2. SYNOPSIS

Name of Sponsor: I.R.I.S., 50 rue Carnot, 92284 Suresnes Cedex – France	*(For National Authority Use only)*
Name of finished product: Not applicable **Name of active ingredient:** S64315	
Title of study: An International Phase Ib multicentre study to characterize the safety and tolerability of intravenously administered S64315, a selective Mcl-1 inhibitor, in combination with orally administered venetoclax, a selective Bcl-2 inhibitor, in patients with Acute Myeloid Leukaemia (AML) Protocol No.: CL1-64315-002 EudraCT No.: 2018-001809-88 CT.gov No.: NCT03672695 The description of the study protocol given hereafter includes the modifications implemented through the 5 substantial amendments to the protocol.	
International coordinator: [redacted]	
Number of study centers and countries: Three countries included 37 patients: Australia (included 14 patients), France (included 9 patients), and the United States of America (included 14 patients).	
Studied period: Initiation date: 28 November 2018 Completion date: 12 November 2022 The study was prematurely terminated (as explained in the 'Overall study design' and 'Discussion and conclusions' sections)."	
Phase of development of the study: Phase I	
Publication (reference): Not applicable	
Background and rationale for the study: In this study S64315 and venetoclax were administered in combination to patients with AML to characterize safety and tolerability of S64315 and venetoclax combination treatment, and to determine a recommended phase 2 dose (RP2D) for future clinical studies. The Sponsor decided to discontinue the study based on strategic considerations. This decision was not a consequence of any safety concerns as confirmed by Data and Safety Monitoring Board (DSMB) during its meeting on 03 June 2022. The discontinuation was effective from 23 June 2022 (last end-of-cohort meeting). The study was discontinued during the dose escalation phase, and the expansion phase of the study was not initiated. In this context, an **abbreviated clinical study report** was written.	

Objectives and endpoints:

Objectives	**Endpoints**
Primary Objective: - To determine the safety profile (including dose limiting toxicities [DLTs], maximum tolerated dose [MTD]), tolerability and the Recommended Phase 2 Dose (RP2D) of the combination of S64315 with venetoclax in patients with AML	Primary Endpoints: - Incidence of DLTs during the first cycle, starting from the first dose of S64315 combined with venetoclax and from the lead-in dose (LiD) 1 in alternative schedule (AS) 3 - Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) o Laboratory tests: hematology with differential, blood biochemistry, thyroid function, coagulation and urinary analysis o Vital signs and performance status o Electrocardiogram (ECG) parameters, cardiac function assessment o Left ventricular ejection fraction (LVEF) assessed by echocardiography or multi-gated acquisition scan (MUGA) scan - Dose interruptions, reductions and dose intensity

Study design:
This was an open-label, multicentre, international, non-randomized, non-comparative phase Ib study, with A Bayesian Logistic Regression Model (BLRM) with overdose control (EWOC) guided the dose escalation and determined the MTD, recommended dose for expansion (RDE) and/or RP2D.
This study was designed with 2 parts, a dose escalation phase and a dose expansion phase. Cohorts of patients were treated with S64315 and venetoclax until the MTD(s) combination and/or RDE are identified.
This study was planned to explore different administration schedules as defined in the protocol.
This study was performed in strict accordance with Good Clinical Practice (GCP).

Number of patients:
Planned: around 40 patients.
Analyzed: 37 patients.
A total of 37 patients were included in the study:
- Safety Set (SS): 35 patients
- DLT Evaluable Set (DLTES): 25 patients

Diagnosis and main criteria for inclusion:

- Male or female patients aged ≥ 18 years.
- Patients with cytologically confirmed and documented *de novo*, secondary or therapy-related AML as defined by World Health Organization (WHO) 2016 classification, excluding acute promyelocytic leukaemia (APL, French-American British M3 classification):
    - With relapsed or refractory disease without established alternative therapy or
    - Secondary to myelodysplastic syndrome (MDS) treated at least with a hypomethylating agent and without established alternative therapy or
    - ≥ 65 years not previously treated for AML and who were not candidates for intensive chemotherapy nor candidates for established alternative therapies
- Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2.
- Able to comply with study procedures.
- Circulating white cell count < 10 x 10^9/L (with or without use of hydroxycarbamide).
- Adequate renal function within 7 days before the inclusion of the patient defined as:
    - Calculated creatinine clearance (determined by MDRD) > 60 mL/min/1.73m^2.
- Adequate hepatic function within 7 days before the inclusion of the patient defined as:
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 1.5 x upper limit of normal (ULN).
    - Total serum bilirubin level ≤ 1.5 x ULN, except for patients with known Gilbert's syndrome, who were excluded if total bilirubin > 3.0 x ULN or direct bilirubin > 1.5 x ULN.
- Women of childbearing potential had been tested negative in a serum pregnancy test within 7 days before the first day of investigational medicinal product (IMP) administration.

Investigational medicinal products:
Venetoclax film-coated tablets were administered orally once a day. Patients were instructed to swallow the tablets whole with water at approximately the same time each day with a meal (ideally during breakfast) to avoid reduced efficacy.
During the ramp-up period, venetoclax was administered in the morning to facilitate biological monitoring.
S64315 was administered 2 to 4 hours after venetoclax intake, via intravenous (IV) infusion, and initially administered over 30 minutes once every week.

Table 1 - Treatment schedules

Schedule	Study treatments	Pharmaceutical form and route of administration	Frequency and/or schedule
[redacted]	S64315	[redacted]	[redacted]
	Venetoclax	[redacted]	[redacted]
[redacted]	S64315	[redacted]	[redacted]
	Venetoclax	[redacted]	[redacted]
[redacted]	S64315	[redacted]	[redacted]
	Venetoclax	[redacted]	[redacted]
[redacted]	S64315	[redacted]	[redacted]
	Venetoclax	[redacted]	[redacted]

** Applicable only when the planned full dose of S64315 was 25 mg QW*

[redacted]

Dose escalation scheme
In this study, an adaptive BLRM with EWOC was used to guide the dose escalation of S64315 and venetoclax administered in combination.
The dose escalation was started at the weekly dose of 50 mg of S64315 and at the daily dose of 100 mg of venetoclax. Patients were included by cohorts of 3 to 6 evaluable patients.
All available data on DLTs were used for updating the model. A DLT was defined as a clinically significant AE graded according to the CTCAE version 4.03, observed during the first administration of the test drugs, assessed as unrelated to disease progression, intercurrent illness, or concomitant medications, considered as at least possibly related to the test drug(s) by the investigator, and that met any of the criteria defined in the study protocol. Before making a decision on dose escalation, the minimum number of patients required according to the model from a cohort should have been treated with one cycle of the combination and be fully evaluable for treatment-related toxicities according to the minimum requirements for inclusion in the DLTES.
The planned dose expansion part of the study was not initiated.

Comparator:
Not applicable.

Duration of treatment:
Screening period/inclusion: within 21 days before the first day of IMP administration.
Ramp-up period of venetoclax: 1 to 4 days to achieve the daily dose evaluated.
Lead-in dose (LiD) period of S64315 (only for AS 3): from end of the ramp-up of venetoclax until the start of Cycle 1 and lasting 2 weeks. If patient did not fulfill administration criteria, venetoclax might have continued for up to 7 additional days as a single agent before the S64315 was administered.
The LiD1 of S64315 was 25 mg and the LiD2 was 50 mg of S64315 in combination with venetoclax administered daily at the planned dose.
Combination treatment period:

- 21 days for patients treated with S64315 and venetoclax in the:
  - Initial Schedule
  - Alternative Schedule 2
  - Alternative Schedule 3
- 28 days for patients treated with S64315 and venetoclax in the:
  - Alternative Schedule 1

Follow-up period:

- Withdrawal visit (WV): Up to 21 days after the last dose of IMP.
- Post-withdrawal follow-up (FU): After the WV, a contact or telephone call was done every 3 months (up to 6 months), except in case of consent withdrawal.

Statistical methodology:

Analysis Sets:

- **Screened Set:** all screened patients (ie, all patients who signed the informed consent form (ICF), whether they were included or not at the end of the screening period).
- **Included Set:** all included patients.
- **Safety Set (SS):** all patients having received at least one full or partial dose of IMP (S64315 or venetoclax).
- **DLT Evaluable Set:** patients from the SS who were evaluable for DLTs according to the DLT assessment at the end of Cycle 1. Patients were analyzed according to the dose level received on C1D1. A patient was not considered evaluable if he/she:
  - Permanently discontinued treatment before the end of Cycle 1 for reasons other than DLT or
  - Did not undergo a DLT assessment at the end of Cycle 1, or
  - Did not receive the minimum exposure criteria ie, minimum number of doses according to the dose administration schedule of both test drugs prescribed from study entry to DLTs assessment visit (end of Cycle 1 D21 or D28), unless treatment was stopped for a DLT.
  - Did receive more than the assigned IMP doses from study entry to DLT occurrence during the DLT assessment period, non-evaluability criteria will be reassessed by Sponsor and investigator

Study patients (disposition, baseline characteristics and FU): Descriptive statistics were provided by dose level and overall.

Pharmacokinetic (PK) analysis: S64315 PK parameters were estimated by non-compartmental analysis (NCA) using the individual serum concentration vs actual sampling time data. Details on the PK analyses are described in the Pharmacokinetic Report.

Safety analysis: All safety analyses were performed on the SS (resp. DLTES for DLT analysis), by treatment dose level group and overall.

SUMMARY OF RESULTS AND CONCLUSIONS

DISPOSITION OF PATIENTS AND ANALYSIS SETS

A total of 46 patients were screened and 37 patients were included in the study. Among included patients, 35 patients were treated, and 2 patients were not treated due to consent withdrawal by the patient and partial hold of the study, respectively.
During the dose escalation part, patients entered either in initial schedule (IS) or AS 3. The overall disposition of patients is presented in **Table 2.**

Table 2 – Overall patient disposition – Included Set (N = 37)

Status		IS - 25 mg S64315 + 400 mg venetoclax (N = 5)		IS - 50 mg S64315 + 100 mg venetoclax (N = 4)		IS - 50 mg S64315 + 200 mg venetoclax (N = 6)		IS - 50 mg S64315 + 400 mg venetoclax (N = 1)		IS - 75 mg S64315 + 200 mg venetoclax (N = 1)		AS - 0 mg S64315 + 200 mg venetoclax (N = 1)		AS - 50 mg S64315 + 200 mg venetoclax (N = 10)		AS - 75 mg S64315 + 100 mg venetoclax (N = 7)		Not treated (N = 2)		ALL (N = 37)	
Included	**n**	**5**		**4**		**6**		**1**		**1**		**1**		**10**		**7**		**2**		**37**	
Withdrawn due to	**n (%)**	**5**	**(100)**	**4**	**(100)**	**6**	**(100)**	**1**	**(100)**	**1**	**(100)**	**1**	**(100)**	**10**	**(100)**	**7**	**(100)**	**2**	**(100)**	**37**	**(100)**
Adverse event	n (%)	1	(20.0)	-	-	1	(16.7)	1	(100)	1	(100)	1	(100)	6	(60.0)	2	(28.6)	-	-	13	(35.1)
Protocol deviation	n (%)	-	-	-	-	1	(16.7)	-	-	-	-	-	-	-	-	-	-	-	-	1	(2.7)
Progressive disease	n (%)	1	(20.0)	2	(50.0)	4	(66.7)	-	-	-	-	-	-	2	(20.0)	4	(57.1)	-	-	13	(35.1)
Withdrawal non-medical reason	n (%)	1	(20.0)	1	(25.0)	-	-	-	-	-	-	-	-	-	-	1	(14.3)	1	(50.0)	4	(10.8)
Physician decision	n (%)	2	(40.0)	1	(25.0)	-	-	-	-	-	-	-	-	2	(20.0)	-	-	1	(50.0)	6	(16.2)

N number of patients by dose combination
n number of patients
Percentages are based on n
IS initial schedule, AS alternative schedule

Included Set consisted of 37 patients, Safety Set of 35 patients, and DLTES of 25 patients.

BASELINE CHARACTERISTICS

For included patients, the mean age was 63.0 ± 16.5 years (median: 67.0 years), and the majority of the patients were male (59.5%) and white (79.4%).

Overall, all included patients were diagnosed with AML and classified as follows: 20 patients as 'AML with myelodysplasia-related changes', 11 as 'AML, not otherwise specified', 5 as 'AML with recurrent genetic abnormalities', and 1 as 'therapy-related myeloid neoplasms'. Sixteen patients had de novo AML and 21 patients had secondary AML. The mean disease duration since diagnosis was 1.6 ± 2.2 years. At entry in the study, 56.8% of the patients were refractory to previous treatment, 24.3% were treatment naive, and 18.9% were in relapse. The cytogenetic risk category was adverse for 56.8% of the patients, intermediate for 24.3%, favorable for 10.8%, and not assessable for 8.1%.

The number of previous treatment lines was distributed as follows: none (24.3%), 1 line (16.2%), 2 lines (8.1%), 3 lines (18.9%), 4-7 lines (29.7%), and more than 7 lines of treatment (2.7%).

Among the 35 patients with a bone marrow (BM) blast value at baseline, 4 patients (11.4%) had a BM blast value in the range of 5%-20%, 14 (40.0%) had a value in the range of 20%-50% and 17 (48.6%) had a value of ≥ 50%.

EXTENT OF EXPOSURE

The mean ± Standard Deviation (SD) treatment duration with S64315 was 8.1 ± 13.7 weeks (median = 6.1 weeks) ranging from 1.0 week to 81.0 weeks. Treatment duration with venetoclax was similar to the one with S64315.

The mean relative dose intensity (RDI) for S64315 was 89.3% ± 12.8% (median = 93.7%) and most of the patients (70.6%) had an RDI between 65% and 100%. The mean RDI for venetoclax was 78.8 ± 22.6% (median = 84.0%) and most of the patients (28.6%) had an RDI between 85% and 100%.

EFFICACY RESULTS

Pharmacokinetic results

S64315 was administered once weekly at the dose of 25, 50 or 75 mg by IV infusion in combination with venetoclax at daily doses of 100, 200 or 400 mg orally. Different combinations have been evaluated in several cohorts. The infusion duration of S64315 ranged from 0.48 hours to 3.38 hours depending on the patient's weight and toxicities observed during the infusion.

For S64315, an increase in exposure was observed with the increased doses from 25 to 75 mg. High variability was observed around the end of infusion timepoint probably due to several imprecisions during sample collection ie, the end of infusion timepoint often collected out of the time window recommended in the protocol.

At 50 mg and 75 mg of S64315, AUC_{last} was similar throughout the different cohorts regardless of the different venetoclax doses administered. Overall, the elimination half-life of S64315 was short and ranged from 1.4 to 4.1 hours across the dosing range investigated in this study.

When comparing data with single agent study CL1-64315-001, high variability was observed on the PK parameters which could be explained by operational issues during blood sample collection (ie, same arm used for administration and collection of PK samples). Nonetheless, PK exposure and parameters of S64315 when given in combination with venetoclax seem to be consistent with the data obtained in single agent study (CL1-64315-001). Therefore, the co-administration of venetoclax with S64315 did not seem to have an impact on the PK of S64315.

For venetoclax, high variability was observed on the derived PK parameters. For each dose, a narrow range of concentration from 0 to 24h was observed with a persistence of a same level of concentration throughout the PK profile. PK exposure and parameters of venetoclax when given in combination with S64315 seem to be consistent with the data of single agent available in the literature. Therefore, the co-administration of S64315 with venetoclax did not seem to have an impact on the PK of venetoclax.

SAFETY RESULTS

Dose limiting toxicities (DLTs)

During dose escalation, S64315 was evaluated in combination with venetoclax at dose levels ranging from 25 mg to 75 mg for S64315 and 50 mg to 400 mg for venetoclax. At the end of Cycle 1, 25 patients were evaluable for DLTs, out of whom 5 patients experienced DLTs: 1 event of Grade 4 supraventricular tachycardia (IS - 50 mg S64315 + 400 mg venetoclax), 1 event of Grade 1 troponin I increased (IS- 75 mg S64315 + 200 mg venetoclax), 2 events of Grade 3 ALT increased (AS – 50 mg S64315 + 200 mg venetoclax), and 1 event of Grade 3 troponin I increased (AS – 75 mg S64315 + 100 mg venetoclax).

Treatment-emergent adverse events (TEAEs)
Main results for AEs in the SS are described in **Table 3**.

Table 3 – Overall summary of treatment-emergent adverse events in the Safety Set

	ALL (N = 35) n (%)
Participants having reported at least one:	
TEAE	35 (100)
Treatment-related* TEAE	31 (88.6)
Severe (Grade ≥ 3) TEAE	34 (97.1)
Severe treatment-related* TEAE	12 (34.3)
Serious TEAE (including death)	33 (94.3)
Serious treatment-related TEAE	13 (37.1)
TEAE leading to treatment withdrawal	17 (48.6)
Treatment-related* TEAE leading to treatment withdrawal	7 (20.0)
TEAE leading to dose reduction	-
TEAE leading to dose delay	5 (14.3)
TEAE leading to temporarily IMP interruption	20 (57.1)
Participants who died during the study	30 (85.7)
During treatment period	10 (28.6)
Treatment-related* TEAE leading to death	-

**Related to S64315 or/and venetoclax*
FU follow-up, IMP investigational medicinal product, TEAE treatment-emergent adverse event.
Note one patient experienced a TEAE leading to death during the FU period (not treatment-related).

All treated patients reported at least one TEAE. The ***most frequently affected System Organ Class (SOC)***, in ≥ 30% of the patients overall, were Investigations (88.6%), Gastrointestinal disorders (85.7%), Metabolism and nutrition disorders (74.3%), Infection and infestations (71.4%), Blood and lymphatic system disorders (68.6%), Injury, poisoning and procedural complications (57.1%), General disorders and administration site conditions and Nervous system disorders (both SOCs: 48.6%), Respiratory, thoracic and mediastinal disorders (42.9%), and Musculoskeletal and connective tissue disorders (40.0%).

The ***most commonly reported TEAEs*** (≥ 10% of the patients overall) were diarrhoea (62.9%), nausea (60.0%), vomiting (45.7%), febrile neutropenia (42.9%), ALT increased and troponin I increased (40.0% each), hypokalaemia and hypophosphataemia (31.4% each), abdominal pain and constipation (28.6% each), AST increased and hypomagnesaemia (25.7% each), hypocalcaemia (22.9%), headache and hyperphosphataemia (20.0% each), fall, hyponatraemia, oedema peripheral, pyrexia, troponin T increased (17.1% each), anaemia, blood bilirubin increased, brain natriuretic peptide increased, dizziness, dyspnoea, infusion related reaction, and lipase increased (14.3% each), abdominal distension, back pain, *Clostridium difficile* colitis, epistaxis, hyperkalaemia, hypervolaemia, pruritus, and thrombocytopenia (11.4% each).

Most of the patients (97.1%) reported at least one ***severe TEAE***. The ***most commonly reported severe TEAEs*** (≥ 10% of the patients overall) were febrile neutropenia (42.9%), hypophosphataemia (28.6%), hypokalaemia (22.9%), anaemia (14.3%), ALT increased (14.3% patients), and thrombocytopenia (11.4%).

Overall, 88.6% of the patients experienced at least one treatment-related TEAE. The ***most commonly reported treatment-related TEAEs*** (≥ 10% of the patients overall) were diarrhea (54.3%), nausea (48.6%), vomiting (37.1%), troponin I increased (31.4%), ALT increased (17.1%), abdominal pain and infusion related reaction (14.3% each) and, brain natriuretic peptide increased (11.4%). Overall, 12 patients (34.3%) experienced at least

one ***severe treatment-related TEAEs***. Among those TEAEs, all were reported in no more than one patient, except ALT increased and hypotension (8.6% each), hypokalaemia, tumour lysis syndrome and diarrhoea (5.7% each).

TEAEs leading to treatment withdrawal were reported in 17 patients (48.6%). Each of those TEAEs were reported in no more than one patient except ALT increased (11.4%), troponin I increased (8.6%), and leukocytosis (5.7%). ***Treatment-related TEAEs leading to treatment withdrawal*** were reported in 7 patients (20.0%). Each of those TEAEs was reported in no more than one patient except for ALT and troponin I increased (5.7% each).

TEAEs leading to dose delay were reported in 5 patients (14.3%). Each of those TEAEs were reported in no more than one patient except for febrile neutropenia (2 patients).

Overall, ***TEAEs leading to temporary interruption of IMP (S64315 or venetoclax)*** were reported in 20 patients (57.1%). The most common TEAEs (in at least 3 patients overall) that led to temporarily IMP interruption were troponin I increased (22.9%) and ALT increased (8.6%).

A total of 33 patients (94.3%) experienced at least one ***serious TEAE***. The serious TEAEs reported in at least 2 patients in any dose group level were febrile neutropenia (42.9% in overall patients), troponin I increased and malignant neoplasm progression (8.6% in overall patients, each), septic shock and gastrointestinal toxicity (5.7% in overall patients, each). Overall, 13 patients (37.1%) reported at least one ***serious treatment-related TEAE***. Among those TEAEs, all were reported in no more than one patient, except for troponin I increased and hypotension (8.6% each), diarrhea and gastrointestinal toxicity (5.7% each).

A total of 30 ***deaths*** (85.7%) were reported during the study. Among those, 10 patients (28.6%) died during the treatment period and 20 during the FU period. Overall, 9 patients (25.7%) experienced at least one fatal TEAE as following: pneumonia (IS - 25 mg S64315 + 400 mg venetoclax); neutropenic sepsis (IS - 50 mg S64315 + 100 mg venetoclax); malignant neoplasm progression and death (as preferred term) (IS - 50 mg S64315 + 200 mg venetoclax); respiratory distress (IS - 75 mg S64315 + 200 mg venetoclax); septic shock and head injury (AS - 50 mg S64315 + 200 mg venetoclax), malignant neoplasm progression, ALT increased, AST increased, blood bilirubin increased and headache (AS – 75 mg S64315 + 100 mg venetoclax); all those occurring in a single patient; and traumatic intracranial haemorrhage in another patient. One additional patient died during the treatment period with progressive disease as reason of death, but no fatal TEAE was reported by the investigator. None of the fatal TEAEs were considered treatment-related.

Out of the 20 patients who died during the FU period, one death was reported as fatal outcome of an AE emergent on treatment (Klebsiella sepsis, not treatment-related).

Laboratory tests

For ***hematological gradable*** parameters, emergent severe (Grade ≥ 3) abnormal values were detected for low lymphocytes (78.8%), low haemoglobin and low leukocytes (60.0% each), low neutrophils (39.4%), and low platelets (25.7%).

For ***blood biochemical gradable*** parameters, the most frequent emergent severe abnormal (≥ 10% of overall patients) were observed for low potassium (25.7%), high glucose (22.9%) and high magnesium (14.3%).

Other safety evaluation

Vital signs, clinical examination and ECOG performance status

Clinically relevant changes in highest heart rate values over time were detected. The mean ± SD worst highest value on treatment was 105.3 ± 23.8 beats per minute (bpm); mean change from baseline: 24.7 ± 20.5 bpm. No clinically relevant changes in mean values were detected for blood pressures.

Half of patients (50.0%) had ECOG performance status maintained on treatment and 47.1% had worsening of ECOG performance.

Electrocardiogram

Overall, 5 patients (15.6%) had a clinically significant emergent ECG abnormality. QTc interval corrected with Fridericia (QTcF) values within]450; 480] ms were detected on treatment in 6 patients (17.6%). A QTcF change from baseline within]30; 60] ms was detected in 4 patients (12.1%) overall, and a QTcF change from baseline > 60 ms was detected in 1 patient (3.0% of the overall patients).

LVEF

At baseline, all assessable patients had an LVEF ≥ 50%, and under treatment, one patient (3.3%) had an LVEF in the 40%-50% class.

Biomarkers assessments
For blood cardiac markers, the most frequent emergent out-of-reference range values (≥ 50% of the overall patients) were detected for high brain natriuretic peptide (18 patients, 78.3%).

CONCLUSION
This was an international, multicentre, open-label, non-randomized, non-comparative phase Ib, dose escalation and expansion study, aimed to characterize the safety profile (including DLT, MTD), tolerability, and to determine the RP2D of intravenously administered S64315 in combination with orally administered venetoclax in patients with AML.

During the dose escalation, the Sponsor decided to discontinue the study for strategic reasons. This decision was not a consequence of any safety concern.

[redacted]

Dose limiting toxicities were reported in 5 patients: Grade 4 supraventricular tachycardia, Grade 1 and Grade 3 troponin I increased, Grade 3 ALT increased (2 patients). The MTD could not be determined.

In overall treated patients, the most common treatment-related TEAEs were gastrointestinal disorders (diarrhea, nausea, vomiting, and abdominal pain), troponin I increased, ALT increased, infusion related reaction, and brain natriuretic peptide increased. Severe treatment-related TEAEs reported in more than one patient were ALT increased, hypotension, hypokalaemia, tumour lysis syndrome and diarrhoea. Serious treatment-related TEAEs reported in more than one patient were troponin I increased, hypotension, diarrhea and gastrointestinal toxicity. None of the reported TEAEs leading to death were related to study treatment.

Date of the report: 11 September 2023