Amsterdam, 12 December 2024
EMA/CHMP/542864/2024
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

Stivarga

International non-proprietary name: Regorafenib

Procedure No. EMEA/H/C/002573/P46/014

## Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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| Status of this report and steps taken for the assessment | | | | |
|---|---|---|---|---|
| **Current step[1]** | **Description** | **Planned date** | **Actual Date** | **Need for discussion[2]** |
| ☐ | Start of procedure | 14 Oct 2024 | 14 Oct 2024 | ☐ |
| ☐ | CHMP Rapporteur Assessment Report | 18 Nov 2024 | 19 Nov 2024 | ☐ |
| ☐ | CHMP members comments | 2 Dec 2024 | n/a | ☐ |
| ☐ | Updated CHMP Rapporteur Assessment Report | 5 Dec 2024 | n/a | ☐ |
| ☒ | CHMP adoption of conclusions: | 12 Dec 2024 | 12 Dec 2024 | ☐ |

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

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**List of abbreviations**

| | |
|---|---|
| ANC | absolute neutrophil count |
| AEs | adverse events |
| ALT | Alanine aminotransferase |
| AUC | area under the curve |
| AST | Aspartate aminotransferase |
| BSA | body surface area |
| CNS | central nervous system |
| CSP | Clinical Study Protocol |
| CSR | clinical study report |
| CR | complete response |
| COVID-19 | coronavirus disease 2019 |
| CPK | Creatine phosphokinase |
| DLT | Dose-limiting toxicity |
| DDI | drug drug interaction |
| EAS | Efficacy analysis set |
| GIST | gastrointestinal stromal tumor |
| HFSR | Hand-foot skin reaction (hand-foot syndrome) |
| MTD | maximum tolerated dose |
| mCRC | metastatic colorectal cancer |
| MKI | multikinase inhibitor |
| NCI-CTCAE | National cancer institute common terminology criteria for adverse events |
| PR | partial response |
| PDCO | pediatric committee |
| PK | pharmacokinetic |
| PBPK | Physiologically based pharmacokinetic modelling |
| PNET | Primitive neuroectodermal tumor |
| PD | progressive disease |
| RP2D | recommended phase II dose |
| RECIST | Response evaluation criteria in solid tumors |
| RMS | rhabdomyosarcoma |
| SAF | Safety analysis set |
| SD | stable disease |
| TTP | time to progression |
| TEAE | treatment emergent adverse events |
| ULN | upper limit of normal |
| VI | vincristine/irinotecan |

# 1. Introduction

On 9 September 2024, the MAH submitted completed paediatric study for regorafenib, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

# 2. Scientific discussion

## *2.1. Information on the development program*

The MAH stated that EMEA-001178-PIP01-11-M06 (P/0495/2021) is a multi-center, open-label, non-randomized, phase I dose escalation study of regorafenib (BAY 73-4506) in pediatrie subjects with solid malignant tumors that are recurrent or refractory to standard therapy BAY 73-4506/15906. This study has been conducted and completed as by the agreed regorafenib Pediatrie Investigation Plan (EMEA-001178-PIP01-11-M06; P/0495/2021).

## *2.2. Information on the pharmaceutical formulation used in the study*

Granulate formulation in the forms of 5 mg and 20 mg regorafenib granulate packaged/contained in sachets was introduced to allow recruitment of children who are not able to swallow tablets.

## *2.3. Clinical aspects*

### 2.3.1. Introduction

The MAH submitted final report for:

- Study no.: 15906 (EudraCT no.: 2013-003579-36 / NCT no.:NCT02085148)

A multi-center, open-label, non-randomized, phase I dose escalation study of regorafenib (BAY 73-4506) in pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy.

Regorafenib (BAY 73-4506) is an oral multikinase inhibitor (MKI) which inhibits tumor growth, progression, and metastasis by inhibiting the proliferation of tumor cells, the formation of new tumor vasculature, and stromal signaling in the tumor microenvironment. Regorafenib has potential activity in various pediatric malignancies, such as neuroblastoma, sarcomas, and brain tumors.

Regorafenib is currently approved for the treatment of patients with metastatic colorectal cancer (mCRC) and unresectable or metastatic gastrointestinal stromal tumors (GIST). Additionally, Regorafenib is authorized for the treatment of adult patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. Currently, there are no data available on efficacy and the toxicity profile of regorafenib in pediatric patients. To enable the use of regorafenib in pediatric cancer patients, this study aimed to establish the safety and pharmacokinetic (PK) profile, maximum tolerated dose (MTD), and recommended phase II dose (RP2D) in pediatric cancer patients as well as help identify the tumor types with potential benefit from regorafenib treatment.

This Phase 1 study was the first study conducted with regorafenib in children from 6 months to less than 18 years old who had a solid malignant tumor that was recurrent or refractory to standard therapy and for which no effective treatment was known. This study was part of a thorough pediatric development plan, which was agreed with the pediatric committee (PDCO) (EMEA-001178-PIP01-11-

M06) with the goal to evaluate regorafenib and to define its safety, tolerability, pharmacokinetics PK and potential antitumor activity in selected pediatric solid malignant tumors that were recurrent or refractory to standard therapy.

The dose-escalation phase of this study enabled the use of regorafenib in pediatric patients, and generated the first data about its safety, tolerability, pharmacokinetics and potential efficacy where regorafenib was administered as a single agent to pediatric patients with solid malignant tumors recurrent or refractory to standard therapy.

The dose-expansion phase was added by amendment in agreement with PDCO to evaluate pharmacokinetics, pharmacodynamics, tolerability, safety, and tumor activity of regorafenib administered orally in combination with backbone chemotherapy at relapse (vincristine and irinotecan (VI)) in pediatric patients with rhabdomyosarcoma and other solid malignant tumors recurrent or refractory to standard therapy.

For further details on study background and rationale, refer to Section 1 of Section 16.1.1 study protocol.

The dose-escalation monotherapy phase results were reported in clinical study report (CSR) PH-38659 (database cut-off date of 19 NOV 2015). The results of the phase 1 monotherapy dose escalation have been published (Eur J Cancer. 2021 Aug;153:142-152).

The second interim report, CSR PH-40803 (data cut-off: 05 MAY 2019), presented the dose-expansion phase results until primary completion, when the last participant required for establishment of the RP2D reached the end of Cycle 2. The results of the phase 1 monotherapy dose expansion have been published (Clin Cancer Res. 2023 Nov 1;29(21):4341-4351) This report has been submitted within an interim compliance check with PDCO and concluded the PIP requirement for Study 5 (Compliance report reference: EMEA-C2-001178-PIP01-11M05).

This final CSR B003223 for the study presents the cumulative results of the escalation and expansion phases of the study as of the final data release of the clinical database (date of clean database 05 APR 2024). This final report is submitted to the agency via Article 46 procedure. Within this report the final CSR for the study will be discussed which main focus on the dose expansion cohorts in which regorafenib has been studied in combination with vincristine and irinotecan.

### 2.3.2. Clinical study

**Clinical study no.: 15906:A multi-center, open-label, non-randomized, phase I dose escalation study of regorafenib (BAY 73-4506) in pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy**

**Description**

This study in pediatric subjects with recurrent or refractory solid malignant tumors was conducted in the scope of an agreed pediatric investigation plan. In order to enable the use of regorafenib in pediatric patients, first data about its safety, tolerability, pharmacokinetics and potential efficacy signal was generated in dose escalation phase of this phase 1 study followed by a dose expansion phase.

**Methods**

Escalation phase: prospective, open-label, multi-center, non-randomized, phase I dose escalation study of oral regorafenib to define the safety profile, MTD, RP2D, PK, pharmacodynamics, preliminary tumor response in pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy and acceptability/palatability of the formulations (tablets and granulates). The starting dose of

60 mg/m$^2$ (Dose Level 1) was derived from a physiologically based pharmacokinetic modelling (PBPK) model developed for regorafenib in adults and scaled to children 2-18 years old. The starting dose was predicted to result in 80% of steady state exposure of total regorafenib defined as the sum of parent, M-2 and M-5, in adults. Steady state exposure was defined as area under the curve (AUC) (0-24)md after 3 weeks of 160 mg regorafenib q.d. Body surface area-based dosing was chosen as it is the most commonly used and the most accurate method in pediatric oncology. A PBPK model for children 6 to less than 24 months of age was also available and recommended a starting dose of 45 mg/m$^2$.

The **dose escalation phase** determined the MTD and the RP2D of **regorafenib monotherapy** in pediatric subjects.

Expansion phase: prospective, open-label, multi-center, non-randomized study. The dose- expansion phase was added by amendment in agreement with PDCO to evaluate pharmacokinetics, pharmacodynamics, tolerability, safety, and tumor activity of regorafenib administered orally in combination with backbone chemotherapy at relapse (vincristine and irinotecan) in pediatric patients with rhabdomyosarcoma and other solid malignant tumors recurrent or refractory to standard therapy.

The **dose expansion phase** determined the safety profile, MTD and the RP2D of regorafenib administered orally in combination with vincristine and irinotecan in pediatric subjects with RMS and other solid malignant tumors recurrent or refractory to standard therapy.

At the beginning of the dose expansion phase, two dosing schedules will be explored. Regorafenib and vincristine/irinotecan will be given concomitantly **(Schedule A)** or sequentially **(Schedule B)**.

At least 15 subjects evaluable for DLTs will be necessary to establish the RP2D of the combination. At least 8 RMS subjects evaluable for safety and tumor response will be included.

**Dose-limiting toxicity (DLT)** will be defined as any of the following occurring during Cycle 1 to be regarded as related to the study treatment. The NCI-CTCAE, v. 4.0 will be used to assess toxicities.

A subject will be eligible for DLT assessments if he/she has received at least 80% of the planned cumulative dose of regorafenib and irinotecan and 2 infusions of vincristine or if a subject develops any toxicity considered dose limiting, regardless of the percentage of planned cumulative dose received.

- Hematological toxicities:
    - absolute neutrophil count (ANC) < 500/mm$^3$ for ≥ 7 days
    - Febrile neutropenia (single temperature of > 38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour) with ANC < 500/mm$^3$.
    - Platelets < 25,000/mm$^3$ for > 7 days despite platelet transfusion or ≥ Grade 3 thrombocytopenic bleeding.
- Non-hematologic Grade 3 or Grade 4 toxicity considered treatment-related, except for:
    - Drug-related Grade 3 diarrhea (but will be classified as DLT if NOT manageable by dose interruption within 3 days/adequate treatment).
    - Drug-related Grade 3 hand-foot skin reaction (HFSR) (hand-foot syndrome) (but will be classified as DLT if NOT manageable by dose interruption within 3 days and adequate treatment).
    - Drug-related Grade 3 aspartate aminotransferase (AST) or alanine aminotransferase ALT ≤ 8 x upper limit of normal (ULN) without bilirubin increase (but will be classified as DLT if NOT manageable [not back to baseline] by dose interruption within 3 days). However, if the

AST and/or ALT increase is > 3 x ULN and associated with concurrent bilirubin increase (> 2 x ULN), it will automatically be considered a DLT.

In addition, the following situations may be considered DLTs after discussion between the investigators and the study sponsor:

- relative dose intensity of less than 80% for regorafenib and irinotecan and 2 infusions of vincristine in Cycle 1 due to an adverse event considered related to the study treatment
- a delay of more than 14 days to start Cycle 2, due to treatment related toxicity

The **maximum tolerated dose (MTD)** is defined as the dose level at which none or 1 of 6 participants experiences a DLT, when at least 2 of 3-6 participants experience a DLT at the next highest dose. According to the Rolling-6 design, enrollment to the subsequent dose cohort can start after 3 to 5 subjects in the preceding cohort complete Cycle 1 and none of them meets criteria for a DLT, with no more than 1 subject with data pending from Cycle 1. Table 1displays decision rules in "rolling-6" design.

*Table 1 Decision rules for dose adjustments in "rolling-6" design.*

| Number of subjects enrolled | Number of subjects with DLT | Number of subjects with data pending | Decision |
|---|---|---|---|
| 1 | - | - | Same dose level |
| 2 | 2 | - | De-escalate [a] |
| | 0 or 1 | - | Same dose level |
| 3 | ≥ 2 | - | De-escalate [a] |
| | 0 | 0 | Escalate [b] |
| | 1 | - | Same dose level |
| 4 | ≥ 2 | - | De-escalate [a] |
| | 0 | 0 | Escalate [b] |
| | 1 | - | Same dose level |
| 5 | ≥ 2 | - | De-escalate [a] |
| | 0 | 0 | Escalate [b] |
| | 1 | - | Same dose level |
| 6 | ≥ 2 | - | De-escalate [a] |
| | ≤ 1 | 1 | Escalate [b] |
| | 0 | | Escalate [b] |

DLT = dose-limiting toxicity, MTD = maximum tolerated dose

[a] If six subjects already entered at the next lower dose level, the MTD has been defined; if-de-escalation occurs at the lowest dose level (level -1), then the study is discontinued

[b] Dose escalation will take place only after comprehensive review of all collected safety data and careful evaluation by the investigators and sponsor.

**Protocol amendments (main changes)**

The original Clinical Study Protocol (CSP) was dated 06 NOV 2013. For the Protocol Amendments 2 to 6, refer to Section 16.1.1 of CSR PH-40803.

Note: Protocol Amendments 1 to 4 were implemented prior to enrolment of the first participant into the expansion phase of the study.

**Protocol amendment 1**

Protocol amendment 1, dated 08 JUL 2014, was globally implemented and specified the following modifications:

-Addition of pediatric granulate formulation: Granulate formulation in the forms of 5 mg and 20 mg regorafenib granulate packaged/contained in sachets was introduced to allow recruitment of children who are not able to swallow tablets.

-Revised eligibility criteria: Age limit in the inclusion criteria was changed to allow recruitment of children from 6 months to less than 18 years old. Inclusion criterion limiting enrolment to children who are able to swallow tablets was removed because the option to take granulate formulation became available. Consequently, dose modifications were introduced separately for children from 6 to less than 24 months old.

**Protocol amendment 2**

Protocol amendment 2, dated 25 MAR 2015, was globally implemented and specified the following modifications:

-Clarified guidance on the initial choice and later change of regorafenib formulation

-Clarified guidance on drug interruption and cycle delay

-Addition of BSA ranges for children 2-5 years old: The table for regorafenib granulate based on BSA was supplemented with additional BSA ranges, to allow calculation of the dose for younger children.

**Protocol amendment 3**

Protocol amendment 3, dated 27 JAN 2016, was a local amendment for France only.

**Protocol amendment 4**

Protocol amendment 4, dated 29 MAY 2017, was globally implemented and specified the following modifications:

-Structural changes - dose expansion phase added: Prior to Amendment 4, a dose escalation phase of the study in pediatric subjects with solid malignant tumors (recurrent or refractory to standard therapy) was completed, and the MTD and the RP2D of regorafenib monotherapy in pediatric subjects was determined. This was the only phase of the study included in the protocol up to integrated protocol Version 3.0 and including global Amendment 2 (dated 25 MAR 2015).

-The dose finding of the combination of regorafenib with vincristine/irinotecan (VI) was conducted as an expansion phase to this ongoing Phase 1 trial in order to leverage the sites already open and initiate recruitment as soon as possible. The goal was to provide speedy access to this combination treatment to children and adolescents if active, and minimize the period in which the study was closed for enrolment while a plan to study regorafenib in pediatric patients was crafted together with the pediatric oncology community and agreed by EMA/Pediatric Committee (PDCO). ‘

-To make the dose expansion phase of the study easier to follow, minimize confusion, and potentially reduce protocol deviations, the structure of the protocol was re-organized for following the sections (study design, study population, treatment, procedure and variables, statistical methods and determination of sample size), in an effort to sequentially present these sections of the ‘new’ dose expansion phase separately from the ‘completed’ dose escalation phase.

-Addition of the objectives of the dose expansion phase: Primary and secondary objectives of the dose expansion phase were added.

-Addition of backbone chemotherapy for the dose expansion phase: Backbone chemotherapy (VI) of the dose expansion phase was added.

-Revised eligibility criteria for the dose expansion phase:

-Added the inclusion criterion concerning diagnosis of the indications to be studied in the dose expansion phase.

**Protocol amendment 5**

Protocol amendment 5, dated 13 JUN 2018, was globally implemented and specified the following modifications:

-PK sampling schedule for irinotecan for the sequential dosing schedule changed: The planned timing of the PK samples for I, irinotecan for the sequential dosing schedule has been moved from Cycle 1 to Cycle 2.

**Protocol amendment 6**

Protocol amendment 6, dated 20 MAR 2019, was globally implemented and specified the following modifications:

-List of regorafenib adverse drug reactions removed and reference to Investigator Brochure added.

-Rescreening criteria clarified to confirm that re-screening was also allowed when a screening failure was caused by a condition directly related to the primary disease which later stabilized such that the patient meets the eligibility criteria.

-The table with recommendations regarding dose adjustments was updated to give more flexibility for dose delays - to allow patients to be delayed up to 2 weeks rather than 1 to 2 weeks.

-Modification of requirement regarding tumor assessments for those patients that stay on treatment after Cycle 12 of treatment added.

Rationale for the amendment:

-The purpose of this Amendment was to remove the list of regorafenib ADR information from the background and reference the IB; to clarify re-screening criteria; to clarify on dose delay requirement to up to 2 weeks instead of 1-2 weeks; to add the requirement for the tumor response assessment for patients that stay on treatment after Cycle 12; to include lower BSA range for tablet dosing; and to include administrative changes.

**Protocol Amendment 7**

Protocol Amendment 7, dated 13 JUL 2020, was globally implemented and specified the following modifications:

-Language added to clarify when participants enter the active follow-up.

-Clarification added that days 2-5 are not mandatory if participant is no longer receiving irinotecan.

-Allowed local control via surgery and/or radiotherapy while continuing study treatment if response to treatment is significant enough for local therapy to be potentially curative.

**Protocol Amendment 8**

Protocol Amendment 8, dated 01 MAR 2022, was globally implemented and specified the following modifications:

-Protocol updated to allow flexibility in collecting the post-treatment biomarker sample.

-Protocol-required procedures updated to account for situations where participants are receiving only the study drug regorafenib to decrease burden while maintaining data collection required for safety monitoring.

***Study participants***

***Treatments***

**Escalation phase**

The following investigational product was used in the study:

- Regorafenib, 20 mg tablets
- Regorafenib, 20 mg granulate packaged/contained in sachets
- Regorafenib, 5 mg granulate packaged/contained in sachets.

The dose levels and dose modifications are shown in Table 2.

*Table 2 The modifications of regorafenib dose for children 2 to less than 18 years old*

| Regorafenib dose [a] | 1st dose modification | 2nd dose modification |
|---|---|---|
| Level -1 (50 mg/m$^2$) | Stop treatment [b] | Stop treatment [b] |
| Level 1 (60 mg/m$^2$) | Level -1 (50 mg/m$^2$) | Stop treatment [b] |
| Level 1a (66.5 mg/m$^2$) | Level 1 (60 mg/m$^2$) | Level -1 (50 mg/m$^2$) |
| Level 2 (72 mg/m$^2$) | Level 1 (60 mg/m$^2$) | Level -1 (50 mg/m$^2$) |
| Level 3 (82 mg/m$^2$) | Level 2 (72 mg/m$^2$) | Level 1 (60 mg/m$^2$) |
| Level 4 (93 mg/m$^2$) | Level 3 (82 mg/m$^2$) | Level 2 (72 mg/m$^2$) |

[a] Calculation of individual doses should be based on protocol Table 14-10, Section 16.1.1.
[b] From Cycle 3 onwards, for subjects who were experiencing clinical benefit with regorafenib, continuation of treatment could be discussed on a case-by-case basis with the sponsor.

**Dose expansion phase**

Regorafenib will be administered once daily for 14 days, in a 14 day on/7 days off schedule (21-day cycle), starting at 72 mg/m$^2$ (subjects 2 to less than 18 years old) or 60 mg/m$^2$ (subjects 6 to less than 24 months old).

Vincristine will be given at a dose of 1.5 mg/m$^2$ (0.05 mg/kg for subjects ≤ 10 kg, maximum 2.0 mg) on Day 1 and Day 8 in 21-day cycles. This is in agreement with the product label, in which the usual dose of vincristine for pediatric patients is 1.5-2 mg/m$^2$.

Irinotecan will be administered at a starting dose of 50 mg/m$^2$/day from Day 1 to Day 5, in 21 day cycles. This dose was given to 170 children with an AE profile comparable to that in adults.

Two dosing schedules will be explored, both of which include a regorafenib dosing regimen in a 21-day cycle:

**Schedule A** - **Concomitant dosing schedule** - Of a 21-day cycle, regorafenib will be concomitantly administered with vincristine and irinotecan (VI), in the following order if 2 or 3 agents of the study treatment are scheduled to be administered in the same day:

- **Vincristine:** intravenous bolus, 1.5 mg/m$^2$, maximum of 2 mg (0.05 mg/kg for subjects ≤ 10 kg), Day 1 and Day 8.
- **Irinotecan:** intravenously over 1 hour, at a starting dose of 50 mg/m$^2$/day, Day 1 to Day 5.

- **Regorafenib**: orally at a starting dose of 72 mg/m$^2$ (subjects 2 to less than 18 years old) or 60 mg/m$^2$ (subjects 6 to less than 24 months old) once daily, from Day 1 to Day 14.

On Cycle 1 Days 3, 4 and 5, when both irinotecan and regorafenib will be administered and PK sampling will be needed, the dose of regorafenib will start approximately 60 to 120 minutes after the start of irinotecan.

**Schedule B** - **Sequential dosing schedule** - Of a 21-day cycle, regorafenib will be dosed sequentially, following administration of VI, in the following order if 2 or 3 agents of the study treatment are scheduled to be administered in the same day:

- **Vincristine**: intravenous bolus, 1.5 mg/m$^2$, maximum of 2 mg (0.05 mg/kg for subjects ≤ 10 kg), Day 1 and Day 8.
- **Irinotecan**: intravenously over 1 hour, at a starting dose of 50 mg/m$^2$/day, Day 1 to Day 5.
- **Regorafenib**: orally at a starting dose of 72 mg/m$^2$ (subjects 2 to less than 18 years old) or 60 mg/m$^2$ (subjects 6 to less than 24 months old) once daily, Day 8 to Day 21.

After the last evaluable subject finishes Cycle 1 in each of the cohorts (Schedule A and Schedule B) at the first dose level and if both treatment schedules are equally tolerated, the concomitant schedule (Schedule A) may be chosen for further evaluation since the concomitant administration might increase the probability of synergy as studied in preclinical models. If neither dosing schedule is tolerated, the dose of irinotecan may be de-escalated only if there is a proven increase in the irinotecan and SN-38 exposure due to a DDI with regorafenib.

***Objective(s)***

**Dose escalation phase of the study**

The primary objectives of the dose escalation phase are:

- To define the safety profile, MTD and recommended phase II dose (RP2D) of regorafenib administered orally as a single agent in a 3 weeks on/1 week off schedule in repeating cycles of 28 days in pediatric subjects with solid malignant tumors recurrent or refractory to standard therapy
- To characterize the PK of regorafenib

The secondary objectives of the dose escalation phase are:

- To evaluate preliminarily anti-tumor activity of regorafenib
- To evaluate pharmacodynamic parameters of regorafenib
- Acceptability and palatability of the formulations - tablets and granulates

**Dose expansion phase of the study**

The primary objectives of the dose expansion phase are:

- To define the safety profile, MTD and the RP2D of regorafenib administered orally in combination vincristine and irinotecan in pediatric subjects with RMS and other solid malignant tumors recurrent or refractory to standard therapy

The secondary objectives of the dose expansion phase are:

- To characterize the PK of regorafenib in combination with vincristine and irinotecan
- To evaluate the anti-tumor activity of regorafenib in combination with vincristine and irinotecan

- To characterize the PK of irinotecan
- To evaluate pharmacodynamic parameters of regorafenib in combination with vincristine and irinotecan
- Acceptability and palatability of the regorafenib formulations - tablets and granulates

***Outcomes/endpoints***

**Escalation:**

Escalation primary variables were adverse events (AEs).

Primary safety endpoints were to define MTD and RP2D of regorafenib administered orally as a single agent in a 3-weeks- on/1-week-off schedule in repeating cycles of 28 days in pediatric participants with solid malignant tumors recurrent or refractory to standard therapy.

**Expansion:**

Expansion primary variable of the dose expansion phase was safety: AEs, including the determination, during the first cycle, of DLTs defined as selected Grade 3/4 toxicities according to the NCI-CTCAE (v. 4.0).

***Sample size***

**Dose escalation phase**

No formal statistical sample size estimation was performed in this exploratory study. Depending on the number of dose-escalating steps and the occurrence of DLTs, the planned numbers of subjects could vary. It is anticipated that at least 6 subjects will be enrolled in the dose escalation phase of the study. Based on experience, the chosen sample size of at least 12 additional subjects at the MTD level should be sufficient to confirm the RP2D for this study.

**Dose expansion phase**

No formal statistical sample size estimation will be performed in this exploratory study. Depending on the number of dose-escalating steps and the occurrence of DLTs, the planned numbers of subjects could vary. It is anticipated that at least 15 subjects evaluable for DLTs (at least 50%, i.e. 8 rhabdomyosarcoma (RMS) subjects evaluable for tumor response), with minimum of 6 RMS patients treated at the RP2D.

***Randomisation and blinding (masking)***

This is an open-label non-randomized study. All analyses will be performed in a non-blinded fashion.

***Statistical Methods***

**Analysis sets**

Safety Analysis Set: all subjects who receive at least one dose of the study drug (regorafenib) will be included in the safety evaluation.

MTD Analysis Set: all subjects who completed Cycle 1 or discontinued during Cycle 1 due to an adverse event or DLT in the dose expansion phase will be included in the MTD evaluation.

Efficacy Analysis Set: all subjects who receive at least 1 dose of regorafenib and either have at least one post-baseline efficacy evaluation or have clinical disease progression before the first post-baseline efficacy assessment (treatment failure) will be included in the efficacy evaluations.

PK Analysis Set regorafenib: all subjects with valid evaluable PK data under regorafenib will be included in the evaluation of PK parameters.

PK Analysis Set irinotecan: all subjects with valid evaluable PK data under irinotecan will be included in the evaluation of PK parameters.

Variables (dose expansion phase)

**Primary variables**

- Safety: AEs, including the determination, during the first cycle, of DLTs defined as selected Grade 3/4 toxicities according to the NCI-CTCAE (v. 4.0).

8.3.2 Secondary variables (dose expansion phase)

- PK variables (for regorafenib BAY 73-4506 parent) derived from population PK analysis: AUC(0-24)md based on nominal dosing, Cmax(0-24)md, Cav(0-24)md, t1/2eff,md, and AUC(0-24)md based on individual dosing

- PK variables for irinotecan and SN-38 derived from population PK analysis: clearance of irinotecan and SN-38

- Overall survival under the study treatment (regorafenib in combination with vincristine and irinotecan)

- Time to progression under the study treatment (regorafenib in combination with vincristine and irinotecan)

- Tumor response: tumor assessment by response evaluation criteria in solid tumors (RECIST) v. 1.1: (complete response (CR,) partial response (PR), stable disease (SD), progressive disease (PD) + semi-quantitative mIBG score for neuroblastoma subjects in whom the disease is not evaluable per RECIST v. 1.1.

- Pharmacodynamic parameters of regorafenib in combination with vincristine and irinotecan (plasma and tissue biomarkers, whenever feasible to collect)

- Taste and texture questionnaire of the regorafenib formulations

The complete list of variables will be provided in the statistical analysis plan.

The decision rules for dose adjustments in the “rolling-6” design are depicted in Table 1.

**Planned Interim Analysis (dose expansion phase)**

An interim analysis to report the main study objectives will be performed after the last evaluable subject has finished Cycle 2 (primary completion). This will be an analysis reporting all available data at this point in time.

**Results**

**Participant flow**

**Escalation phase**

The first patient was included on 11 APR 2014. As of the final data release of the clinical database (clean database 05 APR 2024), all 41 participants treated with ≥1 dose of regorafenib and evaluable for safety in the escalation phase of the study, had discontinued study treatment; 40 of the 41 treated participants had died.

**Expansion phase**

As of the final data release of the clinical database (clean database 05 APR 2024), 20 of the 21 participants, who received ≥1 dose of study treatment (i.e., regorafenib administered orally in combination with the VI backbone chemotherapy) in the expansion phase of the study, had discontinued study treatment (1 participant to continue treatment in roll-over study).

**Protocol deviations**

Protocol deviations were identified in 35 of 41 participants treated in the escalation phase and in all 21 participants treated in the expansion phase. The protocol deviations referred to inclusion/exclusion criteria not met but participant entered treatment, time schedule deviations, procedure deviations, other protocol deviations, and treatment deviations.

No protocol deviations associated with the COVID-19 pandemic were reported in the escalation phase of the study. However, in the expansion phase, 2 participants had important protocol deviations (procedure deviations) due to the pandemic.

***Baseline data***

**Escalation**

The demographics of the safety analysis set are shown in Table 3. Twenty-one of the 41 participants (51.2%) in the escalation phase safety analysis set (SAF) of the study were female and 20 (48.8%) were male. Twenty-one participants (51.2%) did not report their race and 17 participants (41.5%) were White. The participants' median age was 13.0 years (range: 3 to 17 years) (CSR PH-38659 [database cut-off date of 19 NOV 2015]).

*Table 3 Demographics (Safety analysis set)*

| | Level 1 (60 mg/m$^2$) N=6 (100%) | Level 2 (72 mg/m$^2$) N=14 (100%) | Level 3 (82 mg/m$^2$) N=14 (100%) | Level 4 (93 mg/m$^2$) N=7 (100%) | Total N=41 (100%) |
|---|---|---|---|---|---|
| **Sex** | | | | | |
| Female | 2 (33.3%) | 7 (50.0%) | 7 (50.0%) | 5 (71.4%) | 21 (51.2%) |
| Male | 4 (66.7%) | 7 (50.0%) | 7 (50.0%) | 2 (28.6%) | 20 (48.8%) |
| **Race (N)** | | | | | |
| White | 2 (33.3%) | 6 (42.9%) | 8 (57.1%) | 1 (14.3%) | 17 (41.5%) |
| Asian | 0 | 1 (7.1%) | 0 | 1 (14.3%) | 2 (4.9%) |
| Not reported | 4 (66.7%) | 7 (50.0%) | 5 (35.7%) | 5 (71.4%) | 21 (51.2%) |
| Multiple | 0 | 0 | 1 (7.1%) | 0 | 1 (2.4%) |
| **Age (years)** | | | | | |
| Mean | 12.5 | 13.2 | 10.2 | 10.6 | 11.6 |
| SD | 2.3 | 3.2 | 4.7 | 4.5 | 4.0 |
| Min | 9 | 6 | 3 | 5 | 3 |
| Median | 12.5 | 14.0 | 9.5 | 11.0 | 13.0 |
| Max | 15 | 17 | 17 | 17 | 17 |
| **Baseline of weight (kg)** | | | | | |
| Mean | 43.3 | 49.6 | 37.4 | 30.4 | 41.2 |
| SD | 12.5 | 16.5 | 21.8 | 12.9 | 18.4 |
| Median | 42.0 | 48.2 | 31.4 | 28.2 | 39.1 |
| **Baseline of height (cm)** | | | | | |
| Mean | 148.6 | 157.3 | 138.9 | 136.9 | 146.2 |
| SD | 12.8 | 16.0 | 27.4 | 21.2 | 22.2 |
| Median | 149.0 | 161.0 | 129.5 | 133.7 | 150.5 |
| **Baseline of Body Mass Index (kg/m$^2$)** | | | | | |
| Mean | 19.09 | 20.02 | 17.81 | 15.41 | 18.34 |
| SD | 3.64 | 3.91 | 3.97 | 1.95 | 3.87 |
| Median | 18.11 | 19.31 | 16.70 | 14.68 | 17.27 |
| **Baseline of Body Surface Area (m$^2$)** | | | | | |
| Mean | 1.34 | 1.48 | 1.19 | 1.07 | 1.29 |
| SD | 0.22 | 0.32 | 0.46 | 0.32 | 0.39 |
| Min | 1.09 | 0.93 | 0.62 | 0.68 | 0.62 |
| Median | 1.36 | 1.49 | 1.02 | 0.98 | 1.33 |
| Max | 1.56 | 2.01 | 2.10 | 1.60 | 2.10 |

SD = standard deviation.
Multiple: Subject 15906-12002-0003 in Level 3 (82 mg/m$^2$) reported both White and Black that belong to more than one race (Table 14.1/15).
Source: Table 14.1/8

**Expansion**

The most common cancer type reported in the dose-escalation phase was CNS tumor of glial origin (11 reported as CNS of glial origin and 2 reported as diffuse pontine glioma; total of 13 participants, 31.7%), followed by medulloblastoma/ primitive neuroectodermal tumor (PNET) (6 participants, 14.6%) and Ewing's sarcoma/PNET (5 participants, 12.2%) (Table 14.1/17 of CSR PH-38659, database cut-off date of 19 NOV 2015).

The most common cancer type in the expansion phase was RMS (12 participants, 57.1%), of which the most predominant histologic subtype was aRMS (8 participants, 38.1%) followed by eRMS (3 participants, 14.3%). The next most common cancer type was Ewing sarcoma in 5 participants

(23.8%), then neuroblastoma in 3 participants (14.3%). One participant (4.8%) was diagnosed with Wilms tumor (Table 14.1/18 of CSR PH-40803, database cut-off date of 05 MAY 2019).

Eight of the 21 participants (38.1%) in the expansion phase SAF of the study were female and 13 (61.9%) were male; 14 participants (66.7%) were White. The participants' median age was 10.0 years (range: 1.5 to 17.0 years). A summary of demographic characteristics for the participants in the expansion phase of the study data is shown by treatment regimen in Table 4.

*Table 4 Demographics – Expansion (SAF)*

| | Reg72 conc+VI (N=2) n % | Reg72 seq+VI (N=6) n % | Reg82 seq+VI (N=13) n % | Total (N=21) n % |
|---|---|---|---|---|
| **Sex [n (%)]** | | | | |
| Female | 0 | 2 (33.3) | 6 (46.2) | 8 (38.1) |
| Male | 2 (100.0) | 4 (66.7) | 7 (53.8) | 13 (61.9) |
| **Race [n (%)]** | | | | |
| Missing [a] | 0 | 0 | 1 (7.7) | 1 (4.8) |
| White | 1 (50.0) | 3 (50.0) | 10 (76.9) | 14 (66.7) |
| Asian | 0 | 2 (33.3) | 0 | 2 (9.5) |
| Not reported [b] | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Multiple | 0 | 0 | 1 (7.7) | 1 (4.8) |
| **Age [years]** | | | | |
| Mean | 13.50 | 10.50 | 8.73 | 9.69 |
| StD | 4.95 | 4.59 | 4.74 | 4.71 |
| Min | 10.00 | 5.00 | 1.50 | 1.50 |
| Median | 13.50 | 12.00 | 10.00 | 10.00 |
| Max | 17.00 | 15.00 | 16.00 | 17.00 |
| **Weight [kg]** | | | | |
| Mean | 40.10 | 36.77 | 33.89 | 35.31 |
| StD | 27.15 | 14.71 | 21.36 | 19.21 |
| Min | 20.90 | 17.10 | 10.80 | 10.80 |
| Median | 40.10 | 42.85 | 32.90 | 33.90 |
| Max | 59.30 | 49.60 | 77.60 | 77.60 |
| **Height [cm]** | | | | |
| Mean | 146.00 | 140.83 | 128.59 | 133.75 |
| StD | 21.21 | 25.88 | 31.45 | 28.82 |
| Min | 131.0 | 107.0 | 76.5 | 76.5 |
| Median | 146.00 | 150.50 | 132.00 | 138.50 |
| Max | 161.0 | 167.0 | 174.0 | 174.0 |
| **Body Surface Area [$m^2$]** | | | | |
| Mean | 1.2850 | 1.1933 | 1.0838 | 1.1343 |
| StD | 0.5869 | 0.3598 | 0.4641 | 0.4287 |
| Min | 0.870 | 0.710 | 0.500 | 0.500 |
| Median | 1.2850 | 1.3400 | 1.1000 | 1.1400 |
| Max | 1.700 | 1.500 | 1.940 | 1.940 |

SAF = Safety Analysis Set
[a] Participant has no data entry.
[b] Participant has data entry "Not reported".
Source: Table 14.1/5b

**Prior anticancer therapy**

Of the 41 participants treated in the escalation phase of this study, 40 participants (97.6%) had received prior systemic anticancer therapy (chemotherapy, immunotherapy, or high dose chemotherapy/autologous transplant) before study entry (Table 14.1/18 of CSR PH-38659, database cut-off date of 19 NOV 2015).

All of the 21 participants (100%) treated in the expansion phase of the study had already received ≥1 prior systemic anticancer therapy (Table 14.1/19 of CSR PH-40803, database cut-off date of 05 MAY 2019).

***Number analysed***

***Efficacy results***

Efficacy was a secondary endpoint of the study. No clear relationship between dose level and best response was observed. None of the treated escalation participants achieved a CR. There was 1 participant ("alveolar rhabdomyosarcoma") in Dose Level 3 (82 mg/m2) with a PR. There were 15 participants with stable disease as best overall response (Listing 16.2.6/6a).

For a detailed summary of the secondary efficacy variable (tumor response) for the escalation phase of the study, refer to CSR PH-38659 (database cut-off date of 19 NOV 2015).

**Tumor response evaluation (Expansion phase)**

In the dose expansion phase of the study, the evaluation of the antitumor activity of regorafenib in combination with vincristine and irinotecan was a secondary objective. Tumor response in the expansion phase of the study was evaluated by site investigator using RECIST v. 1.1 as per investigator's and/or local radiologist's assessment (CR, PR, SD, PD).

As shown in Table 5, grading of tumor response according to RECIST v. 1.1 was available for 20 of 21 participants treated in the expansion phase. Overall, the response rate (CR+PR) was 47.6%. Seven of the 21 expansion participants in the EAS (33.3%) achieved PR as best overall response during treatment or active follow-up and 7 participants (33.3%) had SD. Three participants (14.3%) had achieved CR as best response. All 3 participants were in the Reg82 seq+VI group.

*Table 5 Best overall response (Expansion; EAS)*

| Best overall response (RECIST 1.1) | Reg72 conc+VI (N=2) n (%) [95% CI] | Reg72 seq+VI (N=6) n (%) [95% CI] | Reg82 seq+VI (N=13) n (%) [95% CI] | Total (N=21) n (%) [95% CI] |
|---|---|---|---|---|
| Response rate (CR + PR) | 2 (100.0) | 2 (33.3) | 6 (46.2) | 10 (47.6) |
| Complete response (CR) | 0 | 0 | 3 (23.1) [5.5; 57.2] | 3 (14.3) [3.2; 37.9] |
| Partial response (PR) | 2 (100.0) [15.8; 100.0] | 2 (33.3) [4.3; 77.7] | 3 (23.1) [5.5; 57.2] | 7 (33.3) [15.4; 59.2] |
| Stable disease (SD) | 0 | 3 (50.0) [11.8; 88.2] | 4 (30.8) [9.9; 65.1] | 7 (33.3) [15.4; 59.2] |
| Non-CR/non-PD[a] | 0 | 1 (16.7) [0.4; 64.1] | 0 | 1 (4.8) [0.1; 24.9] |
| Progressive disease (PD) | 0 | 0 | 2 (15.4) [2.1; 48.4] | 2 (9.5) [1.2; 31.7] |

Source: Table 14.2/1b
CI = Confidence interval; CR = Complete response; EAS = Efficacy analysis set; N = total number of participants (100%); n = number of participants in category/with event; PD = Progressive disease; PR = Partial response; RECIST = Response evaluation criteria in solid tumors; SD = Stable disease
[a] For 1 participant (160019001), no target lesions were available and thus only non-target lesions (not measurable) were assessed.

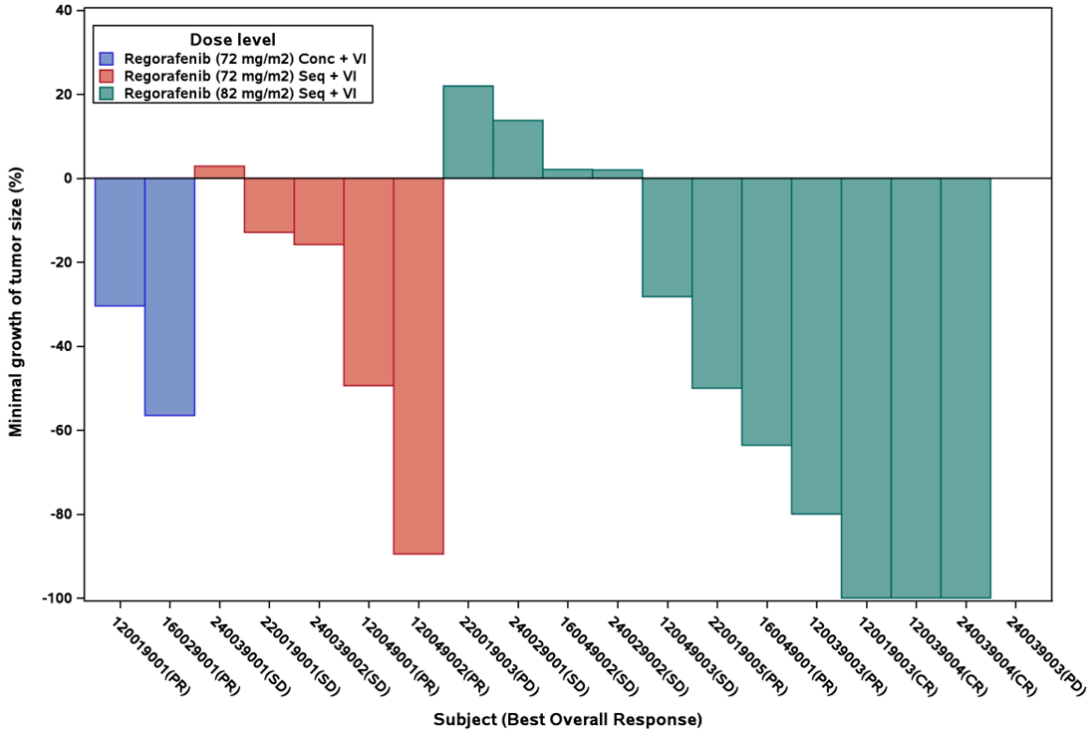
Table 6 shows the details for the 20 participants (12 with RMS) for whom best response assessments according to RECIST 1.1 were available, with the best percentage of change in lesion size from baseline ranging from -100.0% to +22.0%.

Waterfall diagrams for best overall response of target lesions by treatment regimen and tumor type are provided in Figure 1 and Figure 2 respectively.

*Table 6 Listing of best response, treatment duration, disease status at end of treatment and at study entry (Expansion; EAS)*

| Treatment regimen Participant ID | Histology type | Best response | Best percent change from Baseline | Treatment duration [days] | Disease status at EoT visit | Disease status at study entry |
|---|---|---|---|---|---|---|
| **Reg72 conc+VI** | | | | | | |
| 120019001 | Ewing sarcoma | PR | -30.4 | 546 | PD | relapsing |
| 160029001 | Embryonal rhabdomyosarcoma, NOS | PR | -56.5 | 40 | SD | refractory |
| **Reg72 seq+VI** | | | | | | |
| 120049001 | Ewing sarcoma | PR | -49.4 | 84 | PD | Refractory & relapsing |
| 120049002 | Ewing sarcoma | PR | -89.5 | 259 | - | refractory |
| 160019001 | Rhabdomyosarcoma, NOS | Non-CR/ Non-PD | - | 143 | - | refractory |
| 220019001 | Neuroblastoma, NOS | SD | -12.9 | 98 | - | relapsing |
| 240039001 | Ewing sarcoma | SD | 2.9 | 149 | - | refractory |
| 240039002 | Ewing sarcoma | SD | -15.8 | 14 | SD | relapsing |
| **Reg82 seq+VI** | | | | | | |
| 120019003 | Alveolar rhabdomyosarcoma | CR | -100 | 1218 | CR | refractory |
| 120039002 | Alveolar rhabdomyosarcoma | - [b] | - | 14 | - | relapsing |
| 120039003 | Alveolar rhabdomyosarcoma | PR | -80.0 | 161 | - | relapsing |
| 120039004 | Alveolar rhabdomyosarcoma | CR | -100.0 | 98 | CR | relapsing |
| 120049003 | Embryonal rhabdomyosarcoma, NOS | SD | -28.2 | 216 | - | refractory & relapsing |
| 160049001 | Embryonal rhabdomyosarcoma, NOS | PR | -63.6 | 427 | - | relapsing |
| 160049002 | Neuroblastoma, NOS | SD | 2.1 | 35 | NE | relapsing |
| 220019003 | Wilms tumor | PD | 22.0 | 14 | - | relapsing |
| 220019005 | Alveolar rhabdomyosarcoma | PR | -50 | 86 | - | refractory |
| 240029001 | Alveolar rhabdomyosarcoma | SD | 13.8 | 42 | - | relapsing |
| 240029002 | Alveolar rhabdomyosarcoma | SD | 2.0 | 78 | - | relapsing |
| 240039003 | Neuroblastoma, NOS | PD | - | 12 | - | relapsing |
| 240039004 | Alveolar rhabdomyosarcoma | CR | -100 | 1815 | CR | relapsing |

[a] According to investigator's assessment: Clinical progression.
CR = Complete response; EAS = Efficacy analysis set; EoT = End of treatment; ID = Identification; NE = Not evaluable;
NOS = Not otherwise specified; PD = Progressive disease; PR = Partial response; SD = Stable disease
Source: Listing 16.2.4/7b and Listing 16.2.6/9b




EAS = Efficacy analysis set
Source: Figure 14.2/3b
Note: Only participants with best overall response assessed as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

*Figure 1 Best overall response by dose level (Expansion; EAS)*

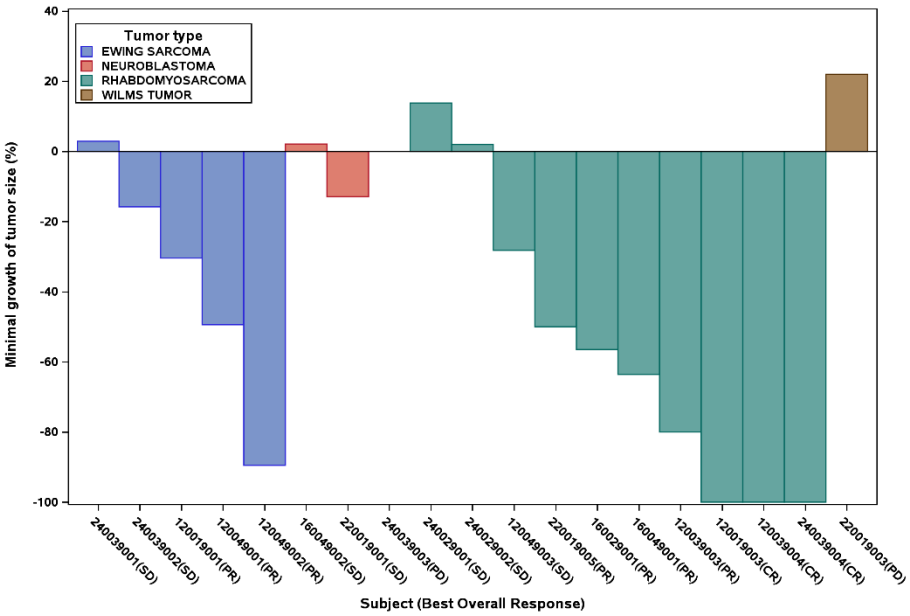



*Figure 2 Best overall response by response category (Expansion; EAS)*

EAS = Efficacy analysis set
Source: Figure 14.2/4b
Note: Only participants with best overall response assessed as complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD).

**Time to death (Expansion; EAS**)

As of the final data release of the clinical database (date of clean database 05 APR 2024), 16 of the 21 expansion participants (76.2%) in the efficacy/safety analysis set had died. None of the on-study deaths were assessed as drug-related. As displayed in Table 7. the median survival time was 391 days (12.85 months), with a lower limit of the 95% CI of 191 days (6.28 months**Error! Bookmark not defined.**), and ranged (including censored values at last known time point) from (censored) 42 to (censored) 1940 days (63.74 months).

*Table 7 Time to death (Expansion; EAS)*

| | **Total (N=21)** |
|---|---|
| Number (%) of participants with event | 16 (76.2%) |
| Number of participants censored | 5 (23.8%) |
| 25th percentile (95% CI) [days] | 191 (42, 266) |
| Median (95% CI) [days] | 391 (191,1149) |
| 75th percentile (95% CI) [days] | 1731 (391, A) |
| Range (including censored values) [days] | (42-1940**) |
| Range (without censored values) [days] | (42-1731) |
| Overall survival rate at | |
| Month 12 (95% CI) | 0.503 (0.284, 0.722) |
| Month 24 (95% CI) | 0.302 (0.100, 0.503) |
| Month 36 (95% CI) | 0.302 (0.100, 0.503) |
| Month 48 (95% CI) | 0.251 (0.061, 0.442) |
| Month 60 (95% CI) | 0.201 (0.025, 0.377) |

EAS = Efficacy analysis set
A: Value cannot be estimated due to censored data
**: Censored at last known time point
Median, percentile and other 95% CIs computed using Kaplan-Meier estimates.
Source: Table 14.2/2b

**Progression-free survival (Expansion phase)**

Eighteen of the 21 participants (85.7%) had experienced disease progression or death, (whichever came first). The corresponding listing by participant, treatment regimen and time of event is provided in Listing 16.2.6/8b.

As displayed in Table 8the median PFS was 212 days (6.97 months), with a lower limit of the 95% CI of 89 days (2.92 months), and ranged (including censored values at last know time point) from 19 to (censored) 1825 days (59.96 months).

*Table 8 Progression-free survival (Expansion; EAS)*

| | Total (N=21) |
|---|---|
| Number (%) of participants with event | 18 (85.7%) |
| Number of participants censored | 3 (14.3%) |
| 25th percentile (95% CI) [days] | 89 (19, 198) |
| Median (95% CI) [days] | 212 (89, 450) |
| 75th percentile (95% CI) [days] | 457 (214,1731) |
| Range (including censored values) [days] | (19-1825**) |
| Range (without censored values) [days] | (19-1731) |
| Progression-free survival rate at | |
| Month 12 (95% CI) | 0.323 (0.111, 0.534) |
| Month 24 (95% CI) | 0.108 (0.000, 0.248) |
| Month 36 (95% CI) | 0.108 (0.000, 0.248) |
| Month 48 (95% CI) | 0.108 (0.000, 0.248) |
| Month 60 (95% CI) | A (A, A) |

CI = Confidence interval; EAS = Efficacy analysis set
A: Value cannot be estimated due to censored data
**: Censored at last known time point: alive with no disease progression
Median, percentile, and other 95% CIs computed using Kaplan-Meier estimates.
Source: Table 14.2/3b

Tumor progression was reported in 16 of the 21 treated expansion participants (76.2%).

As only 1 further participant (no. 120039002) died without radiologically confirmed disease progression, the data for time to progression (TTP) are nearly identical to those displayed for PFS. The median TTP was 214 days (7.03 months ), with a lower limit of the 95% CI of 89 days (2.92 months), and ranged (including censored values at last know time point) from 19 to (censored) 1825 days (59.96 months).

**Pharmacokinetic evaluation**

Regorafenib exposure when administered in combination with vincristine/irinotecan was consistent with the exposure observed in the dose-escalation phase where regorafenib was administered as monotherapy and in the same range as observed in the adult population dosed as 160 mg once daily.

***Safety results***

**Treatment duration (Escalation phase)**

Duration of regorafenib treatment during the treatment period in the escalation phase of the study is summarized in Table 9. Overall, 27 out of 41 subjects (65.9%) had at least one dose modification, and the majority of dose modifications were due to AEs. Dose reductions were reported for 14 (34.1%) of the 41 subjects treated. No subject had more than one dose reduction.

*Table 9 Regorafenib: Duration of treatment (Escalation; SAF)*

| | Regorafenib Level 1 (60 mg/m²) (N=6) | Regorafenib Level 2 (72 mg/m²) (N=14) | Regorafenib Level 3 (82 mg/m²) (N=14) | Regorafenib Level 4 (93 mg/m²) (N=7) | Total (N=41) |
|---|---|---|---|---|---|
| **Overall time on treatment (incl. time off-drug/interruptions) [no. of cycles]** | | | | | |
| Mean | 2.3 | 4.2 | 3.1 | 1.7 | 3.1 |
| (StD) | (1.9) | (7.5) | (1.8) | (0.5) | (4.6) |
| Median | 2.0 | 2.0 | 2.5 | 2.0 | 2.0 |
| Min, Max | 1, 6 | 1, 30 | 1, 8 | 1, 2 | 1, 30 |
| **Overall time on treatment (incl. time off-drug/interruptions) [no. of days] [a]** | | | | | |
| Mean | 53.3 | 110.7 | 80.9 | 35.9 | 79.3 |
| (StD) | (53.6) | (212.0) | (51.4) | (18.0) | (129.1) |
| Median | 36.0 | 49.0 | 68.5 | 43.0 | 49.0 |
| Min, Max | 18, 160 | 7, 834 | 21, 220 | 2, 49 | 2, 834 |
| **Actual time on treatment (excl. time off-drug/interruptions) [no. of days] [b]** | | | | | |
| Mean | 42.8 | 84.8 | 63.0 | 27.6 | 61.4 |
| (StD) | (38.4) | (159.4) | (39.4) | (14.1) | (97.1) |
| Median | 28.5 | 39.5 | 53.0 | 32.0 | 42.0 |
| Min, Max | 18, 119 | 7, 630 | 14, 169 | 2, 42 | 2, 630 |

SAF = Safety analysis set
[a] (Day of last dose minus day of first dose) +1
[b] (Day of last dose minus day of first dose) +1 minus days of interruption
Source: Table 14.3/1a

**Treatment duration (Expansion phase)**

Duration of regorafenib treatment during the treatment period in the expansion phase of the study is summarized in Table 10.

*Table 10 Regorafenib: Duration of treatment (Expansion; SAF)*

| | Reg72 conc+VI (N=2) | Reg72 seq+VI (N=6) | Reg82 seq+VI (N=13) | Total (N=21) |
|---|---|---|---|---|
| **Overall time on treatment (incl. time off-drug/interruptions) [no. of cycles]** | | | | |
| Mean | 11.5 | 5.8 | 14.8 | 12.0 |
| (StD) | (13.4) | (3.8) | (25.2) | (20.3) |
| Median | 11.5 | 5.5 | 4.0 | 4.0 |
| Min, Max | 2, 21 | 1, 12 | 1, 85 | 1, 85 |
| **Overall time on treatment (incl. time off-drug/interruptions) [no. of days] [a]** | | | | |
| Mean | 293.0 | 124.5 | 324.3 | 264.2 |
| (StD) | (357.8) | (82.0) | (554.7) | (448.3) |
| Median | 293.0 | 120.5 | 86.0 | 98.0 |
| Min, Max | 40, 546 | 14, 259 | 12, 1815 | 12, 1815 |
| **Actual time on treatment (excl. time off-drug/interruptions) [no. of days] [b]** | | | | |
| Mean | 142.5 | 77.2 | 202.2 | 160.8 |
| (StD) | (170.4) | (52.1) | (349.5) | (280.5) |
| Median | 142.5 | 71.5 | 54.0 | 55.0 |
| Min, Max | 22, 263 | 14, 166 | 10, 1175 | 10, 1175 |

SAF = Safety analysis set
[a] (Day of last dose minus day of first dose) +1
[b] (Day of last dose minus day of first dose) +1 minus days of interruption
Source: Table 14.3/1b

As of the final data release of the clinical database (clean database 05 APR 2024), the median overall time on treatment with regorafenib (including time off-drug/interruptions) was 98 days or 3.22 months

(range: 12 to 1815 days [0.39 to 59.63 months]), corresponding to a median number of 4 cycles (range: 1 to 85 cycles). The median treatment duration was longer in the Reg72 groups (11.5 and 5.5 cycles) when compared to the Reg82 seq+VI group (4.0 cycles).

Excluding the time off-drug/interruptions, the median actual time on treatment with regorafenib was 55 days (1.81 months; range: 10 days [0.33 months] in a participant on the Reg82 seq+VI regimen to 1175 days [38.60 months[3]] in a participant on the Reg82 seq+VI regimen).

**Dosages of regorafenib, irinotecan, and vincristine (Expansion phase)**

The data displayed in Table 11 show that the difference between planned and actual doses of the 3 drugs was high. Disregarding the data of the 2 participants of the Reg72 conc+VI group, both mean and median percentages of the actual dose in relation to the planned dose were >80% for all drugs.

*Table 11 Actual dosages in relation to planned dosages (Expansion; SAF)*

| | Reg72 conc+VI (N=2) | Reg72 seq+VI (N=6) | Reg82 seq+VI (N=13) | Total (N=21) |
|---|---|---|---|---|
| **Regorafenib** | | | | |
| Percent of planned dose [%] | | | | |
| n | 2 | 5 | 12 | 19 |
| Mean | 66.09 | 80.89 | 89.07 | 84.49 |
| StD | 1.64 | 22.81 | 12.60 | 16.37 |
| Minimum | 64.9 | 53.2 | 63.8 | 53.2 |
| Median | 66.09 | 84.56 | 89.89 | 88.06 |
| Maximum | 67.3 | 104.1 | 107.0 | 107.0 |
| Percent of planned dose, categorical [n (%)] | | | | |
| n | 2 (100.0) | 6 (100.0) | 13 (100.0) | 21 (100.0) |
| Missing | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| >30 to 60% | 0 | 1 (16.7) | 0 | 1 (4.8) |
| >60 to 90% | 2 (100.0) | 2 (33.3) | 6 (46.2) | 10 (47.6) |
| >90 to 110% | 0 | 2 (33.3) | 6 (46.2) | 8 (38.1) |
| **Irinotecan** | | | | |
| Percent of planned dose [%] | | | | |
| n | 2 | 5 | 12 | 19 |
| Mean | 89.47 | 94.72 | 91.68 | 92.25 |
| StD | 3.65 | 10.69 | 9.86 | 9.40 |
| Minimum | 86.9 | 82.4 | 70.2 | 70.2 |
| Median | 89.47 | 95.43 | 95.83 | 95.29 |
| Maximum | 92.1 | 106.8 | 101.0 | 106.8 |
| Percent of planned dose, categorical [n (%)] | | | | |
| n | 2 (100.0) | 6 (100.0) | 13 (100.0) | 21 (100.0) |
| Missing | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| >60 to 90% | 1 (50.0) | 2 (33.3) | 3 (23.1) | 6 (28.6) |
| >90 to 110% | 1 (50.0) | 3 (50.0) | 9 (69.2) | 13 (61.9) |
| **Vincristine** | | | | |
| Percent of planned dose [%] | | | | |
| n | 2 | 5 | 12 | 19 |
| Mean | 60.58 | 93.68 | 85.60 | 85.09 |
| StD | 28.18 | 12.71 | 16.53 | 18.29 |
| Minimum | 40.7 | 79.7 | 59.4 | 40.7 |
| Median | 60.58 | 97.92 | 93.43 | 93.28 |
| Maximum | 80.5 | 108.6 | 102.8 | 108.6 |

| | Reg72 conc+VI (N=2) | Reg72 seq+VI (N=6) | Reg82 seq+VI (N=13) | Total (N=21) |
|---|---|---|---|---|
| Percent of planned dose, categorical [n (%)] | | | | |
| n | 2 (100.0) | 6 (100.0) | 13 (100.0) | 21 (100.0) |
| Missing | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| >30 to 60% | 1 (50.0) | 0 | 2 (15.4) | 3 (14.3) |
| >60 to 90% | 1 (50.0) | 2 (33.3) | 3 (23.1) | 6 (28.6) |
| >90 to 110% | 0 | 3 (50.0) | 7 (53.8) | 10 (47.6) |

SAF = Safety analysis set
Note: For participants 160019001 and 240039001, the body surface area was not reported in the database for all cycles. For the calculation of "percent of planned dose", these values were calculated retrospectively.
Source: Tables 14.3/2b, 14.3/4b and 14.3/6b

**Dose modifications (Expansion phase)**

Table 12 shows that 18 of 21 treated expansion participants (85.7% of the total SAF in the expansion phase of the study) had ≥1 dose modification of regorafenib (dose reduction and/or interruption or delay of dosing).

Dose reductions (n=10) were reported in 8 of 21 participants (38.1%) and all of these reductions were primarily due to a treatment emergent adverse events (TEAE). Two participants in the Reg82 seq+VI group required 2 dose reductions. One of these participants had otitis, asthenia, and neutropenia; initially, backbone chemotherapy was continued for this participant without any changes but was finally interrupted due to neutropenia. In the second participant, the adverse events leading to dose reductions were platelets decreased and creatine phosphokinase (CPK) increased (Listing 16.2.7/7b).

Dose interruptions or delays (n=94) were reported in 18 of 21 expansion participants (85.7%), and 62.8% of the interruptions/delays were primarily due to a TEAE. Fourteen of the 18 participants had up to 4 interruptions/delays.

Drug withdrawal due to a TEAE was reported in 3 expansion participants.

*Table 12 Regorafenib: Dose modifications (Expansion; SAF)*

| | Reg72 conc+VI (N=2) | Reg72 seq+VI (N=6) | Reg82 seq+VI (N=13) | Total (N=21) |
|---|---|---|---|---|
| No. (%) participants with modification(s) | 2/2 (100.0%) | 6/6 (100.0%) | 10/13 (76.9%) | 18/21 (85.7%) |
| Dose reduction: | | | | |
| No. (%) participants with dose reduction | 2/2 (100.0%) | 2/6 (33.3%) | 4/13 (30.8%) | 8/21 (38.1%) |
| No. of dose reductions | 2 | 2 | 6 | 10 |
| No. of dose reductions per participant | | | | |
| 1 | 2/2 (100.0%) | 2/2 (100.0%) | 2/4 (50.0%) | 6/8 (75.0%) |
| 2 | 0 | 0 | 2/4 (50.0%) | 2/8 (25.0%) |
| Primary reason for dose reduction: | | | | |
| Adverse event | 2/2 (100.0%) | 2/2 (100.0%) | 6/6 (100.0%) | 10/10 (100.0%) |
| Dose interruption or delay: | | | | |
| No. (%) participants with dose interruptions/delays | 2/2 (100.0%) | 6/6 (100.0%) | 10/13 (76.9%) | 18/21 (85.7%) |
| No. of dose interruptions/delays | 19 | 16 | 59 | 94 |
| No. of dose interruptions/delays per participant | | | | |
| 1 | 0 | 2/6 (33.3%) | 4/10 (40.0%) | 6/18 (33.3%) |
| 3 | 1/2 (50.0%) | 2/6 (33.3%) | 0 | 3/18 (16.7%) |
| 4 | 0 | 2/6 (33.3%) | 3/10 (30.0%) | 5/18 (27.8%) |
| 6 | 0 | 0 | 1/10 (10.0%) | 1/18 (5.6%) |
| 16 | 1/2 (50.0%) | 0 | 0 | 1/18 (5.6%) |
| 18 | 0 | 0 | 1/10 (10.0%) | 1/18 (5.6%) |
| 19 | 0 | 0 | 1/10 (10.0%) | 1/18 (5.6%) |
| Primary reason for dose interruptions/delays: | | | | |
| Missing | 0 | 1/16 (6.3%) | 0 | 1/94 (1.1%) |
| Adverse event | 13/19 (68.4%) | 13/16 (81.3%) | 33/59 (55.9%) | 59/94 (62.8%) |
| Participant error | 1/19 (5.3%) | 0 | 4/59 (6.8%) | 5/94 (5.3%) |
| Other | 5/19 (26.3%) | 2/16 (12.5%) | 22/59 (37.3%) | 29/94 (30.9%) |

SAF = Safety analysis set
Source: Table 14.3/3b

**Irinotecan**

Table 13 shows that all but 4 participants in the Reg82 seq+VI group (81.0% of the total SAF in the expansion phase of the study) had ≥1 irinotecan dose modification (dose reduction and/or interruption or delay of dosing.

Dose reductions (n=22) were reported in 14 of 21 expansion participants (66.7%) and all of these reductions were primarily due to a TEAE. The maximum number of dose reductions per participant was 2.

Dose interruptions or delays (n=47) were reported in 17 of 21 expansion participants (81.0%), and 78.7% of interruptions were primarily due to a TEAE. Fourteen of the 17 participants had up to 3 interruptions/delays.

Drug withdrawal due to a TEAE was reported in 5 expansion participants

*Table 13 Irinotecan: Dose modifications (Expansion; SAF)*

| | Reg72 conc+VI (N=2) | Reg72 seq+VI (N=6) | Reg82 seq+VI (N=13) | Total (N=21) |
|---|---|---|---|---|
| No. (%) participants with modification(s) | 2/2 (100.0%) | 6/6 (100.0%) | 9/13 (69.2%) | 17/21 (81.0%) |
| Dose reduction: | | | | |
| No. (%) participants with dose reduction | 2/2 (100.0%) | 4/6 (66.7%) | 8/13 (61.5%) | 14/21 (66.7%) |
| No. of dose reductions | 3 | 7 | 12 | 22 |
| No. of dose reductions per participant | | | | |
| 1 | 1/2 (50.0%) | 1/4 (25.0%) | 4/8 (50.0%) | 6/14 (42.9%) |
| 2 | 1/2 (50.0%) | 3/4 (75.0%) | 4/8 (50.0%) | 8/14 (57.1%) |
| Primary reason for dose reduction: | | | | |
| Adverse event | 3/3 (100.0%) | 7/7 (100.0%) | 12/12 (100.0%) | 22/22 (100.0%) |
| Dose interruption or delay: | | | | |
| No. (%) participants with dose interruptions/delays | 2/2 (100.0%) | 6/6 (100.0%) | 9/13 (69.2%) | 17/21 (81.0%) |
| No. of dose interruptions/delays | 15 | 10 | 22 | 47 |
| No. of dose interruptions/delays per participant | | | | |
| 1 | 1/2 (50.0%) | 2/6 (33.3%) | 3/9 (33.3%) | 6/17 (35.3%) |
| 2 | 0 | 4/6 (66.7%) | 1/9 (11.1%) | 5/17 (29.4%) |
| 3 | 0 | 0 | 3/9 (33.3%) | 3/17 (17.6%) |
| 4 | 0 | 0 | 2/9 (22.2%) | 2/17 (11.8%) |
| 14 | 1/2 (50.0%) | 0 | 0 | 1/17 (5.9%) |
| Primary reason for interruptions/delays: | | | | |
| Adverse event | 10/15 (66.7%) | 10/10 (100.0%) | 17/22 (77.3%) | 37/47 (78.7%) |
| Other | 5/15 (33.3%) | 0 | 5/22 (22.7%) | 10/47 (21.3%) |

SAF = Safety analysis set
Source: Table 14.3/5b

**Vincristine**

Table 14 shows that all but 5 participants in the Reg82 seq+VI group (76.2% of the total SAF in the expansion phase of the study) had ≥1 dose modification of vincristine (dose reduction and/or interruption or delay of dosing).

Dose reductions were reported in 1 expansion participant (4.8%).

Dose interruptions or delays (n=47) were reported in 15 of 21 expansion participants (71.4%), and 85.1% of the interruptions/delays were primarily due to a TEAE. Twelve of the 15 participants had up to 3 interruptions/delays.

Drug withdrawal due to a TEAE was reported for 5 expansion participants

*Table 14 Vincristine: Dose modifications (Expansion; SAF)*

| | Reg72 conc+VI (N=2) | Reg72 seq+VI (N=6) | Reg82 seq+VI (N=13) | Total (N=21) |
|---|---|---|---|---|
| No. (%) participants with modification(s) | 2/2 (100.0%) | 6/6 (100.0%) | 8/13 (61.5%) | 16/21 (76.2%) |
| Dose reduction: | | | | |
| No. (%) participants with dose reduction | 0 | 0 | 1/13 (7.7%) | 1/21 (4.8%) |
| Dose interruption or delay: | | | | |
| No. (%) participants with dose interruptions/delays | 1/2 (50.0%) | 6/6 (100.0%) | 8/13 (61.5%) | 15/21 (71.4%) |
| No. of dose interruptions/delays | 1 | 10 | 36 | 47 |
| No. of dose interruptions/delays per participant | | | | |
| 1 | 1/1 (100.0%) | 2/6 (33.3%) | 2/8 (25.0%) | 5/15 (33.3%) |
| 2 | 0 | 4/6 (66.7%) | 1/8 (12.5%) | 5/15 (33.3%) |
| 3 | 0 | 0 | 2/8 (25.0%) | 2/15 (13.3%) |
| 4 | 0 | 0 | 1/8 (12.5%) | 1/15 (6.7%) |
| 6 | 0 | 0 | 1/8 (12.5%) | 1/15 (6.7%) |
| 16 | 0 | 0 | 1/8 (12.5%) | 1/15 (6.7%) |
| Primary reason for interruptions/delays: | | | | |
| Adverse event | 1/1 (100.0%) | 10/10 (100.0%) | 29/36 (80.6%) | 40/47 (85.1%) |
| Other | 0 | 0 | 7/36 (19.4%) | 7/47 (14.9%) |

SAF = Safety analysis set
Source: Table 14.3/7b

**Adverse events**

All treated participants (escalation: N=41; expansion: N=21) were evaluable for the analysis of safety.

Table 15 summarizes the incidences and main characteristics of TEAEs reported in participants in the escalation phase of the study as of the final data release of the clinical database (clean database 05 APR 2024).

All 41 treated participants in the escalation phase of the study experienced ≥1 TEAE, and 40 participants (97.6%) reported ≥1 regorafenib-related TEAE. In the escalation phase, 23 participants (56.1%) experienced ≥1 TESAE (treatment-emergent serious adverse event), and 7 (17.1%) experienced ≥1 drug-related TESAE. The majority of the 41 escalation participants (34; 82.9%) experienced ≥1 TEAE of worst Grade 3 or higher. The severity of drug-related TEAEs by worst grade was most commonly moderate (Grade 2: 22 participants, 53.7%). Fifteen participants (36.6%) experienced ≥1 drug-related TEAE of worst Grade 3 or Grade 4. No Grade 5 drug-related TEAEs were reported.

*Table 15 Overview of treatment-emergent adverse events (Escalation; SAF)*

| | Regorafenib Level 1 (60 mg/m$^2$) N=6; n (%) | Regorafenib Level 2 (72 mg/m$^2$) N=14; n (%) | Regorafenib Level 3 (82 mg/m$^2$) N=14; n (%) | Regorafenib Level 4 (93 mg/m$^2$) N=7; n (%) | Total N=41; n (%) |
|---|---|---|---|---|---|
| **Any TEAE** | **6 (100.0)** | **14 (100.0)** | **14 (100.0)** | **7 (100.0)** | **41 (100.0)** |
| **Worst grade: 1** | 0 | 0 | 0 | 0 | 0 |
| **2** | 1 (16.7) | 2 (14.3) | 1 (7.1) | 3 (42.9) | 7 (17.1) |
| **3** | 3 (50.0) | 3 (21.4) | 9 (64.3) | 4 (57.1) | 19 (46.3) |
| **4** | 1 (16.7) | 4 (28.6) | 2 (14.3) | 0 | 7 (17.1) |
| **5 (death)** | 1 (16.7) | 5 (35.7) | 2 (14.3) | 0 | 8 (19.5) |
| **≥3** | 5 (83.3) | 12 (85.7) | 13 (92.9) | 4 (57.1) | 34 (82.9) |
| Serious | 3 (50.0) | 10 (71.4) | 9 (64.3) | 1 (14.3) | 23 (56.1) |
| Leading to dose modification [a] | 3 (50.0) | 11 (78.6) | 7 (50.0) | 5 (71.4) | 26 (63.4) |
| Leading to permanent discontinuation of regorafenib | 1 (16.7) | 3 (21.4) | 1 (7.1) | 0 | 5 (12.2) |
| Related to protocol-required procedure | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| **Any regorafenib-related TEAE** | **6 (100.0)** | **14 (100.0)** | **14 (100.0)** | **6 (85.7)** | **40 (97.6)** |
| **Worst grade: 1** | 0 | 1 (7.1) | 2 (14.3) | 0 | 3 (7.3) |
| **2** | 5 (83.3) | 9 (64.3) | 5 (35.7) | 3 (42.9) | 22 (53.7) |
| **3** | 0 | 3 (21.4) | 5 (35.7) | 3 (42.9) | 11 (26.8) |
| **4** | 1 (16.7) | 1 (7.1) | 2 (14.3) | 0 | 4 (9.8) |
| **5 (death)** | 0 | 0 | 0 | 0 | 0 |
| **≥3** | 1 (16.7) | 4 (28.6) | 7 (50.0) | 3 (42.9) | 15 (36.6) |
| Serious | 0 | 5 (35.7) | 1 (7.1) | 1 (14.3) | 7 (17.1) |
| Leading to dose modification [a] | 1 (16.7) | 8 (57.1) | 6 (42.9) | 5 (71.4) | 20 (48.8) |
| Leading to permanent discontinuation of regorafenib | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| Related to protocol-required procedure | 0 | 0 | 0 | 0 | 0 |

SAF = Safety analysis set; TEAE = Treatment-emergent adverse event
[a] Modifications include dose delays, interruptions and reductions.
"Any adverse event" also includes participants with grades not available for all adverse events.
Table contains deaths (Grade 5 events) only if due to a TEAE.
Source: Table 14.3.1/1a

**Brief summary of adverse events (Expansion phase)**

Table 16 summarizes the incidences and main characteristics of TEAEs reported in participants of the expansion phase of the study as of the final data release of the clinical database (clean database 05 APR 2024).

All 21 treated participants of the expansion phase of the study experienced ≥1 TEAE, and all of them experienced ≥1 TEAE rated as drug-related (irrespective of the drug). In accordance with the high incidence of drug-related TEAEs, dose modifications due to drug-related TEAEs occurred in 85.7% of the participants. Five participants (23.8%) permanently discontinued at least 1 of the 3 drugs because of TEAEs.

In most participants (20/21; 95.2%), the worst grade TEAEs (any TEAEs, including drug-related ones) were CTCAE (v. 4.0) Grade 3 or higher. TESAEs occurred in 16 participants (76.2%), and in half of them (8 participants [38.1%]), a causal relationship to at least 1 of the 3 drugs was reported.

Two participants reported a Grade 5 event (‘cardiac arrest’ and ‘death NOS’); neither was assessed as drug-related.

*Table 16 Overview of treatment-emergent adverse events (Expansion; SAF)*

| | | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|---|
| **Any TEAE** | | **2 (100.0)** | **6 (100.0)** | **13 (100.0)** | **21 (100.0)** |
| **Worst grade:** | **1** | 0 | 0 | 0 | 0 |
| | **2** | 0 | 0 | 1 (7.7) | 1 (4.8) |
| | **3** | 0 | 3 (50.0) | 8 (61.5) | 11 (52.4) |
| | **4** | 2 (100.0) | 2 (33.3) | 3 (23.1) | 7 (33.3) |
| | **5 (death)** | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| | **≥3** | 2 (100.0) | 6 (100.0) | 12 (92.3) | 20 (95.2) |
| Serious | | 2 (100.0) | 5 (83.3) | 9 (69.2) | 16 (76.2) |
| Leading to dose modification [a] | | 2 (100.0) | 6 (100.0) | 12 (92.3) | 20 (95.2) |
| Leading to permanent discontinuation of study drug | | 1 (50.0) | 1 (16.7) | 3 (23.1) | 5 (23.8) |
| | Regorafenib | 0 | 1 (16.7) | 2 (15.4) | 3 (14.3) |
| | Irinotecan | 1 (50.0) | 1 (16.7) | 3 (23.1) | 5 (23.8) |
| | Vincristine | 1 (50.0) | 1 (16.7) | 3 (23.1) | 5 (23.8) |
| Related to protocol-required procedure | | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |
| **Any drug-related TEAE** | | **2 (100.0)** | **6 (100.0)** | **13 (100.0)** | **21 (100.0)** |
| Related to: | Regorafenib | 2 (100.0) | 6 (100.0) | 11 (84.6) | 19 (90.5) |
| | Irinotecan | 2 (100.0) | 6 (100.0) | 12 (92.3) | 20 (95.2) |
| | Vincristine | 2 (100.0) | 6 (100.0) | 9 (69.2) | 17 (81.0) |
| **Worst grade:** | **1** | 0 | 0 | 2 (15.4) | 2 (9.5) |
| | **2** | 0 | 0 | 0 | 0 |
| | **3** | 0 | 3 (50.0) | 8 (61.5) | 11 (52.4) |
| | **4** | 2 (100.0) | 3 (50.0) | 3 (23.1) | 8 (38.1) |
| | **5 (death)** | 0 | 0 | 0 | 0 |
| | **≥3** | 2 (100.0) | 6 (100.0) | 11 (84.6) | 19 (90.5) |
| Serious | | 2 (100.0) | 2 (33.3) | 4 (30.8) | 8 (38.1) |
| Leading to dose modification [a] | | 2 (100.0) | 6 (100.0) | 10 (76.9) | 18 (85.7) |
| Leading to permanent discontinuation of study drug | | 1 (50.0) | 0 | 2 (15.4) | 3 (14.3) |
| | Regorafenib | 0 | 0 | 1 (7.7) | 1 (4.8) |
| | Irinotecan | 1 (50.0) | 0 | 2 (15.4) | 3 (14.3) |
| | Vincristine | 1 (50.0) | 0 | 2 (15.4) | 3 (14.3) |
| Related to protocol-required procedure | | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |

SAF = Safety analysis set; TEAE = Treatment-emergent adverse event
[a] Modifications include dose delays, interruptions and reductions.
"Any adverse event" also includes participants with grades not available for all adverse events.
Table contains deaths (Grade 5 events) only if due to a TEAE.
Source: Table 14.3.1/1b

**All treatment-emergent adverse events (Escalation phase)**

All 41 treated escalation participants (100%) experienced TEAE(s). Most commonly (≥50% in the total group), the TEAEs referred to the SOCs "investigations" (87.8%), "skin and subcutaneous tissue disorders" (85.4%), "gastrointestinal disorders" and "general disorders and administration site conditions" (82.9% each), "metabolism and nutrition disorders" and "nervous system disorders" (61%

each), "blood and lymphatic system disorders", "infections and infestations", and "respiratory, thoracic and mediastinal disorders" (53.7% each).

Table 17 shows the TEAEs reported by ≥10% of 41 treated escalation participants. The most frequent (≥20% in the total group) TEAEs were fatigue (54%), vomiting (51.2%), rash (51%), pyrexia (48.8%), headache (43.9%), AST increased and nausea (41.5% each), ALT increased, abdominal pain, and hyperbilirubinemia (39% each), thrombocytopenia (37%), palmar-plantar erythrodysaesthesia syndrome (HFSR) (34%), constipation (29.3%), lymphopenia (29%), neutropenia (27%), diarrhea, decreased appetite, and erythema (26.8% each), anemia (24.4%), and hyponatremia (22%).

Overall, there were no apparent differences between the dose levels with regard to the incidence and pattern of TEAEs.

*Table 17 TEAEs reported in ≥10% in the total group (Escalation; SAF)*

| **Primary SOC**<br>PT<br>**MedDRA v. 26.1** | **Level 1 (60 mg/m²) N=6 n (%)** | **Level 2 (72 mg/m²) N=14 n (%)** | **Level 3 (82 mg/m²) N=14 n (%)** | **Level 4 (93 mg/m²) N=7 n (%)** | **Total N=41 n (%)** |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | **2 (33.3)** | **9 (64.3)** | **8 (57.1)** | **3 (42.9)** | **22 (53.7)** |
| Anaemia | 0 | 3 (21.4) | 5 (35.7) | 2 (28.6) | 10 (24.4) |
| Lymphopenia [a] | 2 (33) | 3 (21) | 6 (43) | 1 (14) | 12 (29) |
| Neutropenia [b] | 1 (17) | 7 (50) | 3 (21) | 0 | 11 (27) |
| Thrombocytopenia [c] | 2 (33) | 6 (43) | 5 (36) | 2 (29) | 15 (37) |
| **Cardiac disorders** | **2 (33.3)** | **2 (14.3)** | **3 (21.4)** | **1 (14.3)** | **8 (19.5)** |
| Tachycardia [d] | 1 (17) | 1 (7) | 3 (21) | 1 (14) | 6 (15) |
| **Endocrine disorders** | **1 (16.7)** | **4 (28.6)** | **3 (21.4)** | **0** | **8 (19.5)** |
| Hypothyroidism | 0 | 3 (21.4) | 3 (21.4) | 0 | 6 (14.6) |
| Eye disorders | 1 (16.7) | 4 (28.6) | 2 (14.3) | 1 (14.3) | 8 (19.5) |
| **Gastrointestinal disorders** | **5 (83.3)** | **11 (78.6)** | **12 (85.7)** | **6 (85.7)** | **34 (82.9)** |
| Abdominal pain [e] | 2 (33) | 3 (21) | 7 (50) | 4 (57) | 16 (39) |
| Constipation | 1 (16.7) | 3 (21.4) | 5 (35.7) | 3 (42.9) | 12 (29.3) |
| Diarrhoea | 1 (16.7) | 3 (21.4) | 5 (35.7) | 2 (28.6) | 11 (26.8) |
| Dysphagia | 2 (33.3) | 2 (14.3) | 1 (7.1) | 1 (14.3) | 6 (14.6) |
| Nausea | 2 (33.3) | 6 (42.9) | 4 (28.6) | 5 (71.4) | 17 (41.5) |
| Vomiting | 3 (50.0) | 8 (57.1) | 9 (64.3) | 1 (14.3) | 21 (51.2) |
| **General disorders and administration site conditions** | **6 (100.0)** | **11 (78.6)** | **11 (78.6)** | **6 (85.7)** | **34 (82.9)** |
| Chest pain | 0 | 3 (21.4) | 1 (7.1) | 1 (14.3) | 5 (12.2) |
| Death | 1 (16.7) | 4 (28.6) | 1 (7.1) | 0 | 6 (14.6) |
| Fatigue [f] | 5 (83) | 8 (57) | 5 (36) | 4 (57) | 22 (54) |
| Pyrexia | 1 (16.7) | 7 (50.0) | 8 (57.1) | 4 (57.1) | 20 (48.8) |
| **Hepatobiliary disorders** | **2 (33.3)** | **2 (14.3)** | **2 (14.3)** | **1 (14.3)** | **7 (17.1)** |
| Hyperbilirubinaemia [g] | 3 (50) | 5 (36) | 8 (57) | 0 | 16 (39) |
| **Infections and infestations** | **3 (50.0)** | **8 (57.1)** | **8 (57.1)** | **3 (42.9)** | **22 (53.7)** |
| Urinary tract infection | 0 | 1 (7.1) | 1 (7.1) | 3 (42.9) | 5 (12.2) |
| **Investigations** | **4 (66.7)** | **13 (92.9)** | **13 (92.9)** | **6 (85.7)** | **36 (87.8)** |
| ALT increased | 1 (16.7) | 5 (35.7) | 5 (35.7) | 5 (71.4) | 16 (39.0) |
| AST increased | 1 (16.7) | 5 (35.7) | 7 (50.0) | 4 (57.1) | 17 (41.5) |
| Gamma-glutamyltransferase increased | 1 (16.7) | 2 (14.3) | 0 | 2 (28.6) | 5 (12.2) |
| Weight decreased | 0 | 3 (21.4) | 4 (28.6) | 0 | 7 (17.1) |
| **Metabolism and nutrition disorders** | **3 (50.0)** | **9 (64.3)** | **8 (57.1)** | **5 (71.4)** | **25 (61.0)** |
| Decreased appetite | 1 (16.7) | 6 (42.9) | 1 (7.1) | 3 (42.9) | 11 (26.8) |

| Primary SOC<br>PT<br><br>MedDRA v. 26.1 | Level 1<br>(60 mg/m²)<br>N=6<br>n (%) | Level 2<br>(72 mg/m²)<br>N=14<br>n (%) | Level 3<br>(82 mg/m²)<br>N=14<br>n (%) | Level 4<br>(93 mg/m²)<br>N=7<br>n (%) | Total<br><br>N=41<br>n (%) |
|---|---|---|---|---|---|
| Hyponatraemia | 1 (16.7) | 3 (21.4) | 3 (21.4) | 2 (28.6) | 9 (22.0) |
| Hypophosphataemia | 2 (33.3) | 1 (7.1) | 4 (28.6) | 1 (14.3) | 8 (19.5) |
| **Musculoskeletal and connective tissue disorders** | **2 (33.3)** | **8 (57.1)** | **7 (50.0)** | **2 (28.6)** | **19 (46.3)** |
| Arthralgia | 0 | 3 (21.4) | 2 (14.3) | 0 | 5 (12.2) |
| Back pain | 0 | 2 (14.3) | 2 (14.3) | 1 (14.3) | 5 (12.2) |
| Pain in extremity | 1 (16.7) | 3 (21.4) | 2 (14.3) | 2 (28.6) | 8 (19.5) |
| **Nervous system disorders** | **6 (100.0)** | **9 (64.3)** | **7 (50.0)** | **3 (42.9)** | **25 (61.0)** |
| Headache | 6 (100.0) | 5 (35.7) | 5 (35.7) | 2 (28.6) | 18 (43.9) |
| **Respiratory, thoracic and mediastinal disorders** | **4 (66.7)** | **11 (78.6)** | **5 (35.7)** | **2 (28.6)** | **22 (53.7)** |
| Cough | 1 (16.7) | 4 (28.6) | 1 (7.1) | 1 (14.3) | 7 (17.1) |
| Dyspnoea | 1 (16.7) | 2 (14.3) | 3 (21.4) | 1 (14.3) | 7 (17.1) |
| Epistaxis | 2 (33.3) | 3 (21.4) | 2 (14.3) | 1 (14.3) | 8 (19.5) |
| **Skin and subcutaneous tissue disorders** | **6 (100.0)** | **12 (85.7)** | **11 (78.6)** | **6 (85.7)** | **35 (85.4)** |
| Alopecia | 0 | 1 (7.1) | 5 (35.7) | 0 | 6 (14.6) |
| Dry skin | 0 | 1 (7.1) | 2 (14.3) | 2 (28.6) | 5 (12.2) |
| Erythema | 4 (66.7) | 3 (21.4) | 4 (28.6) | 0 | 11 (26.8) |
| Palmar-plantar erythrodysaesthesia syndrome (HFSR) [h] | 1 (17) | 6 (43) | 4 (29) | 3 (43) | 14 (34) |
| Pruritus [i] | 2 (33) | 0 | 3 (21) | 1 (14) | 6 (15) |
| Rash [j] | 1 (17) | 9 (64) | 6 (43) | 5 (71) | 21 (51) |
| **Vascular disorders** | **1 (16.7)** | **4 (28.6)** | **4 (28.6)** | **1 (14.3)** | **10 (24.4)** |
| Hypertension | 1 (16.7) | 3 (21.4) | 3 (21.4) | 1 (14.3) | 8 (19.5) |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; HFSR = Hand-foot skin reaction (hand-foot syndrome); MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event

[a] Includes PTs lymphopenia and lymphocyte count decreased (Table 14.3.1/4a).

[b] Includes PTs neutropenia and neutrophil count decreased (Table 14.3.1/4a).

[c] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/4a).

[d] Includes PTs tachycardia and sinus tachycardia (Table 14.3.1/4a).

[e] Gastrointestinal and abdominal pains, includes PTs abdominal pain and abdominal pain upper (Table 14.3.1/4a).

[f] Decreased general strength and energy, includes PTs fatigue and asthenia (Table 14.3.1/4a).

[g] Increase in bilirubin, includes PTs blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased (Table 14.3.1/4a).

[h] Hand-foot syndrome, includes PTs palmar-plantar erythrodysaesthesia syndrome and palmar erythema (Table 14.3.1/4a).

[i] Includes PTs pruritus and pruritus allergic (Table 14.3.1/4a).

[j] Includes PTs rash, rash maculo-papular, rash macular, and rash morbilliform (Table 14.3.1/4a).

Source: Table 14.3.1/2a and Table 14.3.1/4a

**All treatment-emergent adverse events (Expansion phase)**

Table 18 shows the TEAEs reported by ≥10% of 21 treated expansion participants in the SAF. The most frequent (≥30% in the total group) TEAEs were diarrhoea (95.2%), anaemia (71.4%), neutropenia and abdominal pain (71% each), pyrexia (66.7%), vomiting (61.9%), decreased appetite (57.1%),

thrombocytopenia (57%), rash (48%), nausea (47.6%), fatigue (43%), ALT increased and AST increased (42.9% each), weight decreased, hypokalemia, and dry skin (38.1% each), leukopenia (38%), and gamma-glutamyltransferase increased and hypophosphatemia (33.3% each).

Overall, there were no apparent differences among treatment groups with regard to the incidence and pattern of TEAEs.

*Table 18 TEAEs reported in ≥10% in the total group (Expansion; SAF)*

| **Primary SOC/** PT **MedDRA v. 26.1** | **Reg72 conc+VI (N=2) n (%)** | **Reg72 seq+VI (N=6) n (%)** | **Reg82 seq+VI (N=13) n (%)** | **Total (N=21) n (%)** |
|---|---|---|---|---|
| **Any category/ any event** | **2 (100.0)** | **6 (100.0)** | **13 (100.0)** | **21 (100.0)** |
| **Blood and lymphatic system disorders** | **2 (100.0)** | **4 (66.7)** | **10 (76.9)** | **16 (76.2)** |
| Anaemia | 2 (100.0) | 4 (66.7) | 9 (69.2) | 15 (71.4) |
| Febrile neutropenia | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Leukopenia [a] | 1 (50) | 3 (50) | 4 (31) | 8 (38) |
| Neutropenia [b] | 2 (100) | 6 (100) | 7 (54) | 15 (71) |
| Lymphopenia [c] | 1 (50) | 1 (17) | 1 (8) | 3 (14) |
| Thrombocytopenia [d] | 1 (50) | 4 (67) | 7 (54) | 12 (57) |
| **Cardiac disorders** | **0** | **2 (33.3)** | **4 (30.8)** | **6 (28.6)** |
| Tachycardia [e] | 0 | 0 | 4 (31) | 4 (19) |
| **Gastrointestinal disorders** | **2 (100.0)** | **6 (100.0)** | **13 (100.0)** | **21 (100.0)** |
| Abdominal distension | 0 | 1 (16.7) | 2 (15.4) | 3 (14.3) |
| Abdominal pain [f] | 2 (100) | 5 (83) | 8 (62) | 15 (71) |
| Constipation | 1 (50.0) | 1 (16.7) | 2 (15.4) | 4 (19.0) |
| Diarrhoea | 2 (100.0) | 5 (83.3) | 13 (100.0) | 20 (95.2) |
| Dyspepsia | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Nausea | 1 (50.0) | 3 (50.0) | 6 (46.2) | 10 (47.6) |
| Stomatitis | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Toothache | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Vomiting | 2 (100.0) | 3 (50.0) | 8 (61.5) | 13 (61.9) |
| **General disorders and administration site conditions** | **2 (100.0)** | **6 (100.0)** | **10 (76.9)** | **18 (85.7)** |
| Fatigue [g] | 2 (100) | 3 (50) | 4 (31) | 9 (43) |
| Pain | 0 | 1 (16.7) | 4 (30.8) | 5 (23.8) |
| Pyrexia | 1 (50.0) | 4 (66.7) | 9 (69.2) | 14 (66.7) |
| **Infections and infestations** | **1 (50.0)** | **6 (100.0)** | **7 (53.8)** | **14 (66.7)** |
| Upper respiratory tract infection | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| **Investigations** | **2 (100.0)** | **6 (100.0)** | **11 (84.6)** | **19 (90.5)** |
| ALT increased | 2 (100.0) | 3 (50.0) | 4 (30.8) | 9 (42.9) |
| AST increased | 2 (100.0) | 3 (50.0) | 4 (30.8) | 9 (42.9) |
| Blood bilirubin increased [h] | 1 (50) | 2 (33) | 2 (15) | 5 (24) |
| Blood creatinine increased | 0 | 0 | 3 (23.1) | 3 (14.3) |
| Blood thyroid stimulating hormone increased | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |
| Gamma-glutamyltransferase increased | 2 (100.0) | 2 (33.3) | 3 (23.1) | 7 (33.3) |
| Weight decreased | 1 (50.0) | 2 (33.3) | 5 (38.5) | 8 (38.1) |
| **Metabolism and nutrition disorders** | **2 (100.0)** | **5 (83.3)** | **10 (76.9)** | **17 (81.0)** |
| Decreased appetite | 2 (100.0) | 5 (83.3) | 5 (38.5) | 12 (57.1) |
| Hypocalcaemia | 1 (50.0) | 0 | 3 (23.1) | 4 (19.0) |
| Hypokalaemia | 2 (100.0) | 1 (16.7) | 5 (38.5) | 8 (38.1) |
| Hyponatraemia | 1 (50.0) | 1 (16.7) | 2 (15.4) | 4 (19.0) |
| Hypophosphataemia | 2 (100.0) | 2 (33.3) | 3 (23.1) | 7 (33.3) |

| Primary SOC/ PT<br>MedDRA v. 26.1 | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|
| **Musculoskeletal and connective tissue disorders** | **1 (50.0)** | **4 (66.7)** | **4 (30.8)** | **9 (42.9)** |
| Myalgia | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |
| Pain in extremity | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Pain in jaw | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| **Nervous system disorders** | **2 (100.0)** | **3 (50.0)** | **6 (46.2)** | **11 (52.4)** |
| Headache | 1 (50.0) | 2 (33.3) | 2 (15.4) | 5 (23.8) |
| Lethargy | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |
| **Renal and urinary disorders** | **1 (50.0)** | **2 (33.3)** | **4 (30.8)** | **7 (33.3)** |
| Leukocyturia | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Proteinuria | 1 (50.0) | 2 (33.3) | 2 (15.4) | 5 (23.8) |
| **Respiratory, thoracic and mediastinal disorders** | **1 (50.0)** | **2 (33.3)** | **5 (38.5)** | **8 (38.1)** |
| Cough | 1 (50.0) | 2 (33.3) | 3 (23.1) | 6 (28.6) |
| Epistaxis | 0 | 1 (16.7) | 3 (23.1) | 4 (19.0) |
| **Skin and subcutaneous tissue disorders** | **2 (100.0)** | **6 (100.0)** | **10 (76.9)** | **18 (85.7)** |
| Alopecia | 0 | 2 (33.3) | 4 (30.8) | 6 (28.6) |
| Dry skin | 0 | 2 (33.3) | 6 (46.2) | 8 (38.1) |
| Palmar-plantar erythro-dysaesthesia syndrome (HFSR) | 0 | 3 (50.0) | 0 | 3 (14.3) |
| Pruritus | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Rash [i] | 2 (100) | 3 (50) | 5 (38) | 10 (48) |
| **Vascular disorders** | **1 (50.0)** | **3 (50.0)** | **4 (30.8)** | **8 (38.1)** |
| Hypertension | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; HFSR = Hand-foot skin reaction (hand-foot syndrome); MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event

[a] Leukopenia (not further specified), includes PT leukopenia and white blood cell count decreased (Table 14.3.1/8b).

[b] Includes PTs neutropenia and neutrophil count decreased (Table 14.3.1/8b).

[c] Includes PTs lymphopenia and lymphocyte count decreased (Table 14.3.1/8b).

[d] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/8b).

[e] Includes PTs tachycardia and sinus tachycardia (Table 14.3.1/8b).

[f] Gastrointestinal and abdominal pains, includes PTs abdominal pain, abdominal pain lower, and abdominal pain upper (Table 14.3.1/8b).

[g] Decreased general strength and energy, includes PTs fatigue and asthenia (Table 14.3.1/8b).

[h] Increase in bilirubin, includes PTs blood bilirubin increased and hyperbilirubinemia (Table 14.3.1/8b).

[i] Includes PTs rash and rash maculo-papular (Table 14.3.1/8b).

Source: Table 14.3.1/2b and Table 14.3.1/8b

**Severity of treatment-emergent adverse events (Escalation phase)**

Table 19 shows the number of escalation participants with at least one TEAE of worst Grade ≥3. Among them, 19 of 41 participants (46.3%) experienced TEAEs of worst Grade 3; 7 participants (17.1%) of worst Grade 4; and 8 participants (19.5%) of worst Grade 5 (i.e., TEAEs with fatal outcomes) (Table 14.3.1/1a). None of the fatal events were considered to be related to study treatment; ).

The most common TEAEs of worst Grade 3 or above (Grades 3/4/5), irrespective of relationship to study drugs, occurring in >2 participants of all 41 treated escalation participants were death (6

participants; 14.6%), thrombocytopenia (5 participants; 12%), lymphopenia (4 participants; 10%); headache (4 participants; 9.8%), ALT increased, dyspnea, hydrocephalus, lymphopenia, neutropenia, rash maculo-papular, and vomiting (3 participants; 7.3% each)).

*Table 19 TEAEs of Grade ≥3 (any Grade ≥3 in >2 participants in the total group) (Escalation; SAF)*

| **Primary SOC/ PT**<br>**MedDRA v. 26.1** | **Worst CTCAE grade** | **Level 1 (60 mg/m²) N=6 n (%)** | **Level 2 (72 mg/m²) N=14 n (%)** | **Level 3 (82 mg/ m²) N=14 n (%)** | **Level 4 (93 mg/ m²) N=7 n (%)** | **Total N=41 n (%)** |
|---|---|---|---|---|---|---|
| **Any category/any event** | Grade 3 | 3 (50.0) | 3 (21.4) | 9 (64.3) | 4 (57.1) | 19 (46.3) |
| | Grade 4 | 1 (16.7) | 4 (28.6) | 2 (14.3) | 0 | 7 (17.1) |
| | Grade 5 | 1 (16.7) | 5 (35.7) | 2 (14.3) | 0 | 8 (19.5) |
| | Total | 5 (83.3) | 12 (85.7) | 13 (92.9) | 4 (57.1) | 34 (82.9) |
| **Blood and lymphatic system disorders** | **Grade 3** | **0** | **3 (21.4)** | **1 (7.1)** | **2 (28.6)** | **6 (14.6)** |
| | **Grade 4** | **1 (16.7)** | **1 (7.1)** | **1 (7.1)** | **0** | **3 (7.3)** |
| Lymphopenia [a] | Grade 3 | 0 | 1 (7) | 2 (14) | 1 (14) | 4 (10) |
| Neutropenia | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| Neutropenia | Grade 4 | 0 | 1 (7.1) | 1 (7.1) | 0 | 2 (4.9) |
| Thrombocytopenia [b] | Grade 3 | 0 | 1 (7) | 0 | 1 (14) | 2 (5) |
| Thrombocytopenia [b] | Grade 4 | 1 (17) | 1 (7) | 1 (7) | 0 | 3 (7) |
| **Gastrointestinal disorders** | **Grade 3** | **1 (16.7)** | **1 (7.1)** | **3 (21.4)** | **1 (14.3)** | **6 (14.6)** |
| Vomiting | Grade 3 | 1 (16.7) | 0 | 2 (14.3) | 0 | 3 (7.3) |
| **General disorders and administration site conditions** | **Grade 3** | **0** | **0** | **1 (7.1)** | **2 (28.6)** | **3 (7.3)** |
| | **Grade 5** | **1 (16.7)** | **4 (28.6)** | **1 (7.1)** | **0** | **6 (14.6)** |
| Death | Grade 5 | 1 (16.7) | 4 (28.6) | 1 (7.1) | 0 | 6 (14.6) |
| **Investigations** | **Grade 3** | **1 (16.7)** | **1 (7.1)** | **4 (28.6)** | **2 (28.6)** | **8 (19.5)** |
| ALT increased | Grade 3 | 1 (16.7) | 1 (7.1) | 0 | 1 (14.3) | 3 (7.3) |
| **Nervous system disorders** | **Grade 3** | **2 (33.3)** | **3 (21.4)** | **1 (7.1)** | **0** | **6 (14.6)** |
| Headache | Grade 3 | 2 (33.3) | 2 (14.3) | 0 | 0 | 4 (9.8) |
| Hydrocephalus | Grade 3 | 2 (33.3) | 1 (7.1) | 0 | 0 | 3 (7.3) |
| **Respiratory, thoracic and mediastinal disorders** | **Grade 3** | **0** | **2 (14.3)** | **2 (14.3)** | **0** | **4 (9.8)** |
| Dyspnoea | Grade 3 | 0 | 2 (14.3) | 1 (7.1) | 0 | 3 (7.3) |
| **Skin and subcutaneous tissue disorders** | **Grade 3** | **0** | **3 (21.4)** | **2 (14.3)** | **1 (14.3)** | **6 (14.6)** |
| Rash maculo-papular [c] | Grade 3 | 0 | 3 (21) | 1 (7) | 0 | 4 (10) |

ALT = Alanine aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event

[a] Includes PTs lymphopenia and lymphocyte count decreased (Table 14.3.1/7a).

[b] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/7a).

[c] Includes PTs rash and rash maculo-papular (Table 14.3.1/7a).

Source: Table 14.3.1/1a, Table 14.3.1/2a and Table 14.3.1/7a

**Severity of treatment-emergent adverse events (Expansion phase)**

Table 20 displays the number of expansion participants with ≥1 TEAE of worst Grade ≥3. Among them, 11 of 21 participants (52.4%) experienced TEAEs of worst Grade 3, 7 participants (33.3%) of worst Grade 4, and 2 participants (9.5%) of worst Grade 5 (i.e., TEAEs with fatal outcomes; 1 case each of cardiac arrest and death, neither were considered related to treatment;

The most common TEAEs of worst Grade 3 or above (Grades 3/4/5), irrespective of relationship to study drugs, occurring in ³20% of all 21 treated expansion participants were neutropenia (71%), anaemia (38.1%), leukopenia and thrombocytopenia (33% each), abdominal pain (24%), and ALT increased (23.8%).

*Table 20 TEAEs of Grade ≥3 (any Grade ≥3 in >2 participants in the total group) (Expansion; SAF)*

| **Primary SOC/ PT**<br>**MedDRA v. 26.1** | **Worst CTCAE grade** | **Reg72 conc+VI (N=2) n (%)** | **Reg72 seq+VI (N=6) n (%)** | **Reg82 seq+VI (N=13) n (%)** | **Total (N=21) n (%)** |
|---|---|---|---|---|---|
| **Any category/ any event** | **Grade 3** | **0** | **3 (50.0)** | **8 (61.5)** | **11 (52.4)** |
| | **Grade 4** | **2 (100.0)** | **2 (33.3)** | **3 (23.1)** | **7 (33.3)** |
| | **Grade 5** | **0** | **1 (16.7)** | **1 (7.7)** | **2 (9.5)** |
| | **Total** | **2 (100.0)** | **6 (100.0)** | **12 (92.3)** | **20 (95.2)** |
| **Blood and lymphatic system disorders** | **Grade 3** | **1 (50.0)** | **2 (33.3)** | **8 (61.5)** | **11 (52.4)** |
| | **Grade 4** | **1 (50.0)** | **2 (33.3)** | **2 (15.4)** | **5 (23.8)** |
| | **Any Grade ≥3** | **2 (100.0)** | **4 (66.7)** | **10 (76.9)** | **16 (76.2)** |
| Anaemia | Grade 3 | 0 | 1 (16.7) | 7 (53.8) | 8 (38.1) |
| | Any Grade ≥3 | 0 | 1 (16.7) | 7 (53.8) | 8 (38.1) |
| Febrile neutropenia | Grade 3 | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| | Any Grade ≥3 | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Leukopenia [a] | Grade 3 | 1 (50) | 3 (50) | 3 (23) | 7 (33) |
| | Any Grade ≥3 | 1 (50) | 3 (50) | 3 (23) | 7 (33) |
| Neutropenia [b] | Grade 3 | 0 | 4 (67) | 4 (31) | 8 (38) |
| | Grade 4 | 2 (100) | 2 (33) | 3 (23) | 7 (33) |
| | Any Grade ≥3 | 2 (100) | 6 (100) | 7 (54) | 15 (71) |
| Thrombocytopenia [c] | Grade 3 | 1 (50) | 0 | 4 (31) | 5 (24) |
| | Grade 4 | 0 | 2 (33) | 0 | 2 (10) |
| | Any Grade ≥3 | 1 (50) | 2 (33) | 4 (31) | 7 (33) |
| **Gastrointestinal disorders** | **Grade 3** | **2 (100.0)** | **3 (50.0)** | **5 (38.5)** | **10 (47.6)** |
| | **Any Grade ≥3** | **2 (100.0)** | **3 (50.0)** | **5 (38.5)** | **10 (47.6)** |
| Abdominal pain [d] | Grade 3 | 2 (100) | 2 (33) | 1 (8) | 5 (24) |
| | Any Grade ≥3 | 2 (100) | 2 (33) | 1 (8) | 5 (24) |
| Diarrhoea | Grade 3 | 0 | 1 (16.7) | 3 (23.1) | 4 (19.0) |
| | Any Grade ≥3 | 0 | 1 (16.7) | 3 (23.1) | 4 (19.0) |
| Vomiting | Grade 3 | 2 (100.0) | 0 | 2 (15.4) | 4 (19.0) |
| | Any Grade ≥3 | 2 (100.0) | 0 | 2 (15.4) | 4 (19.0) |

| Primary SOC/ PT<br><br>MedDRA v. 26.1 | Worst CTCAE grade | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|---|
| **Investigations** | **Grade 3** | **1 (50.0)** | **3 (50.0)** | **4 (30.8)** | **8 (38.1)** |
| | **Grade 4** | **1 (50.0)** | **2 (33.3)** | **1 (7.7)** | **4 (19.0)** |
| | **Any Grade ≥3** | **2 (100.0)** | **5 (83.3)** | **5 (38.5)** | **12 (57.1)** |
| ALT increased | Grade 3 | 2 (100.0) | 2 (33.3) | 1 (7.7) | 5 (23.8) |
| | Any Grade ≥3 | 2 (100.0) | 2 (33.3) | 1 (7.7) | 5 (23.8) |
| AST increased | Grade 3 | 2 (100.0) | 2 (33.3) | 0 | 4 (19.0) |
| | Any Grade ≥3 | 2 (100.0) | 2 (33.3) | 0 | 4 (19.0) |
| **Metabolism and nutrition disorders** | **Grade 3** | **1 (50.0)** | **1 (16.7)** | **3 (23.1)** | **5 (23.8)** |
| | **Any Grade ≥3** | **1 (50.0)** | **1 (16.7)** | **3 (23.1)** | **5 (23.8)** |
| Hypokalaemia | Grade 3 | 1 (50.0) | 0 | 3 (23.1) | 4 (19.0) |
| | Any Grade ≥3 | 1 (50.0) | 0 | 3 (23.1) | 4 (19.0) |
| Hypophosphataemia | Grade 3 | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| | Any Grade ≥3 | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event
[a] Leukopenia (not further specified), includes PT leukopenia and white blood cell count decreased (Table 14.3.1/14b).
[b] Includes PTs neutropenia and neutrophil count decreased (Table 14.3.1/14b).
[c] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/14b).
[d] Gastrointestinal and abdominal pains, includes PTs abdominal pain, abdominal pain lower, and abdominal pain upper (Table 14.3.1/14b).
Source: Table 14.3.1/3b and Table 14.3.1/14b

**Drug-related treatment-emergent adverse events (Escalation)**

In total, 40 of 41 participants (97.6%) treated in the escalation phase of the study experienced ≥1 TEAE considered by the investigator as regorafenib-related. Majority of the events were of worst Grade 2 (22 participants).

Table 21 displays regorafenib-related TEAEs reported by ≥ 10% of 41 treated escalation participants.

Drug-related TEAEs occurring in ≥20% of escalation participants in the SAF were fatigue and rash (41% each), blood bilirubin increased (37%), AST increased (34.1%), palmar-plantar erythrodysaesthesia syndrome (HFSR) (34%), thrombocytopenia (32%), nausea and ALT increased (31.7% each), pyrexia (29.3%), decreased appetite (26.8%), neutropenia (24.4%), lymphopenia (22%), and abdominal pain (20%).

Table 20 displays regorafenib-related TEAEs of CTCAE Grade ≥ 3. Eleven participants (26.8%) experienced drug-related TEAE of worst CTCAE severity Grade ≥3, and 4 participants (9.8%) had drug-related TEAEs of worst Grade 4. Drug-related TEAEs of CTCAE Grade 5 did not occur.

Common drug-related TEAEs of worst Grade ≥3, occurring in ≥2 participants of all 41 treated escalation participants were thrombocytopenia (4 participants [10%]), rash maculo-papular (3 participants [7.3%]), and blood bilirubin increased, lymphopenia, and neutropenia (2 participants [5%] each). (see Table 22)

*Table 21 Regorafenib-related TEAEs (≥10% in the total group) (Escalation; SAF)*

| Primary SOC/ • PT MedDRA v. 26.1 | Level 1 (60 mg/m²) N=6 n (%) | Level 2 (72 mg/m²) N=14 n (%) | Level 3 (82 mg/m²) N=14 n (%) | Level 4 (93 mg/m²) N=7 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|
| **Blood and lymphatic system disorders** | 2 (33.3) | 7 (50.0) | 8 (57.1) | 3 (42.9) | 20 (48.8) |
| Anaemia | 0 | 2 (14.3) | 5 (35.7) | 1 (14.3) | 8 (19.5) |
| Lymphopenia [a] | 1 (17) | 2 (14) | 5 (36) | 1 (14) | 9 (22) |
| Neutropenia | 1 (16.7) | 6 (42.9) | 3 (21.4) | 0 | 10 (24.4) |
| Thrombocytopenia [b] | 2 (33) | 4 (29) | 5 (36) | 2 (29) | 13 (32) |
| **Endocrine disorders** | 1 (16.7) | 3 (21.4) | 3 (21.4) | 0 | 7 (17.1) |
| Hypothyroidism | 0 | 3 (21.4) | 3 (21.4) | 0 | 6 (14.6) |
| **Gastrointestinal disorders** | 4 (66.7) | 6 (42.9) | 8 (57.1) | 4 (57.1) | 22 (53.7) |
| Abdominal pain [c] | 1 (17) | 2 (14) | 3 (21) | 2 (29) | 8 (20) |
| Diarrhoea | 1 (16.7) | 1 (7.1) | 2 (14.3) | 2 (28.6) | 6 (14.6) |
| Nausea | 2 (33.3) | 4 (28.6) | 3 (21.4) | 4 (57.1) | 13 (31.7) |
| Vomiting | 0 | 3 (21.4) | 3 (21.4) | 1 (14.3) | 7 (17.1) |
| **General disorders and administration site conditions** | 4 (66.7) | 10 (71.4) | 7 (50.0) | 4 (57.1) | 25 (61.0) |
| Fatigue [d] | 4 (67) | 6 (43) | 3 (21) | 4 (57) | 17 (41) |
| Pyrexia | 0 | 5 (35.7) | 5 (35.7) | 2 (28.6) | 12 (29.3) |
| **Investigations** | 2 (33.3) | 10 (71.4) | 11 (78.6) | 4 (57.1) | 27 (65.9) |
| ALT increased | 0 | 4 (28.6) | 5 (35.7) | 4 (57.1) | 13 (31.7) |
| AST aminotransferase increased | 0 | 4 (28.6) | 7 (50.0) | 3 (42.9) | 14 (34.1) |
| Blood bilirubin increased [e] | 2 (33) | 5 (36) | 8 (57) | 0 | 15 (37) |
| **Metabolism and nutrition disorders** | 2 (33.3) | 7 (50.0) | 6 (42.9) | 3 (42.9) | 18 (43.9) |
| Decreased appetite | 1 (16.7) | 6 (42.9) | 1 (7.1) | 3 (42.9) | 11 (26.8) |
| Hypophosphataemia | 1 (16.7) | 1 (7.1) | 4 (28.6) | 0 | 6 (14.6) |
| **Skin and subcutaneous tissue disorders** | 6 (100.0) | 12 (85.7) | 8 (57.1) | 6 (85.7) | 32 (78.0) |
| Alopecia | 0 | 1 (7.1) | 5 (35.7) | 0 | 6 (14.6) |
| Dry skin | 0 | 1 (7.1) | 2 (14.3) | 2 (28.6) | 5 (12.2) |
| Erythema | 4 (66.7) | 1 (7.1) | 3 (21.4) | 0 | 8 (19.5) |
| Palmar-plantar erythrodysaesthesia syndrome (HFSR) [f] | 1 (17) | 6 (43) | 4 (29) | 3 (43) | 14 (34) |
| Rash [g] | 1 (17) | 6 (43) | 5 (36) | 5 (71) | 17 (41) |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; HFSR = Hand-foot skin reaction (hand-foot syndrome); MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event

[a] Includes PTs lymphopenia and lymphocyte count decreased (Table 14.3.1/5a).

[b] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/5a).

[c] Gastrointestinal and abdominal pains, includes PTs abdominal pain and abdominal pain upper (Table 14.3.1/5a).

[d] Decreased general strength and energy, includes PTs fatigue and asthenia (Table 14.3.1/5a).

[e] Increase in bilirubin, includes PTs blood bilirubin increased, hyperbilirubinemia, bilirubin conjugated increased, and blood bilirubin unconjugated increased (Table 14.3.1/5a).

[f] Hand-foot syndrome, includes PTs palmar-plantar erythrodysaesthesia syndrome and palmar erythema (Table 14.3.1/5a).

[g] Includes PTs rash and rash maculo-papular (Table 14.3.1/5a).

Source: Table 14.3.1/3a and Table 14.3.1/5a

*Table 22 Regorafenib-related TEAEs by worst CTCAE grade (Grade ≥3) (Escalation; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | Worst CTCAE grade | Level 1 (60 mg/m²) N=6 n (%) | Level 2 (72 mg/m²) N=14 n (%) | Level 3 (82 mg/m²) N=14 n (%) | Level 4 (93 mg/m²) N=7 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|
| **Any category/any event** | Grade 3 | 0 | 3 (21.4) | 5 (35.7) | 3 (42.9) | 11 (26.8) |
| | Grade 4 | 1 (16.7) | 1 (7.1) | 2 (14.3) | 0 | 4 (9.8) |
| **Blood and lymphatic system disorders** | **Grade 3** | 0 | 1 (7.1) | 1 (7.1) | 2 (28.6) | 4 (9.8) |
| | **Grade 4** | 1 (16.7) | 1 (7.1) | 1 (7.1) | 0 | 3 (7.3) |
| Anaemia | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| Haemolysis | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| Lymphopenia | Grade 3 | 0 | 0 | 1 (7.1) | 1 (14.3) | 2 (4.9) |
| Neutropenia | Grade 4 | 0 | 1 (7.1) | 1 (7.1) | 0 | 2 (4.9) |
| Thrombocytopenia [a] | Grade 3 | 0 | 1 (7) | 0 | 1 (14) | 2 (5) |
| Thrombocytopenia [a] | Grade 4 | 1 (17) | 0 | 1 (7) | 0 | 2 (5) |
| Thrombocytopenia [a] | Total | 1 (17) | 1 (7) | 1 (7) | 1 (14) | 4 (10) |
| **General disorders and administration site conditions** | **Grade 3** | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| Pyrexia | Grade 3 | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| **Infections and infestations** | **Grade 3** | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| Pneumonia | Grade 3 | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| **Injury, poisoning and procedural complications** | **Grade 3** | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| Wound dehiscence | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| **Investigations** | **Grade 3** | 0 | 0 | 2 (14.3) | 0 | 2 (4.9) |
| | **Grade 4** | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| Blood bilirubin increased [b] | Grade 3 | 0 | 0 | 2 (14) | 0 | 2 (5) |
| **Skin and subcutaneous tissue disorders** | **Grade 3** | 0 | 3 (21.4) | 1 (7.1) | 1 (14.3) | 5 (12.2) |
| Dermatitis exfoliative generalised | Grade 3 | 0 | 0 | 0 | 1 (14.3) | 1 (2.4) |
| Palmar-plantar erythrodysaesthesia syndrome (HFSR) | Grade 3 | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| Rash maculo-papular | Grade 3 | 0 | 3 (21.4) | 0 | 0 | 3 (7.3) |
| **Vascular disorders** | **Grade 3** | 0 | 0 | 0 | 1 (14.3) | 1 (2.4) |
| Hypertension | Grade 3 | 0 | 0 | 0 | 1 (14.3) | 1 (2.4) |

CTCAE = Common Terminology Criteria for Adverse Events; HFSR = Hand-foot skin reaction (hand-foot syndrome); MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event
[a] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/6a).
[b] Increase in bilirubin, includes PTs blood bilirubin increased and blood bilirubin unconjugated increased (Table 14.3.1/6a).
Source: Table 14.3.1/3a and Table 14.3.1/6a

**Drug-related treatment-emergent adverse events (Expansion)**

All 21 treated participants (100.0%) in the expansion phase of the study experienced ≥1 TEAE considered by the investigator as drug-related (i.e., considered related to any of the 3 drugs: regorafenib, irinotecan, vincristine); 19 expansion participants (90.5%) experienced ≥1 drug-related TEAE of Grade 3 or 4.

The highest incidence of drug-related TEAEs were seen in the SOCs "gastrointestinal disorders" and "investigations" (85.7% each), followed by "blood and lymphatic system disorders" (76.2%). These were also the SOCs with the highest incidences of drug-related Grade 3/4 (worst grades) TEAEs.

The most commonly reported drug-related TEAEs (occurring in ≥30% in the total group) were diarrhoea (81%), neutropenia (71%), anaemia (66.7%), vomiting (52.4%), thrombocytopenia (52%),

abdominal pain and decreased appetite (47.6% each), nausea, ALT increased, and AST increased (42.9% each), and leukopenia and fatigue (38% each) diarrheal and vomiting were mainly of Grade 1 or 2, whereas anaemia and neutropenia of Grade 3 or 4 occurred in 38.1% and 47.6% of the participants, respectively. Grade 3 AST and ALT increased occurred in 19% and 23.8% of participants, respectively.

Table 23 shows by treatment regimen drug-related TEAEs reported by ≥ 10% of 21 treated expansion participants.

*Table 23 Drug-related TEAEs (≥10% in the total group) (Expansion; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|
| **Any category/ any event** | **2 (100.0)** | **6 (100.0)** | **13 (100.0)** | **21 (100.0)** |
| Worst CTCAE grade: Grade 1 | 0 | 0 | 2 (15.4) | 2 (9.5) |
| Grade 2 | 0 | 0 | 0 | 0 |
| Grade 3 | 0 | 3 (50.0) | 8 (61.5) | 11 (52.4) |
| Grade 4 | 2 (100.0) | 3 (50.0) | 3 (23.1) | 8 (38.1) |
| **Blood and lymphatic system disorders** | **2 (100.0)** | **4 (66.7)** | **10 (76.9)** | **16 (76.2)** |
| Anaemia | 2 (100.0) | 3 (50.0) | 9 (69.2) | 14 (66.7) |
| Leukopenia [a] | 1 (50) | 3 (50) | 4 (31) | 8 (38) |
| Neutropenia [b] | 2 (100) | 6 (100) | 7 (54) | 15 (71) |
| Thrombocytopenia [c] | 1 (50) | 4 (67) | 6 (46) | 11 (52) |
| **Gastrointestinal disorders** | **2 (100.0)** | **5 (83.3)** | **11 (84.6)** | **18 (85.7)** |
| Abdominal pain | 1 (50.0) | 3 (50.0) | 6 (46.2) | 10 (47.6) |
| Constipation | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Diarrhoea | 2 (100.0) | 4 (66.7) | 11 (84.6) | 17 (81.0) |
| Nausea | 0 | 3 (50.0) | 6 (46.2) | 9 (42.9) |
| Toothache | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Vomiting | 1 (50.0) | 2 (33.3) | 8 (61.5) | 11 (52.4) |
| **General disorders and administration site conditions** | **2 (100.0)** | **3 (50.0)** | **5 (38.5)** | **10 (47.6)** |
| Fatigue [d] | 1 (50) | 3 (50) | 4 (31) | 8 (38) |
| **Investigations** | **2 (100.0)** | **6 (100.0)** | **10 (76.9)** | **18 (85.7)** |
| ALT increased | 2 (100.0) | 3 (50.0) | 4 (30.8) | 9 (42.9) |
| AST increased | 2 (100.0) | 3 (50.0) | 4 (30.8) | 9 (42.9) |
| Blood bilirubin increased [e] | 1 (50) | 2 (33) | 2 (15) | 5 (24) |
| Blood thyroid stimulating hormone increased | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |
| Gamma-glutamyltransferase increased | 2 (100.0) | 1 (16.7) | 2 (15.4) | 5 (23.8) |
| Weight decreased | 1 (50.0) | 1 (16.7) | 4 (30.8) | 6 (28.6) |
| **Metabolism and nutrition disorders** | **2 (100.0)** | **5 (83.3)** | **6 (46.2)** | **13 (61.9)** |
| Decreased appetite | 2 (100.0) | 4 (66.7) | 4 (30.8) | 10 (47.6) |
| **Musculoskeletal and connective tissue disorders** | **1 (50.0)** | **3 (50.0)** | **3 (23.1)** | **7 (33.3)** |
| Pain in extremity | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Pain in jaw | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| **Nervous system disorders** | **2 (100.0)** | **3 (50.0)** | **4 (30.8)** | **9 (42.9)** |
| Headache | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| Lethargy | 0 | 2 (33.3) | 2 (15.4) | 4 (19.0) |
| **Renal and urinary disorders** | **1 (50.0)** | **2 (33.3)** | **2 (15.4)** | **5 (23.8)** |
| Proteinuria | 1 (50.0) | 2 (33.3) | 0 | 3 (14.3) |

| Primary SOC/ PT<br>MedDRA v. 26.1 | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|
| **Skin and subcutaneous tissue disorders** | **2 (100.0)** | **5 (83.3)** | **7 (53.8)** | **14 (66.7)** |
| Alopecia | 0 | 2 (33.3) | 4 (30.8) | 6 (28.6) |
| Dry skin | 0 | 2 (33.3) | 1 (7.7) | 3 (14.3) |
| Palmar-plantar erythrodysaesthesia syndrome (HFSR) | 0 | 3 (50.0) | 0 | 3 (14.3) |
| Rash [f] | 1 (50) | 2 (33) | 3 (23) | 6 (29) |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; HFSR = Hand-foot skin reaction (hand-foot syndrome); MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event

[a] Leukopenia (not further specified), includes PTs leukopenia and white blood cell count decreased (Table 14.3.1/9b).

[b] Includes PTs neutropenia and neutrophil count decreased (Table 14.3.1/9b).

[c] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/9b).

[d] Decreased general strength and energy, includes PTs fatigue and asthenia (Table 14.3.1/9b).

[e] Increase in bilirubin, includes PTs blood bilirubin increased and hyperbilirubinemia (Table 14.3.1/9b).

[f] Includes PTs rash and rash maculo-papular (Table 14.3.1/9b).

Source: Table 14.3.1/4b and Table 14.3.1/9b

In addition, the investigator could indicate the specific drug(s) assessed as most likely contributing to the TEAE.

Table 24 summarizes all drug-related TEAEs for which a causal relationship to at least 1 of the 3 drugs was assumed in at least 2 expansion participants of the safety population (irrespective of treatment regimen). The data show that 90.5%, 95.2%, and 81.0% of the 21 expansion participants experienced TEAEs with a causal relationship to regorafenib, irinotecan, and vincristine, respectively. Considering the small sample size, the proportions of participants with TEAEs related to the different drugs were comparable. No relevant differences between TEAEs related to regorafenib and TEAEs related to the backbone chemotherapy were seen. The highest incidence of severe (worst CTCAE Grade ≥3) drug-related TEAEs were seen for irinotecan (90.5%; manually calculated from Table 24).

*Table 24 Drug-related [a] TEAEs by drug (Expansion; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | | Number (%) of participants with TEAEs related to: Regorafenib (N=21) | Irinotecan (N=21) | Vincristine (N=21) |
|---|---|---|---|---|
| **Any category / any event** | | **19 (90.5)** | **20 (95.2)** | **17 (81.0)** |
| Worst CTCAE grade: | Grade 1 | 2 (9.5) | 1 (4.8) | 1 (4.8) |
| | Grade 2 | 3 (14.3) | 0 | 1 (4.8) |
| | Grade 3 | 7 (33.3) | 11 (52.4) | 12 (57.1) |
| | Grade 4 | 7 (33.3) | 8 (38.1) | 3 (14.3) |
| **Blood and lymphatic system disorders** | | **11 (52.4)** | **16 (76.2)** | **12 (57.1)** |
| Anaemia | | 9 (42.9) | 13 (61.9) | 8 (38.1) |
| Leukopenia [b] | | 6 (29) | 8 (38) | 8 (38) |
| Lymphopenia [c] | | 2 (10) | 3 (14) | 1 (5) |
| Neutropenia [d] | | 11 (52) | 15 (71) | 11 (52) |
| Thrombocytopenia [e] | | 7 (33) | 11 (52) | 5 (24) |

| Primary SOC/ PT<br>MedDRA v. 26.1 | Number (%) of participants with TEAEs related to:<br>Regorafenib (N=21) | Irinotecan (N=21) | Vincristine (N=21) |
|---|---|---|---|
| **Endocrine disorders** | **2 (9.5)** | **0** | **0** |
| Hypothyroidism | 2 (9.5) | 0 | 0 |
| **Gastrointestinal disorders** | **8 (38.1)** | **16 (76.2)** | **14 (66.7)** |
| Abdominal pain | 3 (14.3) | 8 (38.1) | 7 (33.3) |
| Constipation | 0 | 0 | 3 (14.3) |
| Diarrhoea | 5 (23.8) | 15 (71.4) | 4 (19.0) |
| Nausea | 3 (14.3) | 8 (38.1) | 7 (33.3) |
| Oral pain | 0 | 2 (9.5) | 2 (9.5) |
| Stomatitis | 2 (9.5) | 1 (4.8) | 1 (4.8) |
| Toothache | 0 | 0 | 3 (14.3) |
| Vomiting | 3 (14.3) | 11 (52.4) | 8 (38.1) |
| **General disorders and administration site conditions** | **7 (33.3)** | **9 (42.9)** | **5 (23.8)** |
| Fatigue [f] | 6 (29) | 7 (33) | 5 (24) |
| Pyrexia | 1 (4.8) | 2 (9.5) | 0 |
| **Investigations** | **16 (76.2)** | **14 (66.7)** | **10 (47.6)** |
| ALT increased | 7 (33.3) | 6 (28.6) | 4 (19.0) |
| AST increased | 9 (42.9) | 7 (33.3) | 4 (19.0) |
| Blood bilirubin increased [g] | 5 (24) | 1 (5) | 2 (10) |
| Blood thyroid stimulating hormone increased | 4 (19.0) | 0 | 0 |
| Gamma-glutamyltransferase increased | 4 (19.0) | 1 (4.8) | 3 (14.3) |
| Prothrombin time ratio increased | 2 (9.5) | 0 | 0 |
| Weight decreased | 6 (28.6) | 5 (23.8) | 2 (9.5) |
| **Metabolism and nutrition disorders** | **10 (47.6)** | **11 (52.4)** | **8 (38.1)** |
| Decreased appetite | 6 (28.6) | 10 (47.6) | 6 (28.6) |
| Hypokalaemia | 1 (4.8) | 2 (9.5) | 0 |
| **Musculoskeletal and connective tissue disorders** | **2 (9.5)** | **2 (9.5)** | **7 (33.3)** |
| Myalgia | 2 (9.5) | 1 (4.8) | 2 (9.5) |
| Pain in extremity | 0 | 0 | 3 (14.3) |
| Pain in jaw | 0 | 1 (4.8) | 3 (14.3) |
| **Nervous system disorders** | 5 (23.8) | 6 (28.6) | 8 (38.1) |
| Headache | 2 (9.5) | 2 (9.5) | 2 (9.5) |
| Lethargy | 0 | 4 (19.0) | 4 (19.0) |
| Peripheral sensory neuropathy | 0 | 0 | 2 (9.5) |
| **Renal and urinary disorders** | 5 (23.8) | 2 (9.5) | 2 (9.5) |
| Proteinuria | 3 (14.3) | 1 (4.8) | 0 |
| **Skin and subcutaneous tissue disorders** | **12 (57.1)** | **7 (33.3)** | **4 (19.0)** |
| Alopecia | 2 (9.5) | 5 (23.8) | 4 (19.0) |
| Dry skin | 3 (14.3) | 0 | 1 (4.8) |
| Erythema | 2 (9.5) | 0 | 0 |
| Palmar-plantar erythrodysaesthesia syndrome (HFSR) | 3 (14.3) | 0 | 0 |
| Rash [h] | 6 (29) | 1 (5) | 1 (5) |
| Skin hyperpigmentation | 1 (4.8) | 2 (9.5) | 2 (9.5) |
| **Vascular disorders** | **4 (19.0)** | **1 (4.8)** | **0** |
| Hypertension | 2 (9.5) | 0 | 0 |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; HFSR = Hand-foot skin reaction (hand-foot syndrome); MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event

[a] All TEAEs assessed as "related" to at least 1 of the 3 drugs in ≥2 participants (9.5%) are listed by PT.

[b] Leukopenia (not further specified), includes PTs leukopenia and white blood cell count decreased (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).

[c] Includes PT lymphocyte count decreased (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).

[d] Includes PTs neutropenia and neutrophil count decreased (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).

| Primary SOC/ PT<br>MedDRA v. 26.1 | Number (%) of participants with TEAEs related to: Regorafenib (N=21) | Irinotecan (N=21) | Vincristine (N=21) |
|---|---|---|---|

[e] Includes PTs thrombocytopenia and platelet count decreased (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).
[f] Decreased general strength and energy, includes PTs fatigue and asthenia (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).
[g] Increase in bilirubin, includes PTs blood bilirubin increased and hyperbilirubinemia (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).
[h] Includes PTs rash and rash maculo-papular (Tables 14.3.1/10b, 14.3.1/11b, and 14.3.1/12b).
Source: Tables 14.3.1/5b, 14.3.1/6b, 14.3.1/7b, Table 14.3.1/10b, Table 14.3.1/11b, and Table 14.3.1/12b

Severe TEAEs (worst CTCAE Grade ≥3) assessed as any drug-related most frequently were laboratory abnormalities referring to the SOCs "blood and lymphatic disorders" (71.4%) and "investigations" (57.1%) (manually calculated from Table 14.3.1/4b). No reliable comparisons between treatment regimens can be made because of the very different group sizes.

All Grade ≥3 TEAEs assessed as related to regorafenib that occurred in ≥2 expansion participants of the total group are presented by treatment regimen and worst CTCAE grade in Table 25.

*Table 25 Regorafenib-related TEAEs of CTCAE Grade ≥3 (≥2 participants in the total group) (Expansion; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|
| **Any category/any event** | | | | |
| Worst CTCAE grade: | | | | |
| Grade 3 | 0 | 1 (16.7) | 6 (46.2) | 7 (33.3) |
| Grade 4 | 2 (100.0) | 3 (50.0) | 2 (15.4) | 7 (33.3) |
| **Blood and lymphatic system disorders** | | | | |
| **Grade 3** | **0** | **1 (16.7)** | **4 (30.8)** | **5 (23.8)** |
| **Grade 4** | **1 (50.0)** | **2 (33.3)** | **2 (15.4)** | **5 (23.8)** |
| Anaemia | | | | |
| Grade 3 | 0 | 1 (16.7) | 2 (15.4) | 3 (14.3) |
| Neutropenia [a] | | | | |
| Grade 3 | 0 | 1 (17) | 3 (23) | 4 (19) |
| Grade 4 | 2 (100) | 2 (33) | 2 (15) | 6 (29) |
| Leukopenia [b] | | | | |
| Grade 3 | 1 (50) | 1 (17) | 1 (8) | 3 (14) |
| Thrombocytopenia [c] | | | | |
| Grade 3 | 1 (50) | 0 | 3 (23) | 4 (19) |
| **Investigations** | | | | |
| **Grade 3** | **1 (50.0)** | **2 (33.3)** | **4 (30.8)** | **7 (33.3)** |
| **Grade 4** | **1 (50.0)** | **1 (16.7)** | **0** | **2 (9.5)** |
| ALT increased | | | | |
| Grade 3 | 2 (100.0) | 2 (33.3) | 1 (7.7) | 5 (23.8) |
| AST increased | | | | |
| Grade 3 | 2 (100.0) | 2 (33.3) | 0 | 4 (19.0) |
| **Metabolism and nutrition disorders** | | | | |
| **Grade 3** | **1 (50.0)** | **1 (16.7)** | **2 (15.4)** | **4 (19.0)** |
| Decreased appetite | | | | |
| Grade 3 | 1 (50.0) | 0 | 1 (7.7) | 2 (9.5) |

ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities;

| Primary SOC/ PT<br><br>MedDRA v. 26.1 | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|

PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TEAE = Treatment-emergent adverse event
[a] Includes PTs neutropenia and neutrophil count decreased (Table 14.3.1/13b).
[b] Leukopenia (not further specified), includes PTs leukopenia and white blood cell count decreased (Table 14.3.1/13b).
[c] Includes PTs thrombocytopenia and platelet count decreased (Table 14.3.1/13b).
Source: Table 14.3.1/5b and Table 14.3.1/13b

**Deaths**

**Escalation phase**

A total of 40 of 41 (97.6%) participants died during the escalation phase of the study; of which 8 participants died within 30 days after last dose Table 26. Of these 8 participants, 7 died of PD, and 1 participant's cause of death was AE (general physical condition, abnormal) not related to regorafenib and was associated with clinical disease progression.

*Table 26 Number of deaths by time period (Escalation; SAF)*

| | Regorafenib Level 1 (60 mg/m²) N=6 n (%) | Regorafenib Level 2 (72 mg/m²) N=14 n (%) | Regorafenib Level 3 (82 mg/m²) N=14 n (%) | Regorafenib Level 4 (93 mg/m²) N=7 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|
| **Any death** | 6 (100.0) | 14 (100.0) | 13 (92.9) | 7 (100.0) | 40 (97.6) |
| **Before treatment** | 0 | 0 | 0 | 0 | 0 |
| **During treatment and within 30 days post permanent treatment discontinuation** | 1 (16.7) | 5 (35.7) | 2 (14.3) | 0 | 8 (19.5) |
| **More than 30 days post permanent treatment discontinuation** | 5 (83.3) | 9 (64.3) | 11 (78.6) | 7 (100.0) | 32 (78.0) |

SAF = Safety analysis set
Source: Table 14.3.2/5a

**Expansion phase**

A total of 16 of 21 (76.2%) participants died during the expansion phase of the study; of which 2 participants died within 30 days after last dose (Table 27):

- Participant no. 120049001 (Reg72 seq+VI group) with Ewing sarcoma died of cardiac arrest 30 days after receiving last dose (121 days after treatment start) (and 12 days after decision of treatment discontinuation, which was due to progressive disease).

- Participant no. 120039002 (Reg82 seq+VI group) with RMS died 21 days after receiving last dose (42 days after treatment start). The participant was noted to have clinical progressive disease on

study, which was later confirmed radiologically locally, and participant went home for palliative care (Listing 16.2.8.3/5b).

Of the 14 expansion participants that died >30 days after permanent treatment discontinuation, the primary cause of death was PD in 13 participants and AE (cardiac arrest) in 1 participant (Listing 16.2.7/3b). This participant (no. 120049002; Reg72 seq+VI group) with Ewing sarcoma died of cardiac arrest 443 days after receiving last dose (709 days after treatment start).

None of the on-study deaths were assessed as drug-related.

*Table 27 Number of deaths by time period (Expansion; SAF)*

| | Regorafenib (72 mg/m²) Conc + VI N=2 n (%) | Regorafenib (72 mg/m²) Seq + VI N=6 n (%) | Regorafenib (82 mg/m²) Seq + VI N=13 n (%) | Total N=21 n (%) |
|---|---|---|---|---|
| **Any death** | 2 (100.0) | 6 (100.0) | 8 (61.5) | 16 (76.2) |
| **Before treatment** | 0 | 0 | 0 | 0 |
| **During treatment and within 30 days post permanent treatment discontinuation** | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| **More than 30 days post permanent treatment discontinuation** | 2 (100.0) | 5 (83.3) | 7 (53.8) | 14 (66.7) |

SAF = Safety analysis set
Source: Table 14.3.2/6b

**Serious adverse events (Escalation phase)**

Twenty-three escalation participants (56.1%) experienced ≥1 TESAE; 21 of them experienced TESAEs of CTCAE Grade ≥3.

**Common TESAEs**

The following TESAEs were reported in ≥2 escalation participants: pyrexia (in 7 participants [17.1%]; mostly worst Grade 1), death (in 6 participants [14.6%]), hydrocephalus (in 3 participants [7.3%]; all worst Grade 3), and abdominal pain, pneumonia, and vomiting (in 2 participants [4.9%] each; all worst Grade 3) (Table 28).

**Severity of TESAEs (worst grade)**

In 11 of the 23 dose-escalation participants, TESAEs were of worst Grade 3.

Two participants experienced Grade 4 TESAEs as worst grade. These were cases of cerebral salt-wasting syndrome, and leukemia (all in participants in escalation Level 2 [72 mg/m2]). Eight participants experienced Grade 5 TESAEs. These included death in 6 participants (4 of these in escalation Level 2 [72 mg/m$^2$]) and general physical condition abnormal in 2 participants (1 in escalation Level 2 [72 mg/m$^2$] and 1 in Level 3 [82 mg/m$^2$]).

**Drug-related TESAEs**

Overall, regorafenib-related TESAEs were reported for 7 escalation participants (17.1%). None of the drug-related TESAEs were of CTCAE Grade >3.

Table 29 shows the number of participants with drug-related TESAEs by MedDRA terms and worst CTCAE grade. The Grade 3 drug-related TESAEs were hemolysis, pyrexia, pneumonia, wound dehiscence, rash maculo-papular, and hypertension.

*Table 28 TESAEs by worst CTCAE grade (≥2 participants in total group) (Escalation; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | Worst CTCAE grade | Level 1 (60 mg/m²) N=6 n (%) | Level 2 (72 mg/m²) N=14 n (%) | Level 3 (82 mg/m²) N=14 n (%) | Level 4 (93 mg/m²) N=7 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|
| **Any category/any event** | Grade 3 | 2 (33.3) | 3 (21.4) | 5 (35.7) | 1 (14.3) | 11 (26.8) |
| | Grade 4 | 0 | 2 (14.3) | 0 | 0 | 2 (4.9) |
| | Grade 5 | 1 (16.7) | 5 (35.7) | 2 (14.3) | 0 | 8 (19.5) |
| **Gastrointestinal disorders** | | | | | | |
| | **Grade 3** | **0** | **0** | **3 (21.4)** | **1 (14.3)** | **4 (9.8)** |
| Abdominal pain | Grade 3 | 0 | 0 | 1 (7.1) | 1 (14.3) | 2 (4.9) |
| Vomiting | Grade 3 | 0 | 0 | 2 (14.3) | 0 | 2 (4.9) |
| **General disorders and administration site conditions** | | | | | | |
| | **Grade 1** | **0** | **1 (7.1)** | **2 (14.3)** | **0** | **3 (7.3)** |
| | **Grade 2** | **0** | **1 (7.1)** | **1 (7.1)** | **0** | **2 (4.9)** |
| | **Grade 3** | **0** | **0** | **1 (7.1)** | **1 (14.3)** | **2 (4.9)** |
| | **Grade 5** | **1 (16.7)** | **4 (28.6)** | **1 (7.1)** | **0** | **6 (14.6)** |
| Death | Grade 5 | 1 (16.7) | 4 (28.6) | 1 (7.1) | 0 | 6 (14.6) |
| Pyrexia | Grade 1 | 0 | 2 (14.3) | 2 (14.3) | 0 | 4 (9.8) |
| | Grade 2 | 0 | 2 (14.3) | 0 | 0 | 2 (4.9) |
| | Grade 3 | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| **Infections and infestations** | | | | | | |
| | **Grade 3** | **0** | **1 (7.1)** | **1 (7.1)** | **0** | **2 (4.9)** |
| Pneumonia | Grade 3 | 0 | 1 (7.1) | 1 (7.1) | 0 | 2 (4.9) |
| **Injury, poisoning and procedural complications** [a] | | | | | | |
| | **Grade 3** | **0** | **1 (7.1)** | **1 (7.1)** | **0** | **2 (4.9)** |
| **Investigations** | | | | | | |
| | **Grade 5** | **0** | **1 (7.1)** | **1 (7.1)** | **0** | **2 (4.9)** |
| General physical condition abnormal | Grade 5 | 0 | 1 (7.1) | 1 (7.1) | 0 | 2 (4.9) |
| **Metabolism and nutrition disorders** [b] | | | | | | |
| | **Grade 3** | **0** | **1 (7.1)** | **1 (7.1)** | **0** | **2 (4.9)** |
| **Nervous system disorders** | | | | | | |
| | **Grade 2** | **1 (16.7)** | **2 (14.3)** | **1 (7.1)** | **0** | **4 (9.8)** |
| | **Grade 3** | **2 (33.3)** | **1 (7.1)** | **0** | **0** | **3 (7.3)** |
| Hydrocephalus | Grade 3 | 2 (33.3) | 1 (7.1) | 0 | 0 | 3 (7.3) |

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TESAE = Treatment-emergent serious adverse event

[a] SOC "Injury, poisoning and procedural complications" included PTs shunt occlusion and wound dehiscence, 1 participant each (both worst Grade 3).

[b] SOC "Metabolism and nutrition disorders" included PTs cerebral salt-wasting syndrome (worst Grade 4), dehydration (worst Grade 3), and hypophagia (worst Grade 3), 1 participant each.

Source: Table 14.3.2/1a

*Table 29 Regorafenib-related TESAEs by worst CTCAE grade (Escalation; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | Worst CTCAE grade | Level 1 (60 mg/m²) N=6 n (%) | Level 2 (72 mg/m²) N=14 n (%) | Level 3 (82 mg/m²) N=14 n (%) | Level 4 (93 mg/m²) N=7 n (%) | Total N=41 n (%) |
|---|---|---|---|---|---|---|
| **Any category/any event** | Grade 1 | 0 | 2 (14.3) | 0 | 0 | 2 (4.9) |
| | Grade 2 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| | Grade 3 | 0 | 2 (14.3) | 1 (7.1) | 1 (14.3) | 4 (9.8) |
| **Blood and lymphatic system disorders** | | | | | | |
| Haemolysis | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| **General disorders and administration site conditions** | | | | | | |
| Pyrexia | Grade 1 | 0 | 2 (14.3) | 0 | 0 | 2 (4.9) |
| | Grade 2 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| | Grade 3 | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| Systemic inflammatory response syndrome | Grade 1 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| **Infections and infestations** | | | | | | |
| Pneumonia | Grade 3 | 0 | 0 | 1 (7.1) | 0 | 1 (2.4) |
| **Injury, poisoning and procedural complications** | | | | | | |
| Wound dehiscence | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| **Skin and subcutaneous tissue disorders** | | | | | | |
| Rash maculo-papular | Grade 3 | 0 | 1 (7.1) | 0 | 0 | 1 (2.4) |
| **Vascular disorders** | | | | | | |
| Hypertension | Grade 3 | 0 | 0 | 0 | 1 (14.3) | 1 (2.4) |

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TESAE = Treatment-emergent serious adverse event
Source: Table 14.3.2/3a

**Common TESAEs**

The following TESAEs were reported in ≥2 expansion participants: pyrexia (in 6 participants [28.6%]; Grade 3 pyrexia in 1 participant [4.8%]), febrile neutropenia (in 3 participants [14.3%]; all worst Grade 3), and abdominal pain, diarrhoea, and vomiting (in 2 participants [9.5%] each; all worst Grade 3) (Table 30).

**Severity of TESAEs (worst grade)**

In 9 of the 16 expansion participants concerned TESAEs were of worst Grade 3.

Two participants experienced Grade 4 TESAEs. These were 1 case of cardiac failure in a participant of the Reg72 seq+VI group; and hepatic hematoma and sepsis, both in a participant of the Reg82 seq+VI group. Two worst Grade 5 events were reported in the expansion phase of the study: cardiac arrest was reported in a participant of the Reg72 seq+VI group and death in a participant of the Reg82 seq+VI group.

**Drug-related TESAEs**

Overall, drug-related TESAEs occurred in 8 expansion participants (38.1%) in the SAF. None of the drug-related TESAEs were of CTCAE Grade >3 (Table 14.3.2/2b). A causal relationship between a TESAE and regorafenib was assumed in 5 participants (23.8%). The corresponding percentages for irinotecan and vincristine were 33.3% and 19.0%.

All of the drug-related TESAEs occurred in single participants, except for 2 occurrences of irinotecan-related diarrhoea and vomiting. A causal relationship was seen for more than 1 drug in ~50% of the cases (Table 31).

TESAEs related to regorafenib occurred in 5 expansion participants (Listing 16.2.7/5b):

- 120019001 (Reg72 conc+VI): hepatic pain, pyrexia
- 160029001 (Reg72 conc+VI): abdominal pain, febrile bone marrow aplasia, vomiting
- 220019001 (Reg72 seq+VI): febrile neutropenia
- 120039004 (Reg82 seq+VI): hypotension
- 160049001 (Reg82 seq+VI): ear infection

*Table 30 Common (≥2 participants in the total group) TESAEs by worst CTCAE grade (Expansion; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | | Reg72 conc+VI (N=2) n (%) | Reg72 seq+VI (N=6) n (%) | Reg82 seq+VI (N=13) n (%) | Total (N=21) n (%) |
|---|---|---|---|---|---|
| **Any category/ any event** | | 2 (100.0) | 5 (83.3) | 9 (69.2) | 16 (76.2) |
| Worst CTCAE grade: | Grade 2 | 0 | 0 | 3 (23.1) | 3 (14.3) |
| | Grade 3 | 2 (100.0) | 3 (50.0) | 4 (30.8) | 9 (42.9) |
| | Grade 4 | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| | Grade 5 | 0 | 1 (16.7) | 1 (7.7) | 2 (9.5) |
| **Blood and lymphatic system disorders** | | | | | |
| | **Grade 3** | **2 (100.0)** | **1 (16.7)** | **1 (7.7)** | **4 (19.0)** |
| Febrile neutropenia | | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| | Grade 3 | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| **Cardiac disorders [a]** | | | | | |
| | **Grade 4** | **0** | **1 (16.7)** | **0** | **1 (4.8)** |
| | **Grade 5** | **0** | **1 (16.7)** | **0** | **1 (4.8)** |
| **Gastrointestinal disorders** | | | | | |
| | **Grade 3** | **2 (100.0)** | **1 (16.7)** | **4 (30.8)** | **7 (33.3)** |
| Abdominal pain | | 2 (100.0) | 0 | 0 | 2 (9.5) |
| | Grade 3 | 2 (100.0) | 0 | 0 | 2 (9.5) |
| Diarrhoea | | 0 | 0 | 2 (15.4) | 2 (9.5) |
| | Grade 3 | 0 | 0 | 2 (15.4) | 2 (9.5) |
| Vomiting | | 1 (50.0) | 0 | 1 (7.7) | 2 (9.5) |
| | Grade 3 | 1 (50.0) | 0 | 1 (7.7) | 2 (9.5) |
| **General disorders and administration site disorders** | | | | | |
| | **Grade 1** | **0** | **0** | **2 (15.4)** | **2 (9.5)** |
| | **Grade 2** | **1 (50.0)** | **1 (16.7)** | **2 (15.4)** | **4 (19.0)** |
| | **Grade 3** | **0** | **0** | **1 (7.7)** | **1 (4.8)** |
| | **Grade 5** | **0** | **0** | **1 (7.7)** | **1 (4.8)** |
| Pyrexia | | 1 (50.0) | 1 (16.7) | 4 (30.8) | 6 (28.6) |
| | Grade 1 | 0 | 0 | 2 (15.4) | 2 (9.5) |
| | Grade 2 | 1 (50.0) | 1 (16.7) | 1 (7.7) | 3 (14.3) |
| **Hepatobiliary disorders [b]** | | | | | |
| | **Grade 3** | **1 (50.0)** | **0** | **0** | **1 (4.8)** |
| | **Grade 4** | **0** | **0** | **1 (7.7)** | **1 (4.8)** |
| **Infections and infestations [c]** | | | | | |
| | **Grade 2** | **0** | **1 (16.7)** | **0** | **1 (4.8)** |
| | **Grade 3** | **1 (50.0)** | **2 (33.3)** | **2 (15.4)** | **5 (23.8)** |
| | **Grade 4** | **0** | **0** | **1 (7.7)** | **1 (4.8)** |

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TESAE = Treatment-emergent serious adverse event

[a] Cardiac disorders included 1 participant each with cardiac arrest (fatal) and cardiac failure.

[b] Hepatobiliary disorders included 1 case each of drug-induced liver injury, hepatic hematoma, and hepatic pain.

[c] Infections and infestations included 1 participant each with bacteremia, *Clostridium difficile* infection, cytomegalovirus infection, ear infection, pneumonia, rhinitis, sepsis, tonsillitis, and tooth infection.

Source: Table 14.3.2/1b

*Table 31 Drug-related TESAEs (Expansion; SAF)*

| Primary SOC/ PT<br>MedDRA v. 26.1 | | Number (%) of participants with TESAEs related to: Regorafenib (N=21) | Irinotecan (N=21) | Vincristine (N=21) |
|---|---|---|---|---|
| **Any category/ any event** | | **5 (23.8)** | **7 (33.3)** | **4 (19.0)** |
| Worst CTCAE grade: | Grade 1 | 0 | 0 | 1 (4.8) |
| | Grade 3 | 5 (23.8) | 7 (33.3) | 3 (14.3) |
| **Blood and lymphatic system disorders** | | **2 (9.5)** | **2 (9.5)** | **1 (4.8)** |
| Febrile bone marrow aplasia | | 1 (4.8) | 1 (4.8) | 1 (4.8) |
| Febrile neutropenia | | 1 (4.8) | 1 (4.8) | 0 |
| **Gastrointestinal disorders** | | **1 (4.8)** | **5 (23.8)** | **1 (4.8)** |
| Abdominal pain | | 1 (4.8) | 1 (4.8) | 1 (4.8) |
| Colitis | | 0 | 1 (4.8) | 0 |
| Diarrhoea | | 0 | 2 (9.5) | 0 |
| Vomiting | | 1 (4.8) | 2 (9.5) | 1 (4.8) |
| **General disorders and administration site conditions** | | **1 (4.8)** | **1 (4.8)** | **0** |
| Pyrexia | | 1 (4.8) | 1 (4.8) | 0 |
| **Hepatobiliary disorders** | | **1 (4.8)** | **1 (4.8)** | **1 (4.8)** |
| Drug-induced liver injury | | 0 | 0 | 1 (4.8) |
| Hepatic pain | | 1 (4.8) | 1 (4.8) | 1 (4.8) |
| **Infections and infestations** | | **1 (4.8)** | **1 (4.8)** | **1 (4.8)** |
| Ear infection | | 1 (4.8) | 1 (4.8) | 0 |
| Tooth infection | | 0 | 0 | 1 (4.8) |
| **Metabolism and nutrition disorders** | | **0** | **1 (4.8)** | **0** |
| Dehydration | | 0 | 1 (4.8) | 0 |
| **Nervous system disorders** | | **0** | **0** | **1 (4.8)** |
| Peripheral sensory neuropathy | | 0 | 0 | 1 (4.8) |
| **Reproductive system and breast disorders** | | **0** | **1 (4.8)** | **1 (4.8)** |
| Oedema genital | | 0 | 1 (4.8) | 1 (4.8) |
| **Vascular disorders** | | **1 (4.8)** | **1 (4.8)** | **0** |
| Hypotension | | 1 (4.8) | 1 (4.8) | 0 |

CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical dictionary for regulatory activities; PT = Preferred term; SAF = Safety analysis set; SOC = System organ class; TESAE = Treatment-emergent serious adverse event
Source: Table 14.3.2/3b, 14.3.2/4b and 14.3.2/5b

**Adverse events of special interest**

Adverse events of special safety interest listed in the original study protocol were considered outdated based on new safety data generated from other studies. Therefore, these were removed from the Clinical Study Protocol with Amendment 1.

**Other significant adverse events**

An increased incidence of Grades 3/4 hematological events was observed across dose levels in the escalation phase of the study, and it appears that participants with a prior history of myelosuppressive therapies such as high dose chemotherapy with stem cell rescue or craniospinal irradiation may be at a higher risk (for further details, refer to CSR PH-38659 (database cut-off date of 19 NOV 2015).

**Evaluation of each laboratory parameter (Escalation phase)**

Clinical laboratory data for hematology, biochemistry, urinalysis, coagulation, and thyroid function tests are displayed in Listings 16.2.8.1/1a to 16.2.8.1/5a by dose level and by visit for all escalation participants assigned to treatment.

In the escalation phase, CTCAE Grades 3/4 treatment-emergent hematological and biochemical abnormalities were most commonly reported for lymphocyte count decreased (7/41 participants or 17.1%), followed by platelet count decreased (6/41 participants or 14.6%), ALT increased and neutrophil count decreased (4/41 participants or 9.8% each) (percentages calculated manually; Listing 16.2.7/9a).

For further details on evaluation of each laboratory parameter and for summaries of laboratory abnormalities and toxicities in participants of the escalation phase of the study, refer to CSR PH-38659 (database cut-off date of 19 NOV 2015).

**Evaluation of each laboratory parameter (Expansion phase)**

Clinical laboratory data for hematology, biochemistry, urinalysis, coagulation, and thyroid function tests are displayed by treatment regimen and by visit for all participants assigned to treatment in Listings 16.2.8.1/1b to 16.2.8.1/5b.

Clinical laboratory data for thyroid function tests included thyrotropin (also known as TSH), thyroxine free (also known as free T4), and free triiodothyronine (also known as free T3). At least transient abnormal results for these tests were reported for most of the expansion participants (Listing 16.2.8.1/5b). In 3 participants of the Reg72 seq+VI group and in 2 participants of the Reg82 seq+VI group, the abnormalities were assessed as clinically relevant and reported as (non-serious) TEAEs (CTCAE Grades 1 and 2; Listing 16.2.7/1b).

Clinically relevant findings in urinalysis, which were also reported as TEAEs, were seen in 11 participants in total. These included glycosuria (Grade 1 in a participant of the Reg72 conc+VI group and Grade 2 in a participant of the Reg82 seq+VI group), hematuria (Grade 2 in a participant of the Reg82 seq+VI group), leukocyturia (Grade 1 in 2 participants of the Reg72 seq+VI group and in 1 participant of the Reg82 seq+VI group), and proteinuria (Grade 1 in 2 participants of the Reg72 seq+VI group and in 2 participants of the Reg82 seq+VI group and Grade 2 in 1 participant of the Reg72 conc+VI group; Table 14.3.1/2b). One case of hematuria (Grade 1) and 3 cases of proteinuria (2 Grade 1 and 1 Grade 2) were assessed as related to regorafenib (Table 14.3.1/5b).

Laboratory results for parameters of hematology and general chemistry were further classified according to NCI-CTCAE grading, independent of being reported as AEs or not.

**Hematological and biochemical toxicities (CTCAE Grade ≥3; Expansion phase)**

In this section, CTCAE severity grading for laboratory abnormalities are based on applicable laboratory threshold values according to NCI-CTCAE. If any laboratory abnormality was additionally reported as a TE(S)AE, this information is included within Sections 10.2 and 10.3.

For summaries of pretreatment (baseline), of treatment-emergent hematological and of change in worst CTCAE grade during treatment for biochemical toxicities (CTCAE Grade ≥3) in the expansion phase of the study, refer to CSR PH-40803 (database cut-off date of 05 MAY 2019).

**Hematological and biochemical toxicities: Change in CTCAE grade from pretreatment (Expansion phase)**

The number of expansion participants and the incidence of changes in grade from pretreatment (Baseline) for hematological and biochemical parameters by CTCAE category and term in the safety analysis set are shown in Table 14.3.4/1b.

As only a few pretreatment toxicities were present, improvements in CTCAE grades of the respective laboratory parameters occurred in single participants only. Most frequently, laboratory parameters either remained unchanged or worsened by 1 grade.

**A worsening by 3 grades** was observed in >1 participant with the following parameters:

- Neutrophil count decreased (8/21 participants or 38.1%)
- Alanine aminotransferase increased (6/20 participants or 30.0%)
- White blood cell decreased (6/21 participants or 28.6%)
- Hypokalemia (5/21 participants or 23.8%)
- Platelet count decreased (3/21 participants or 14.3%)
- Aspartate aminotransferase increased (2/20 participants or 10.0%)
- Lipase increased (2/20 participants or 10.0%)
- Anemia (2/21 participants or 9.5%)
- Lymphocyte count decreased (2/21 participants or 9.5%)

**A worsening by 4** grades was observed with the following parameters:

- Neutrophil count decreased (4/21 participants or 19.0%)
- Lymphocyte count decreased (1/21 participants or 4.8%)
- Platelet count decreased (1/21 participants or 4.8%)
- White blood cell count decreased (1/21 participants or 4.8%)

**Other safety variables or evaluations - DLTs, MTD, and RP2D**

**Escalation phase**

Dose-limiting toxicities observed in the escalation phase of the study were thrombocytopenia at 60 mg/m$^2$, rash maculo-papular at 72 mg/m$^2$, fever at 82 mg/m$^2$, hypertension and erythroderma at 93 mg/m$^2$ (Table 32). Based on the overall safety profile and drug exposure across dose levels observed in the dose-escalation phase of this study, 82 mg/m$^2$ once daily in a 3-weeks-on/1-week-off schedule was selected as the RP2D (CSR PH-38659).

*Table 32 Overview of dose-limiting toxicities (MTD analysis set)*

| Investigator term (Standard Toxicity Grade) | Level 1 (60 mg/m²) N=6 (100%) | Level 2 (72 mg/m²) N=6 (100%) | Level 3 (82 mg/m²) N=6 (100%) | Level 4 (93 mg/m²) N=5 (100%) | Total N=23 (100%) |
|---|---|---|---|---|---|
| **Any DLT** | 1 (16.7%) | 1 (16.7%) | 1 (16.7%) | 2 (40.0%) | 5 (21.7%) |
| Thrombocytopenia (Grade 4) | 1 (16.7%) | 0 | 0 | 0 | 1 (4.3%) |
| Rash maculo-papular (Grade 3) | 0 | 1 (16.7%) | 0 | 0 | 1 (4.3%) |
| Fever (Grade 3) | 0 | 0 | 1 (16.7%) | 0 | 1 (4.3%) |
| Hypertension (Grade 3) | 0 | 0 | 0 | 1 (20%) | 1 (4.3%) |
| Erythroderma (Grade 3) | 0 | 0 | 0 | 1 (20%) | 1 (4.3%) |

Source: Table 14.3.2/16 and Table 14.3.2/17.

**Expansion phase**

In the expansion phase of the study, 4 participants of the MTD analysis set, which served as the primary analysis set for dose decisions, experienced a total of 11 DLTs (all Grade 3). Eight of these DLTs (peripheral sensory neuropathy, increased ALT/AST values, hepatic pain and drug induced liver injury) occurred in 2 participants in the Reg72 conc+VI group, 2 (maculopapular rash and increased AST levels) in 1 participant in the Reg72 seq+VI group, and 1 (worsening of thrombocytopenia) in the Reg82 seq+VI group (CSR PH-40803). Thus, the MTD of regorafenib was 82 mg/m2 when used in combination with a backbone chemotherapy with vincristine and irinotecan. For further details, refer to CSR PH-40803 (database cut-off date of 05 MAY 2019).

**Escalation phase**

New findings or a worsening of baseline findings for blood pressure were reported as TEAEs for 8 escalation participants (19.5%) as hypertension (Table 14.3.1/2a). Drug-related hypertension as TEAEs of any CTCAE grade were reported for 4 participants (9.8%) (Table 14.3.1/3a). One participant had drug-related TESAE hypertension of Grade 3 (Table 14.3.2/2a), which was considered as a DLT and led to study drug interruption (Listing 16.2.7/7a; and CSR PH-38659, database cut-off date of 19 NOV 2015).

Pyrexia was reported as a TEAE for 20 escalation participants (48.8%). Drug-related pyrexia TEAEs were reported for 12 participants (29.3%). One participant had drug-related pyrexia of Grade 3. Pyrexia was also reported as a TESAE for 7 participants (17.1%), and 4 of them (9.8%) were drug-related. Three participants had pyrexia TEAEs leading to study drug interruption (Listing 16.2.7/7a).

For further analysis and summaries of vital sign data in the escalation phase of the study, refer to CSR PH-38659 (database cut-off date of 19 NOV 2015).

**Expansion phase**

In participants of the expansion phase, mean blood pressure (systolic and diastolic) remained nearly unchanged during treatment (Listing 16.2.8.2/3b). Two cases of transient Grade 3 hypotension (in 1 of the participants together with Grade 1 sinus tachycardia) were reported in the Reg82 seq+VI group as TEAEs. Three participants (2 in the Reg72 seq+VI and 1 in the Reg82 seq+VI groups) were reported with treatment-emergent Grade 1 hypertension and 1 participant in the Reg82 seq+VI group with Grade 2 (Listing 16.2.7./1b).

In participants with values at Screening and EoT visit, a trend towards increase in heart rate was noted (Listing 16.2.8.2/3b). Transient Grade 1 tachycardia deemed as unrelated to regorafenib was reported as a TEAE in 4 participants in the Reg82 seq+VI group (Listing 16.2.7./1b).

No relevant changes in mean body temperature and respiratory rate were observed (Listing 16.2.8.2/3b).

A trend towards decreased body weight was noted (Listing 16.2.8.2/3b). None of the participants with available data had a weight gain. The maximum weight loss was -27.8 kg in participant 120039003 (Reg82 seq+VI group). The overall rate of participants with the corresponding TEAE weight decreased was 38.1% (including 7 participants with worst Grades of 1–2 [2 participants in the Reg72 seq+VI group, and 5 participants in the Reg82 seq+VI group] and 1 participant in the Reg72 conc+VI group with worst Grade of 3 [deemed as unrelated to regorafenib]) (Table 14.3.1/2b).

**Electrocardiograms**

Individual ECG data for rhythm and cycle measurements, as well as findings by participant are presented in Listings 16.2.8.2/1a and 16.2.8.2/2a and Listings 16.2.8.2/1b and 16.2.8.2/2b for escalation and expansion participants, respectively.

In the escalation phase of the study, 1 participant in Dose Level 2 (72 mg/m$^2$) and 1 participant in Dose Level 4 (93 mg/m$^2$) experienced a sinus tachycardia and ECG QT prolonged reported as medical history findings, respectively. Most ECG abnormalities in escalation participants were assessed as clinically insignificant. One participant in Dose Level 4 (93 mg/m2) had ECG interpreted as abnormal and clinically significant at Screening and EoT visits (CSR PH-38659).

**In the expansion phase**, there were 2 participants with abnormal and clinically significant findings in ECG. However, the participants' performance status remained unchanged.

- Participant no. 160029001 in the Reg72 conc+VI group with normal sinus rhythm at screening reported ventricular extrasystole at EoT that was assessed as abnormal and clinically significant (Listing 16.2.8.2/2b). No associated TEAEs were reported.

- Participant no. 240039002 in the Reg72 seq+VI group had normal sinus rhythm at screening, which persisted until EoT. At EoT, the participant had QTC interval prolongation, which was assessed as abnormal and clinically significant (Listing 16.2.8.2/2b). The participant had TEAE cardiac failure reported, unrelated to study treatment (Listing 16.2.7/6b). In addition, the participant had intercurrent hemophagocytic lymphohistiocytosis and disease progression at the time of EoT (Listing 16.2.7/4b).

All other ECG findings in the expansion participants in SAF were assessed as normal/normal variant.

**Karnofsky performance status / Lansky Play performance status**

Respective participant listings of Lansky PS and Karnofsky Play PS are provided in Listings 16.2.8.2/7a and 16.2.8.2/8a for escalation and in Listings 16.2.8.2/7b and 16.2.8.2/8b for expansion phase. The results for Karnofsky PS and Lansky Play PS during the escalation phase are presented in CSR PH-38659 and during the expansion phase in Tables 14.3.4/2b and 14.3.4/3b. The PS was generally stable with no significant changes when compared to the baseline data from Section 8.5.2 of CSR PH-38659 for the escalation phase and CSR PH 40803 for the expansion phase.

**Skin and subcutaneous tissue**

**Escalation phase**

Thirty-five escalation participants (85.4% of 41 treated in escalation phase) experienced skin and subcutaneous tissue disorder TEAEs. Most commonly reported TEAEs by PTs were palmar-plantar erythrodysaesthesia syndrome (31.7%), rash (29.3%), and erythema (26.8%) (Table 14.3.1/2a).

Thirty-two participants (78.0%) experienced drug-related TEAEs by skin and subcutaneous tissue disorders SOC, most commonly reported by PTs were palmar-plantar erythrodysaesthesia syndrome (31.7%), rash (22.0%), and rash maculo-papular (19.5%).

Six participants (14.6%) experienced Grade ≥3 TEAEs by skin and subcutaneous tissue disorders SOC (all reported as Grade 3), with rash maculo-papular reported in 3 participants in Dose Level 2, palmar-plantar erythrodysesthesia syndrome and rash each reported in 1 participant in Dose Level 3, and dermatitis exfoliative generalized reported in 1 participant in Dose Level 4,.

Five participants (12.2%) experienced Grade ≥ 3 drug-related TEAEs by skin and subcutaneous tissue disorders SOC (all reported as Grade 3), with rash maculo-papular reported in 3 participants in Dose Level 2, palmar-plantar erythrodysesthesia syndrome reported in 1 participant in Dose Level 3, and erythroderma/dermatitis exfoliative reported in 1 participant in Dose Level 4, respectively.

One participant (2.4% of 41) in Dose Level 2 experienced a Grade 3 drug-related TESAE rash maculo-papular.

**Expansion phase**

Eighteen expansion participants (85.7% of 21 treated in expansion phase) experienced skin and subcutaneous tissue disorder TEAEs. Most commonly reported TEAEs by PTs were rash (42.9%), dry skin (38.1%), and alopecia (28.6%).

Fourteen participants (66.7%) experienced drug-related TEAEs by skin and subcutaneous tissue disorders SOC, most commonly reported by PTs were alopecia (28.6%) and rash (19.0%).

Three participants (14.3%) experienced Grade ≥ 3 TEAEs by skin and subcutaneous tissue disorders SOC (all reported as Grade 3), with pain of skin, palmar-plantar erythrodysesthesia syndrome, and rash maculo-papular reported in 1 participant, each.

Two participants (9.5%) experienced Grade ≥3 drug-related (i.e., considered related to any of the 3 drugs: regorafenib, irinotecan, vincristine) TEAEs by skin and subcutaneous tissue disorders SOC, with Grade 3 palmar-plantar erythrodysesthesia syndrome and rash maculo-papular reported in 1 participant, each (Table 14.3.1/4b), events were assessed as related to regorafenib in both cases.

There were no TESAEs from the skin and subcutaneous tissue disorders SOC reported in the expansion phase of the study.

Bone growth and dental examination

Bone and teeth growth were monitored annually (or more often, if deemed necessary) for at least 2 years regardless of subsequent clinical trial participation. Participant listings of hand wrist radiography are provided in Listings 16.2.8.2/9a (escalation phase) and 16.2.8.2/6b (expansion phase). Participant listings of dental examination are provided in Listings 16.2.8.2/6a (escalation phase) and 16.2.8.2/7b (expansion phase).

**Bone growth and dental examination (Escalation phase)**

Hand-wrist X-ray

Hand-wrist X-rays are available for all 41 participants treated in the escalation phase of the study (Listings 16.2.8.2/6a). For 5 of these, interpretation was reported as ‘abnormal’ at screening.

**Dental examination**

Dental examination at screening are available for 29 of the 41 participants. Baseline dental examination results were reported as normal for 27 participants and abnormal for two participants (120020004 and 120020006; post-baseline evaluations are not available). Of those 29 participants, post-baseline dental examinations were only available for 4 participants and all were reported as normal.

**Bone growth and dental examination (Expansion phase)**

All of the 21 expansion participants had baseline hand-wrist X-rays and dental examination at screening. Of the 21 participants, 14 had post-baseline hand-wrist X-rays (Listing 16.2.8.2/6b) and 11 participants had dental examinations.

**Hand-wrist X-ray**

Of the 14 expansion participants with post baseline hand-wrist X-rays, 3 participants had abnormal hand-wrist X-ray at baseline with findings of delayed bone age (220019003 and 120039004) and advanced bone age (160049001). These findings were maintained at EoT assessment.

Abnormal post-baseline hand-wrist X-ray findings of "advanced bone age" were reported for 3 expansion participants (120019003, 240039004, and 120049003):

- Participant 120019003, an 11-year-old male with metastatic RMS, reported abnormal "advanced bone age" on X-rays C22D1 and C38D1. The participant was receiving treatment for hypothyroidism (Listing 16.2.4/5b) that could explain the advance bone age (1).

- Participant 240039004, a 10-year-old female with metastatic RMS, had abnormal "advanced bone age" at X-ray in C36D1 and C43D1 by investigator. The participant was receiving treatment for hypothyroidism (Listing 16.2.4/5b) (that could explain the advance bone age (1)) and received radiation therapy around the time of the abnormality.

- Participant 120049003, a 2-year-old male with metastatic RMS, had the 'abnormal' "advanced bone age" at the EoT. This participant did not have additional X-rays reported. Follow-up information: The investigator commented that the "abnormal; "advanced' bone age was also observed at baseline X-ray before the start of study treatment.

Further to the investigator assessments, an independent pediatric endocrinologist consultation assessed the hand-wrist X-rays of patients (240039003 and 120049003) and these were assessed as "normal variants" for age.

**Dental examination**

One participant had 'abnormal' reported in baseline dental examination (120039004). Of 11 participants with post-baseline dental examinations, one reported 'microdontia and blunted roots' (240039004).

Participant 240039004 is also presented above diagnosed with "advanced bone age" at X-ray findings in C36D1 and C43D1 by investigator. Participant was receiving treatment for hypothyroidism (Listing 16.2.4/5b) and received radiation therapy around the time of the abnormality in the dental X-ray (Listing 16.2.8.2/5b) that confounds the causal evaluation of this case (2).

Overall, based on the assessment of the participants with post baseline hand-wrist and dental X-rays, there is insufficient evidence to support a causal association between regorafenib and risk to teeth and skeletal growth.

**Other variables and evaluations**

**Palatability of regorafenib tablets/granulate**

Palatability of the regorafenib tablets/granulate was assessed as at least neutral, and none of the participants found it difficult to swallow (CSR PH-40803 [database cut-off date of 05 MAY 2019]).

**Discussion on clinical aspects**

**Escalation phase**

Four dose levels (60, 72, 82 and 93 mg/m$^2$) were studied in the single agent dose escalation phase, and 5 subjects had DLTs reported during the assessment of MTD. For Dose Level 4, due to the incidence of 2 DLTs in 7 subjects treated (5 were considered evaluable for MTD analysis), 93 mg/m$^2$ was deemed not tolerable, and 82 mg/m$^2$ was considered the MTD. In addition, dose modifications were required for almost all subjects in this cohort, corroborating the poor tolerability of Dose Level 4.

During the safety expansion of the MTD cohort (82 mg/m$^2$ dose level) to establish the RP2D, the incidence of 2 treatment related Grade 4 hematological toxicities (neutropenia and platelet count decreased) during the first cycle of study treatment prompted the call for additional safety discussion with investigators and the Sponsor's study team. After preliminary evaluation of the available laboratory data, and based on the expected safety profile, it was noted that for this study, there seemed to be a myelosuppressive effect of regorafenib on thrombocytes, lymphocytes and neutrophils, with no clinically relevant effect on erythropoiesis. This was observed at different dose levels, and although no clear dose dependency was observed, an additional safety expansion at 72 mg/m$^2$ was initiated to have a better understanding of the regorafenib safety profile in pediatric subjects with recurrent or refractory solid tumors. On 07 DEC 2015, a meeting was held between the Sponsor and the study Investigators to determine the RP2D and the 72 mg/m$^2$ dose was selected. On 18 MAY 2016, based on the availability of all PK data and an analysis demonstrating that the observed geometric mean exposure at the 82 mg/m$^2$ dose level is closer to that observed in adults at a dose level of 160 mg dose q.d. for 21 days, the decision was made to revisit the RP2D. In addition, aggregated safety data showed that the hematologic toxicity in this trial is not limited to a specific dose level, nor showed higher incidence when the dose was increased (Grade 4 hematological related events occurred at all dose levels, and in the majority of cases appeared to be associated to the extent of prior treatment received, with subjects receiving prior high dose chemotherapy with stem cell transplantation or craniospinal irradiation at a higher risk). A new meeting was held between the Sponsor and the study investigators and 82 mg/m$^2$ was selected as the RP2D of single agent regorafenib in pediatric subjects with solid malignant tumors to be studied in subsequent trials.

**Dose expansion phase**

The results of the dose expansion phase of study have been submitted in CSR B003223. The safety of regorafenib in combination with vincristine and irinotecan as backbone chemotherapy was investigated in pediatric subjects with solid malignant tumors that were recurrent or refractory to standard therapy included 41 patients.

The most common cancer type in the expansion phase was RMS (12 participants, 57.1%). Eight of the 21 participants (38.1%) in the expansion phase SAF of the study were female and 13 (61.9%) were male; 14 participants (66.7%) were White. The participants' median age was 10.0 years (range: 1.5 to 17.0 years). All of the 21 participants (100%) treated in the expansion phase of the study had already received ≥1 prior systemic anticancer therapy.

In the dose expansion phase of the study, the evaluation of the **antitumor activity** of regorafenib in combination with vincristine and irinotecan was a secondary objective. The response rate (CR+PR) was 47.6%. Seven of the 21 expansion participants in the EAS (33.3%) achieved PR as best overall

response during treatment or active follow-up and 7 participants (33.3%) had SD. Three participants (14.3%) had achieved CR as best response. All 3 participants were in the Reg82 seq+VI group. As of the final data release of the clinical database (date of clean database 05 APR 2024), 16 of the 21 expansion participants (76.2%) in the efficacy/safety analysis set had died.

Based on the limited amount of data generated during the expansion phase of the study, regorafenib at doses between 72 mg/m$^2$ and 82 mg/m$^2$ in combination with vincristine and irinotecan as backbone chemotherapy demonstrated a clear signal of efficacy, with 3 participants (14.3%) who achieved CR and were alive at the time of data release, in the studied patient population with relapsed/refractory RMS or other solid malignant tumors.

As of the final data release of the clinical database (clean database 05 APR 2024), the median overall time on treatment with regorafenib (including time off-drug/interruptions) was 98 days or 3.22 months (range: 12 to 1815 days [0.39 to 59.63 months[3]]), corresponding to a median number of 4 cycles (range: 1 to 85 cycles). The **median treatment duration** was longer in the Reg72 groups (11.5 and 5.5 cycles) when compared to the Reg82 seq+VI group (4.0 cycles).

**Dose reductions** of regorafenib (n=10) were reported in 8 of 21 participants (38.1%) and all of these reductions were primarily due to a TEAE. All but 4 participants in the Reg82 seq+VI group (81.0% of the total SAF in the expansion phase of the study) had ≥1 irinotecan dose modification (dose reduction and/or interruption or delay of dosing. All but 5 participants in the Reg82 seq+VI group (76.2% of the total SAF in the expansion phase of the study) had ≥1 dose modification of vincristine (dose reduction and/or interruption or delay of dosing).

A summary of the **pharmacokinetic** data was not provided with the study report. The MAH has completed the pharmacokinetic analysis and evaluation of regorafenib in paediatric patients. The pharmacokinetic data are included in section 9.4 of interim CSR PH-40803 (version 1.0, dated 06 January 2020, with cut-off date of May 05, 2019).

This report was submitted on June 25, 2020, as part of an interim compliance check with PDCO and concluded the PIP requirement for Study 5 (Compliance report reference: EMEA-C2-001178-PIP01-11M05) and was referenced in section 9.4 of the final CSR.

All 21 treated participants of the expansion phase of the study experienced ≥1 **TEAE**, and all of them experienced ≥1 TEAE rated as drug-related (irrespective of the drug). The most frequent (≥30% in the total group) TEAEs were diarrhoea (95.2%), anaemia (71.4%), neutropenia and abdominal pain (71% each), pyrexia (66.7%), vomiting (61.9%), decreased appetite (57.1%), thrombocytopenia (57%), rash (48%), nausea (47.6%), fatigue (43%), ALT increased and AST increased (42.9% each), weight decreased, hypokalemia, and dry skin (38.1% each), leukopenia (38%), and gamma-glutamyltransferase increased and hypophosphatemia (33.3% each). Eleven (11) of 21 participants (52.4%) experienced TEAEs of worst Grade 3, 7 participants (33.3%) of worst Grade 4, and 2 participants (9.5%) of worst Grade 5. The most commonly reported **drug-related TEAEs** (occurring in ≥30% in the total group) were diarrhea (81%), neutropenia (71%), anemia (66.7%), vomiting (52.4%), thrombocytopenia (52%), abdominal pain and decreased appetite (47.6% each), nausea, ALT increased, and AST increased (42.9% each), and leukopenia and fatigue (38% each).

A total of 16 of 21 (76.2%) participants died during the expansion phase of the study; of which 2 participants died within 30 days after last dose.

In the expansion phase of the study, 4 participants of the **MTD** analysis set, which served as the primary analysis set for dose decisions, experienced a total of 11 DLTs (all Grade 3). Eight of these DLTs (peripheral sensory neuropathy, increased ALT/AST values, hepatic pain and drug induced liver injury) occurred in 2 participants in the Reg72 conc+VI group, 2 (maculopapular rash and increased

AST levels) in 1 participant in the Reg72 seq+VI group, and 1 (worsening of thrombocytopenia) in the Reg82 seq+VI group (CSR PH-40803). Thus, the MTD of regorafenib was 82 mg/m$^2$ when used in combination with a backbone chemotherapy with vincristine and irinotecan.

# 3. CHMP's overall conclusion and recommendation

The MAH submitted the final CSR for study 73-4506/15906, PIP study 5: A multi-center, open-label, non-randomized, phase 1 dose escalation study of regorafenib (BAY 73-4506) in pediatric subjects with solid malignant tumors that are recurrent or refractory to standard therapy.

Regorafenib 82 mg/m$^2$ in combination with vincristine and irinotecan as backbone chemotherapy demonstrated a signal of efficacy in the studied pediatric patient population with relapsed/refractory RMS or other solid malignant tumors. The adverse events profile of the combination therapy is severe. The combination is further being evaluated in a comparative clinical trial for the treatment of relapse rhabdomyosarcoma i children aged >6 months and older. The multi-centre, randomised, controlled, open label trial to evaluate the activity, safety and efficacy of regorafenib in combination with vincristine (V) and irinotecan (I) compared to VI alone in the paediatric population from 6 months to less than 18 years with a first and subsequent relapses of rhabdomyosarcoma is ongoing. The results of the comparative PIP study 7 need to be awaited for further evaluation of the B/R of regorafenib in combination with vincristine and irinotecan versus VI alone in the paediatric population with a first and subsequent relapses of rhabdomyosarcoma.

Pediatric PK data were gathered and evaluated in a popPK model, as mentioned in the study methods. The MAH completed the pharmacokinetic analysis and evaluation of regorafenib in paediatric patients. The pharmacokinetic data are included in section 9.4 of interim CSR PH-40803 (version 1.0, dated 06 January 2020, with cut-off date of May 05, 2019). In addition, the MAH commits to providing a commentary on the suitability of the inclusion into the SmPC upon completion of Study 7.

## ☒ Fulfilled:

No regulatory action required.

## ☐ Not fulfilled:

<Based on the data submitted, the MAH should provide <description of the additional clarifications requested per study>as part of this procedure. (see section "Request for supplementary information")