3 months after EOT unless the participant is in PFS follow-up at that time. OS follow-up will continue until all participants have died, withdrawn consent, or are lost to follow-up, or up to 2 years after the last participant enrolled, or the sponsor terminates the study, whichever comes first.

For the details on study design and measurements to be collected in each period, refer to the Section 4.1.2 of the clinical study protocol.

1.2.2. Type of randomization

Not applicable.

1.3. Determination of sample size

It is estimated that up to approximately 92 participants will be enrolled in this Phase 1/2 study, with approximately 6 to 12 DLT-evaluable patients in the Safety Lead-in phase and up to approximately 40 patients in each Expansion phase cohort. The number of participants in the Expansion phase cohorts include the participants enrolled in the Safety Lead-in phase and treated at the RCD.
Due to the exploratory nature of this study, the planned sample sizes are not determined based on formal evaluation using statistical power and type I error, but to provide a reasonable precision of the estimation of ORR.

[redacted]

[redacted]

[redacted]

2. STATISTICAL HYPOTHESES AND MULTIPLICITY HANDLING

2.1. Statistical hypotheses

Not applicable.

2.2. Multiplicity handling

Not applicable.

3. ANALYSIS SETS / TREATMENT GROUPS

3.1. Analysis sets

The following analysis sets will be evaluated and used for presentation of the data:

- DLT-Evaluable Set: All participants enrolled during the Safety Lead-in phase who have received any dose of the combination therapy and experienced a DLT through Cycle 2, or who have received at least 2 doses of nivolumab and ipilimumab, respectively, and at least 75% of ivosidenib at the planned dose through Cycle 2 without experiencing a DLT through Cycle 2 will be considered evaluable for DLT assessment. This analysis set will be the primary set to determine the RCD, which will be further investigated at the Expansion phase.
- Safety Analysis Set: All participants enrolled who have received any amount of study treatment (ivosidenib in combination with nivolumab and ipilimumab). The Safety Analysis Set will be the primary analysis set for clinical anti-tumor activity, safety, and other analyses, unless otherwise specified.
- Response-Evaluable Set: All participants in the Safety Analysis Set for whom a baseline disease assessment and at least one post-baseline response assessment are available and evaluable. The Response-Evaluable Set will be used for the supportive analysis for the primary endpoint of objective response (OR).
  Since the study does not proceed to the Expansion phase, the primary endpoint OR for the Expansion phase will not be evaluated. Hence, the Response-Evaluable Set is not applicable.
- Pharmacokinetic Analysis Set: All participants who have had at least one blood sample providing evaluable PK data for ivosidenib in combination with nivolumab and ipilimumab.
- Pharmacodynamic Analysis Set: All participants who have had at least one blood sample providing evaluable plasma 2-HG data for ivosidenib in combination with nivolumab and ipilimumab.
- ADA Analysis Set: All participants with a baseline ADA assessment and at least one post-treatment ADA assessment.

3.2. Treatment groups

Treatment considered is ivosidenib in combination with nivolumab and ipilimumab.

For Safety Lead-in phase, 2 sequential dose groups will be considered:

- Ivosidenib 500 mg QD PO + nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)
- Ivosidenib 250 mg QD PO + nivolumab (3 mg/kg) + ipilimumab (1 mg/kg)

The total number of dose levels tested will depend on the DLT observed. The RCD will be used for the Expansion phase.

In the unlikely event of a patient taking a different dose level from the planned dose level at Cycle 1 Day 1 (C1D1), the patient will be considered in the group corresponding to initial dose level taken at C1D1.

4. GENERAL STATISTICAL CONSIDERATIONS

4.1. Descriptive statistics

For qualitative data, number of observed values, number and percentage of patients per class will be presented. Unless otherwise specified in the TLG, no class "Missing" is considered. Percentages will be rounded to one decimal place.

For quantitative data, number of observed values, mean, standard deviation, median, first and third quartiles, minimum and maximum will be presented. The geometric mean and standard deviation will also be provided for log-distributed data (if applicable).
Minimum and maximum will be displayed with the same accuracy as the original data. Means, median and quartiles will be presented to one more decimal place than the data precision, and standard deviations to two more decimal places.

4.2. General definitions

- Baseline is defined as the last available observation prior to the first dose of any investigational medicinal product (IMP) on C1D1. Assessments performed on the same day of first dose will be assumed to happen before first dose, unless the protocol schedule states otherwise or information about the time is available.
- In general, the on-treatment period is defined as the time from the date of the first dose of any IMP to 30 days from the last dose of IMPs. For immune-mediated adverse events (IMAEs), the on-treatment period is defined as the time from the date of the first dose of any IMP to 100 days from the last dose of nivolumab.

4.3. Dates imputation

Fully or partially missing dates of AEs, concomitant medications and procedures will be imputed for the summary tables as detailed below. These dates will be presented as reported in the data listings.

- For missing start dates the following will be applied:
    a. If day is missing, impute as the 1st of the month unless month is the same as month of the first dose of any IMP then impute as first dose date.
    b. If month is missing, impute as ‘January’ unless the year is the same as the year of the first dose of any IMP then impute as first dose date.
    c. If both day and month are missing, impute as ‘01 January’ unless year is the same as first dose date then impute first dose date.
    d. If date is completely missing, impute the first dose date unless the end date suggests it must have started prior to this in which case impute the 1st of January of the same year as the end date.
    e. If end date is a complete date and imputed start date is greater than end date, then start date is imputed to end date.
- For missing end dates (not ongoing), the following will be applied:

a. If day is missing, impute as the last day of the month unless the End of Study visit date or data cut-off date or death date is before in which case impute the corresponding date whichever occurs first.

b. If month is missing, impute as 'December' unless the End of Study visit date or data cut-off date or death date is before in which case impute the corresponding month whichever occurs first.

c. If both day and month are missing, impute as '31 December' unless the End of Study visit date or data cut-off date or death date is before in which case impute the day and the month whichever occurs first.

4.4. Other statistical considerations

- If retests or repeat measurements are performed on the same visit/timepoint, only the last one will be used in summaries, unless otherwise specified. All measurements will be displayed in listings.
- Data collected from unscheduled visits will be displayed in listings, but it will not be considered in the analyses, unless otherwise specified.
- Summaries, listings and analyses will be performed by dose level and total in the Safety Lead-in phase, and by cohort and total in the Expansion phase, unless otherwise specified.
- All data analyses will be performed using SAS® Version 9.4 or higher.

5. STATISTICAL ANALYSES

The study stopped enrollment after enrolling 7 patients for the Safety Lead-in phase and did not proceed to the Expansion phase, therefore limited listings will be generated as appropriate. Tables and figures will not be generated in general, unless specifically mentioned.

5.1. Study patients

5.1.1. Disposition

The size of each analysis set, and reasons for exclusion will be described.

Disposition of participants, including reasons for treatment discontinuation and study withdrawal, will be presented on the Safety Analysis Set. A listing of screen failures will also be provided.

Tables and listings will be presented.

5.1.2. Protocol deviations

Important protocol deviations (IPD) before or at inclusion, as well as after inclusion, will be described by category of deviation (based on International Council for Harmonization (ICH) E3 guideline and ICH E3 Q&A).

All the IPDs will be listed in the Safety Analysis Set.

5.1.3. Demographic data and baseline characteristics

Demographic data and baseline characteristics will be descriptively summarized based on the Safety Analysis Set.

5.1.3.1. Demographics and physical measurements

Demographic characteristics and physical measurements at baseline will be summarized as follows:

- Demographic characteristics:
  - Sex: Male, Female
  - Race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other, Missing
  - Ethnicity: Hispanic or Latino, Non Hispanic or non Latino, Missing
  - Age (years): summary statistics
  - Age categories:
    - <65 years, ≥65 years
  - Country
- Physical measurements:
  - Height (cm)
  - Weight (kg)
  - Body Mass Index (BMI) (kg/m^2): Weight (kg) / [Height (m)]^2

Tables and listings will be presented.

5.1.3.2. Baseline characteristics

The following baseline characteristics of the underlying disease will be summarized:

- Diagnosis: Intrahepatic cholangiocarcinoma, Perilhilar cholangiocarcinoma, Distal cholangiocarcinoma, Unknown cholangiocarcinoma
- Disease duration (months): (date informed consent form signed – date of first diagnosis + 1) / 30.4375
- Grade at initial diagnosis: Well differentiated, Moderately differentiated, Poorly differentiated, Undifferentiated, Unknown
- Primary Tumor (T): TX, T0, Tis, T1, T1a, T1b, T2, T3, T4, T4a, T4b, Missing
- Regional Lymph Nodes (N): NX, N0, N1, N1a, N1b, N1c, N2, N2a, N2b, N3, N3a, N3b, Missing
- Distant Metastasis (M): MX, M0, M1, M1a, M1b, Missing
- IDH1 mutation: Yes, No
  - Type: R132C, R132L, R132G, R132H, R132S

- Eastern Cooperative Oncology Group Performance Status (ECOG-PS) at baseline: 0, 1, 2, 3, 4

Tables and listings will be presented.

5.1.3.3. Prior therapies for studied disease

5.1.3.3.1. Prior systemic anti-cancer therapy

Prior therapies will be listed based on the Safety Analysis Set. The listing will include the following variables but not limited to them:

- Line of therapy
- Therapy setting: Adjuvant, Palliative, Neoadjuvant
- Duration of last line of therapy (months): (end date of the last line of therapy – start date of the last line of therapy + 1) / 30.4375
- Time from last line of therapy to enrollment (months): (first dose date – end date of the last line of therapy +1) / 30.4375
- Best response: Complete Response, Partial Response, Stable Disease, Progressive Disease, Unknown

In case there are multiple drugs within one line of therapy, the outer window rule will be applied to calculate the duration: the earliest start date of all drugs will be the start date, and the latest end date will be the end date for that line. The line that has contributed to the eligibility will be flagged as appropriate.

5.1.3.3.2. Prior local or regional therapy

A data listing will be provided for prior local or regional therapy, including the type of prior local/regional therapy, anatomical location, start date, end date, therapy setting, best response, and date of progression.

5.1.3.3.3. Prior surgery for cholangiocarcinoma

A data listing will be provided for prior surgery, including procedure, location, date of procedure, whether disease recur or progress after the procedure, and date of recurrence or progression.

5.1.3.4. Relevant medical and surgical history

Medical and surgical history other than for the studied disease will be presented in a listing with system organ class (SOC) and preferred term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA).

Listing will include onset date and grade, if applicable.

5.2. Treatments of patients

Treatment of patients will be described on the Safety Analysis Set.

5.2.1. Extent of exposure and treatment compliance

Ivosidenib in combination with nivolumab and ipilimumab will be administered every 21 days for the first four cycles and every 28 days for cycle 5 and beyond until the end of treatment for each patient.

The following variables are derived using non-zero doses of the IMPs:

- Cycles of exposure: number of cycles where patient received at least one dose
- Treatment duration (months): (last dose date - first dose date + 1) / 30.4375
- Planned cumulative dose (mg): sum of the planned doses administered for each cycle
    - Ivosidenib: planned dose level (mg) * x days
    - Nivolumab and ipilimumab: planned total dose (mg)
- Actual cumulative dose (mg): sum of the actual doses administered for each cycle
    - Ivosidenib: (tablets dispensed - tablets returned) * actual dose (mg)
    - Nivolumab and ipilimumab: actual total dose (mg)
- Planned Dose Intensity (PDI):
    - Ivosidenib: schedule dose level (mg/day)
    - Nivolumab and ipilimumab (mg/cycle): planned cumulative dose (mg) / number of planned cycles
- Actual Dose Intensity (ADI):
    - Ivosidenib (mg/day): actual cumulative dose (mg) / treatment duration (days)
    - Nivolumab and ipilimumab (mg/cycle): actual cumulative dose (mg) / cycle of exposure (cycles)
- Relative Dose Intensity (RDI) (%):
    - Ivosidenib: 100 × ADI (mg/day) / PDI (mg/day)
    - Nivolumab and ipilimumab: 100 × ADI (mg/cycle) / PDI (mg/cycle)

These exposure variables will be presented in listings for each drug. Cycles of exposure and treatment duration will be presented also for the overall treatment (any drug).

Treatment compliance will be presented in listings using the number of doses administered, the number of dose interruptions, number of dose delays, number of dose missed and number of dose reductions for each of the three drugs. Reasons for these actions will be included.

5.2.2. Prior and concomitant medications

Prior medications other than for the studied disease are defined as non-study medications taken prior to or at the time of the first dose of IMPs.

Concomitant medications are defined as non-study medications taken at the time of or after the first dose of IMPs and prior to the last dose plus 35 days.

All non-study medications will be coded according to World Health Organization Drug Dictionary (WHODD).

Prior and concomitant medications will be presented in listing according to Anatomical Therapeutic Chemical (ATC) code into 4 levels (Pharmacological class, Pharmacological subclass, Therapeutic class, Preferred name).

All non-study medications will be listed, including indication, dose, frequency, route, start date and end date.

A listing of medical and surgical procedures coded according to MedDRA dictionary will also be provided.

5.2.3. Subsequent therapies

Subsequent therapies are defined as anti-cancer therapies that are started after the last dose of IMPs.

Subsequent anti-cancer therapies will be coded according to WHODD and presented in a listing by ATC code classification level 3 and preferred name.

5.3. Efficacy analyses

Tumor response is evaluated as per RECIST v1.1 (Eisenhauer, et al., 2009) in patients by the investigator.

Since the study stopped enrollment after enrolling 7 patients for the Safety Lead-in phase and did not proceed to the Expansion phase, only listings will be generated for efficacy analyses for the Safety Lead-in phase. The listings will be based on the Safety Analysis Set and will include response assessments and best overall response (BOR).

BOR will be based on all post-baseline disease assessments until the first documentation of progressive disease (PD) or end of treatment, and prior to the initiation of a subsequent anti-cancer therapy, whichever occurs first.

BOR may include the following categories: CR, PR, stable disease (SD), PD and non evaluable (NE). Definitions of the response categories are the following:

- CR: at least two CRs at least 4 weeks apart.
- PR: at least two PRs or better (PR followed by PR or PR followed by CR) at least 4 weeks apart, and not qualifying for a CR.
- SD: at least one SD assessment (or better) ≥ 36 days after start of IMPs, and not qualifying for CR or PR.
- PD: documentation of PD after start of IMPs (and not qualifying for CR, PR, SD).
- NE: all other cases.

5.4. Safety analyses

All safety analyses will be performed in the Safety Analysis Set and summaries will contain only data collected during the on-treatment period, unless otherwise specified.

5.4.1. Adverse events

5.4.1.1. Dose Limiting Toxicity (Safety Lead-in phase)

DLT is defined for the DLT evaluation period (first 42 days of dosing (i.e., Cycles 1 and 2) of the Safety Lead-in phase) and it is described in protocol Section 4.1.4.2. Details of the observed DLTs will be presented in a listing based on the DLT-Evaluable Set and only for the Safety Lead-in phase.

5.4.1.2. Adverse Events

Definition:

- Treatment-Emergent Adverse Events (TEAEs) are defined as all adverse events:

- which occur or worsen between the first IMP administration date of any drug (included) and the last IMP administration date of any drug + 30 days (included), or between the first IMP administration date of any drug (included) and the last nivolumab administration + 100 days (included) for IMAEs,

- The seriousness and the relationship with the IMPs of the adverse event are based on investigator opinion.

Analysis:

Adverse events will be coded according to MedDRA dictionary, and their severity classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0.

Number of events, number and percentage of patients reporting at least one event will be presented in a summary table for TEAEs by SOC, PT and severity.

An overall summary with number and percentage of patients in the following categories will be presented:

- All TEAEs.
- Treatment-related (for any drug) TEAEs.
- Ivosidenib-related TEAEs.
- Nivolumab-related TEAEs.
- Ipilimumab-related TEAEs.
- Grade 3 or higher TEAEs.
- Grade 3 or higher treatment-related TEAEs.
- SAEs.
- Treatment-related SAEs.
- AESIs.
- TEAEs leading to treatment discontinuation of any study drug.
- TEAEs leading to dose reduction of ivosidenib.
- TEAEs leading to on-treatment deaths.

Listings will be provided for TEAEs, SAEs, TEAEs leading to treatment discontinuation of any study drug, and TEAEs leading to on-treatment death.

The date/time of onset, date/time of recovery, action taken with IMPs, seriousness criteria and outcome will also be included in listings.

5.4.2. Death

A listing for deaths, along with the cause of death, will be provided for the following categories:

- On-treatment death: Deaths after the first dose of any IMP and on or before 30 days after the last dose of IMPs.
- Post-treatment death: Deaths more than 30 days after the last dose of IMPs.

5.4.3. Clinical laboratory evaluation

The following laboratory parameters are collected in the study as per protocol and will be presented in the SI units:

Table (5.4.3) 1 Gradable Laboratory Parameters

	Parameter	Worst highest	Worst lowest
Hematology	**Hemoglobin**	Hemoglobin increased	Anemia
	Eosinophils	Eosinophilia	NA
	Lymphocytes	Absolute lymphocytes count increased	Absolute lymphocytes count decreased
	Neutrophils	NA	Absolute neutrophils count decreased
	White blood cell (WBC) count	Leukocytosis	WBC decreased
	Platelet count	NA	Platelet count decreased
Serum chemistry	**Alanine aminotransferase (ALT)**	ALT increased	NA
	Albumin	NA	Hypoalbuminemia
	Alkaline phosphatase (ALP)	ALP increased	NA
	Aspartate aminotransferase (AST)	AST increased	NA
	Total bilirubin	Blood bilirubin increased	NA
	Gamma glutamyl transferase (GGT)	GGT increased	NA
	Calcium	Hypercalcemia	Hypocalcemia
	Serum creatinine	Creatinine increased	NA
	Glucose	Hyperglycemia	Hypoglycaemia
	Magnesium	Hypermagnesemia	Hypomagnesemia
	Potassium	Hyperkalemia	Hypokalemia
	Sodium	Hypernatremia	Hyponatremia
Coagulation	**Activated Partial thromboplastin time (aPTT)**	aPTT prolonged	NA
	International Normalized Ratio (INR)	INR increased	NA

Table (5.4.3) 2 Non Gradable Laboratory Parameters

	Parameter	Worst highest	Worst lowest
Hematology	**Basophils**	High basophils	Low basophils
	Hematocrit	High hematocrit	Low hematocrit
	Monocytes	High monocytes	Low monocytes
	Red blood cell (RBC) count	High RBC	Low RBC
Serum chemistry	**Direct bilirubin**	High direct bilirubin	Low direct bilirubin
	Indirect bilirubin	High indirect bilirubin	Low indirect bilirubin
	Blood urea nitrogen (BUN)	High BUN	Low BUN
	Carbon dioxide	High carbon dioxide	Low carbon dioxide
	Chloride	High chloride	Low chloride
	Phosphorus	High phosphorus	Low phosphorus
	Urea	High urea	Low urea
Coagulation	**Prothrombin time (PT)**	High PT	Low PT
Thyroid function tests	**Free thyroxine**	High free thyroxine	Low free thyroxine
	Thyroid stimulating hormone (TSH)	High TSH	Low TSH
	Triiodothyronine (T3) or free T3	High T3	Low T3

For serum chemistry, creatinine clearance will also be derived as per the Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = (140 - \text{Age(years)}) * [\text{Weight (kg)}] * (0.85 \text{ if Female}) / 72 * [\text{Serum creatinine (mg/dL)}]$$

For calcium, CTCAE grading is based on corrected calcium and ionized calcium. Corrected calcium is calculated from albumin and calcium as follows:

$$\text{Corrected calcium (mmol/L)} = \text{Total calcium (mmol/L)} + 0.02 * [40 - \text{Albumin (g/L)}]$$

Corrected calcium is derived based on calcium and albumin from the same date and visit. Lower reference range will be 2.1 mmol/L and upper reference range will be 2.6 mmol/L.

For laboratory tests covered by the NCI CTCAE v5.0, grades will be assigned for these tests as per Appendix A. For laboratory tests not covered by the NCI CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

Listings will be generated separately for hematology, serum chemistry, coagulation and thyroid function laboratory tests.

A listing of pregnancy tests will also be provided.

5.4.4. Vital signs, clinical examination and other observations related to safety

5.4.4.1. Vital signs and clinical examination

The following vital signs and clinical examination will be analysed:

- Weight (kg)
- BMI (kg/m²)
- Systolic Blood Pressure (SBP) (mmHg)
- Diastolic Blood Pressure (DBP) (mmHg)
- Heart Rate (b.p.m.)
- Respiratory Rate (breaths/minute)
- Temperature (ºC)

They will be listed, in terms of value at baseline, value at each post-baseline visit under treatment as well as in terms of change from baseline to each post-baseline visit under treatment.

5.4.4.2. Electrocardiogram

The actual values and change from baseline over time will be presented for each electrocardiogram (ECG) parameter:

- Heart Rate (b.p.m.)
- PR interval (msec)
- QT interval (msec)
- Duration of QRS (msec)
- RR interval (msec)
- QTcF (msec) (Fridericia's correction). QTcF (msec) = [QT (msec)] / [RR interval (sec)]$^{1/3}$ (values as per eCRF, not derived)

A listing will be provided. The listing will flag the maximum values and its maximum change from baseline.

5.4.4.3. ECOG-PS

ECOG-PS scores will be presented in a listing.

5.5. Quality of Life

Not applicable.

5.6. Pharmacokinetics analyses

Individual concentrations of ivosidenib (in plasma and tumor tissue), nivolumab and ipilimumab (in serum) for each visit and timepoint of collection by subject, will be presented as listings. Spaghetti plots of individual plasma concentration-time profiles for ivosidenib on Cycle 2 Day 1 will be plotted on linear-linear scale and log linear scales using nominal time.

Plots of concentrations of nivolumab and ipilimumab by visit may be presented based on available data. The Pharmacokinetic Analysis Set will be used for listings and figures of concentration data for ivosidenib, nivolumab and ipilimumab.

5.7. Pharmacodynamics analyses

Individual plasma and tumor 2-HG concentrations, at each visit and collection timepoint by subject will be listed. Spaghetti plots of individual 2-HG concentrations by visit may be plotted based on available data. The Pharmacodynamic Analysis Set will be the primary analysis set for listings and figures of 2-HG concentrations.

5.8. Immunogenicity analyses

A separate analysis plan will be developed on the immunogenicity analyses if needed.

5.9. Biomarkers analyses

A separate analysis plan will be developed on the biomarker analyses if needed.

6. INTERIM ANALYSIS

Since the study stopped enrollment after enrolling 7 patients for the Safety Lead-in phase and did not proceed to the Expansion phase, the futility interim analysis during the Expansion phase will not be conducted.

7. CHANGES TO PROTOCOL-PLANNED ANALYSES

Not applicable.

8. REFERENCES

Eisenhauer, E. A., Therasse, P., Bogaerts, J., Schwartz, L. H., Sargent, D., Ford, R., . . . Verweij, J. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer, 228*(47), 45.

9. APPENDICES

9.1. Appendix A: Laboratory parameters toxicity grading

Following there's a list of study laboratory parameters with the corresponding rules for toxicity grade classification based on the NCI CTCAE v5.0. Reference ranges are used: lower limit of normal (LLN) and upper limit of normal (ULN).

In case there are several grades for the same record, choose the worst grade (i.e., grade with the highest number).

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Table (A) 1 - Laboratory Parameters Toxicity Grading

Parameter (unit)	Grade	Low Grade	High Grade
Albumin (g/L)	Grade 0	≥LLN	
	Grade 1	[30; LLN[	
	Grade 2	[20; 30[	
	Grade 3	<20	
ALP (IU/L)	Grade 0		If baseline value normal or not available: ≤ULN If baseline value abnormal and post-baseline: <2.0*baseline
	Grade 1		If baseline value normal or not available:]ULN; 2.5*ULN] If baseline value abnormal and post-baseline: [2.0*baseline; 2.5*baseline]
	Grade 2		If baseline value normal or not available:]2.5*ULN; 5.0*ULN] If baseline value abnormal and post-baseline:]2.5*baseline; 5.0*baseline]
	Grade 3		If baseline value normal or not available:]5.0*ULN ; 20.0*ULN] If baseline value abnormal and post-baseline:]5.0*baseline; 20.0*baseline]
	Grade 4		If baseline value normal or not available: > 20.0*ULN If baseline value abnormal and post-baseline: >20.0*baseline
ALT (IU/L)	Grade 0		If baseline value normal or not available: ≤ULN If baseline value abnormal or post-baseline: <1.5*baseline
	Grade 1		If baseline value normal or not available:]ULN; 3.0*ULN] If baseline value abnormal or post-baseline: [1.5*baseline; 3.0*baseline]
	Grade 2		If baseline value normal or not available:]3.0*ULN; 5.0*ULN] If baseline value abnormal or post-baseline:]3.0*baseline; 5.0*baseline]
	Grade 3		If baseline value normal or not available:]5.0*ULN; 20.0*ULN] If baseline value abnormal or post-baseline:]5.0*baseline; 20.0*baseline]
	Grade 4		If baseline value normal or not available: >20.0*ULN If baseline value abnormal or post-baseline: >20.0*baseline
aPTT (sec)	Grade 0		≤ULN
	Grade 1		]ULN; 1.5*ULN]
	Grade 2		]1.5*ULN; 2.5*ULN]
	Grade 3		>2.5*ULN
AST (IU/L)	Grade 0		If baseline value normal or not available: ≤ULN If baseline value abnormal or post-baseline: <1.5*baseline
	Grade 1		If baseline value normal or not available:]ULN; 3.0*ULN]

Parameter (unit)	Grade	Low Grade	High Grade
			If baseline value abnormal or post-baseline: [1.5*baseline; 3.0*baseline]
	Grade 2		If baseline value normal or not available:]3.0*ULN; 5.0*ULN] If baseline value abnormal or post-baseline:]3.0*baseline; 5.0*baseline]
	Grade 3		If baseline value normal or not available:]5.0*ULN; 20.0*ULN] If baseline value abnormal or post-baseline:]5.0*baseline; 20.0*baseline]
	Grade 4		If baseline value normal or not available: >20.0*ULN If baseline value abnormal or post-baseline: >20.0*baseline
Corrected calcium (mmol/L)	Grade 0	≥LLN	≤ULN
	Grade 1	[2.0; LLN[	]ULN; 2.9]
	Grade 2	[1.75; 2.0[	]2.9; 3.1]
	Grade 3	[1.5; 1.75[	]3.1; 3.4]
	Grade 4	<1.5	>3.4
Eosinophils (G/L)	Grade 0		≤ULN or If post-baseline: ≤baseline
	Grade 1		>ULN and If post-baseline: >baseline
GGT (IU/L)	Grade 0		If baseline value normal or not available: ≤ULN If baseline value abnormal or post-baseline: <2.0*baseline
	Grade 1		If baseline value normal or not available:]ULN; 2.5*ULN] If baseline value abnormal or post-baseline: [2.0*baseline; 2.5*baseline]
	Grade 2		If baseline value normal or not available:]2.5*ULN; 5.0*ULN] If baseline value abnormal or post-baseline:]2.5*baseline; 5.0*baseline]
	Grade 3		If baseline value normal or not available:]5.0*ULN; 20.0*ULN] If baseline value abnormal or post-baseline:]5.0*baseline; 20.0*baseline]
	Grade 4		If baseline value normal or not available: >20.0*ULN If baseline value abnormal: >20.0*baseline
Glucose (mmol/L)	Grade 0	≥LLN	If baseline available and >ULN: ≤baseline If baseline available and ≤ULN: ≤ULN If baseline not available: ≤ULN
	Grade 1	[3.0; LLN[	If baseline available and >ULN: >baseline If baseline available and ≤ULN: >ULN If baseline not available: >ULN
	Grade 2	[2.2; 3.0[	
	Grade 3	[1.7; 2.2[	

Parameter (unit)	Grade	Low Grade	High Grade
	Grade 4	<1.7	
Hemoglobin (g/L)	Grade 0	≥LLN	≤ULN
	Grade 1	[100; LLN[	]ULN; ULN + 20]
	Grade 2	[80; 100[	]ULN + 20; ULN + 40]
	Grade 3	<80	>ULN + 40
INR	Grade 0		If not on anticoagulant or baseline not available: ≤1.2 If on anticoagulant and baseline available: ≤baseline
	Grade 1		If not on anticoagulant or baseline not available:]1.2; 1.5] If on anticoagulant and baseline available:]baseline; 1.5*baseline]
	Grade 2		If not on anticoagulant or baseline not available:]1.5; 2.5] If on anticoagulant and baseline available:]1.5*baseline; 2.5*baseline]
	Grade 3		If not on anticoagulant or baseline not available: >2.5 If on anticoagulant and baseline available: >2.5*baseline
Ionized calcium (mmol/L)	Grade 0	≥LLN	≤ULN
	Grade 1	[1.0; LLN[	]ULN; 1.5]
	Grade 2	[0.9; 1.0[	]1.5; 1.6]
	Grade 3	[0.8; 0.9[	]1.6; 1.8]
	Grade 4	<0.9	>1.8
Lymphocytes (G/L)	Grade 0	≥LLN	≤4
	Grade 1	[0.8; LLN[	
	Grade 2	[0.5; 0.8[	]4.0; 20.0]
	Grade 3	[0.2; 0.5[	>20
	Grade 4	<0.2	
Magnesium (mmol/L)	Grade 0	≥LLN	≤ULN
	Grade 1	[0.5; LLN[	]ULN; 1.23]
	Grade 2	[0.4; 0.5[	
	Grade 3	[0.3; 0.4[	]1.23; 3.30]
	Grade 4	<0.3	>3.30
Neutrophils (G/L)	Grade 0	≥LLN	
	Grade 1	[1.5; LLN[	
	Grade 2	[1.0; 1.5[	
	Grade 3	[0.5; 1.0[	
	Grade 4	<0.5	
Platelets (G/L)	Grade 0	≥LLN	
	Grade 1	[75; LLN[	
	Grade 2	[50; 75[	
	Grade 3	[25; 50[	
	Grade 4	<25	
Potassium (mmol/L)	Grade 0	≥LLN	≤ULN
	Grade 1		]ULN; 5.5]
	Grade 2	[3.0; LLN[	]5.5; 6]
	Grade 3	[2.5; 3.0[	]6; 7]
	Grade 4	<2.5	>7

Parameter (unit)	Grade	Low Grade	High Grade
Serum creatinine (umol/L)	Grade 0		≤ULN
	Grade 1		]ULN; 1.5*ULN]
	Grade 2		If baseline available:]1.5*baseline; 3.0*baseline] If baseline not available:]1.5*ULN; 3.0*ULN]
	Grade 3		If baseline available:]3.0*baseline; 6.0*baseline] If baseline not available:]3.0*ULN; 6.0*ULN]
	Grade 4		>6.0*ULN
Sodium (mmol/L)	Grade 0	≥LLN	≤ULN
	Grade 1	[130; LLN[	]ULN; 150]
	Grade 2		]150; 155]
	Grade 3	[120; 130[	]155; 160]
	Grade 4	<120	>160
Total bilirubin (umol/L)	Grade 0		If baseline value normal or not available: ≤ULN If baseline value abnormal or post-baseline: ≤baseline
	Grade 1		If baseline value normal or not available:]ULN; 1.5*ULN] If baseline value abnormal or post-baseline:]baseline; 1.5*baseline]
	Grade 2		If baseline value normal or not available:]1.5*ULN; 3.0*ULN] If baseline value abnormal or post-baseline:]1.5*baseline; 3.0*baseline]
	Grade 3		If baseline value normal or not available:]3.0*ULN; 10.0*ULN] If baseline value abnormal or post-baseline:]3.0*baseline; 10.0*baseline]
	Grade 4		If baseline value normal or not available: >10.0*ULN If baseline value abnormal or post-baseline: >10.0*baseline
WBC (G/L)	Grade 0	≥LLN	≤100
	Grade 1	[3.0; LLN[	
	Grade 2	[2.0; 3.0[	
	Grade 3	[1.0; 2.0[	>100
	Grade 4	<1.0	