Amsterdam, 27 February 2025
EMA/46449/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cyramza

Ramucirumab

Procedure no: EMEA/H/C/002829/P46/010

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	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	30/12/2024	30/12/2024	☐
☐	CHMP Rapporteur Assessment Report	03/02/2025	03 Feb 2025	☐
☐	CHMP members comments	17/02/2025	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	20/02/2025	n/a	☐
☒	CHMP adoption of conclusions:	27/02/2025	27/02/2025	☐

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1. Introduction

On 10 december 2024, the MAH submitted a completed paediatric study for ramucirumab, 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 study J1S-MC-JV01 (JV01) is part of a clinical development program. Study JV01 is not planned to be submitted as part of a future variation.

Study JV01 is a randomised, multicentre, global, Phase 1/2 study to evaluate the efficacy, safety, and tolerability of ramucirumab in combination with low-dose cyclophosphamide and vinorelbine in paediatric patients and young adults diagnosed with relapsed, recurrent, or refractory desmoplastic small round cell tumour (DSRCT).

Ramucirumab has been approved for use in adults as a single-agent and in combination with various chemotherapeutic agents or erlotinib in the European Union. The adult registered doses of ramucirumab are 8 mg/kg intravenous (IV) formulation administered every 2 weeks (Q2W) in gastric cancer, colorectal cancer, and hepatocellular carcinoma indications; 10 mg/kg IV formulation administered Q2W in epidermal growth factor receptor-mutated non-small cell lung cancer (NSCLC); and 10 mg/kg IV formulation administered every 3 weeks in NSCLC in patients with disease progression after platinum-based chemotherapy (Cyramza SmPC).

Ramucirumab has not been approved in paediatric patients, however, it has been studied previously in the paediatric I4T-MC-JVDA (JVDA) trial that was completed in 2020 and in the Phase 1/2 Study J1S-MC-JV02 (JV02) in 2023. Study JV01 and JV02 were conducted under the construct of the CAMPFIRE Master Protocol JAAA that defined common elements across both studies.

JVDA was a multicentre, open-label, dose-finding, and dose-escalation study of ramucirumab monotherapy in children aged at least 12 months and patients 21 years of age or below with recurrent solid tumours, including central nervous system tumours. JVDA was submitted to EMA through an Article 46 submission on 03 February 2021 (EMA/H/C/002829/P46/008). Relevant information was included in the SmPC.

Study JV02 was a randomised, multicentre, global, Phase 1/2 study in paediatric patients and young adults with relapsed, recurrent, or refractory synovial sarcoma (SS), evaluating the efficacy of ramucirumab in combination with chemotherapy versus chemotherapy alone. JV02 was submitted to EMA through an Article 46 submission on 29 August 2023 (EMA/H/C/002829/P46/009). Relevant information was included in the SmPC.

Study JV01 is not part of a paediatric investigation plan (PIP). Product specific waivers were granted for all subsets of the paediatric population for the treatment of gastric cancer and gastro-oesophageal junction adenocarcinoma, intestinal malignant neoplasm, lung malignant neoplasm and liver cancer and urinary tract malignant neoplasm (P/0282/2017).

Study JV01 passed the interim futility analysis and completed enrolment. The primary analysis data cutoff date was 14 June 2024. The last patient last visit is not completed, as there is 1 remaining patient on trial to have the last patient last visit to occur. This patient has been moved to a continued access program and no additional analyses are planned to be conducted once the remaining last

patient completes the last visit. The MAH does not plan to create and submit a clinical study report addendum. This is considered acceptable.

Study JV01 did not meet the pre-specified success criterion for the study. The safety assessment did not reveal any new or unexpected safety findings. The MAH did not propose any changes to the product information, however, a proposal for a SmPC update was submitted in case the CHMP would consider the results in general to be meaningful enough to request an update to the SmPC.

2.2. Information on the pharmaceutical formulation used in the study

Ramucirumab was administered as an intravenous infusion over 60 minutes (12 mg/kg) at day 1 and day 15 of 28-day cycles. All study drugs were administered at the investigational site; at-home intravenous administration was not permitted in the study. Treatment was to continue until evidence of disease progression or other discontinuation criteria were met.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- J1S-MC-JV01: A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Paediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumour.

2.3.2. Clinical study

J1S-MC-JV01: A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Paediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumour.

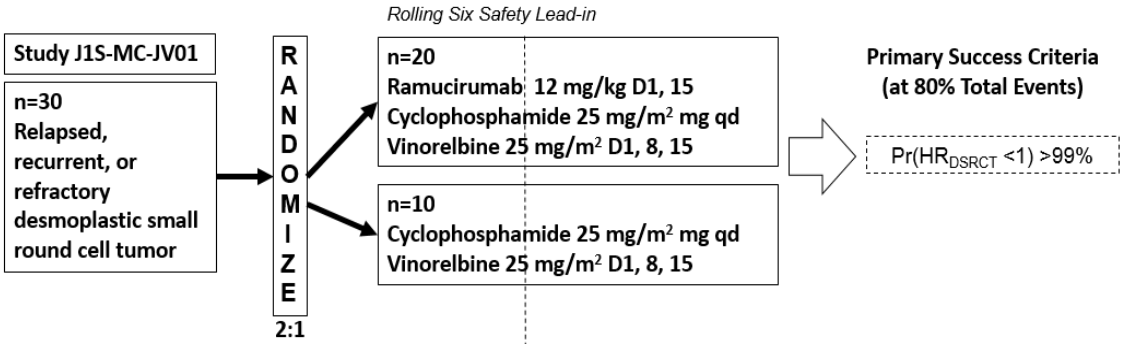
Description

Study JV01 was a randomised, multi-centre, global, Phase 1/2 study in paediatric and young adult patients with relapsed, recurrent, or refractory DSRCT evaluating the efficacy of ramucirumab in combination with chemotherapy versus chemotherapy alone.

A total of approximately 30 patients were to be randomised at a ratio of 2:1 to receive ramucirumab in combination with a tumour-specific chemotherapy (RAM + CV) backbone versus chemotherapy alone (CV) (Figure 1).

To assess excessive toxicity associated with the experimental ramicurimab-based combination, a safety lead-in period was observed via the rolling 6 decision framework (Skolnik et al, 2008).

Figure 1 ***JV01 Study Design****. Abbreviations: D = day; DSRCT = desmoplastic small round cell tumour; HR = hazard ratio; n = approximate number of patients per treatment arm; Pr = probability*



Methods

Study participants

Key inclusion criteria:

- patients of 12 months to 29 years of age at the time of study enrolment, while patients from countries in EU should be 36 months to 29 years of age and weighing greater than 11 kg at the time of study enrolment
- patients with relapsed, recurrent, or refractory DSRCT
- patients with measurable or evaluable disease by Response Evaluation Criteria in Solid Tumours 1.1
- patients had received at least 1 prior line of systemic treatment for which they were eligible, unless the patient was not a suitable candidate for the approved therapy
- patients must not be eligible for surgical resection at the time of enrolment

Key exclusion criteria:

- patients were taking any prohibited medications
- patients with bleeding or had a history of significant bleeding event within 3 months prior to enrolment
- patients with bleeding diathesis or vasculitis
- patients with a history of deep vein thrombosis requiring medical intervention, haemoptysis or other signs of pulmonary haemorrhage within 3 months prior to study enrolment
- patients with central nervous system, arterial or venous thromboembolic events, transient ischemic attack, cerebrovascular accident, myocardial infarction within 6 months prior to study enrolment
- patients who had a nonhealing wound, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of enrolment
- patients previously treated and progressed on combination CV regimen
- patients with hepatic impairment

- patients with bowel obstruction, history or presence of inflammatory enteropathy or extensive intestinal resection, Crohn's disease, ulcerative colitis, or chronic diarrhoea
- patients with urinary outflow obstruction
- patients with Grade 2 haematuria or non-infectious cystitis at the time of screening
- patients with central nervous system involvement.

Treatments

The dosing schedule is shown in **Error! Reference source not found.** for the intervention (1) and control (2) arm. The treatments were administered in a 4-week (28-day) cycle. Patients received premedication with diphenhydramine or alternative antihistamine within 30 to 60 minutes prior to each infusion with ramucirumab.

Ramicurumab was administered first, followed by vinorelbine on days when both were given. During the first 2 ramicurimab infusions, patients were closely monitored for a 1-hour observation period following the ramicurimab infusions before receiving vinorelbine. On these visits, cyclophosphamide was taken in the clinic following the ramicurimab infusion observation period. On all other days, including days of study treatment, cyclophosphamide was taken at home prior to clinic visits. In addition, vinorelbine was given without the post- ramicurimab observation period after the first 2 ramicurimab infusions, unless an infusion-related reaction (IRR) had occurred.

Table 1 ***Study interventions administered****. Abbreviations: IV = intravenous; kg = kilogram; mg = milligram; PO = by mouth.*

Study drug	Arm	Dose	Route	Timing
Ramucirumab	1	12 mg/kg	IV	Approximately 1-hour infusion on Days 1 and 15 of each 28-day cycle
Cyclophosphamide	1 & 2	25 mg/m^2	PO	Daily on Days 1-28 of each 28-day cycle
Vinorelbine	1 & 2	25 mg/m^2	IV	Days 1, 8, and 15 of each 28-day cycle

Dose reductions are described in **Error! Reference source not found.**. Any patient who required a dose reduction continued to receive a reduced dose for the remainder of the study. For ramicurimab, cyclophosphamide, or vinorelbine, any patient who had 2 dose reductions in the same agent and who experienced a toxicity that would cause a third dose reduction were discontinued from that study treatment. During the rolling-6 safety lead-in, de-escalation of ramucirumab to 8 mg/kg was possible.

Table 2 ***Dose reductions*** *for treatment-related toxicities*

Study drug	Starting dose	Dose reduction	
		First	Second
Ramicurimab	12 mg/kg	10 mg/kg	8 mg/kg
if de-escalated	8 mg/kg	6 mg/kg	5 mg/kg
Cyclophosphamide	25 mg/m^2	20 mg/m^2	15 mg/m^2
Vinorelbine	25 mg/m^2	20 mg/m^2	15 mg/m^2

Objective(s)

The primary objective was:

- to evaluate the efficacy of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in paediatric and young adult patients with DSRCT.

The secondary objectives were:

- to evaluate the safety and tolerability of ramucirumab in combination with cyclophosphamide and vinorelbine compared with cyclophosphamide and vinorelbine in paediatric and young adult patients with DSRCT.
- to characterise the PK and immunogenicity of ramucirumab when co administered with cyclophosphamide and vinorelbine in paediatric and young adult patients with DSRCT.

Outcomes/endpoints

The primary endpoint was PFS.

Secondary endpoints were:

- SAEs, AEs, safety laboratory assessments, and vital signs
- overall response rate (ORR), duration of response (DoR) and complete response (CR)
- C_{max} and Ctrough
- Incidence of immunogenicity

Sample size, randomisation and blinding (masking)

A total of approximately 30 patients were randomised at a ratio of 2:1 to receive ramucirumab in combination with a tumour-specific chemotherapy backbone versus chemotherapy alone. Randomization was stratified according to staging at relapse (metastatic versus locally advanced). Study JV01 was an open-label study.

Statistical Methods

Primary outcome - PFS

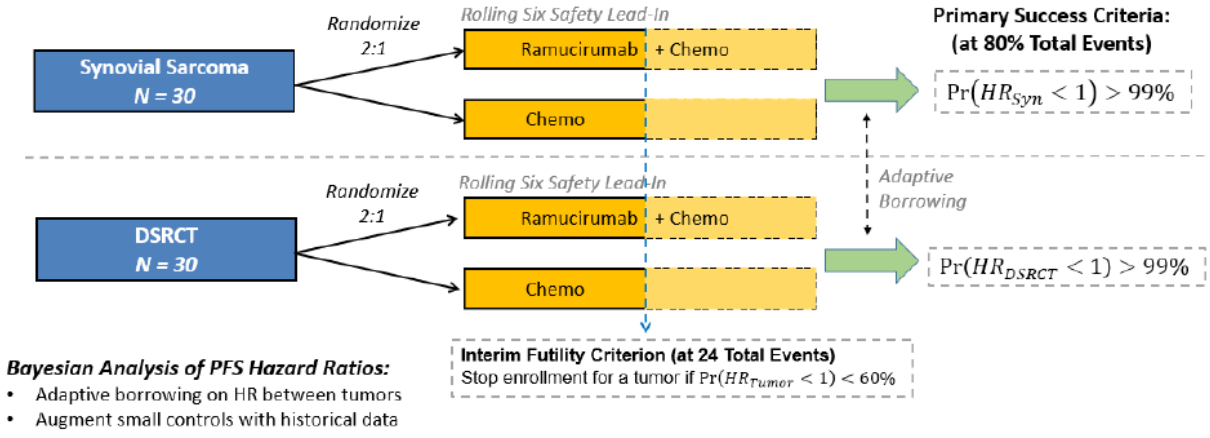
PFS was defined as the time from randomization until the first investigator-determined objective progression as defined by RECIST v1.1, or death from any cause in the absence of progressive disease. Patients known to be alive and without disease progression were censored at the time of the last adequate tumour assessment (Table 3).

Table 3 PFS Event/Censoring scheme

Situation	Event/Censor	Date of Event or Censor
Investigator assessed tumour progression or death	Event	Earliest date of PD or death
No tumour progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)
Unless		
No baseline radiological tumour assessment available	Censored	Date of randomisation
No adequate postbaseline radiological tumour assessment available and death reported after 2 scan intervals following randomization	Censored	Date of randomisation
New anticancer treatment started and no tumour progression or death within 14 days	Censored	Date of adequate radiological assessment before (start of new therapy +14 days) or date of randomization (whichever is later)
Tumour progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumour assessment or randomization (whichever is later)	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)

The primary endpoint of PFS was analysed via a Bayesian hierarchical Weibull model that allows (1) adaptive borrowing on effect-size (log hazard ratio) between studies JV01 and JV02 and (2) augmenting with historical control data via the use of informative prior distributions constructed from real-world (RW) control outcomes. A schematic diagram of the studies and their statistical/timing linkages is provided in Figure 2.

Figure 2 JVAA study design



Secondary outcomes - efficacy

Overall response rate (ORR) was defined as the number of patients who achieve a best overall response of CR or PR divided by the total number of patients randomized to the corresponding treatment arm (ITT population). The confirmation of CR and PR was required.

The CR rate was defined as the number of patients who achieve a best overall response of CR divided by the total number of patients randomized to the corresponding treatment arm (ITT population). The confirmation of CR was required.

Duration of response was defined as the time from the date measurement criteria for CR or PR (whichever is first recorded) were first met until the first date that disease was recurrent or objective progression was observed, per RECIST 1.1, or the date of death from any cause in the absence of objectively determined disease progression or recurrence. DoR was calculated only for patients with confirmed PR or CR. DoR was summarized for each treatment arm using descriptive statistics.

Secondary outcomes - pharmacokinetics

In study JV01, ramucirumab concentrations were collected following administration of ramucirumab 12 mg/kg on Day 1 and Day 15 of a 28-day cycle.

Ramucirumab PK sampling was performed at the following time:

- At end of infuction on Day 1
- Pre-dose on Day 15 of Cycle 1
- Pre-dose on Day 1 of Cycle 2
- Pre-dose on Day 1 of Cycle 4
- Pre-dose on Day 1 of Cycle 7, and
- Pre-dose on Day 1 of Cycle 10.

Interim futility analysis

An interim futility analysis was triggered when approximately 24 total PFS events had been observed across studies JV01 and JV02 with a minimum of 8 events in each study. At the interim futility look for study JV01, the Bayesian analysis must have provided a minimum of 60% confidence in treatment superiority (PFS HR less than 1 for patients with DSRCT) for enrolment on study JV01 to continue. Otherwise, enrolment on study JV01 would be stopped.

Study JV01 passed the futility analysis and completed enrolment. Historical control data (see below) were not included in the futility analysis due to insufficient data available at the time of the analysis. The omission of these data in this circumstance was prespecified in the statistical analysis plan.

Primary analysis

If a study passed the futility analysis, the primary analysis was triggered when PFS events had occurred for approximately 80% of the enrolled patients across both Study JV01 and Study JV02, regardless of whether or not 1 stopped for futility. To conclude success for the investigation in Study

JV01, the Bayesian analysis were to yield a minimum of 99% confidence in treatment superiority (PFS HR less than 1) for the DSRCT population.

Historical controls

To augment the control arm, a retrospective chart review was conducted to collect real-world data for paediatric and young adult patients with relapsed, recurrent, or refractory DSRCT. The chart review was conducted at the US sites where site personnel entered requested data variables into a study-specific electronic case report form. Data collection was intended to allow for estimation of PFS of systemic anti-cancer regimens for relapsed, recurrent, or refractory DSRCT.

Eligibility criteria included

- age at initial DSRCT diagnosis of at least 12 months to 39 years or below
- initial diagnosis on or after 01 January 2005
- documentation of at least 1 systemic anti-cancer therapy regimen in the relapsed or recurrent setting

This age limit is higher than the eligibility criterion for study JV01, as pathology and outcomes were not expected to vary based on age in these diseases; therefore, the age range was expanded to facilitate improved matching on other important prognostic factors. Variables to be extracted include patient and baseline/disease characteristics, as well as treatments (surgery, radiotherapy, chemotherapy) and outcomes since initial DSRCT diagnosis. Progression dates were based primarily on physician notes and no re-interpretation of radiologic scans was required. The target sample size was 100 charts at the time of the final analysis.

Expert prior elicitation

During the design phase of studies JV01 and JV02, a formal prior elicitation exercise (Garthwaite et al. 2005) was conducted to characterize expert opinion regarding the anticipated duration of median PFS on the control arms. The elicitation interviews were conducted with 6 investigators or academic pediatric oncologists specializing in the treatment and clinical research for cancers including SS and DSRCT.

The expert elicited priors were constructed according to the following procedure:

- each of the 6 experts was interviewed (independently) with prespecified questions designed specifically to elicit gamma priors for the 2 Weibull parameters for the control arm in each of studies JV01 and JV02, and
- the resulting gamma priors (for 1 shape parameter and 1 rate parameter for each of Studies JV01 and JV02) were synthesized using a fixed-effects approach in which the combined prior was the product of the individual gamma priors (from each expert).

Sensitivity analyses

Besides the primary Bayesian analysis, the following sensitivity analyses were performed:

- Traditional frequentist analysis (1-sides alpha level of .1, 2-sides coverage equal to 80%)

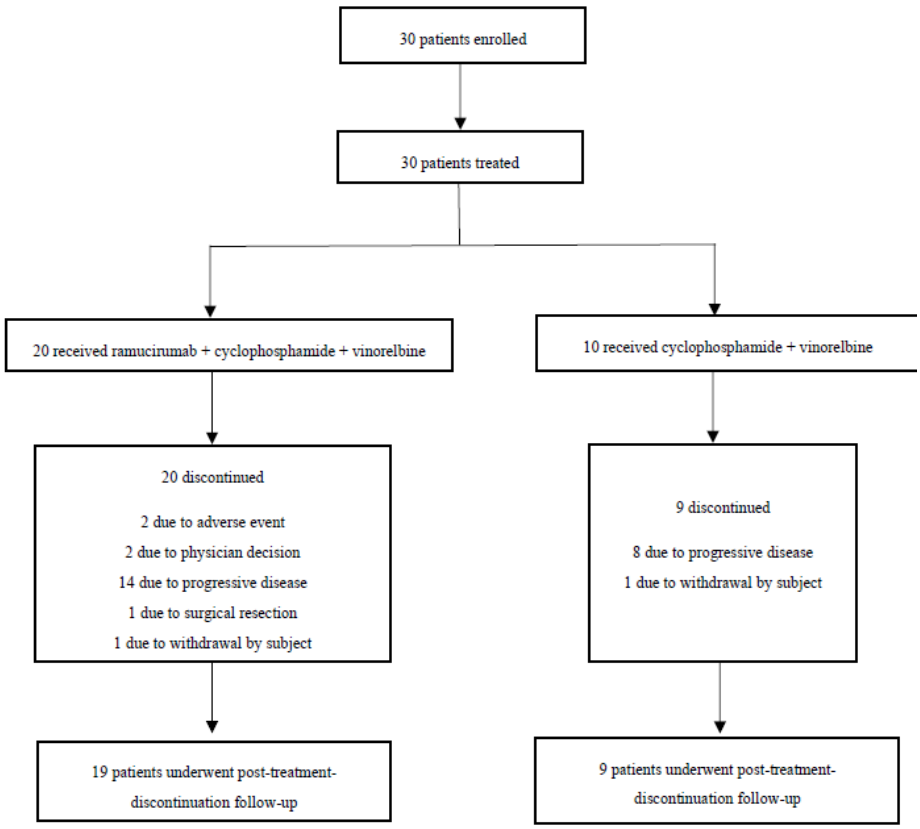
- Sensitivity analysis 1: eliminates borrowing from the study JV02 PFS effect-size but maintains borrowing from historical controls
- Sensitivity analysis 2: eliminates borrowing from historical controls but maintains borrowing from the study JV02.
- Sensitivity analysis 3: removes borrowing from all exogenous data (historical controls and study JV02)
- Sensitivity analysis 4: studies the effect of using Mahalanobis distance matching (instead of the prespecified propensity base approach) to identify the matched historical controls
- Sensitivity analysis 5: effect of using formal expert elicitation priors in lieu of the power priors constructed from historical controls but maintains borrowing from the study JV02
- Sensitivity analysis 6: removes the influence of the study JV02 matched historical data on the study JV02 HR, which is borrowed by the model for estimation of the study JV01 HR

Results

Participant flow

A total of 30 patients at 20 sites were enrolled. A total of 20 patients received at least 1 dose of ramucirumab. The participant flow is shown in Figure 3.

Figure 3 Study participant disposition



Recruitment

The first patient enrollment to the study was on 22 January 2020 and the last patient visit was on 14 June 2024. The results presented are based on the data cutoff date of 14 June 2024. Of note, the last patient last visit was not completed, as there is 1 remaining patient on trial to have the last patient last visit to occur. This patient has been moved to a continued access program and no additional analyses are planned to be conducted once the remaining last patient completes the last visit.

Baseline data

Baseline characteristics are shown in Table 4. Patients were mainly white (56.7%) and male (83.3%). The median age of the patients was 21 years (range 7 to 28 years), with 11 (36.7%) patients being 17 years or younger (8 in the intervention arm; 3 in the control arm). The median body weight of the patients was 59.9 kg (range 26 kg to 130 kg). More male patients were enrolled in the control treatment arm (CV) compared with the interventional treatment arm (RAM+CV, 100% versus 75%).

Table 4 Patient demographics and baseline characteristics (ITT)

	RAM + CV (N = 20)	CV (N = 10)	Total (N = 30)
Demographic Parameter	**n (%)**	**n (%)**	**n (%)**
Sex, n (%)			
Male	15 (75.0)	10 (100.0)	25 (83.3)
Female	5 (25.0)	0	5 (16.7)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	2 (10.0)	4 (40.0)	6 (20.0)
Black or African American	4 (20.0)	1 (10.0)	5 (16.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	13 (65.0)	4 (40.0)	17 (56.7)
Multiple	0	0	0
Missing	1 (5.0)	1 (10.0)	2 (6.7)
Ethnicity, n (%)			
Hispanic or Latino	3 (15.0)	1 (10.0)	4 (13.3)
Not Hispanic or Latino	16 (80.0)	8 (80.0)	24 (80.0)
Not reported	1 (5.0)	1 (10.0)	2 (6.7)
Age group, n (%)			
≤17 years	8 (40.0)	3 (30.0)	11 (36.7)
>17 years	12 (60.0)	7 (70.0)	19 (63.3)
Weight (kg)			
N	18	10	28
Median	59.9	60.4	59.9
Min-max	26-130	35-100	26-130
Missing	2	0	2
Lansky PS (< 16 years)			
N	5	3	8
Median	100	80	85
Min-max	70-100	80-90	70-100
Missing	15	7	22
Karnofsky PS (≥16 years)			
N	3	0	3
Median	100	NA	100
Min-Max	90-100	NA	90-100
Missing	17	10	27
ECOG PS			
0	8 (40.0)	5 (50.0)	13 (43.3)
1	1 (5.0)	2 (20.0)	3 (10.0)
2	0	0	0
Missing	11 (55.0)	3 (30.0)	14 (46.7)

Baseline disease characteristics are shown in Table 5. The median duration of disease prior to the start of study treatment was 16 months in the interventional treatment arm compared with 23 months in the control treatment arm. At study entry, the majority (73.3%) of patients had metastatic disease at relapse. More patients (50%) in the interventional arm (RAM + CV) had relapse in less than 1 year compared with the control arm (CV, 20%).

Table 5 Baseline disease characteristics

	RAM + CV (N = 20)	CV (N = 10)	Total (N = 30)
Duration of Disease (Months)[a]			
N	19	10	29
Mean (SD)	20.2 (12.39)	32.8 (22.97)	24.5 (17.49)
Median (Q1, Q3)	16 (11, 28)	23 (17, 53)	19 (12, 31)
Min-max	5-53	5-69	5-69
Missing	1	0	1
Metastatic Disease at Relapse, n (%)			
No	1 (5.0)	0	1 (3.3)
Yes	14 (70.0)	8 (80.0)	22 (73.3)
Missing	[b]5 (25.0)	[b]2 (20.0)	7 (23.3)
Lines of Therapy, n (%)			
1	9 (45.0)	2 (20.0)	11 (36.7)
≥2	11 (55.0)	8 (80.0)	19 (63.3)
Time-to-Relapse Group, n (%)			
<1 year	10 (50.0)	2 (20.0)	12 (40.0)
≥1 year	4 (20.0)	2 (20.0)	6 (20.0)
Missing	6 (30.0)	6 (60.0)	12 (40.0)
Tumor Size Group at Initial Diagnosis, n (%)			
<10 cm	6 (30.0)	4 (40.0)	10 (33.3)
≥10 cm	6 (30.0)	1 (10.0)	7 (23.3)
Missing	8 (40.0)	5 (50.0)	13 (43.3)

Abbreviations: CV = cyclophosphamide and vinorelbine; ITT = intention to treat; max = maximum; min = minimum; n = number of patients in the specified category; N = number of patients in the intent-to-treat population within the treatment group; Q = quartile; RAM = ramucirumab; SD = standard deviation.

[a] Duration of disease is the time from date of initial diagnosis to date of start of study treatment

[b] of 5 patients in the RAM + CV treatment arm with missing CRF data for metastatic disease at study entry, 4 had metastatic disease and 1 had locally advanced disease per interactive web-response system. And the 2 patients in the CV arm with missing CRF data for metastatic disease at study entry, had metastatic disease per interactive web-response system.

A summary of prior cancer therapy and surgery is shown in Table 6. Patients in the interventional treatment arm received a median of 1 prior anticancer regimen compared with a median of 3 prior regimens in the control treatment arm.

	RAM + CV (N = 20)	CV (N = 10)	Total (N = 30)
	n (%)	n (%)	n (%)
Prior anticancer therapy			
Surgical procedure	14 (70.0)	8 (80.0)	22 (73.3)
Radiotherapy	8 (40.0)	7 (70.0)	15 (50.0)
Systemic therapy	20 (100.0)	10 (100.0)	30 (100.0)
Surgical procedure: intent			
Curative intent	10 (50.0)	5 (50.0)	15 (50.0)
Palliative intent	6 (30.0)	4 (40.0)	10 (33.3)
Missing	1 (5.0)	0	1 (3.3)
Radiotherapy: reason			
Adjuvant	6 (30.0)	2 (20.0)	8 (26.7)
Advanced/metastatic	2 (10.0)	5 (50.0)	7 (23.3)
Systemic therapy: reason and type			
Neoadjuvant	8 (40.0)	4 (40.0)	12 (40.0)
Adjuvant	6 (30.0)	3 (30.0)	9 (30.0)
Metastatic	9 (45.0)	6 (60.0)	15 (50.0)
Locally advanced	4 (20.0)	3 (30.0)	7 (23.3)
Systemic therapy: median number of regimens for any setting			
Median	1	3	2
Min-max	1-6	1-6	1-6

Table 6 Prior cancer therapy and surgery

Number analysed

The numbers analysed are presented in Table 7.

Population/Dataset	Definition	Number
Intention-to-treat (ITT) population	All randomized patients regardless of assigned dose.	30
Safety analysis set	All randomized patients who received any quantity of study treatment, regardless of their eligibility for the study.	30
Pharmacokinetic analysis set (ramucirumab)	All randomized patients who received at least 1 full dose of study treatment and have at least 1 postbaseline evaluable PK sample	18
Historical control set	All lines of therapy from historical control patients that are eligible for matching	26

Table 7 Analysis populations

Pharmacokinetic results

Ramucirumab serum PK data were available in 18 patients and included 64 quantifiable concentrations and 20 below-limit-of quantification concentrations. The results of the Ctrough values are shown in Table 8. The C_{max} at the end-of-infusion on Day 1 of Cyle 1 was 238 µg/mL (CV%=35).

Table 8 Ramucirumab concentrations in combination with vinorelbine and cyclophosphamide

	Day 15 Cycle 1 (n=13)	Day 1 Cycle 2 (n=9)	Day 1 Cycle 4 (n=7)	Day 1 Cycle 7 (n=4)	Day 1 Cycle 10 (n=2)
C_{trough} (µg/mL)	41.6 (CV%=57)	88.7 (CV%=47)	157 (CV%=37)	155 (CV%=28)	151-207

The exposure was comparable to that previously measured in study JVDA in which paediatric and young adult patients were treated with ramucirumab. The C_{max} at the end-of-infusion on Day 1 of Cyle 1 was 285 µg/mL (CV%=26) in study JVDA (n=14). The C_{trough} was 48.3 µg/mL (CV%=41) at Day 15 Cycle 1 (n=19) and 80.2 µg/mL (CV%=44) Day 1 Cycle 2 (n=9) at in study JVDA. No C_{trough} values were available for other Cycles.

Immunogenicity

The formation of antidrug-antibody (ADA) was performed in 13 of the 14 subjects treated with ramucircumab before and after treatment. None of the subjects were ADA-positive at baseline (before treatment) and after treatment with ramucirumab.

Efficacy results

Primary endpoint PFS

Of the 30 patients in the intent-to-treat population, 6 (20.0%) patients were censored in this study. These included

- 3 patients (2 in the RAM + CV treatment arm and 1 in the CV treatment arm) who had no documented progressive disease with regular assessment, and
- 3 patients (2 in the RAM + CV treatment arm and 1 in the CV treatment arm) who discontinued study treatment prior to disease progression and started on new anti-cancer treatment.

A total of 24 PFS events were observed, with 16 in the RAM + CV treatment arm and 8 in the CV treatment arm.

A summary of the key PFS results performed based on the data cutoff date of 14 June 2024 is shown in Table 1.

Analysis	Median (months) 98% CrI[a]	Median (months) 98% CrI	HR (98% CrI)[b] Pr (HR <1) (%)
	RAM + CV	CV	
Primary Bayesian Analysis	5.69 (3.20, 10.01)	3.73 (1.76, 8.29)	0.69 (0.25, 1.69) 0.864
Sensitivity 6	5.93 (3.41, 10.29)	3.46 (1.70, 6.93)	0.60 (0.24, 1.28) 0.950
Frequentist Analysis[c]	6.75 (5.54, 10.36)	1.71 (1.41, 2.66)	0.465 (0.261, 0.827) p-value = 0.082
Sensitivity 1	6.01 (3.42, 10.57)	3.41 (1.65, 7.08)	0.58 (0.23, 1.35) 0.944
Sensitivity 2	6.03 (3.43, 10.44)	3.84 (1.71, 8.32)	0.66 (0.26, 1.51) 0.905
Sensitivity 3	6.07 (3.41, 10.65)	3.80 (1.66, 8.75)	0.66 (0.24, 1.63) 0.890
Sensitivity 4[d]	5.69 (3.23, 10.00)	3.68 (1.77, 7.92)	0.68 (0.25, 1.60) 0.878
Sensitivity 5	5.52 (3.12, 9.91)	2.65 (1.78, 3.76)	0.48 (0.23, 0.86) 0.999

Abbreviations: CI = confidence interval; CrI = credible interval; CV = cyclophosphamide and vinorelbine; HR = hazard ratio; PFS = progression-free survival; Pr = probability; RAM = ramucirumab.

a Posterior median.

b Posterior mean displayed.

c 80% CI.

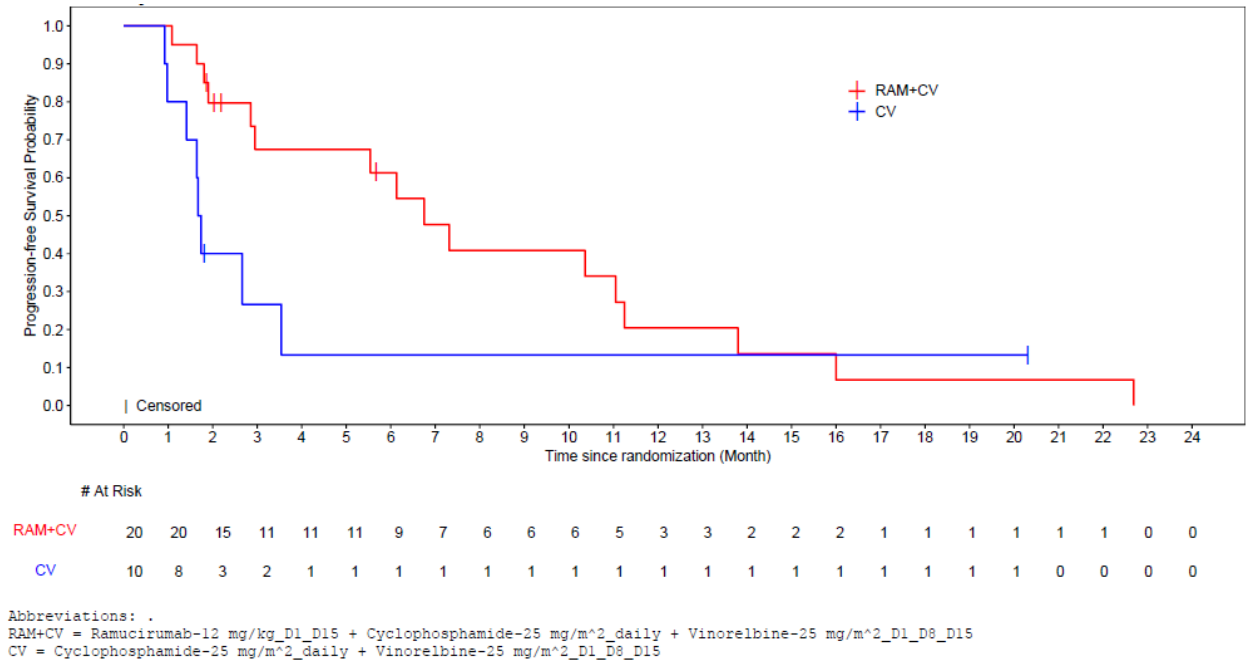
d Mahalanobis distance matching.

Table 9 PFS Results

The analysis of PFS was based on a Bayesian hierarchical model that allowed the use of an informative prior distribution for the control arm constructed from a matched subset of DSRCT and adaptive borrowing on PFS effects-size (log HR) observed in study JV02. The Bayesian model yielded an estimated posterior Pr of 86.4% of an HR of less than 1. The corresponding estimated posterior mean PFS HR was 0.69 (98% credible interval: 0.25, 1.69). The results did not meet the prespecified success criterion for the study, which required a Pr(HR <1) greater than 99% to declare success for the intervention.

According to the frequentist analysis the median PFS was 6.75 months in the RAM + CV treatment arm and 1.71 months in the CV treatment arm (HR 0.465 [80% CI: 0.261, 0.827]). These results corresponded to a numerical improvement of approximately 5-months in the median PFS for patients treated with RAM + CV. The risk of disease progression or death was reduced by 53% for patients treated with RAM + CV compared to CV. However, this result comes from a prespecified sensitivity analysis that was not designed to confirm statistical significance. The Kaplan-Meier plot for progression-free survival by treatment arm is shown in Figure 4.

Figure 4 ***Kaplan-Meier plot for PFS*** *by treatment arm*

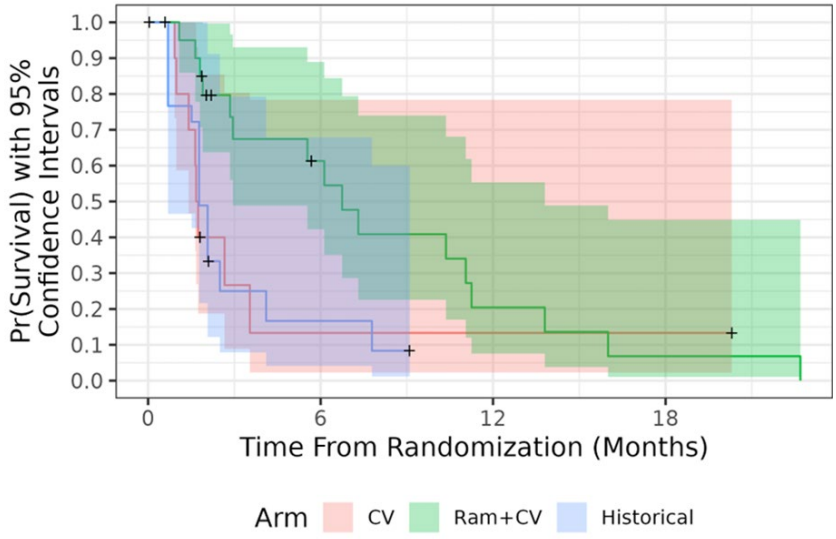


Abbreviations: .
RAM+CV = Ramucirumab-12 mg/kg_D1_D15 + Cyclophosphamide-25 mg/m^2_daily + Vinorelbine-25 mg/m^2_D1_D8_D15
CV = Cyclophosphamide-25 mg/m^2_daily + Vinorelbine-25 mg/m^2_D1_D8_D15

Sensitivity Analysis 6 was conducted to remove the influence of the study JV02 matched historical data on the JV02 HR, which is borrowed by the model for estimation of the JV01 HR. This sensitivity analysis yielded a posterior Pr of 0.950 that the HR was less than 1. The estimated posterior mean PFS HR was 0.60, with a 98% credible interval of 0.24 to 1.28. This suggests an improvement in the estimation process.

The Kaplan-Meier plot of survival estimates treatment arm with weighted historical matched patients is shown in Figure 4.

Figure 5 ***Kaplan-Meier survival estimates*** *by arm with historical matched patients (propensity) based on primary Bayesian analysis. Abbreviations: CV = cyclophosphamide + vinorelbine; Pr = probability; RAM = ramucirumab..*



Historical controls

Historical data were available for 20 patients with DSRCT of which 14 patients had at least 1 line of therapy eligible for matching. Historical patients with multiple eligible lines of therapy were used as distinct observations for matching, with PFS calculated from the relevant line of therapy. Based on the algorithm, a line of therapy from the historical control data could be matched to multiple clinical trial patients (that is, matching was conducted with replacement).

These 14 patients provided a total of 26 lines of therapy for matching. Of these 26 lines of therapy, 12 were classified as first line and 14 were classified as second or later lines. The median PFS for the first line was 4.2 months (80% CI: 2.1, not estimable), and the median PFS for the second or later lines was 2.2 months (80% CI: 1.5, 4.1).

Expert prior elicitation

Based on the combined expert prior for study JV01, the expected median PFS for the control arm in study JV01 was 2.5 months (95% CI: 1.6, 3.6 months).

Secondary efficacy endpoints

- Tumour response was not evaluable for 1 patient (5.0%) in the RAM + CV treatment arm.
- Complete response was recorded in 1 patient (5.0%) in the RAM + CV treatment arm.
- Partial response was recorded in 1 patient each in the RAM + CV treatment arm and in the CV treatment arm (5.0% and 10.0%).
- Stable disease persisting for 6 months or more was observed as the best response in 8 patients (40.0%) in the RAM + CV treatment arm and none in the CV treatment arm.
- The disease control rate in the RAM + CV treatment arm versus in the CV treatment arm was 80.0% versus 40.0%.
- The clinical benefit rate in the RAM + CV treatment arm versus the CV treatment arm was 50.0% versus 10.0%.
- Two (10.0%) patients qualified for duration of response analysis in the RAM + CV treatment arm with a median duration of response of 9.6 months.
- One (10.0%) patient qualified for duration of response analysis in the CV treatment arm; this patient had no documented PD during regular assessment, thus censored at the primary outcome analysis.

Safety results

All 20 patients enrolled in the RAM + CV treatment arm received at least 1 dose of ramicurimab. The total median exposure was 11.1 weeks, with 19.6 weeks in the RAM+CV arm and 7.1 weeks in the CV arm.

An overview of the number of subjects with adverse events is provided in Table 10.

Number of Subjects*a	RAM+CV (N=20) n	(%)	CV (N=10) n	(%)	Total (N=30) n	(%)
Subjects with >= 1 TEAE	20	(100.0)	10	(100.0)	30	(100.0)
Related to Study Treatment*b	19	(95.0)	10	(100.0)	29	(96.7)
Subjects with >=1 CTCAE Grade >= 3 TEAE	20	(100.0)	9	(90.0)	29	(96.7)
Related to Study Treatment*b	17	(85.0)	8	(80.0)	25	(83.3)
Subjects with >=1 SAE	6	(30.0)	3	(30.0)	9	(30.0)
Related to Study Treatment*b	3	(15.0)	1	(10.0)	4	(13.3)
Subjects who discontinued study treatment due to AE	2	(10.0)	0	(0.0)	2	(6.7)
Related to Study Treatment*b	1	(5.0)	0	(0.0)	1	(3.3)
Subjects who discontinued study treatment due to SAE	0	(0.0)	0	(0.0)	0	(0.0)
Related to Study Treatment*b	0	(0.0)	0	(0.0)	0	(0.0)
Subjects who died due to AE on study treatment*c	0	(0.0)	0	(0.0)	0	(0.0)
Related to Study Treatment*b	0	(0.0)	0	(0.0)	0	(0.0)
Subjects who died due to AE within 30 days of discontinuation from study treatment*c	0	(0.0)	0	(0.0)	0	(0.0)
Related to Study Treatment*b	0	(0.0)	0	(0.0)	0	(0.0)

Table 10 Overview of adverse events

Treatment-Emergent Adverse Events

A summary of TEAE's is provided in Table 11. Neutropenia was the most common (85.0%) TEAE in the RAM + CV treatment arm, while neutropenia and leukopenia were the most commonly reported (60.0% each) TEAE in the CV treatment arm.

	RAM + CV (N = 20)				CV (N = 10)			
	Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5	
MedDRA Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Patients with ≥1 TEAE	20	100.0	20	100.0	10	100.0	9	90.0
Neutropenia[a]	17	85.0	15	75.0	6	60.0	5	50.0
Leukopenia[a]	13	65.0	9	45.0	6	60.0	4	40.0
Abdominal pain[a]	11	55.0	2	10.0	2	20.0	1	10.0
Alanine aminotransferase increased	10	50.0	0	0.0	2	20.0	0	0.0
Headache	10	50.0	0	0.0	1	10.0	0	0.0
Pyrexia	7	35.0	1	5.0	4	40.0	0	0.0
Anemia[a]	8	40.0	3	15.0	2	20.0	0	0.0
Constipation	7	35.0	0	0.0	3	30.0	0	0.0
Fatigue[a]	6	30.0	0	0.0	4	40.0	1	10.0
Vomiting	6	30.0	0	0.0	4	40.0	0	0.0
Aspartate aminotransferase increased	7	35.0	1	5.0	2	20.0	0	0.0
Back pain	7	35.0	0	0.0	2	20.0	0	0.0
Proteinuria	9	45.0	2	10.0	0	0.0	0	0.0
Diarrhoea	7	35.0	1	5.0	1	10.0	0	0.0
Epistaxis	8	40.0	0	0.0	0	0.0	0	0.0
Lymphocyte count decreased	5	25.0	4	20.0	3	30.0	1	10.0
Nausea	5	25.0	1	5.0	3	30.0	0	0.0
Cough	6	30.0	0	0.0	1	10.0	0	0.0
Hyponatraemia[a]	5	25.0	0	0.0	2	20.0	0	0.0
Thrombocytopenia[a]	6	30.0	2	10.0	1	10.0	0	0.0

Table 11 Summary of Treatment-Emergent Adverse Events Occurring in ≥5 patients.

Deaths

Overall, 19 (63.3%) deaths occurred:

- 12 (60.0%) in the RAM + CV treatment arm, and

- 7 (70.0%) in the CV treatment arm.

The reason for fatal events was reported as either "death" or "study disease". All fatal events, except one, were reported as related to the study disease. The fatal event reported as death was observed in the RAM + CV treatment arm during the long-term follow-up period. This patient discontinued study treatment due to disease progression, 11 months since randomisation, and died 8 months and 15 days later. Most deaths (17/19) occurred after 30 days of treatment discontinuation.

AEs leading to dose modifications

In the RAM + CV arm,

- 2 patients required a reduction in ramucirumab dose: 1 due to neutropenia and 1 due to thrombocytopenia
- 2 patients required a delay in ramucirumab dosing: 1 due to AST increased and 1 due to proteinuria, and
- 2 patients required withholding the ramucirumab dose: 1 due to neutropenia and 1 due to proteinuria.

AEs leading to study drug discontinuations

In the RAM + CV treatment arm, overall 3 (15.0%) patients discontinued ramucirumab due to the following AEs:

- 2 patients discontinued due to Grade 2 or Grade 3 proteinuria, and
- 1 patient discontinued due to Grade 2 AST increased.

In the CV treatment arm, no patients discontinued study drug due to AEs.

Adverse events of special interest for Ramucirumab

Overall, 18 patients (90%) in the RAM + CV arm experienced a treatment-emergent AESI. The most frequently reported AESIs for ramucirumab observed in at least 15% of the patients include

- liver failure and other significant liver injury: the most frequent PTs were alanine aminotransferase increased (10 patients, 50%) and AST increased (7 patients, 35%)
- bleeding/haemorrhage (10 patients, 50%): the most frequent PT was epistaxis (8 patients, 40%)
- proteinuria (9 patients, 45%)
- infusion-related reactions (4 patients, 20%), and
- hypertension (3 patients, 15%).

The majority of the treatment-emergent AESIs were low-grade events. Overall, the AESI profile of ramucirumab observed in Study JV01 was largely consistent with the known AESI profile of ramucirumab in previous studies with adult patients.

Events under the following AESI categories were not observed in the study: gastrointestinal perforation, posterior reversible encephalopathy syndrome, congestive heart failure, and fistula formation.

Clinical laboratory evaluation

The results of haematology showed a general decrease from baseline of neutrophil count, lymphocytes, white blood cell count, creatinine, and magnesium.

Analysis showed worsening of the following haematological parameters:

- neutrophil count: 4 Grade 4 events of neutropenia and 6 Grade 4 events of neutrophil count decreased. No definition of neutropenia or neutrophil count decreased was provided.
- white blood cell count: 4 Grade 4 events of white blood cell decreased
- lymphocyte count: 1 Grade 4 event of lymphocyte count decreased, and
- platelet count: 1 Grade 4 event of platelet count decreased.

No substantial changes from the baseline were reported for the other laboratory analysis.

Growth plate abnormalities

Of the 8 patients below 18 years of age in the RAM + CV treatment arm, 5 patients had baseline growth plate assessment via a plain anteroposterior radiograph of the proximal tibia. All 5 patients had an open growth plate at baseline that required monitoring every 4 cycles while on treatment and at short-term follow-up, or until the growth plate was closed.

Only 2 patients had at least 4 cycles of ramucirumab exposure to perform a protocol-specified post-baseline evaluation. In both patients, no clinically relevant change was noted in the post-baseline height compared to their baseline height, and both had an open growth plate at their last evaluation before study discontinuation or during short-term follow-up.

2.3.3. Discussion on clinical aspects

Study JV01 was a randomised, multi-centre, global, Phase 1/2 study in paediatric and young adult patients with relapsed, recurrent, or refractory DSRCT evaluating the efficacy of ramucirumab in combination with chemotherapy versus chemotherapy alone.

Study conduct

There were two amendments to the statistical analysis plan. Before the interim futility analysis, per communications with the FDA, an analysis plan was developed for the scenario when no or limited real-world evidence would be available. The eligible regimens for the historical controls were expanded. Furthermore, "missing" as factor level was added to several matching variables. All changes were made before the database lock for interim analysis.

Sensitivity analyses and the management of missing data should be pre-specified (EMA/CHMP/150527/2024). The changes were made before the interim analysis, however due to the open-label study design it cannot be excluded that these were data-driven as the number of matched historical controls (n=26) was substantially lower than the target sample size (n=100). Because DSRCT is a rare cancer, a feasibility assessment for the number of historical controls prior to the start of the study including options to increase feasibility would have been preferred.

A total of 20 (66.7%) patients had at least 1 important protocol deviation (IPD) in this study. Of these, 15 patients were from the interventional RAM + CV treatment arm. IPDs were mainly related to assessments not followed according to the study schedule per protocol and are not considered to have impacted the patient safety.

Methods

Patients with missed visits or start of anti-cancer therapy prior to progression were censored, which is not in line with the EMA guidance (EMA/CHMP/27994/2008/Rev.1). In total 6 (20%) patients were censored, including 3 patients (2 in the RAM +CV and 1 in the CV arm) who discontinued study treatment prior to disease progression and started on new anti-cancer treatment. To what extent this potentially informative censoring might have influenced the results is unclear, as no sensitivity analysis using a different approach was performed.

For the analysis of the primary endpoint PFS, data from historical controls were used to augment the control arm. Supplementation of the control arm with historical controls allows a randomization in favour of the interventional treatment. In study JV01, patients were randomized in a ratio of 2:1. The acceptability of a historical control group in combination with randomized can be assessed using Pocock's criteria (Pocock, 1976). When using Pocock's criteria, there are concerns about the acceptability of the historical controls. First, the requirements for eligibility were different from the randomized controls, as older patients were eligible for inclusion. Furthermore, as historical controls with an initial diagnosis on or after 01 January 2005 were eligible, the historical controls could have received different treatments compared to the randomized controls. In fact, only 3 historical controls received the same treatment as the randomized controls (cyclophosphamide and vinorelbine). Therefore, the quality and usability of the historical controls is questionable. There was also adaptive borrowing of effects size between studies JV01 (DSRCT) and JVO2 (SS). The assumption that the hazard ration in DSRCT and SS is similar could be questionable. However, as sensitivity analyses without borrowing from exogenous data were included, the use of historical controls and borrowing from study JV02 is deemed acceptable in the context of this phase 2 study.

A stringent success criterion of 99% was used, resulting in a low type I error rate with a low probability of false positives. This might be acceptable in the context of a phase 2 study, although this results in an increased risk of abandoning a potentially effective therapy (type II error).

Pharmacokinetics

The 12 mg/kg dose is currently not registered for any of the registered indications for Cyramza. The current recommended dose is 8 mg or 10 mg/kg every 2 weeks. No link between exposure and efficacy-safety in the paediatric population appears possible at this stage. For gastric cancer, exposure-response analyses indicated that efficacy and safety of ramucirumab were correlated with ramucirumab exposure. Efficacy, as measured by improvements in OS and PFS, was associated with increasing ramucirumab exposure range. The incidences of Grade ≥ 3 hypertension, neutropenia, and leukopenia were also increased with higher ramucirumab exposure).

The C_{max} at end-of-infusion of 238 µg/mL (CV%=35) following 12 mg/kg (JV01) is comparable with the C_{max} at end-of-infusion of 285 µg/mL (CV%=26) following 12 mg/kg (study JVDA). The C_{max} at end-of-infusion following 9 mg/kg (study JV02) is also comparable when corrected for dose (corrected value of 308 µg/mL assuming dose-proportional PK). Therefore the data are considered consistent with data from other studies in paediatric patients, teenagers, and young adults.

The Rapporteur considers that the data do not add new information as compared to the currently reported information for the adolescent population based on previous Study JVDA in section 5.2 of the SmPC. However, the Applicant is requested to include information from study JV01 to section 5.2 of the SmPC.

Efficacy

The median PFS was 6.75 months in the RAM + CV treatment arm and 1.71 months in the CV treatment arm (HR 0.465 [80% CI: 0.261, 0.827]). The median PFS in the control arm was in line with the anticipated median PFS based on expert opinion.

The Bayesian model yielded an estimated posterior Pr of 86.4% of an HR of less than 1. Although there was a numerically improvement in PFS, the results did not meet the prespecified success criterion for the study which required a 99% posterior probability of superiority (HR<1). In general sensitivity analyses confirmed the robustness of the findings, with a slight improvement in the estimation process after removal of borrowing from historical controls and study JV02.

In the intervention treatment arm, there was 1 patient with complete response, 1 patient with partial response and 8 patients with stable disease. In the control treatment arm, there were no patients with complete response, 1 patient with partial response and no patients with stable disease. Due to the very limited number of patients contributing to DoR analysis, no conclusions on DoR can be made. Although the response rate results were numerically in favour of the intervention treatment arm, the study did not meet the primary endpoint and the data are not robust enough to ascertain a definitive treatment benefit.

Safety

The safety was based on a limited dataset of 20 patients treated with ramucirumab for a median of 19.6 weeks. Eight patients were <18 years of age. TEAEs more frequently reported in the intervention arm compared to the comparator arm were neutropenia, anaemia, headache, abdominal pain, alanine aminotransferase increased, proteinuria, epistaxis and cough. Except for cough, this are known adverse events associated with ramucirumab (SmPC ramucirumab). All cough TEAEs were low grade.

The data did not reveal any new safety concerns. It was not possible to assess the effect of ramucirumab on growth plate abnormalities due to the short exposure to ramucirumab. Safety data were not presented separately for the paediatric population, however, given the limited data and the lack of efficacy this issue is not further pursued.

3. Rapporteur's overall conclusion and recommendation

The MAH submitted a completed paediatric study for ramucirumab in accordance with Article 46 of Regulation (EC) No1901/2006. Study JV01 was a randomised, multicentre, global, Phase 1/2 study in paediatric and young adult patients with relapsed, recurrent, or refractory DSRCT evaluating the efficacy of ramucirumab 12 mg/kg in combination with cyclophosphamide and vinorelbine versus cyclophosphamide and vinorelbine alone. Study JV01 was not part of a paediatric investigation plan (PIP).

The primary objective (PFS) in study JV01 was planned using a Bayesian analysis incorporating information regarding historical control outcomes to augment the control arm of study JV01 as well as

effect-size observed in study JV02 that would provide a posterior probability of treatment superiority. Study JV02 was a multicentre, global, randomized Phase 2 study in paediatric patients and young adults with relapsed, recurrent, or refractory synovial sarcoma (SS) evaluating the efficacy of ramucirumab in combination with gemcitabine and docetaxel versus chemotherapy alone. Both studies JV01 and study JV02 were performed under the construct of the ongoing CAMPFIRE Master Protocol JAAA.

Study JV01 passed the futility analysis and thus completed enrollment. The primary endpoint PFS was not met, as the results did not meet the prespecified success criterion for the study. The data did not reveal any new safety concerns.

The Applicant proposes no changes to the ramucirumab SmPC based on the efficacy and safety data, but a suggestion for updates to SmPC section 4.8 and 5.1 is provided in case an update to the SmPC is requested by the EMA. Acknowledging the limited number of patients included in study JV01, the data are considered relevant for the prescriber, even as the efficacy results did not meet the pre-specified success criterion. Therefore, data should be included in the SmPC. This is also in line with the previous decision to include data from study JVDA and JV02.

☒ Fulfilled:

In view of the available data regarding efficacy and safety of ramucirumab in paediatric patients from study JV01, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

- SmPC section 4.8 Undesirable effects: The proposal made by the applicant is considered acceptable:
    - No new safety concerns were reported in the limited number of paediatric patients treated with ramucirumab in combination therapy in ~~**study**~~ **studies J1S-MC-JV01** and J1S-MC-JV02 (see Section 5.1).
- SmPC section 5.1 Pharmacodynamic properties: The following changes should be implemented in the proposal made by the applicant:
    - The efficacy and safety of ramucirumab in combination with cyclophophamide and vinorelbine versus cyclophosphamide and vinorelbine alone was evaluated in J1S-MCJV01 (JV01), a randomised, multicentre, global, Phase 2 study in 30 paediatric patients and young adults aged 36 months to 29 years, with relapsed, recurrent, or refractory desmoplastic small round cell tumour (DSRCT). Randomisation (2:1) was stratified by staging at relapse (metastatic disease versus locally advanced). JV01 did not meet the pre-specified success criterion for the study, which required **a 99% posterior probability of superiority (HR<1)** ~~that a Pr(HR <1) had to be greater than 99%~~ to declare success for the intervention. **At the final analysis, according to the frequentist analysis, the median PFS was 6.75 months in the experimental arm and 1.71 months in the control arm (HR 0.465 [80% CI: 0.261, 0.827]).** There was one partial response and one complete response in the experimental arm. One partial response and no complete response was observed in the control arm. **Due to the limited size of this study, it is not possible to conclude that the benefits of the use outweigh the risks.** ~~Analysis results from the randomised clinical data~~

~~showed the addition of ramucirumab to conventional chemotherapy resulted in a numerical difference.~~

- SmPC section 5.2 Pharmacokinetic properties: The Applicant is requested to include PK information from studies in paediatric patients to section 5.2. The following changes should be implemented in the proposal made by the Applicant:

  Paediatric population

  The mean peak concentration was 165 µg/mL following 8 mg/kg (study JVDA), 231 µg/mL following 9 mg/kg (study JV02), 238 µg/mL (CV%=35) following 12 mg/kg (study JV01) and 285 µg/mL (CV%=26) following 12 mg/kg (study JVDA), respectively. The C_{trough} was 41.6 (CV%=57) and 48.3 µg/mL (CV%=41) at Day 15 Cycle 1 (n=19) in study JV01 and study JVDA, respectively. Exposure to ramucirumab in paediatric and young adult patients (children >12 months and <21 years) with refractory solid tumours, including CNS tumours following a single dose or multiple doses of 8 mg/kg or 12 mg/kg was similar to the exposure obtained in adult patients. Further, ramucirumab exposure following 12 mg/kg dose was similar across the age range of >12 months to <21 years.

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Cyramza Active substance: Ramucirumab

Study title	Study number	Date of completion	Date of submission of final study report
Thirty-Nine-Week Toxicity Study of IMC-1121B in Cynomolgus Monkeys.	1163-110	14 October 2005	Submitted with EU initial marketing authorisation application for ramucirumab (H0002829) in August 2013

Clinical studies

Product Name: Cyramza Active substance: Ramucirumab

Study title	Study number	Date of completion	Date of submission of final study report
A Phase 1 Study of Ramucirumab, A Human Monoclonal Antibody Against the Vascular Endothelial Growth Factor-2 (VEGFR-2) Receptor in Children with Refractory Solid Tumors, Including CNS Tumors.	I4T-MC-JVDA (ADVL1416)	31 August 2020	Submitted to EMA (EMEA/H/C/002829/P46/008) on 03 February 2021.
A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma.	J1S-MC-JV02	18 August 2023	Submitted to EMA (EMA/H/C/002829/P46/ 009) on 29 August 2023.
A Randomized, Open-Label Phase 1/2 Study Evaluating Ramucirumab in Pediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Desmoplastic Small Round Cell Tumor.	J1S-MC-JV01	14 June 2024	Provided within the current submission.