PASS Information

Title	Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry (I4T-MC-JVDD)
Version identifier of the final study report	1.0
Date of last version of the final study report	N/A
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Procedure number:	MEA 001
Marketing authorisation holder(s)	Eli Lilly Nederland B.V., Papendorpseweg 83 3528 BJ Utrecht, The Netherlands
Joint PASS	No
Research question and objectives	Primary objective: • To evaluate the safety of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer. Secondary objectives: • To describe the safety profile for the following subgroups of interest: o Elderly patients, o Patients with cardiac comorbidities, o Patients with hepatic impairment, and o Patients with renal impairment. • To describe the effectiveness of ramucirumab administered as a monotherapy or in in combination therapy for second-line treatment of adult patients with advanced gastric cancer.
Countries of study	Austria, Belgium, France, Germany, Italy, Spain, Switzerland, the United States
Author	PPD Phone: PPD E-mail: PPD
Signature of principal investigator	Signature on file/see approval date below

Approval Date: 10-Dec-2021 GMT

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V., Papendorpseweg 83 3528 BJ Utrecht, The Netherlands
MAH contact person	PPD Eli Lilly and Company, Lilly Corporate Center Indianapolis, IN 46285 United States

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1. Abstract

Title

Safety and Effectiveness of Ramucirumab in Patients with Advanced Gastric Cancer in the European Union and North America: A Prospective Observational Registry (Study I4T-MC-JVDD [JVDD])

Keywords

Gastric cancer; safety; non-interventional; observational; GEJ adenocarcinoma

Rationale and background

In response to the Pharmacovigilance Risk Assessment Committee's request during the review of the initial marketing authorisation application for ramucirumab in the treatment of gastric cancer, Eli Lilly and Company proposed a PASS to be conducted to characterise the safety and effectiveness of ramucirumab in patients with gastric cancer under real-world disease conditions.

Research question and objectives

The overall study objective was to describe the safety and effectiveness of ramucirumab under real-world disease conditions in Europe and North America.

Primary objective:

- To describe the safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions.

Secondary objectives:

- To describe the safety profile in the following subgroups:
  - Elderly patients (aged ≥65 years),
  - Patients with cardiac comorbidities,
  - Patients with hepatic impairment,
  - Patients with renal impairment.
- To describe the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions.

Study design

This was a prospective non-interventional, non-comparative, observational study in Europe and North America. This study design reflected real-life clinical management of patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma (henceforth, referred to as "gastric cancer"). Patients were to be followed for up to 12 months after initiation of ramucirumab treatment, until death, or loss to follow-up/withdrawal of consent, whichever occurred first. Type and frequency of patient visits and all evaluations were performed, as for routine clinical practice, for this patient population.

Setting

Seventy-eight sites in Europe and North America were utilised to reach the targeted number of patients. This final study report presents data retrieved from 8 countries including Austria, Belgium, France, Germany, Italy, Spain, Switzerland, and the United States.

Subjects and study size, including dropouts

The study planned to include approximately 600 patients from Europe and North America with advanced gastric cancer whose disease had progressed after prior chemotherapy and who were treated with ramucirumab, alone or in combination therapy as second-line therapy, under real-world disease conditions.

Variables and data sources

Demographics and baseline characteristics including medical history, disease characteristics, prior anti-cancer treatment and prior medications were collected. At baseline and throughout treatment, Eastern Cooperative Oncology Group performance status, vital signs, supportive care and laboratory values were collected for analysis. Treatment discontinuation, safety outcomes, effectiveness outcomes and supportive care were collected when available throughout the study. The safety variables included in this report were exposure of ramucirumab, dose adjustments and adverse events (AEs); including serious adverse events (SAEs), adverse events of special interest (AESIs), and deaths.

For information recorded per routine clinical practice, the investigators were instructed to collect all the variables of interest, but given the observational nature of the study, some variables may have not been collected as per routine clinical practice or were not entered by sites in the study database.

Results

Overall safety analysis

Overall, 606 patients were eligible and included in this analysis: 51 (8.4%) in ramucirumab monotherapy cohort; 547 (90.3%) in ramucirumab plus paclitaxel cohort; and 8 (1.3%) in ramucirumab plus anti-cancer agents other than paclitaxel cohort. Approximately 55.0% of patients enrolled in the study were ≥65 years of age. The proportion of patients with cardiac comorbidities was 22.8% and with hepatic or renal impairment was 11.2% and 6.4%, respectively.

The median duration of treatment with ramucirumab received as monotherapy and in combination with paclitaxel were 8 weeks (interquartile range [IQR]: 4.0 to 10.6) and 15 weeks (IQR: 8.4 to 26.7), respectively. Overall, 55.4% of patients had at least 1 ramucirumab dose adjustment. The reporting of dose delay, dose omission, and dose reduction due to AEs in ramucirumab monotherapy cohort and ramucirumab plus paclitaxel cohort were 11.8% and 24.3%, 5.9% and 25.0%, 7.8% and 9.9%, respectively.

Overall, 97.7% of patients experienced at least 1 AE: 96.1% in ramucirumab monotherapy cohort and 97.8% in ramucirumab plus paclitaxel cohort. The 2 most frequently reported AEs in ramucirumab monotherapy cohort were nausea (21.6%), and asthenia and general physical health deterioration (17.6% each), and in ramucirumab plus paclitaxel cohort were fatigue (28.3%) and neutropenia (23.6%). A total of 41.3% of patients experienced at least 1 SAE; malignant neoplasm progression was the most frequently reported SAE in both cohorts (7.8% and 4.9%, respectively). Overall, 65.5% of deaths were reported, regardless of causality, with 37.1% of these deaths due to study disease and 5.4% due to AEs that occurred on or within 90 days of last dose of ramucirumab. General physical health deterioration was the primary reason to discontinue from ramucirumab treatment in both cohorts.

Overall, 39.9% experienced an AESI. Bleeding/haemorrhage events (20.8%), hypertension (10.9%), and liver injury/failure (8.1%) were the most frequently reported AESI categories.

Safety analysis in subgroups of interest

Among patients in subgroups of interest, 97.6% of elderly patients (N=333) experienced at least 1 AE, of which 42.0% were SAEs. The most common reason for discontinuation of ramucirumab in elderly patients was worsening of general health condition. Bleeding/haemorrhage events were the most frequently reported AESIs in elderly patient populations in both the ramucirumab monotherapy (9.1%) and ramucirumab plus paclitaxel (22.0%) cohorts.

Overall, 99.3% of patients with cardiac comorbidities (N=138) experienced at least 1 AE, of which 47.1% were SAEs. The most common reason for discontinuations of ramucirumab in patients with cardiac comorbidities was worsening of general health condition. Liver injury/failure (17.6%) in ramucirumab monotherapy cohort and bleeding/haemorrhage events (27.4%) in ramucirumab plus paclitaxel cohort were the most frequently reported AESIs.

Overall, 95.6% of patients with hepatic impairment (N=68) experienced at least 1 AE, of which 48.5% were SAEs. No discontinuations of ramucirumab due to AEs occurred in the monotherapy subgroup. For the patients in ramucirumab plus paclitaxel cohort who discontinued ramucirumab due to AEs, each AE was reported once and none of these AEs were associated with the liver. Liver injury/failure (22.2%) in ramucirumab monotherapy cohort and bleeding/haemorrhage events (19.3%) in ramucirumab plus paclitaxel cohort were the most frequently reported AESIs.

All patients with renal impairment (N=39) experienced at least 1 AE, of which 56.4% were SAEs. The majority of patients discontinued ramucirumab due to underlying disease such as general health deterioration, weight decreased, ileus, and intestinal obstruction. One patient in ramucirumab plus paclitaxel cohort discontinued ramucirumab due to a non-serious event of proteinuria, from which the patient recovered; relatedness to study treatment was not reported. Bleeding/haemorrhage events (16.7%) were the most frequently reported AESIs in the ramucirumab plus paclitaxel cohort.

Effectiveness

The median overall survival (OS) for patients in this study was 3.6 months (95% confidence interval [CI]: 2.7, 4.3) in the ramucirumab monotherapy cohort and 7.6 months (95% CI: 7.0, 8.4) in the ramucirumab plus paclitaxel cohort. The median real-world progression-free survival (rwPFS) for patients in this study was 1.9 months (95% CI: 1.4, 2.2) in the ramucirumab monotherapy cohort and 4.0 months (95% CI: 3.8, 4.5) in the ramucirumab plus paclitaxel cohort.

Discussion

The patients enrolled in the study were representative of patients in the real-world setting that included patients receiving ramucirumab, alone or in combination with paclitaxel, and in combination with other chemotherapies.

The safety profile observed in this study was generally consistent with the established safety profile of ramucirumab in the clinical settings for this patient population, and no new safety concerns or notable findings were identified. Review of available safety data for the elderly patients and patients with comorbidities of interest did not identify any new safety findings. Therefore, ramucirumab as monotherapy or in combination with paclitaxel has a similar safety profile in patients with gastric cancer in the real-world setting to that established in clinical trial settings.

The rwPFS observed in this study was in line with the PFS reported from clinical trial settings. The OS observed was reflective of the real-world patient characteristics which included a sizeable population of elderly patients with lower or reduced performance status and comorbidities.

Conclusion

- In patients with advanced gastric cancer, the observed safety profile of ramucirumab administered as monotherapy or in combination with paclitaxel, in the real-world setting was manageable and consistent with the established safety profile of ramucirumab identified from clinical trials in this patient population.
- No new safety concerns or notable findings were observed in the overall population or in the subgroups of interest, including elderly patients and patients with cardiac comorbidities, hepatic impairment, or renal impairment.
- In this study conducted in a real-world setting, the effectiveness of ramucirumab treatment as monotherapy or in combination with paclitaxel is in line with what has been observed in clinical trials, in the light of a sizeable population of elderly patients with lower or reduced performance status and comorbidities.

Overall, results of this study indicate that the benefit-risk profile of ramucirumab remains positive in the real-world setting.

2. List of Abbreviations

Term	Definition
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
BMI	body mass index
rwBOR	real-world best overall response
CHF	congestive heart failure
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GEJ	gastro-oesophageal junction
HER2	human epidermal growth factor receptor 2
HSR	hypersensitivity reaction
IQR	interquartile range
KM	Kaplan-Meier
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NE	not evaluable
OS	overall survival
PASS	post-authorisation safety study
PD	progressive disease
PR	partial response
rwPFS	real-world progression-free survival
PRAC	Pharmacovigilance Risk Assessment Committee

PS	performance status
PTX	paclitaxel
PT	preferred term
Ram	ramucirumab
RECIST	Response Evaluation Criteria in Solid Tumours
RPLS	reversible posterior leukoencephalopathy syndrome
SAE	serious adverse event
SD	stable disease
SMQ	standardized MedDRA query
SOC	system organ class
US	United States

3. Investigators

PPD

E-mail: PPD

The listing of clinical sites that participated and contact details and list of all investigators are in a standalone document referred to in Annex 1 and is available upon request.

4. Other Responsible Parties

Sponsor:
Eli Lilly and Company
Global Patient Safety Pharmacoepidemiologist
Eli Lilly and Company
Indianapolis, IN 46285
United States

Third party (Contract Research Organization):
IQVIA
Real World Evidence Solutions
https://www.iqvia.com/solutions/real-world-evidence

5. Milestones

Milestone	Planned date	Actual date
Start of data collection	Estimated Q4 2015	09 December 2015[a]
End of data collection (last patient follow-up date)	Estimated Q4 2020	23 July 2021
Registration in the EU PAS register (ENCePP)	Subject to the final protocol approval date, estimated Q3 2015	Initial registration was submitted to ENCePP on 30 November 2015
Interim report	Interim analysis was planned when the targeted sample size reached one-half of the targeted study size (that was, 300)	24 May 2019
Final report of study results	One year from the end of data collection, estimated Q4 2021	See electronic approval date stamp on cover page

Abbreviations: ENCePP = European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; EU = European Union; NA = not applicable; PAS = post-authorisation studies; Q = quarter.

[a] This is the date of first patient visit.

6. Rationale and Background

Ramucirumab is a human receptor-targeted monoclonal antibody that specifically binds vascular endothelial growth factor receptor 2. Cumulatively, at the time of study design, ramucirumab or placebo had been administered either as a single agent or in combination with various antineoplastic agents to approximately 7222 patients with different oncologic conditions in Phase 1/1b, Phase 2, and Phase 3 clinical trials. Based on actual exposure data from completed clinical trials and the enrolment/randomisation schemes for ongoing trials, an estimated 4122 patients had received ramucirumab, with 991 patients receiving single-agent ramucirumab and 3131 patients receiving ramucirumab in combination with other antineoplastic agents. These were the available data provided at the time of the prior submission for the PASS protocol versions (dated August 2014 and December 2014, respectively).

Ramucirumab as a monotherapy (N=236) in the pivotal Phase 3 REGARD trial was well-tolerated with an overall mostly similar AE profile between the ramucirumab and placebo groups.[1] The safety profile of ramucirumab in combination with paclitaxel (N=327) in the pivotal Phase 3 RAINBOW trial demonstrated that the combination was well-tolerated in patients with gastric cancer, with manageable AEs.[2]

During the initial CHMP's review of the marketing authorisation application for ramucirumab in the treatment of gastric cancer, the PRAC requested a PASS to be conducted to characterise the safety and effectiveness of ramucirumab in patients with gastric cancer under real-world disease conditions. In addition, the safety profile of ramucirumab was to be further described in the subgroups of special interest (see definitions in Section 9.3.1), including:

- Elderly patients (aged ≥65 years),
- Patients with cardiac comorbidities,
- Patients with hepatic impairment, and
- Patients with renal impairment.

Therefore, Lilly proposed this prospective, non-interventional, non-comparative observational cohort Study JVDD in the EU and North America. Patient enrolment into this study was based on ramucirumab approval and reimbursement status in the respective countries. However, due to the loss of countries with reimbursement approval, contingency countries had to be identified to meet the enrolment goal. After assessment, it was agreed to include Switzerland as part of the European Economic Area, as the patients were identical to western patients in the EU. Hence, this study enrolled patients from EU including Switzerland (henceforth, referred to as "Europe") and North America.

7. Research Question and Objectives

The overall study objective was to describe the safety and effectiveness of ramucirumab in gastric or GEJ adenocarcinoma (henceforth, referred to as "gastric cancer") under real-world disease conditions in Europe and North America, and specifically:

Primary Objective:

To describe the safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions.

Secondary Objectives:

- To describe the safety profile in the following subgroups:
    - Elderly patients,
    - Patients with cardiac comorbidities,
    - Patients with hepatic impairment, and
    - Patients with renal impairment.
- To describe the effectiveness of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer under real-world disease conditions.

8. Amendments and Updates

None.

9. Research Methods

9.1. Study Design

This was a prospective, non-interventional, non-comparative, observational cohort study/registry in Europe and North America to evaluate the safety and effectiveness of ramucirumab in patients with locally advanced and unresectable or metastatic gastric cancer whose disease had progressed after prior chemotherapy. The study design reflected real-life clinical management of patients with advanced gastric cancer. The type and frequency of actual patient visits and all evaluations were done as for routine clinical practice. Patients were required to sign an informed consent form after a physician-required eligibility review and no visits were mandated as part of this study.

Patients were treated with ramucirumab as a monotherapy, combination therapy with paclitaxel or combination therapy with anticancer agents other than paclitaxel as a second-line therapy under real-world disease conditions.

Patients were to be followed for up to 12 months after initiation of ramucirumab treatment, until death, or loss to follow-up/withdrawal of consent, whichever occurred first. At the time of the study design, data from REGARD and RAINBOW indicated the median OS time for patients with gastric cancer receiving second-line therapy was approximately 5 to 9 months, thus, the available follow-up time allowed for the evaluation of long-term safety and effectiveness. Of note, the median treatment duration for patients with gastric cancer receiving ramucirumab observed in clinical trials is approximately 2 to 5 months.

9.2. Setting

Potential study sites were identified based on physicians who had a recognised competency in treating advanced gastric cancer.

A reasonable number of sites in Europe and North America were utilised to reach the targeted patient number.

The country selection was based on multiple factors, such as:

- number of sites with a recognised competency in oncology per capita,
- favourable regulatory and ethical environment to conduct observational studies, and
- ramucirumab approval status and reimbursement ability.

The site selection was determined at the country level and included criteria (as applicable) such as:

1. physician speciality,
2. geographical location (for example, rural, urban, suburban),
3. practice setting (hospital-based, academic setting, private practice),
4. estimated eligible patient availability within the 5 years' enrolment period, and
5. staffing availability, including physician availability.

9.3. Subjects

The study planned to include approximately 600 patients from Europe and North America with advanced gastric cancer whose disease had progressed after prior chemotherapy and who were treated with ramucirumab, alone or in combination therapy, as second-line therapy under real-world conditions. The decision to initiate the use of ramucirumab was made by the participants and their healthcare providers independently of their willingness to participate to the study. Physicians were instructed to refer to the local prescribing information for ramucirumab.

All patients presented during the enrolment period were assessed for eligibility according to the defined inclusion/exclusion criteria, and all patients considered eligible by the participating physicians were asked to sign informed consent to be included in the study.

Inclusion Criteria

1. Adult patients (age at least 18 years at enrolment) with advanced gastric cancer whose disease had progressed after prior chemotherapy.
2. Patients who initiated ramucirumab treatment either as a single agent or in combination with chemotherapy.
3. Patients who had been fully informed and had given written consent to the use of the needed information to be part of the observational study.

Exclusion Criteria

4. Patients who had received more than 1 line of chemotherapy for advanced gastric cancer.
5. Patients concurrently participating in any study including administration of any investigational drug (including ramucirumab) or procedure (including survival follow-up).

9.3.1. Subgroups of Special Interest

Elderly population was defined as patients aged ≥65 years. An additional cut-off point of 75 years was considered in the analysis. Patients' pre-existing health conditions/medical history were collected based on general Medical History form in the eCRF reported by the treating physicians. In addition to the Medical History Form, sites were asked to explicitly indicate in the Comorbidities of Special Interest form if patients had hepatic impairment, renal impairment, or cardiac comorbidity to increase the chance to capture these important study variables.

Upon review of Medical History and Comorbidities of Special Interest forms, several patients were identified to have cardiac comorbidities reported either in each or both forms. In this study, patients were considered to have cardiac comorbidities if they have reported it in at least 1 form. In order to identify patients with renal and hepatic impairment most accurately on entry into the study, the treating physician was required to state specifically whether the patient had any renal or hepatic impairment in the Comorbidities of Special Interest form. Identifying these patients based on preferred terms reported in the Medical History form was considered to be a less reliable method and therefore, not implemented in this study for these impairments.

9.4. Variables

It is important to note that this is an observational study and the treatment of the patients under real-world conditions and all evaluations, assessments and data capture were performed per routine clinical practice. The investigators were instructed to collect all the variables of interest, but given the observational nature of the study, some variables may have not been collected as per routine clinical practice or were not entered by sites in the study database.

The complete list of variables can be found in Study JVDD protocol version 2.0 (dated 21 April 2015). The following section summarises the variables discussed in the final study report.

9.4.1. Study Treatment

The following information was collected at ramucirumab treatment initiation or at various times throughout the study, if available:

- Treatment (ramucirumab, alone or in combination with other anti-cancer agents), reason for treatment choice and chemotherapy regimen (if administered in combination),
- Dates of administration,
- Pre-medications administered, if any,
- Dosage and administration details,
- Reason for dose reductions and dose delays, and
- Reason for treatment discontinuation (Section 9.4.4).

9.4.2. Demographics and Baseline Characteristics

The following information was collected prior to or at the start of treatment, if available:

- Demographic and baseline (pre-treatment) characteristics such as age, gender, weight, height, blood pressure, ethnicity, smoking status, alcohol use, weight loss ≥10% over the 3 months prior to ramucirumab initiation.
- Medical history (including history of hepatic impairment, renal impairment, or cardiac morbidity) and pre-existing conditions. One single form was used for collecting both medical history and pre-existing conditions. Pre-existing conditions were defined as ongoing and historical conditions as ended prior to the study initiation.
- Cancer diagnosis and characteristics, such as date of initial diagnosis, initial and current stage, histology, grading, sites of metastases and HER2 status.
- Prior anti-cancer treatment for gastric cancer: type of therapy (for example, surgery, radiotherapy, systemic anti-cancer), overall response and ongoing complications from prior anti-cancer treatment.
- Prior medications other than anti-cancer therapy, received within 14 days to initiation of ramucirumab.

9.4.3. Information to be Collected at Baseline and during Treatment

The following information was collected at baseline and during treatment, if available:

- ECOG performance status,
- Blood pressure,
- Supportive care and procedure information,
    - Hospitalisations including:
        - Type of hospitalisation,
        - Admission and discharge dates,
        - Main reason for hospitalisation at admission,
    - Concomitant medications,
    - Transfusions,
    - Radiation therapy,
- Laboratory (Refer to Study JVDD protocol version 2.0 Section 9.3.3 for additional details):
    - Haematology profile,
    - Coagulation profile,
    - Serum chemistry, and
    - Urinalysis.

9.4.4. Treatment Discontinuation and Post-discontinuation

The following information was collected, if available:

- The date and main reason for ramucirumab and chemotherapy discontinuation, and
- Post-discontinuation systemic anti-cancer therapy.

9.4.5. Safety Outcomes

- Regardless of the relatedness to ramucirumab, AEs or SAEs from first administration of ramucirumab up to and including 90 days after last ramucirumab administration and any associated corrective medications, transfusions or supportive care were recorded.
- For the relationship to anti-cancer treatment, the physician could only select ‘yes’ or ‘no,’ but for a relationship to a specific drug including ramucirumab, the physician could select ‘yes,’ ‘no,’ or ‘unknown.’ Only when ‘yes’ or ‘unknown’ was selected, the event was counted as possibly related to the drug.
- Post 90 days after last ramucirumab infusion only AEs (including SAEs) related to ramucirumab were recorded.

9.4.6. Effectiveness Outcomes

The effectiveness measures constituted secondary objective of the study and included OS and rwPFS. Response to treatment was evaluated and summarized as well.

- Overall survival (OS): was estimated from the date of first administration of ramucirumab to the date of death (all causality). Patient known to be alive at the end of the 12 months follow-up period were censored at the last date when the survival status

was confirmed. Patients who were lost to follow-up or withdrew from the study were censored at the last date the patient was known to be alive.

- Real-world progression-free survival (rwPFS): was estimated from the date of first administration of ramucirumab to the recorded date of disease progression (determined by the physicians based on their routine clinical practice) or death (all causality). Among patients who had no record for disease progression or death, patient data were censored at the end of follow-up period. Otherwise, patients' data were censored at the last contact date if they were lost to follow-up or withdrew from the study.
- Tumour response: was determined by the treating physicians based on their routine clinical practice, including the frequency of re-evaluations, and may not be evaluated based on any response criteria (e.g., RECIST criteria) or as per standard follow-up frequency of tumour re-evaluation as performed in clinical trials for disease progression and tumour response. Physicians were asked to classify the overall response assessment into 'complete remission/complete response (CR), partial remission/partial response (PR), stable disease (SD), progressive disease (PD), or Not evaluable (NE).' Progressive disease was counted when best response over treatment was either clinical or radiological progression.

9.5. Data Sources

Information collected as part of routine clinical practice was transcribed directly by the study site personnel to an eCRF. To ensure accurate, complete, and reliable data, the study site personnel were to keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents. Consistency between eCRF and source documents were ensured through monitoring activities.

9.6. Potential Bias

This section highlights the potential bias seen in epidemiological studies in terms of selection bias and information (or misclassification) bias.

Selection bias:

In cohort studies, a group of study participants are sampled from a source population and followed up over time to ascertain the occurrence of outcomes of interest. Selection bias occurs when the patients selected into the study are not representative of the exposure or outcome pattern in the source population. This study attempted to reduce potential bias in patient selection by asking participating physicians to invite all patients who met the study eligibility criteria to participate.

Loss to follow-up is another source of bias in cohort studies. A low loss to follow-up rate was expected in this study, in part due to the ability of physicians to follow up directly with patients at the hospital or by phone.

Information bias:

Misclassification bias arises when any information used in a study (exposure, outcome, or covariates) is either measured or recorded inaccurately. In this study, information on the disease

status and treatment received has a high probability of accuracy because it is directly provided by treating physicians. However, ascertainment rate may not be constant across different clinical endpoints. For example, certain comorbidities influencing physicians' treatment decision-making or require monitoring/managing would be more likely to be captured in the medical chart/clinical notes than other comorbidities that do not affect treatment decisions, resulting in underestimation of the frequency.

9.7. Study Size

Study JVDD planned to enrol approximately 600 patients treated with ramucirumab as monotherapy or in combination therapy.

For the primary objective of safety outcomes, the study size was determined, based both on the probability of observing at least 1 event for infrequent events and based on the width of CIs around event occurrence for more common events. For a study size of 600 patients and a true event incidence of 1%, the probability of observing at least 1 event was 99%, whereas, for a study size of 300 patients, it would have been 95%. For a subgroup with an expected sample size of 60, the probability to observe a safety event was expected to be >90% if the event occurred in approximately 5/100 patients. Similarly, for a study size of 600 patients and an observed event incidence of 5%, the 95% CI would have spanned ±1.7% % and with an observed event incidence of 45% would have spanned ±4.0%. Both the probability of observing an event and the 95% CI width were considered sufficient and did not increase substantially on increasing the study size. Refer to Study JVDD Protocol version 2.0 Section 9.5 for additional details.

The study size was also based on feasibility considerations including, but not restricted to, the relatively low occurrence and prevalence of gastric cancer in Europe and North America and predicted ramucirumab market uptake for monotherapy and combination therapy.

9.8. Data Transformation

9.8.1. Data Management

A data management plan was created before data collection began and described all functions, processes and specifications for data collection, cleaning, and validation. Processes and procedures were utilised to repeatedly ensure that the data were as clean and accurate as possible when presented for analysis. Data quality was enhanced through a series of programmed data quality checks that automatically detect out-of-range or anomalous data.

Datasets and analytic programs were kept on a secure server and archived according to Lilly's record retention procedures. The data collection of the study was conducted by a third party, the datasets were stored and archived according to the vendor's procedures. These datasets were transferred to the Lilly data repository via a secure transfer system.

9.8.1.1. Data Collection Schedule

This is a non-interventional, observational study. Type and frequency of actual patient visits and all evaluations were done as for routine clinical practice.

9.8.2. Data Collected

9.8.2.1. Site/Physician Questionnaire

Before starting recruitment, each participating physician completed a site questionnaire. The following information was collected and entered in the clinical database:

- Site address, and
- Type of centre (academic/non-academic, public or private practice).

9.8.2.2. Patient Data

Information collected as part of routine clinical practice was transcribed directly by the study site personnel to an eCRF.

9.8.2.3. Patient Withdrawal

Patients could withdraw consent and discontinue participation in the study at any time, with no effect on their medical care or access to treatment. All information already collected as part of the study was retained for analysis; however, no further information was collected from patients after withdrawal.

9.8.2.4. Lost to Follow-up Patients

The participating physician were asked to contact the patients who were lost to follow-up to confirm survival and identify the reason for not willing to participate.

All available information in the patient's file through the date of last contact or visit was entered in the eCRF. For patients who were lost to follow-up or withdrew from the study, OS and rwPFS data were censored at the last date the patient was known to be alive.

9.9. Statistical Methods

9.9.1. Main Summary Measures

For the primary objective of safety, the focus of AE reporting was based on the AEs reported between the date of first dose of ramucirumab and 90 days (≥5 half-lives) after the last dose. Regardless of the relatedness to ramucirumab, AEs (including SAEs) and AESIs from first administration of ramucirumab up to and including 90 days after last ramucirumab administration were summarised. The AEs were summarised by MedDRA® version 24.0 SOC and PT.

- For the AEs reported after 90 days following last ramucirumab infusion only AEs (including SAEs) related to ramucirumab were recorded.
- In addition, AEs and AESIs reported within 30 days of the last ramucirumab dose were summarised.
- Deaths from any cause were also summarised.

The following summary statistics were used for description of quantitative variables: total number of patients, number of patients with available or missing information, mean, standard deviation, standard error of the mean, median, quartiles and extreme values. For the categorical variables frequencies and percentages were reported, normal approximation for binominal

distribution was used for the calculation of the CI, unless the observed counts were too low for approximation and the exact CI was derived.

9.9.2. Main Statistical Methods

9.9.2.1. Analysis Population

This population includes all patients who had given informed consent and received at least 1 dose of ramucirumab, alone or in combination therapy, after prior chemotherapy for advanced/metastatic gastric cancer.

9.9.2.2. Primary Analyses

For the primary objective of safety, data analyses on all patients were stratified on the basis of whether patients received ramucirumab as monotherapy, ramucirumab plus paclitaxel or ramucirumab plus agents other than paclitaxel at the first administration of ramucirumab. Safety endpoints (including overall AEs/SAEs, AESIs, and deaths) were summarised as counts and percentages.

9.9.2.3. Secondary Analyses

As described in Section 9.9.2.2, similar safety analyses were conducted for the following subgroups of interest:

- Elderly patients,
- Patients with cardiac comorbidities,
- Patients with hepatic impairment, and
- Patients with renal impairment.

A descriptive analysis was conducted to evaluate the effectiveness of ramucirumab (as described in Section 9.9.1) and data analyses was stratified on the basis of whether patients received ramucirumab as monotherapy, combination therapy with paclitaxel, or combination therapy with anticancer agents other than paclitaxel.

Effectiveness end points (OS and rwPFS) were summarised as median and survival rates at given time points (3 months, 6 months, 9 months, and 12 months) with their 95% CIs using the Kaplan-Meier method.

The real-world treatment patterns in patients with gastric cancer treated with ramucirumab were summarised to include:

- dosage and administration details, and
- treatment modification (delay, reduction, omissions or discontinuation) and reasons.

Other measures summarised were:

- real-world best overall response (when available),
- healthcare resource utilisation, and
- supportive care.

9.9.3. Missing Values

The eCRF was designed to require certain items to be completed prior to advancing to the next item, thereby, minimising missing data for required items. Certain items may not have been applicable to all patients and were recorded appropriately in the eCRF. There was no imputation of missing data in this report.

9.9.4. Sensitivity Analyses

Sensitivity analysis was planned if there were more than 30 patients (5% of the study cohort) identified in the full analysis data set that had potential deviation from study inclusion criteria, such as patients who received more than 1 line of therapy in the advanced or metastatic setting. In such cases, the primary safety analysis was repeated, excluding patients with potential deviations.

9.9.5. Amendments to the Statistical Analysis Plan

Not applicable.

9.10. Quality Control

Information recorded as part of routine clinical practice was transcribed to an eCRF. Data queries were generated to confirm or modify data, as necessary. In addition, data collection and validation procedures were detailed in appropriate operational documents.

Data quality control was performed on active sites (which have enrolled at least 1 patient). Quality control was performed by qualified designated personnel in each country.

9.10.1. Summary of COVID-19 Impact on Study Conduct

The data collection for this study began in December 2015 and completed in August 2021, which included the period during which the COVID-19 pandemic was occurring globally. The study was completed despite the disruption that occurred, and the objectives were achieved. When the pandemic disruption occurred, the trial was in its last phase of enrolment, and as such, the impact was minimal, and the study was able to reach its targeted enrolment. No protocol amendments or addenda were implemented as a result of the pandemic. For sites affected by the COVID-19 outbreak where onsite monitoring visit was planned, visits were either converted to remote monitoring visit following sponsor approval or rescheduled once the situation allowed. Less availability of site staff impacted site responsiveness, which led to some delayed safety reporting. However, this did not impact the final study results and conclusions.

10. Results

The results presented in this study report are based on final database lock date of 19 August 2021. Overall, 606 patients met the eligibility criteria and signed inform consent and were included in the analysis.

In addition to the primary and secondary analyses, the PRAC had requested specific analyses from the MAH. The additional analyses along with the sections in which the results from these analyses have been described are as follows:

Type of Analyses	Section No.
Premedication - whether or not before each administration, - administration after previous infusion related reaction, which drug(s), which doses.	Section 10.4.1.6.2.5
Frequency of dose reductions of ramucirumab due to hypertension	Section 10.4.1.3
Frequency of discontinuation of treatment with ramucirumab due to hypertension	Section 10.4.1.6.2.3
Frequency of gastrointestinal perforation and fistula	Section 10.4.1.6.2.2

10.1. Participants

Overall, 614 patients' records were entered in this database, of which 3 entries consisted of only patient identification numbers without any further information and, hence, these patients were not included in any analysis. Of the remaining 611 patients who signed the informed consent form, 5 patients did not meet the eligibility criteria (4 patients did not receive any dose of ramucirumab and 1 patient received multiple lines of prior chemotherapy in the advanced/metastatic setting), and hence, were not included in the full analysis dataset (Table ANN.2.1.). A total of 606 patients were included in the final analysis. The study was conducted across 78 sites in 8 countries. As treatment may have been modified during the course of this study, patients were assigned to a cohort according to the regimen reported at first dose of treatment:

- 51 (8.4%) in ramucirumab monotherapy cohort,
- 547 (90.3%) in ramucirumab plus paclitaxel cohort, and
- 8 (1.3%) in ramucirumab plus any chemotherapeutic agent other than paclitaxel cohort (hereafter, referred to as the "ramucirumab plus other cohort"). The "other" refers to chemotherapeutic agents received by patients in this cohort which included 5-fluorouracil (bolus or continuous infusion), docetaxel, and irinotecan.

Summary of ramucirumab disposition

All 606 patients received ramucirumab treatment. Figure JVDD.10.1 presents a summary of ramucirumab disposition by cohort.

Overall:

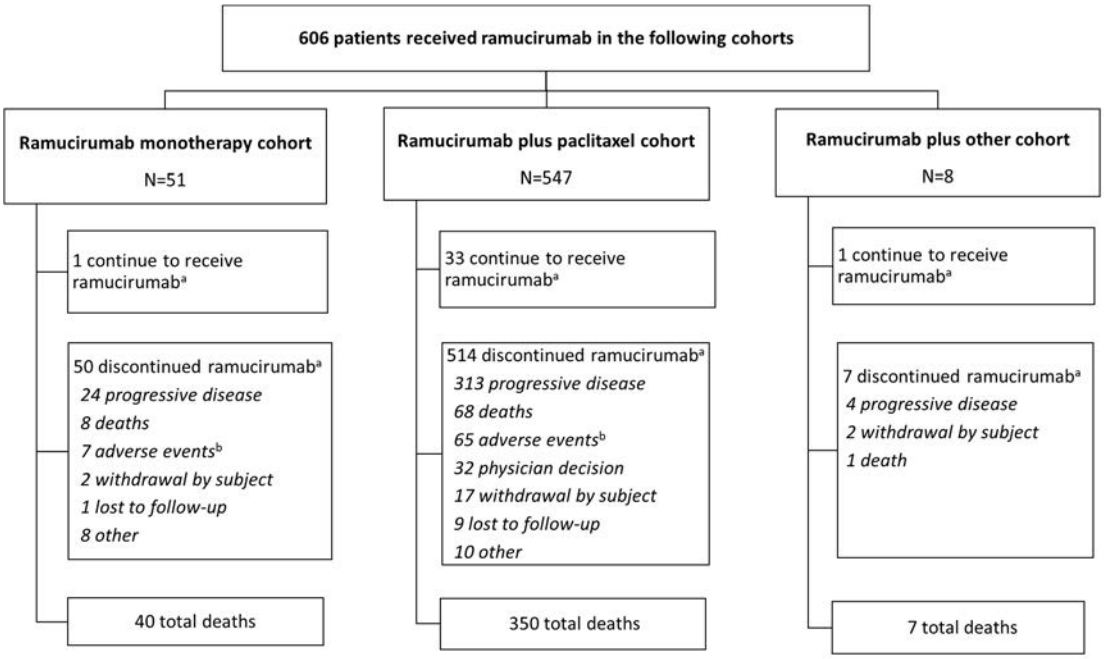
- 35 patients (5.8%) continue to receive ramucirumab treatment at the end of 12 months follow-up period;
- 571 patients (94.2%) discontinued ramucirumab treatment;

- the primary reasons for discontinuation from ramucirumab treatment were:
  - progressive disease (341 patients, 56.3%),
  - death (77 patients, 12.7%), and
  - adverse events (72 patients, 11.9%);
- 397 deaths (65.5%) due to all causalities occurred at any time during the study, of which:
  - 167 deaths (27.6%) occurred between 30 and 90 days of the last ramucirumab dose; and
  - 138 deaths (22.8%) occurred after 90 days of the last ramucirumab dose.

Summary of paclitaxel disposition

Table ANN.2.2. presents a summary of paclitaxel disposition. At the end of 12 months follow-up period, 17 patients (3.1%) continue to receive paclitaxel treatment. A total of 530 patients (96.9%) discontinued paclitaxel treatment, primarily due to:

- progressive disease (267 patients, 48.8%),
- deaths (62 patients, 11.3%), and
- adverse events (117 patients, 21.4%).



a At the end of 12 months follow-up period.
b Discontinuation due to death where primary reason for death is 'Adverse Event' is not included.
Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdsram.rtf; /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf.

Figure JVDD.10.1. Summary of ramucirumab disposition for Study JVDD.

10.2. Descriptive Data

10.2.1. Patient Demographics and Other Baseline Characteristics

The majority of patients were male (421 patients, 69.5%), White (590 patients, 97.4%), and aged 65 years and above (333 patients, 55.0%), with a baseline ECOG performance status of 0 or 1 (489 patients, 80.7%). The median age was 66 years (range, 24 to 88 years), including 22.3% aged 75 years and above. The study site or personnel reported 127 patients (21%) who experienced at least 10% weight loss over 3 months prior to the initiation of ramucirumab treatment (Table JVDD.10.1).

Table JVDD.10.1. Summary of Patient Demographics and Baseline Characteristics
Full Analysis Set
I4T-MC-JVDD

Variables	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Sex, n (%)				
Female	16 (31.4)	165 (30.2)	4 (50.0)	185 (30.5)
Male	35 (68.6)	382 (69.8)	4 (50.0)	421 (69.5)
Age, years				
Median (range)	70 (35-88)	66 (24-86)	64.5 (34-82)	66 (24-88)
Mean (SD)	69.2 (11.6)	64.1 (11.4)	61.3 (15.9)	64.5 (11.5)
Age groups, n (%)				
<65 years	18 (35.3)	251 (45.9)	4 (50.0)	273 (45.0)
≥65 to <70 years	6 (11.8)	96 (17.6)	1 (12.5)	103 (17.0)
≥70 to <75 years	5 (9.8)	89 (16.3)	1 (12.5)	95 (15.7)
≥75years	22 (43.1)	111 (20.3)	2 (25.0)	135 (22.3)
Race, n (%)				
Asian	0	2 (0.4)	0	2 (0.3)
Black/African American	0	6 (1.1)	0	6 (1.0)
White	50 (98.0)	532 (97.3)	8 (100.0)	590 (97.4)
Missing	1 (2.0)	7 (1.3)	0	8 (1.3)
Ethnicity, n (%)				
Hispanic or Latino	2 (3.9)	36 (6.6)	0	38 (6.3)
Not Hispanic or Latino	45 (88.2)	490 (89.6)	7 (87.5)	542 (89.4)
Not reported	4 (7.8)	21 (3.8)	1(12.5)	26 (4.3)
Weight (kg)	**n=51**	**n=523**	**n=8**	**n=582**
Median (range)	63.0 (36-137)	66.5 (36-135)	54.7 (45-105)	66.0 (36-137)
Mean (SD)	64.3 (17.1)	67.2 (14.6)	61.6 (19.6)	66.9 (14.9)
Height (cm)	**n=50**	**n=524**	**n=8**	**n=582**
Median (range)	168.0 (152-193)	170.0 (143-198)	169.0 (154-177)	170.0 (143-198)
Mean (SD)	168.7 (8.7)	169.4 (9.5)	167.4 (7.0)	169.3 (9.4)
BMI (kg/m^2)	**n=50**	**n=523**	**n=8**	**n=581**
Median (range)	21.7 (14-37)	22.9 (13-44)	18.9 (17-36)	22.8 (13-44)
Mean (SD)	22.4 (4.4)	23.3 (4.4)	21.9 (6.4)	23.2 (4.4)

Variables	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Blood pressure (mmHg), n (%)[a]	**n=49**	**n=491**	**n=8**	**n=548**
Systolic blood pressure at baseline				
Normal, <120	22 (43.1)	165 (30.2)	3 (37.5)	190 (31.4)
Grade 1, 120-139	17 (33.3)	248 (45.3)	3 (37.5)	268 (44.2)
Grade 2, 140-159	9 (17.6)	63 (11.5)	1 (12.5)	73 (12.0)
Grade 3, ≥160	1 (2.0)	15 (2.7)	1 (12.5)	17 (2.8)
Critical, ≥180	0	0	0	0
Diastolic blood pressure at baseline				
Normal, <80	28 (54.9)	301 (55.0)	5 (62.5)	334 (55.1)
Grade 1, 80-89	16 (31.4)	157 (28.7)	2 (25.0)	175 (28.9)
Grade 2, 90-99	4 (7.8)	26 (4.8)	1 (12.5)	31 (5.1)
Grade 3, ≥100	1 (2.0)	7 (1.3)	0	8 (1.3)
Critical, ≥120	0	0	0	0
Tobacco consumption, n (%)				
Current smoker	5 (9.8)	61 (11.2)	1 (12.5)	67 (11.1)
Former smoker	17 (33.3)	206 (37.7)	2 (25.0)	225 (37.1)
Never smoker	24 (47.1)	253 (46.3)	3 (37.5)	280 (46.2)
Missing	5 (9.8)	27 (4.9)	2 (25.0)	34 (5.6)
Alcohol consumption, n (%)				
Current	3 (5.9)	91 (16.6)	2 (25.0)	96 (15.8)
Former	14 (27.5)	94 (17.2)	1 (12.5)	109 (18.0)
Never	31 (60.8)	331 (60.5)	2 (25.0)	364 (60.1)
Missing	3 (5.9)	31 (5.7)	3 (37.5)	37 (6.1)
≥10% weight loss over 3 months prior to Ram initiation, n (%)				
Yes	13 (25.5)	113 (20.7)	1 (12.5)	127 (21.0)
No	37 (72.5)	428 (78.2)	6 (75.0)	471 (77.7)
Missing	1 (2.0)	6 (1.1)	1 (12.5)	8 (1.3)
ECOG PS (at baseline), n (%)[b]				
0	9 (17.6)	201 (36.7)	1 (12.5)	211 (34.8)
1	23 (45.1)	252 (46.1)	3 (37.5)	278 (45.9)
2	10 (19.6)	41 (7.5)	2 (25.0)	53 (8.7)
3	3 (5.9)	2 (0.4)	1 (12.5)	6 (1.0)
Missing	6 (11.8)	51 (9.3)	1 (12.5)	58 (9.6)
Country, n (%)				
Austria	4 (7.8)	37 (6.8)	3 (37.5)	44 (7.3)
Belgium	0	22 (4.0)	0	22 (3.6)
France	1 (2.0)	5 (0.9)	0	6 (1.0)
Germany	22 (43.1)	125 (22.9)	3 (37.5)	150 (24.8)
Italy	17 (33.3)	260 (47.5)	0	277 (45.7)
Spain	1 (2.0)	70 (12.8)	0	71 (11.7)
Switzerland	1 (2.0)	11 (2.0)	0	12 (2.0)
United States of America	5 (9.8)	17 (3.1)	2 (25.0)	24 (4.0)

Abbreviations: BMI = body mass index; ECOG = Eastern Cooperative Oncology Group; Mono = monotherapy; N = number of patients in the study; n = number of patients in the specified category; PS = performance status; PTX = paclitaxel; Ram = ramucirumab; SD = standard deviation.

a Patients may be counted in multiple rows.

b 0=Fully active, without restriction; 1=Restricted in physically strenuous activity; 2=Ambulatory and capable of all selfcare; 3=Capable of only limited selfcare.

Note: Denominators are based on the total number of patients in the full analysis set.

Final database lock date: 19 August 2021.
Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdemog.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tvscat.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsubsuse.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/twtlos.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tecog_baseline.rtf.

10.2.2. Baseline Diagnosis and Disease Characteristics

Table JVDD.10.2 summarises baseline diagnosis and disease characteristics reported in this study. At the time of study entry, 552 patients (95.7%) were reported with metastatic cancer and 367 patients (60.6%) had metastases in more than 1 organ. The most common sites of metastases included lymph nodes (334 patients, 55.1%), liver (259 patients, 42.7%), peritoneum (256 patients, 42.2%), and lungs (119 patients, 19.6%). A total of 131 patients (21.6%) were reported to have HER2-positive tumours.

Table JVDD.10.2. Summary of Baseline Diagnosis and Disease Characteristics
Full Analysis Set
I4T-MC-JVDD

Variables	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Primary tumour location				
Gastric	17 (33.3)	168 (30.7)	4 (50.0)	189 (31.2)
GEJ	34 (66.7)	379 (69.3)	4 (50.0)	417 (68.8)
Histological/Pathological type				
Intestinal	8 (15.7)	160 (29.3)	1 (12.5)	169 (27.9)
Diffuse	14 (27.5)	106 (19.4)	3 (37.5)	123 (20.3)
Mixed type	2 (3.9)	32 (5.9)	0	34 (5.6)
Unknown	27 (52.9)	249 (45.5)	4 (50.0)	280 (46.2)
HER2 status				
Positive finding	8 (15.7)	121 (22.1)	2 (25.0)	131 (21.6)
Negative finding	36 (70.6)	385 (70.4)	6 (75.0)	427 (70.5)
Not done	4 (7.8)	13 (2.4)	0	17 (2.8)
Unknown	3 (5.9)	27 (4.9)	0	30 (5.0)
Missing	0	1 (0.2)	0	1 (0.2)
Grade at diagnosis				
Well-differentiated (low grade)	4 (7.8)	19 (3.5)	0	23 (3.8)
Moderately differentiated (intermediate grade)	13 (25.5)	127 (23.2)	3 (37.5)	143 (23.6)
Poorly differentiated (high grade)	22 (43.1)	264 (47.7)	3 (37.5)	289 (47.7)
Unable to determine	9 (17.6)	121 (22.1)	2 (25.0)	132 (21.8)
Missing	3 (5.9)	16 (2.9)	0	19 (3.1)

Variables	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Disease stage at initial diagnosis[a]	**50 (100.0)**	**534 (100.0)**	**8 (100.0)**	**592 (100.0)**
Stage IA	0	2 (0.4)	1 (12.5)	3 (0.5)
Stage IB	1 (2.0)	8 (1.5)	0	9 (1.5)
Stage IIA	0	21 (3.9)	0	21 (3.5)
Stage IIB	1 (2.0)	22 (4.1)	0	23 (3.9)
Stage IIIA	7 (14.0)	63 (11.8)	2 (25.0)	72 (12.2)
Stage IIIB	3 (6.0)	32 (6.0)	1 (12.5)	36 (6.1)
Stage IIIC	4 (8.0)	28 (5.2)	0	32 (5.4)
Stage IV	34 (68.0)	358 (67.0)	4 (50.0)	396 (66.9)
Disease stage at study entry[a]	**51 (100.0)**	**519 (100.0)**	**7 (100.0)**	**577 (100.0)**
Stage IIIA	2 (3.9)	12 (2.3)	1 (14.3)	15 (2.6)
Stage IIIB	0	5 (1.0)	0	5 (0.9)
Stage IIIC	1 (2.0)	4 (0.8)	0	5 (0.9)
Stage IV	48 (94.1)	498 (96.0)	6 (85.7)	552 (95.7)
Primary tumour present				
Yes	29 (56.9)	333 (60.9)	7 (87.5)	369 (60.9)
No	22 (43.1)	214 (39.1)	1 (12.5)	237 (39.1)
Presence of ascites				
Yes	9 (17.6)	136 (24.9)	3 (37.5)	148 (24.4)
No	41 (80.4)	411 (75.1)	5 (62.5)	457 (75.4)
Missing	1 (2.0)	0	0	1 (0.2)
Site of metastases[b]				
Adrenal gland	2 (3.9)	17 (3.1)	0	19 (3.1)
Bone	7 (13.7)	65 (11.9)	1 (12.5)	73 (12.0)
Brain	2 (3.9)	9 (1.6)	0	11 (1.8)
Intestine	1 (2.0)	12 (2.2)	0	13 (2.1)
Liver	28 (54.9)	226 (41.3)	5 (62.5)	259 (42.7)
Lung	6 (11.8)	112 (20.5)	1 (12.5)	119 (19.6)
Skin	1 (2.0)	4 (0.7)	0	5 (0.8)
Lymph nodes	30 (58.8)	302 (55.2)	2 (25.0)	334 (55.1)
Pleural	1 (2.0)	24 (4.4)	1 (12.5)	26 (4.3)
Peritoneal	18 (35.3)	234 (42.8)	4 (50.0)	256 (42.2)
Soft tissue	2 (3.9)	18 (3.3)	0	20 (3.3)
Unknown organ	0	5 (0.9)	0	5 (0.8)
No metastatic disease	1 (2.0)	5 (0.9)	0	6 (1.0)
Number of organs involved				
1	16 (31.4)	209 (38.2)	3 (37.5)	228 (37.6)
2	22 (43.1)	207 (37.8)	4 (50.0)	233 (38.4)
3	10 (19.6)	93 (17.0)	1 (12.5)	104 (17.2)
4+	2 (3.9)	28 (5.1)	0	30 (5.0)
Missing/Unknown	1 (2.0)	10 (1.8)	0	11 (1.8)

Abbreviations: GEJ = gastro-oesophageal junction; HER2 = human epidermal growth factor receptor 2; Mono = monotherapy; N = number of patients; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

a Percent is calculated based on the number of patients with corresponding diagnosis available.

b All reported sites of metastases including non-measurable disease.

Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tptdc.rtf.

10.2.3. Comorbidities of Interest

As part of the secondary objective to describe safety in subgroups of interest, sites were asked to identify if patients had cardiac comorbidity, hepatic impairment, or renal impairment based on their medical history (Table JVDD.10.3). Refer to Section 9.3.1 for a detailed description of how sites identified these subgroups of interest. A total of 138 patients (22.8%) had cardiac comorbidity, 68 (11.2%) had hepatic impairment, and 39 (6.4%) had renal impairment.

Table JVDD.10.3. Summary of Comorbidities of Interest
Full Analysis Set
I4T-MC-JVDD

Variables	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Patients with any comorbidities of interest[a]	**22 (43.1)**	**169 (30.9)**	**4 (50.0)**	**195 (32.2)**
Cardiac comorbidity[b]	17 (33.3)	117 (21.4)	4 (50.0)	138 (22.8)
Hepatic impairment	9 (17.6)	57 (10.4)	2 (25.0)	68 (11.2)
Renal impairment	3 (5.9)	36 (6.6)	0	39 (6.4)

Abbreviations: Mono = monotherapy; N = number of patients in population; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] As reported in medical history. Patients may have multiple comorbidities.

[b] Cardiac comorbidity included, but was not limited to, angina, myocardial infarction, congestive heart failure or arrhythmia.

Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tcomorb.rtf.

10.2.4. Medical History

Table JVDD.10.4 summarises historical medical conditions by MedDRA PT in at least 3% of total patients. A total of 58.3% of patients had at least 1 historical medical condition. Hypertension (24.8%) was the most frequently reported condition.

Medical history in subgroups of special interest by SOC is described below:

- Cardiac disorders: 42 patients (6.9%) had cardiac disorders, of which atrial fibrillation (12 patients, 2%) and coronary artery disease (6 patients, 1%) were the 2 most commonly reported conditions.
- Hepatobiliary disorders: 22 patients (3.6%) had hepatobiliary disorders, of which hepatic cirrhosis and hepatic steatosis (each 6 patients, 1%) were the 2 most commonly reported conditions.
- Renal and urinary disorders: 29 patients (4.8%) had renal and urinary disorders, of which hydronephrosis (6 patients, 1%) and chronic kidney disease (5 patients, 0.8%) were the 2 most commonly reported conditions.

Table JVDD.10.4. Summary of Historical Medical Conditions Occurring in at least 3% of Patients (Total) by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Patients with at least 1 historical medical condition	**37 (72.5)**	**311 (56.9)**	**5 (62.5)**	**353 (58.3)**
Hypertension	21 (41.2)	128 (23.4)	1 (12.5)	150 (24.8)
Anaemia	4 (7.8)	53 (9.7)	0	57 (9.4)
Benign prostatic hyperplasia[a]	5 (14.3)	28 (7.3)	1 (25.0)	34 (8.1)
Type 2 diabetes mellitus	6 (11.8)	39 (7.1)	1 (12.5)	46 (7.6)
Abdominal pain	4 (7.8)	29 (5.3)	1 (12.5)	34 (5.6)
Fatigue	1 (2.0)	25 (4.6)	2 (25.0)	28 (4.6)
Gastro-oesophageal reflux disease	1 (2.0)	19 (3.5)	1 (12.5)	21 (3.5)
Hypothyroidism	3 (5.9)	18 (3.3)	0	21 (3.5)
Paraesthesia	0	21 (3.8)	0	21 (3.5)
Hypercholestrolaemia	0	20 (3.7)	0	20 (3.3)
Dysphagia	1 (2.0)	17 (3.1)	1 (12.5)	19 (3.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in population; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

All medical history that is not classified as ongoing based on available dates.

[a] Denominator adjusted because gender-specific event for males: N=35 (Ram mono), N=382 (Ram + PTX), N=4 (Ram + Other), N=421 (Total).

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tmhhistor.rtf.

10.2.5. Pre-existing Conditions

Table JVDD.10.5 summarises pre-existing conditions by MedDRA PT in at least 3% of total patients. Overall, 83.8% of patients had at least 1 pre-existing condition. Pre-existing conditions reported in at least 10% of patients were:

- hypertension (36.6%),
- anaemia (13.9%),
- benign prostatic hyperplasia (12.1%), and
- type 2 diabetes mellitus (11.7%).

Table JVDD.10.5. Summary of Pre-Existing Conditions Occurring in at least 3% of Patients (Total) by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Patients with any pre-existing condition	**44 (86.3)**	**458 (83.7)**	**6 (75.0)**	**505 (83.8)**
Hypertension	26 (51.0)	194 (35.5)	2 (5.0)	222 (36.6)
Anaemia	5 (9.8)	79 (14.4)	0	84 (13.9)
Benign prostatic hyperplasia[a]	5 (14.3)	45 (11.8)	1 (25.0)	51 (12.1)
Type 2 diabetes mellitus	9 (17.6)	61 (11.2)	1 (12.5)	71 (11.7)
Abdominal pain	4 (7.8)	40 (7.3)	1 (12.5)	45 (7.4)
Paraesthesia	0	39 (7.1)	0	39 (6.4)
Hypercholesterolaemia	0	35 (6.4)	0	35 (5.8)
Gastro-oesophageal reflux disease	3 (5.9)	30 (5.5)	1 (12.5)	34 (5.6)
Hypothyroidism	4 (7.8)	29 (5.3)	0	33 (5.4)
Fatigue	3 (5.9)	28 (5.1)	2 (25.0)	33 (5.4)
Dyslipidaemia	0	26 (4.8)	0	26 (4.3)
Dysphagia	2 (3.9)	23 (4.2)	1 (12.5)	26 (4.3)
Nausea	2 (3.9)	19 (3.5)	1 (12.5)	22 (3.6)
Depression	3 (5.9)	18 (3.3)	0	21 (3.5)
Atrial fibrillation	6 (11.8)	13 (2.4)	1 (12.5)	20 (3.3)
Ascites	3 (5.9)	15 (2.7)	1 (12.5)	19 (3.1)
Chronic obstructive pulmonary disease	2 (3.9)	16 (2.9)	1 (12.5)	19 (3.1)
Constipation	2 (3.9)	16 (2.9)	0	18 (3.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in population; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Denominator adjusted because gender-specific event for males: N=35 (Ramucirumab monotherapy), N=382 (Ramucirumab + paclitaxel), N=4 (Ramucirumab + Other), N=421 (Total).

Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpreexist.rtf.

10.2.6. Prior Therapies

Table JVDD.10.6 summarises prior therapy and surgery for gastric cancer. A total of 159 patients (26.2%) underwent surgical procedures with curative or palliative intent, and 84 patients (13.9%) received radiotherapy in any settings prior to study initiation. All patients had received prior systemic therapy, predominantly in the metastatic setting (442 patients, 72.9%).

The most commonly used classes of prior systemic anticancer therapy in all settings in at least 10% of patients were:

- platinum (585 patients, 96.5%),
- fluoropyrimidine (584 patients, 96.4%),
- taxane (178 patients, 29.4%), and
- HER2-targeted agent (106 patients, 17.5%).

The most commonly used anticancer medications in at least 20% of patients were fluorouracil (303 patients, 50.0%) and oxaliplatin (284 patients, 46.9%).

Table JVDD.10.7 summarises non-anticancer medications received within 14 days prior to ramucirumab infusion by at least 5% of patients in total study cohort. Majority of patients (405 patients, 66.8%) had received premedications 14 days prior to ramucirumab infusion.

Table ANN.2.3. presents a complete summary of concomitant medications received by patients within 14 days prior to ramucirumab infusion. Overall, the majority of concomitant medications reported were premedications.

Table JVDD.10.6. Summary of Prior Therapy and Surgery for Gastric Cancer
Full Analysis Set
I4T-MC-JVDD

Variables	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Prior anticancer therapy				
Systemic therapy	51 (100.0)	547 (100.0)	8 (100.0)	606 (100.0)
Surgical procedure	14 (27.5)	142 (26.0)	3 (37.5)	159 (26.2)
Radiotherapy	8 (15.7)	73 (13.3)	3 (37.5)	84 (13.9)
Type of systemic therapy by setting				
Neoadjuvant	7 (13.7)	130 (23.8)	5 (62.5)	142 (23.4)
Adjuvant	16 (31.4)	112 (20.5)	2 (25.0)	130 (21.5)
Locally advanced	3 (5.9)	36 (6.6)	0	39 (6.4)
Metastatic disease	35 (68.6)	404 (73.9)	3 (37.5)	442 (72.9)
Missing	0	2 (0.4)	0	2 (0.3)
Systemic therapy: number of regimens for locally advanced or metastatic disease				
Overall				
1	35 (68.6)	410 (75.0	3 (37.5)	448 (73.9)
2	1 (2.0)	21 (3.8)	0	22 (3.6)
3	2 (3.9)	3 (0.5)	0	5 (0.8)
5	0	1 (0.2)	0	1 (0.2)
Class of prior anti-cancer therapy (any setting)[a]				
At least 1 prior therapy	51 (100.0)	547 (100.0)	8 (100.0)	606 (100.0)
Platinum	51 (100.0)	527 (96.3)	7 (87.5)	585 (96.5)
Fluoropyrimidine	49 (96.1)	529 (96.7)	6 (75.0)	584 (96.4)
Taxane	19 (37.3)	153 (28.0)	6 (75.0)	178 (29.4)
HER2-targeted agent	5 (9.8)	99 (18.1)	2 (25.0)	106 (17.5)
Anthracycline	4 (7.8)	37 (6.8)	0	41 (6.8)
Topoisomerase I inhibitor	2 (3.9)	20 (3.7)	0	22 (3.6)
Immunotherapy	0	15 (2.7)	0	15 (2.5)
Investigational	0	6 (1.1)	0	6 (1.0)
Anti-angiogenic	0	2 (0.4)	0	2 (0.3)
Antifolate	0	1 (0.2)	0	1 (0.2)
Topoisomerase II inhibitor	0	1 (0.2)	0	1 (0.2)
Other chemotherapy	0	4 (0.7)	0	4 (0.7)

Variables	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Systemic therapy medications: all settings (n≥10% of total)[b]				
Fluorouracil	25 (49.0)	275 (50.3)	3 (37.5)	303 (50.0)
Oxaliplatin	23 (45.1)	260 (47.5)	1 (12.5)	284 (46.9)
Fluorouracil; folinic acid; oxaliplatin	14 (27.5)	105 (19.2)	1 (12.5)	120 (19.8)
Capecitabine	8 (15.7)	109 (19.9)	1 (12.5)	118 (19.5)
Cisplatin	6 (11.8)	107 (19.6)	2 (25.0)	115 (19.0)
Docetaxel	14 (27.5)	100 (18.3)	1 (12.5)	115 (19.0)
Trastuzumab	5 (9.8)	99 (18.1)	2 (25.0)	106 (17.5)

Abbreviations: HER2 = human epidermal growth factor receptor 2; Mono = monotherapy; N = number of subjects in population; n number of subjects in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Patients may be counted in multiple medication classes.

[b] Sites could enter individual drug or combination of drugs as a single record.

Final database lock date: 19 August 2021.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tprioth.rtf; /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpriorthcl.rtf.

Table JVDD.10.7. Non-Anticancer Medications Taken by at least 5% of Patients (Total) within 14 Days Prior to Ramucirumab Infusion Full Analysis Set I4T-MC-JVDD

Prior Non-Anticancer Medications	Ram Mono (N=51) n (%)	Ram + PTX (N=547 n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Patients with at least 1 medication	**39 (76.5)**	**360 (65.8)**	**6 (75.0)**	**405 (66.8)**
Dexamethasone	21 (41.2)	262 (47.9)	6 (75.0)	289 (47.7)
Ranitidine hydrochloride	3 (5.9)	129 (23.6)	0	132 (21.8)
Ondansetron	5 (9.8)	121 (22.1)	2 (25.0)	128 (21.1)
Ranitidine	9 (17.6)	118 (21.6)	0	127 (21.0)
Chlorphenamine	6 (11.8)	75 (13.7)	0	81 (13.4)
Chlorphenamine maleate	0	66 (12.1)	0	66 (10.9)
Metoclopramide	1 (2.0)	62 (11.3)	0	63 (10.4)
Dimetindene maleate	8 (15.7)	36 (6.6)	0	44 (7.3)
Clemastine fumarate	2 (3.9)	41 (7.5)	0	43 (7.1)
Dexamethasone sodium phosphate	1 (2.0)	40 (7.3)	0	41 (6.8)
Granisetron	0	40 (7.3)	0	40 (6.6)
Diphenhydramine hydrochloride	6 (11.8)	26 (4.8)	3 (37.5)	35 (5.8)
Diphenhydramine	1 (2.0)	33 (6.0)	0	34 (5.6)

Abbreviations: Mono = monotherapy; N = number of subjects in population; n = number of subjects in the specified category; PTX = paclitaxel; Ram = ramucirumab.

Final database lock date: 19 August 2021.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpricm.rtf.

10.3. Outcome Data

The primary outcome of interest was overall safety profile of ramucirumab administered as monotherapy or in combination therapy for second-line treatment of adult patients with advanced gastric cancer in the real-world setting. All AEs were outlined as data collection variables in the study objectives and detailed data are provided in the following section.

10.4. Main Results

10.4.1. Primary Objective – Safety

Data are summarised separately for the 3 treatment cohorts for ramucirumab exposure. The ramucirumab plus other cohort contained a small number of patients, and diverse anti-cancer therapies may have heterogeneous effects on safety. Hence, this cohort is included in the total number of patients for the outcomes analyses only to give a complete representation of ramucirumab treatment.

10.4.1.1. Ramucirumab and Paclitaxel Exposure

Table JVDD.10.8 summarises dose exposure for ramucirumab and paclitaxel.

Based on intended regimen, over 90% of patients were planned to receive ramucirumab infusion once every 14 days.

The median duration of treatment with ramucirumab received as monotherapy and in combination with paclitaxel were 8 weeks (IQR: 4.0 to 10.6) and 15 weeks (IQR: 8.4 to 26.7), respectively. The median duration of treatment with paclitaxel in ramucirumab plus paclitaxel cohort was 14 weeks (IQR: 8.1 to 24.3). This means that 50% of patients in ramucirumab monotherapy cohort were treated between 4 and 10.6 weeks and in ramucirumab plus paclitaxel cohort between 8.4 and 26.7 weeks.

Ramucirumab and paclitaxel were administered only at the study sites by the authorised study site personnel. As a result, treatment compliance was ensured.

Table JVDD.10.8. Summary of Drug Exposure and Dose Intensity for Ramucirumab and Paclitaxel
Full Analysis Set
I4T-MC-JVDD

Variables	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Ramucirumab				
Infusion received per patient[a]				
n	51	547	8	606
Median	3	4	3.5	4
Q1-Q3	2-4	2-6	1.5-4.5	2-6
Mean (SD)	3.8 (3.5)	4.9 (3.8)	3.9 (3.2)	4.8 (3.8)
Duration on treatment (weeks)[b]				
n	51	542	8	601
Median	8	15	9.5	13.9
Q1-Q3	4.0-10.6	8.4-26.7	5.5-13.5	8.0-25.3
Mean (SD)	9.4 (8.3)	19.7 (14.7)	12.9 (13.3)	18.8 (14.6)
Cumulative dose (mg)				

Variables	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
n	51	547	8	606
Median	1680	3500	2370	3200
Q1-Q3	1000-2590	1920.0- 5954.6	1200-3150	1728-5700
Mean (SD)	2279.6 (2172.5)	4482.3 (3627.4)	2679.3 (2275.4)	4273.1 (3568.3)
Dose intensity[c] (mg/kg per week)				
n	51	532	8	591
Median	3.9	3.6	3.6	3.6
Q1-Q3	3.7-4.0	3.1-3.9	3.4-3.9	3.1-4.0
Mean (SD)	3.8 (0.4)	3.5 (0.7)	3.6 (0.4)	3.5 (0.7)
Relative dose intensity[d], (%)				
n	51	531	8	590
Median	97.8	86.7	94.2	87.7
Q1-Q3	90.3-100.0	73.6-97.2	86.7-98.8	74.1-97.8
Mean (SD)	89.4 (23.6)	81.8 (22.1)	94.2 (9.1)	82.6 (22.2)
Paclitaxel				
Infusion received per patient[a]	NA		NA	
Median		4		4
Q1-Q3		2-6		2-6
Mean (SD)		4.2 (2.9)		4.2 (2.9)
Duration on treatment (weeks)	NA		NA	
Median		14		14
Q1-Q3		8.1-24.3		8.1-24.3
Mean (SD)		17.6 (12.7)		17.6 (12.7)
Cumulative dose (mg/m^2)	NA		NA	
Median		681		681
Q1-Q3		396.4-1070.9		396.4-1070.9
Mean (SD)		788.8 (556.1)		788.8 (556.1)
Dose intensity[e] (mg/kg per week)	NA		NA	
n		528		528
Median		47		47
Q1-Q3		38.9-54.2		38.9-54.2
Mean (SD)		46 (10.7)		46 (10.7)
Relative dose intensity[f], (%)	NA		NA	
n		515		515
Median		77.7		77.7
Q1-Q3		63.8-89.8		63.8-89.8
Mean (SD)		84.3 (129.6)		84.3 (129.6)

Abbreviations: Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; NA = not applicable; PTX = paclitaxel; Q = quarter; Ram = ramucirumab; SD = standard deviation.

[a] Patient is considered to have received a treatment cycle after receiving at least one dose of ramucirumab (either partial or complete).

[b] Difference between last and first infusion dates + lag based on intended regimen and cycle length.

[c] Dose intensity is defined as actual cumulative amount of drug taken mg/kg per week of ramucirumab treatment.

[d] Relative dose intensity is calculated as (actual amount of ramucirumab taken [mg/kg per week]/amount of ramucirumab prescribed [mg/kg per week])*100%.

[e] Dose intensity is defined as actual cumulative amount of drug taken mg/m^2 per week of paclitaxel treatment.

[f] Relative dose intensity is calculated as (actual amount of paclitaxel taken (mg/m^2 per week) /amount of Paclitaxel prescribed [mg/m^2 per week])*100%.

Final database lock date: 19 August 2021.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texpram.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texppac.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texintram.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texintpac.rtf.

10.4.1.2. Premedications

Table JVDD.10.9 summarises the premedications reported in this study. Overall, 547 patients (90.3%) were reported to have received at least 1 premedication. The most commonly observed premedication classes in at least 10% patients were:

- corticosteroids (512 patients, 84.5%),
- H1 antagonists (503 patients, 83.0%),
- gastric acid suppressants (425 patients, 70.1%), and
- antiemetics (402 patients, 66.3%).

Table JVDD.10.9. Summary of Premedications
Full Analysis Set
I4T-MC-JVDD

Parameters	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Patients with at least 1 premedication	**45 (88.2)**	**494 (90.3)**	**8 (100.0)**	**547 (90.3)**
Premedication classes[a]				
Corticosteroids	28 (54.9)	477 (87.2)	7 (87.5)	512 (84.5)
H1 antagonists	37 (72.5)	461 (84.3)	5 (62.5)	503 (83.0)
Gastric acid suppressants	19 (37.3)	406 (74.2)	0	425 (70.1)
Antiemetics	11 (21.6)	383 (70.0)	8 (100.0)	402 (66.3)
Paracetamol	3 (5.9)	41 (7.5)	0	44 (7.3)
Intravenous fluids/electrolytes	2 (3.9)	6 (1.1)	0	8 (1.3)
Antidiarrheal	0	0	2 (25.0)	2 (0.3)
Other	1 (2.0)	10 (1.8)	0	11 (1.8)
Premedication agents (n>10% of total)				
Dexamethasone	26 (51.0)	438 (80.1)	7 (87.5)	471 (77.7)
Ranitidine	13 (25.5)	339 (62.0)	0	352 (58.1)
Chlorphenamine	11 (21.6)	230 (42.0)	0	241 (39.8)
Ondansetron	9 (17.6)	222 (40.6)	3 (37.5)	234 (38.6)
Clemastine	7 (13.7)	77 (14.1)	2 (25.0)	86 (14.2)
Granisetron	1 (2.0)	80 (14.6)	0	81 (13.4)
Metoclopramide	1 (2.0)	76 (13.9)	0	77 (12.7)
Diphenhydramine	8 (15.7)	61 (11.2)	3 (37.5)	72 (11.9)

Abbreviations: Mono = monotherapy; N = number of patients in full analysis set; n = number of patients who received medication; PTX = paclitaxel; Ram = ramucirumab.

[a] Patients may be counted in multiple medication classes.

Final database lock date: 19 August 2021.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpremedcl.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpremed.rtf

10.4.1.3. Dose Adjustments

A summary of dose reductions, omissions, and delays for ramucirumab and paclitaxel administration is presented in Table ANN.2.4. and Table ANN.2.5., respectively.

Adverse events that led to ramucirumab dose adjustments

Table JVDD.10.10 summarises AEs that led to dose adjustment of ramucirumab in at least 3 patients.

Overall, 336 patients (55.4%) had at least 1 ramucirumab dose adjustment. This included:

- 207 patients (34.2%) with at least 1 dose delay of which 140 (23.1%) were due to AEs,
- 179 patients (29.5%) with at least 1 dose omission of which 141 (23.3%) were due to AEs, and
- 59 patients (9.7%) with at least 1 dose reduction of which 58 (9.6%) were due to AEs.

The reporting of dose delay, dose omission and dose reduction due to AEs in ramucirumab monotherapy cohort and ramucirumab plus paclitaxel cohort were 11.8% and 24.3%, 5.9% and 25.0%, 7.8% and 9.9%, respectively.

The most frequently reported AEs in at least 2% of patients that led to dose delay were neutropenia (37 patients, 6.1%) and neutrophil count decreased (12 patients, 2.0%), dose omission was neutropenia (33 patients, 5.4%), and dose reduction was weight decreased (18 patients, 3.0%). Dose adjustments due to neutropenia were only reported in the ramucirumab plus paclitaxel cohort.

Additional analysis from PRAC

The PRAC had requested Lilly to provide frequency of dose reductions of ramucirumab due to hypertension. This data is provided as follows:

- 1 patient (0.2%) in ramucirumab plus paclitaxel cohort had a ramucirumab dose reduction due to hypertension, which was a non-serious event. This event occurred in a PPD patient with no cardiac, hepatic or renal comorbidities. The patient recovered from this event.

Adverse events that led to paclitaxel dose adjustments

Overall, 371 patients (61.2%) had at least 1 paclitaxel dose adjustment. This included:

- 189 patients (31.2%) with at least 1 dose delay of which 130 (21.5%) were due to AEs,
- 218 patients (36.0%) with at least 1 dose omission of which 132 (21.8%) were due to AEs, and
- 181 patients (29.9%) with at least 1 dose reduction of which 178 (29.4%) were due to AEs.

Neutropenia was the most frequently reported AEs in at least 2% of patients that led to dose delay (43 patients, 7.1%), dose omission (26 patients, 4.3%) and dose reduction (37 patients,

6.1%). Additional AEs that were reported in at least 2% of patients that led to dose reduction were paraesthesia (19 patients, 3.1%), weight decreased (14 patients, 2.3%), neuropathy peripheral (13 patients, 2.1%), asthenia and fatigue (12 patients, 2.0%, each; Table ANN.2.5.).

Table JVDD.10.10. Adverse Events Leading to Dose Adjustment of Ramucirumab Occurring in at least 3 Patients (Total) by MedDRA Preferred Term
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram +Other (N=8) n (%)	Total (N=606) n (%)
Patients with any AE leading to dose delay	**6 (11.8)**	**133 (24.3)**	**1 (12.5)**	**140 (23.1)**
Neutropenia	0	37 (6.8)	0	37 (6.1)
Neutrophil count decreased	0	12 (2.2)	0	12 (2.0)
Pyrexia	0	7 (1.3)	0	7 (1.2)
Diarrhoea	0	6 (1.1)	0	6 (1.0)
Pneumonia	1 (2.0)	4 (0.7)	0	5 (0.8)
Cough	0	4 (0.7)	0	4 (0.7)
Hypertension	1 (2.0)	3 (0.5)	0	4 (0.7)
Platelet count decreased	0	4 (0.7)	0	4 (0.7)
Asthenia	0	3 (0.5)	0	3 (0.5)
Hypertransaminasaemia	0	3 (0.5)	0	3 (0.5)
Urinary tract infection	0	3 (0.5)	0	3 (0.5)
Vomiting	0	3 (0.5)	0	3 (0.5)
Patients with any AE leading to dose reduction	**4 (7.8)**	**54 (9.9)**	0	**58 (9.6)**
Weight decreased	2 (3.9)	16 (2.9)	0	18 (3.0)
Asthenia	1 (2.0)	6 (1.1)	0	7 (1.2)
Neutropenia	0	7 (1.3)	0	7 (1.2)
Fatigue	0	4 (0.7)	0	4 (0.7)
Epistaxis	0	3 (0.5)	0	3 (0.5)
Patients with any AE leading to dose omission	**3 (5.9)**	**137 (25.0)**	**1 (12.5)**	**141 (23.3)**
Neutropenia	0	33 (6.0)	0	33 (5.4)
Neutrophil count decreased	0	11 (2.0)	0	11 (1.8)
General physical health deterioration	0	9 (1.6)	0	9 (1.5)
Proteinuria	0	9 (1.6)	0	9 (1.5)
Epistaxis	0	6 (1.1)	0	6 (1.0)
Diarrhoea	0	5 (0.9)	0	5 (0.8)
Intestinal obstruction	0	4 (0.7)	0	4 (0.7)
Mucosal inflammation	0	4 (0.7)	0	4 (0.7)
Platelet count decreased	0	4 (0.7)	0	4 (0.7)
Anaemia	0	3 (0.5)	0	3 (0.5)
Asthenia	0	3 (0.5)	0	3 (0.5)
Fatigue	0	3 (0.5)	0	3 (0.5)
Leukopenia	0	3 (0.5)	0	3 (0.5)
Malignant neoplasm progression	0	3 (0.5)	0	3 (0.5)
Pyrexia	0	3 (0.5)	0	3 (0.5)
Thrombocytopenia	0	3 (0.5)	0	3 (0.5)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category, PTX = paclitaxel; Ram = ramucirumab.

Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf.

10.4.1.4. Overview of Adverse Events

The study physician or other site personnel recorded via eCRF all AEs that they became aware of that occurred in temporal association with ramucirumab. Severity grades for real-world outcomes were not available as commonly used AE severity scales such as CTCAE grading scales were designed for clinical trial purposes and are not typically used in routine clinical practice settings.

Table JVDD.10.11 provides high level overview of the reported AEs, SAEs, ramucirumab discontinuation due to an AE and deaths. More detailed descriptions of these events (with or without the relationship to anti-cancer treatment including ramucirumab) are presented in the following sections of this report.

Adverse events, including SAEs, from the first administration of ramucirumab up to 30 days, 90 days and post 90 days after last administration of ramucirumab were summarised. As the occurrence of AEs reported within 30 days after last administration of ramucirumab is almost identical to data reported within 90 days, all AE data presented in this report will focus on the period from the first administration of ramucirumab up to and including 90 days after the last infusion, as specified in the study protocol, unless otherwise specified. A summary of AEs by PTs is summarised by frequency in Table JVDD.10.15.

Table JVDD.10.11. Overview of Adverse Events Regardless of Causality
Full Analysis Set
I4T-MC-JVDD

Number of Subjects[a,b]	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other[c] (N=8)	Total[c] (N=606)
Patients with AE				
within 30 days of last ram dose	49 (96.1)	531 (97.1)	8 (100.0)	588 (97.0)
within 90 days of last ram dose	49 (96.1)	535 (97.8)	8 (100.0)	592 (97.7)
after 90 days of last ram dose	0	12 (2.2)	0	12 (2.0)
Patients with SAE[c]				
within 30 days of last ram dose	22 (43.1)	197 (36.0)	5 (62.5)	224 (37.0)
within 90 days of last ram dose	24 (47.1)	220 (40.2)	6 (75.0)	250 (41.3)
after 90 days of last ram dose	0	6 (1.1)	0	6 (1.0)
Discontinuation due to AE[b]				
any treatment	7 (13.7)	130 (23.8)	0	137 (22.6)
ramucirumab	7 (13.7)	68 (12.4)	0	75 (12.4)
paclitaxel	0	122 (22.3)	0	122 (20.1)
Discontinuation due to SAE[b]				
any treatment	2 (3.9)	32 (5.9)	0	34 (5.6)
ramucirumab	2 (3.9)	28 (5.1)	0	30 (5.0)
paclitaxel	0	29 (5.3)	0	29 (4.8)
AE leading to death				
within 30 days of last ram dose	7 (13.7)	55 (10.1)	1 (12.5)	63 (10.4)
within 90 days of last ram dose	10 (19.6)	67 (12.2)	1 (12.5)	78 (12.9)
after 90 days of last ram dose	0	3 (0.5)	0	3 (0.5)

Abbreviations: AE = adverse event; Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.

[a] Patients may be counted in more than 1 category.

[b] Some of the AEs lead to discontinuation of both drugs and are counted in both totals.

[c] Deaths are also included as SAEs.
Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov.rtf.

10.4.1.5. Deaths, Other Serious Adverse Events and Other Adverse Events of Interest

10.4.1.5.1. Deaths

Table JVDD.10.12 presents a summary of deaths observed in this study. Overall, 397 (65.5%) deaths were reported, regardless of causality. There were 259 (42.7%) deaths on or within 90 days of last ramucirumab dose, of which 225 (37.1%) deaths were due to study disease, 33 (5.4%) due to AEs and 1 (0.2%) for which the reason was reported as death. Of the 33 deaths due to AEs, 5 (9.8%) were in the ramucirumab monotherapy cohort and 28 (5.1%) in ramucirumab plus paclitaxel cohort.

There were no AEs reported to be the primary cause of death in more than 1 patient in ramucirumab monotherapy arm. The most frequently reported AEs considered to be the primary cause of death in 2 or more patients in ramucirumab plus paclitaxel arm were malignant neoplasm progression (4 patients, 0.7%) and gastrointestinal haemorrhage (3 patients, 0.5%).

A total of 9 (1.5%) deaths due to AEs were considered to be related to ramucirumab treatment as per physician's assessment. These included:

- gastric perforation (2 deaths, 0.3%), and
- gastrointestinal haemorrhage, intestinal perforation, myocardial infarction, oesophageal perforation, pneumocystis jirovecii pneumonia and small intestinal perforation (1 death, 0.2% each).

Among the 138 (22.6%) deaths occurring after 90 days of the last ramucirumab dose, the majority were due to study disease (134 deaths, 22.1%). Of the 2 deaths due to AEs, the primary reasons for death were acute kidney injury and death not further specified. In both cases the events were considered not related to ramucirumab. It was reported that the patient with acute kidney injury suffered post puncture renal insufficiency due to tumour progression.

A complete summary of death is included in Table ANN.2.6.

Table JVDD.10.12. Summary of Deaths
Full Analysis Set
I4T-MC-JVDD

Variables	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram +Other (N=8) n (%)	Total (N=606) n (%)
Deaths, all causality	**40 (78.4)**	**350 (64.0)**	**7 (87.5)**	**397 (65.5)**
Related to study treatment	**2 (3.9)**	**14 (2.6)**	**0**	**16 (2.6)**
Deaths on or within 30 days of last ram dose	**15 (29.4)**	**75 (13.7)**	**2 (25.0)**	**92 (15.2)**
Related to study treatment	**1 (2.0)**	**6 (1.1)**	**0**	**7 (1.2)**
Deaths between 30 and 90 days of last ram dose	**17 (33.3)**	**148 (27.1)**	**2 (25.0)**	**167 (27.6)**
Related to study treatment	**0**	**1 (0.2)**	**0**	**1 (0.2)**
Deaths on or within 90 days of last ram dose	**32 (62.7)**	**223 (40.8)**	**4 (50.0)**	**259 (42.7)**
Primary reason for deaths (within 90 days)[a]				
Adverse events reported to be primary cause of death in at least 2 patients	5 (9.8)	28 (5.1)	0	33 (5.4)
Malignant neoplasm progression	0	4 (0.7)	0	4 (0.7)
Gastrointestinal haemorrhage	0	3 (0.5)[b]	0	3 (0.5)
Gastric perforation	0	2 (0.4)	0	2 (0.3)
General physical health deterioration	0	2 (0.4)	0	2 (0.3)
Death	0	1 (0.2)	0	1 (0.2)
Study disease	27 (52.9)	194 (35.5)	4 (50.0)	225 (37.1)
Deaths due to adverse events related to study treatment	**1 (2.0)**	**7 (1.3)**	**0**	**8 (1.3)**
Deaths after 90 days of last ram dose	**8 (15.7)**	**127 (23.2)**	**3 (37.5)**	**138 (22.8)**

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

a Patients may be counted in more than 1 category.

b One additional patient (patient ID: PPD was reported to have gastrointestinal haemorrhage that resulted in a fatal outcome; however, the treating physician reported the primary cause of death was reported as study disease.

Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf.

10.4.1.5.2. Serious Adverse Events

Overall, 250 patients (41.3%) experienced at least 1 SAE reported during treatment or within 90 days of the last dose of ramucirumab; 24 patients (47.1%) in ramucirumab monotherapy cohort and 220 patients (40.2%) in ramucirumab plus paclitaxel cohort.

Table JVDD.10.13 summarises SAEs experienced by at least 1% of patients. The most commonly reported SAEs in at least 2% of patients in ramucirumab monotherapy cohort were malignant neoplasm progression (4 patients, 7.8%) and haematemesis and device related infection (2 patients, 3.9% each). The most commonly reported SAEs in at least 2% of patients in ramucirumab plus paclitaxel cohort were malignant neoplasm progression (27 patients, 4.9%), general physical health deterioration (16 patients, 2.9%), intestinal obstruction (15 patients, 2.7%), abdominal pain (14 patients, 2.6%), and pneumonia (12 patients, 2.2%). A full summary

of SAEs by SOC and PTs occurring on or within 90 days of last dose of ramucirumab are presented in Table ANN.2.7.

Table JVDD.10.13. Summary of Serious Adverse Events Experienced by at least 1% of Patients (Total) by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Patients with at least 1 SAE on or within 90 days of Ram[a]	**24 (47.1)**	**220 (40.2)**	**6 (75.0)**	**250 (41.3)**
Malignant neoplasm progression	4 (7.8)	27 (4.9)	1 (12.5)	32 (5.3)
General physical health deterioration	1(2.0)	16 (2.9)	0	17 (2.8)
Abdominal pain	1 (2.0)	14 (2.6)	0	15 (2.5)
Intestinal obstruction	0	15 (2.7)	0	15 (2.5)
Pneumonia	1 (2.0)	12 (2.2)	0	13 (2.1)
Ascites	1 (2.0)	9 (1.6)	0	10 (1.7)
Vomiting	1 (2.0)	9 (1.6)	0	10 (1.7)
Pyrexia	1 (2.0)	8 (1.5)	0	9 (1.5)
Anaemia	1 (2.0)	7 (1.3)	0	8 (1.3)
Febrile neutropenia	0	8 (1.5)	0	8 (1.3)
Dysphagia	1 (2.0)	5 (0.9)	1 (12.5)	7 (1.2)
Dyspnoea	0	7 (1.3)	0	7 (1.2)
Gastrointestinal haemorrhage	0	6 (1.1)	1 (12.5)	7 (1.2)
Haematemesis	2 (3.9)	5 (0.9)	0	7 (1.2)
Ileus	1 (2.0)	6 (1.1)	0	7 (1.2)
Nausea	0	7 (1.3)	0	7 (1.2)
Pulmonary embolism	0	7 (1.3)	0	7 (1.2)
Urinary tract infection	1 (2.0)	6 (1.1)	0	7 (1.2)
Device related infection	2 (3.9)	4 (0.7)	0	6 (1.0)
Pleural effusion	1 (2.0)	4 (0.7)	1 (12.5)	6 (1.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.

[a] SAE from initiation of ramucirumab until up to 90 days after last dose of ramucirumab.

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf.

10.4.1.5.3. Adverse Events Leading to Treatment Discontinuation

Overall, 137 patients (22.6%) discontinued any study treatment due to AEs, of which 34 patients (5.6%) discontinued due to SAEs.

AEs leading to ramucirumab discontinuation

Table ANN.2.8 summarises AEs leading to ramucirumab discontinuation. Overall, 75 patients (12.4%) discontinued ramucirumab treatment due to AEs: 7 patients (13.7%) in ramucirumab monotherapy cohort and 68 patients (12.4%) in ramucirumab plus paclitaxel cohort. Of the

overall 75 patients, 45 patients (7.4%) discontinued ramucirumab treatment due to non-serious AEs. Majority of the patients, both in ramucirumab monotherapy (4 patients, 7.8%) and ramucirumab plus paclitaxel (14 patients, 2.6%) cohorts discontinued primarily due to general physical health deterioration. Additionally, no other AEs occurred in more than 1 patient in ramucirumab monotherapy cohort and in more than 2 patients in ramucirumab plus paclitaxel cohort. AEs leading to ramucirumab discontinuation in 2 patients (0.4%) in ramucirumab plus paclitaxel cohort were:

- asthenia,
- cerebral ischaemia,
- haematemesis,
- ileus,
- intestinal obstruction,
- malignant neoplasm progression,
- peripheral sensory neuropathy, and
- proteinuria.

SAEs leading to ramucirumab discontinuation

Table JVDD.10.14 summarises SAEs leading to ramucirumab discontinuation in 2 or more patients. Thirty patients (5.0%) discontinued ramucirumab treatment due to SAEs: 2 patients (3.9%) in ramucirumab monotherapy cohort and 28 (5.1%) in ramucirumab plus paclitaxel cohort.

AEs leading to paclitaxel discontinuation

Table ANN.2.9 summarises AEs leading to paclitaxel discontinuation. Overall, 122 patients (20.1%) discontinued paclitaxel treatment due to AEs, of which 93 patients (15.3%) discontinued due to non-serious AEs. Majority of the patients (38 patients, 6.9%) discontinued primarily due to neuropathy peripheral (including neuropathy peripheral, peripheral sensory neuropathy, neurotoxicity, paraesthesia, and polyneuropathy).

SAEs leading to paclitaxel discontinuation

Twenty-nine patients (4.8%) discontinued paclitaxel treatment due to SAEs. SAEs leading to paclitaxel discontinuation in 2 patients (0.3%) were febrile neutropenia, haematemesis and ileus. None of these SAEs occurred in more than 2 patients (Table ANN.2.9).

Table JVDD.10.14. Serious Adverse Events Leading to Ramucirumab Discontinuation in 2 or More Patients (Total) by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MV-JVDD

MedDRA Preferred Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram +other (N=8) n (%)	Total (N=606) n (%)
Patients who discontinued ramucirumab due to SAE[a]	**2 (3.9)[b]**	**28 (5.1)**	**0**	**30 (5.0)**
Cerebral ischaemia	0	2 (0.4)	0	2 (0.3)
General physical health deterioration	0	2 (0.4)	0	2 (0.3)
Haematemesis	0	2 (0.4)	0	2 (0.3)
Ileus	0	2 (0.4)	0	2 (0.3)
Intestinal obstruction	0	2 (0.4)	0	2 (0.3)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Patients may be counted in more than 1 category.

[b] The 2 patients in ramucirumab monotherapy cohort discontinued treatment due to disease progression and jaundice cholestatic.

Final database lock date: 19 August 2021.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_ser_ram.rtf.

10.4.1.6. Overall Adverse Event Profile

Table JVDD.10.15 summarises AEs experienced by at least 5% of total patients on or within 90 days of last dose of ramucirumab. Overall, 592 patients (97.7%) experienced at least 1 AE. The most frequently reported AEs were fatigue (163 patients, 26.9%), nausea and neutropenia (129 patients, 21.3% each), and diarrhoea (125 patients, 20.6%). Table ANN.2.10 presents a complete summary of AEs by SOC and PTs occurring on or within 90 days of last ramucirumab dose.

Adverse events in ramucirumab monotherapy cohort

Forty-nine patients (96.1%) experienced at least 1 AE on or within 90 days of last dose of ramucirumab. The 2 most frequently reported AEs were nausea (11 patients, 21.6%), and asthenia and general physical health deterioration (9 patients, 17.6% each).

Adverse events in ramucirumab plus paclitaxel cohort

Five hundred and thirty-five patients (97.8%) experienced at least 1 AE on or within 90 days of last dose of ramucirumab. The 2 most frequently reported AEs were fatigue (155 patients, 28.3%) and neutropenia (129 patients, 23.6%).

Table ANN.2.11 provides an overview of AEs with relatedness to study treatment.

Table JVDD.10.15. Summary of Adverse Events Experienced by at least 5% of Patients (Total) on or within 90 Days of Last Ramucirumab Dose by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram +Other (N=8) n (%)	Total (N=606) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**49 (96.1)**	**535 (97.8)**	**8 (100.0)**	**592 (97.7)**
Fatigue	7 (13.7)	155 (28.3)	1 (12.5)	163 (26.9)
Nausea	11 (21.6)	116 (21.2)	2 (25.0)	129 (21.3)
Neutropenia	0	129 (23.6)	0	129 (21.3)
Diarrhoea	3 (5.9)	121 (22.1)	1 (12.5)	125 (20.6)
Anaemia	6 (11.8)	105 (19.2)	2 (25.0)	113 (18.6)
Asthenia	9 (17.6)	102 (18.6)	0	111 (18.3)
Pyrexia	4 (7.8)	95 (17.4)	0	99 (16.3)
Abdominal pain	6 (11.8)	83 (15.2)	0	89 (14.7)
Epistaxis	1 (2.0)	77 (14.1)	1 (12.5)	79 (13.0)
Weight decreased	4 (7.8)	72 (13.2)	0	76 (12.5)
Vomiting	7 (13.7)	69 (12.6)	0	76 (12.5)
Decreased appetite	5 (9.8)	69 (12.6)	0	74 (12.2)
Paraesthesia	1 (2.0)	72 (13.2)	0	73 (12.0)
Constipation	6 (11.8)	57 (10.4)	3 (37.5)	66 (10.9)
Hypertension	4 (7.8)	60 (11.0)	0	64 (10.6)
General physical health deterioration	9 (17.6)	55 (10.1)	0	64 (10.6)
Oedema peripheral	4 (7.8)	47 (8.6)	0	51 (8.4)
Cough	2 (3.9)	42 (7.7)	1 (12.5)	45 (7.4)
Malignant neoplasm progression	4 (7.8)	40 (7.3)	1 (12.5)	45 (7.4)
Neuropathy peripheral	1 (2.0)	39 (7.1)	1 (12.5)	41 (6.8)
Dyspnoea	2 (3.9)	37 (6.8)	0	39 (6.4)
Dysphagia	1 (2.0)	34 (6.2)	2 (25.0)	37 (6.1)
Mucosal inflammation	0	37 (6.8)	0	37 (6.1)
Abdominal pain upper	4 (7.8)	30 (5.5)	1 (12.5)	35 (5.8)
Ascites	5 (9.8)	29 (5.3)	0	34 (5.6)
Stomatitis	2 (3.9)	30 (5.5)	1 (12.5)	33 (5.4)
Alopecia	0	33 (6.0)	0	33 (5.4)
Neutrophil count decreased	0	31 (5.7)	0	31 (5.1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.
Final database lock date: 19 August 2021.
Source: lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf.

10.4.1.6.1. Consolidated Adverse Events

In addition to the AEs summarised by PTs in Table JVDD.10.15, supplemental displays were prepared in which selected similar PTs were consolidated and data summarised in Table JVDD.10.16.

Consolidated AEs experienced by at least 10% of total patients on or within 90 days of last ramucirumab dose in ramucirumab monotherapy cohort were:

- fatigue (16 patients, 31.4%),
- abdominal pain (10 patients, 19.6%), and
- anaemia (7 patients, 13.7%).

Consolidated AEs experienced by at least 10% of total patients on or within 90 days of last ramucirumab dose in ramucirumab and paclitaxel cohort were:

- fatigue (249 patients, 45.5%),
- neuropathy (167 patients, 30.5%),
- neutropenia (155 patients, 28.3%)
- anaemia (111 patients, 20.3%), and
- abdominal pain (108 patients, 19.7%).

Table JVDD.10.16. Summary of Consolidated Adverse Events Experienced by at least 5% of Patients (Total) on or within 90 Days of Last Ramucirumab Dose by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

Consolidated AE category MedDRA Preferred Term[a]	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + other (N=8) n (%)	Total (N=606) n (%)
Patients with at least 1 consolidated AE on or within 90 days of Ram	**29 (56.9)**	**443 (81.0)**	**4 (50.0)**	**476 (78.5)**
Fatigue	**16 (31.4)**	**249 (45.5)**	**1 (12.5)**	**266 (43.9)**
Fatigue	7 (13.7)	155 (28.3)	1 (12.5)	163 (26.9)
Asthenia	9 (17.6)	102 (18.6)	0	111 (18.3)
Neuropathy	**5 (9.8)**	**167 (30.5)**	**2 (25.0)**	**174 (28.7)**
Paraesthesia	1 (2.0)	72 (13.2)	0	73 (12.0)
Neuropathy peripheral	1 (2.0)	39 (7.1)	1 (12.5)	41 (6.8)
Polyneuropathy	2 (3.9)	25 (4.6)	1 (12.5)	28 (4.6)
Neurotoxicity	1 (2.0)	18 (3.3)	0	19 (3.1)
Neutropenia	**0**	**155 (28.3)**	**0**	**155 (25.6)**
Neutropenia	0	129 (23.6)	0	129 (21.3)
Neutrophil count decreased	0	31 (5.7)	0	31 (5.1)
Abdominal pain	**10 (19.6)**	**108 (19.7)**	**1 (12.5)**	**119 (19.6)**
Abdominal pain	6 (11.8)	83 (15.2)	0	89 (14.7)
Abdominal pain upper	4 (7.8)	30 (5.5)	1 (12.5)	35 (5.8)
Anaemia	**7 (13.7)**	**111 (20.3)**	**2 (25.0)**	**120 (19.8)**
Anaemia	6 (11.8)	105 (19.2)	2 (25.0)	113 (18.6)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Consolidated Adverse Events observed from initiation of Ram to 90 days after the last dose of Ram.

Final database lock date: 19 August 2021.

Source: lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taecon_soc90.rtf.

10.4.1.6.2. Adverse Events of Special Interest

The following AEs are considered to be AESIs for ramucirumab: IRR, hypertension, proteinuria, arterial and venous thromboembolic events, bleeding/haemorrhagic events, GI perforation, CHF, wound healing complications, fistula, liver failure/liver injury and RPLS.

Overall AESIs

Table JVDD.10.17 summarises AESIs experienced by at least 3 patients on or within 90 days of last ramucirumab dose. Overall, 242 patients (39.9%) experienced at least 1 AESI on or within 90 days of last ramucirumab dose. The most frequently reported AESIs categories observed in at least 5% of patients were bleeding/haemorrhage events (126 patients, 20.8%), which constituted mainly of epistaxis (79 patients, 13.0%) and GI haemorrhage events (34 patients, 5.6%), hypertension (66 patients, 10.9%), and liver injury/failure (49 patients, 8.1%).

Additionally, 7 patients (1.2%) experienced arterial thromboembolic events, 5 (0.8%) had CHF, 4 (0.7%) had fistula, 2 (0.3%) had pulmonary haemorrhage events and 1 (0.2%) each, had hepatic haemorrhage events and RPLS.

Serious AESIs

Table JVDD.10.18 summarises serious AESIs experienced by at least 2 patients on or within 90 days of last ramucirumab dose. Sixty-four patients (10.6%) experienced at least 1 serious AESI on or within 90 days of last ramucirumab dose. The most frequently reported AESIs categories observed in at least 1% of patients were bleeding/haemorrhage events (26 patients, 4.3%, including GI haemorrhage events (21 patients, 3.5%), gastrointestinal perforation (12 patients, 2.0%), liver injury/failure (8 patients, 1.3%), and venous thromboembolic events (7 patients, 1.2%).

Table JVDD.10.17. Summary of Adverse Events of Special Interests on or within 90 Days of Last Ramucirumab Dose in at least 3 Patients by MedDRA Preferred Term by Decreasing Frequency Full Analysis Set I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram+ Other (N=8) n (%)	Total (N=606) n (%)
Patients with any AESI on or within 90 days of Ram	15 (29.4)	224 (41.0)	3 (37.5)	242 (39.9)
Bleeding/haemorrhage events	4 (7.8)	119 (21.6)	3 (37.5)	126 (20.8)
Epistaxis	1 (2.0)	77 (14.1)	1 (12.5)	79 (13.0)
Gastrointestinal haemorrhage events	3 (5.9)	30 (5.5)	1 (12.5)	34 (5.6)
Gastrointestinal haemorrhage	1 (2.0)	8 (1.5)	1 (12.5)	10 (1.7)
Haematemesis	2 (3.9)	8 (1.5)	0	10 (1.7)
Gastric haemorrhage	0	4 (0.7)	0	4 (0.7)
Haemorrhoidal haemorrhage	0	3 (0.5)	0	3 (0.5)
Gingival bleeding	0	6 (1.1)	0	6 (1.0)
Haematuria	0	6 (1.1)	0	6 (1.0)
Haematoma	0	2 (0.4)	1 (12.5)	3 (0.5)
Hypertension	**4 (7.8)**	**62 (11.3)**	**0**	**66 (10.9)**
Hypertension	4 (7.8)	60 (11.0)	0	64 (10.6)
Liver injury/failure	**4 (7.8)**	**45 (8.2)**	**0**	**49 (8.1)**
Aspartate aminotransferase increased	1 (2.0)	12 (2.2)	0	13 (2.1)
Blood bilirubin increased	1 (2.0)	9 (1.6)	0	10 (1.7)
Alanine aminotransferase increased	1 (2.0)	7 (1.3)	0	8 (1.3)
Hypertransaminasaemia	0	8 (1.5)	0	8 (1.3)
Gamma-glutamyltransferase increased	0	6 (1.1)	0	6 (1.0)
Hepatotoxicity	0	4 (0.7)	0	4 (0.7)
Jaundice	0	4 (0.7)	0	4 (0.7)
Transaminases increased	0	3 (0.5)	0	3 (0.5)
Venous thromboembolic events	**2 (3.9)**	**17 (3.1)**	**0**	**19 (3.1)**
Pulmonary embolism	0	9 (1.6)	0	9 (1.5)
Deep vein thrombosis	1 (2.0)	4 (0.7)	0	4 (0.7)
Proteinuria	**1 (2.0)**	**17 (3.1)**	**0**	**18 (3.0)**
Proteinuria	1 (2.0)	17 (3.1)	0	18 (3.0)
Gastrointestinal perforation	**2 (3.9)**	**11 (2.0)**	**0**	**13 (2.1)**
Gastric perforation	0	3 (0.5)	0	3 (0.5)
Peritonitis bacterial	1 (2.0)	2 (0.4)	0	3 (0.5)
Healing complication	**0**	**4 (0.7)**	**0**	**4 (0.7)**
Impaired healing	0	4 (0.7)	0	4 (0.7)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Patients may be counted in more than 1 category.

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_pt.rtf.

Table JVDD.10.18. Summary of Serious Adverse Events of Special Interests on or within 90 Days of Last Ramucirumab Dose in at least 2 Patients by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram+ Other (N=8) n (%)	Total (N=606) n (%)
Patients with any serious AESI on or within 90 days of Ram	6 (11.8)	56 (10.2)	2 (25.0)	64 (10.6)
Bleeding/haemorrhage events	**2 (3.9)**	**23 (4.2)**	**1 (12.5)**	**26 (4.3)**
Gastrointestinal haemorrhage events	2 (3.9)	18 (3.3)	1 (12.5)	21 (3.5)
Gastrointestinal haemorrhage	0	6 (1.1)	1 (12.5)	7 (1.2)
Haematemesis	2 (3.9)	5 (0.9)	0	7 (1.2)
Gastric haemorrhage	0	3 (0.5)	0	3 (0.5)
Gastrointestinal perforation	**2 (3.9)**	**10 (1.8)**	**0**	**12 (2.0)**
Gastric perforation	0	3 (0.5)	0	3 (0.5)
Intestinal perforation	0	2 (0.4)	0	2 (0.3)
Peritonitis bacterial	1 (2.0)	1 (0.2)	0	2 (0.3)
Liver injury/failure	**2 (3.9)**	**6 (1.1)**	**0**	**8 (1.3)**
Jaundice	0	3 (0.5)	0	3 (0.5)
Venous thromboembolic events	**0**	**7 (1.3)**	**0**	**7 (1.2)**
Pulmonary embolism	0	7 (1.3)	0	7 (1.2)
Arterial thromboembolic events	**0**	**4 (0.7)**	**1 (12.5)**	**5 (0.8)**
Cerebral ischaemia	0	2 (0.4)	0	2 (0.3)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.
Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_ser.rtf.

The following sub-section describes AESIs of bleeding/haemorrhage events, liver injury/failure events, hypertension, gastrointestinal perforation, and gastrointestinal/non-gastrointestinal fistula in detail.

10.4.1.6.2.1. Bleeding/Haemorrhage Events

Overall, 126 patients (20.8%) experienced bleeding/haemorrhage events. These included:

- 4 patients (7.8%) in ramucirumab monotherapy cohort. The most frequently reported PT was:
  - haematemesis (2 patients, 3.9%);
- 119 patients (21.6%) in ramucirumab plus paclitaxel cohort. The most frequently reported PTs were:
  - epistaxis (77 patients, 14.1%); and
  - gastrointestinal haemorrhage and haematemesis (8 patients, 1.5% each).

Two patients (3.9%) in ramucirumab monotherapy cohort experienced serious events of haematemesis. None of these events resulted in a fatal outcome in this cohort. Twenty-

three patients (4.2%) experienced serious bleeding/haemorrhage events in the ramucirumab plus paclitaxel cohort, primarily due to gastrointestinal haemorrhage events (18 patients, 3.3%): 4 due to gastrointestinal haemorrhage and 1 each due to gastric haemorrhage, haematemesisand tumour haemorrhage. The majority of these events occurred in the context of progressive disease or due to tumour bleeding. Of these, the events experienced by 2 patients, 1 with gastrointestinal haemorrhage and 1 with gastric haemorrhage, were considered to be possibly related to study treatment per physician's assessment.

10.4.1.6.2.2. Gastrointestinal Perforation and Gastrointestinal and Non-Gastrointestinal Fistula

Additional analysis from PRAC

The PRAC had requested Lilly to provide frequency of gastrointestinal perforation and fistula. This data is provided as follows:

Gastrointestinal perforation

Overall, 13 patients (2.1%) experienced GI perforation. These included:

- 2 patients (3.9%) in ramucirumab monotherapy cohort:
  - 1 patient, (2.0%) each, with peritonitis bacterial and small intestinal perforation;
- 11 patients (2.0%) in ramucirumab plus paclitaxel cohort:
  - 3 patients (0.5%) with gastric perforation;
  - 2 patients (0.4%) with peritonitis bacterial and intestinal perforation;
  - 1 patient, (0.2%) each, with gastric ulcer and oesophageal perforation, peritonitis, and pneumoperitoneum.

Except for 1 patient with peritonitis bacterial in ramucirumab plus paclitaxel cohort, the remaining 11 patients experienced serious perforations. A total of 7 of these perforations resulted in fatal outcome: 2 (0.3%) due to gastric perforation, 1 (0.2%), each, due to oesophageal perforation, peritonitis, peritonitis bacterial, intestinal perforation and small intestinal perforation. Of these, 5 cases of perforations were considered possibly related to ramucirumab treatment per physician's assessment: 2 (0.3%) due to gastric perforation and 1 (0.2%), each due to oesophageal perforation, intestinal perforation and small intestinal perforation. Four of these events were reported by the investigator to have occurred in the context of progressive disease, with three reporting extensive peritoneal disease. Two patients had symptomatic treatment. One patient with small intestinal perforation had small bowel metastases, underwent resection, post which their condition worsened, and the patient developed sepsis and died. Three patients (0.5%) discontinued due to SAEs of GI perforation in ramucirumab plus paclitaxel cohort: 1 (0.2%), each, due to gastric perforation, gastric ulcer perforation and oesophageal perforation.

Fistula

There were 4 patients (0.7%) with fistula; all were in ramucirumab plus paclitaxel cohort. These included:

- 2 patients (0.4%) with fistula, and
- 2 patients (one, 0.2% each) with anal and GI fistula.

Of these, 1 patient who experienced anal fistula had a serious event. None of these events resulted in a fatal outcome.

One patient (0.2%) in ramucirumab plus paclitaxel cohort discontinued from ramucirumab treatment due to non-serious event of fistula.

10.4.1.6.2.3. Hypertension

Overall, 66 patients (10.9%) were reported having hypertension. These included:

- 4 patients (7.8%) in ramucirumab monotherapy cohort, and
- 62 patients (11.3%) in ramucirumab plus paclitaxel cohort.

None of the events in ramucirumab monotherapy cohort were serious. Two patients (0.4%) in ramucirumab plus paclitaxel cohort experienced SAE of hypertension, 1 (0.2%), each, due to hypertension and hypertensive crisis. Both patients were elderly with a medical history of hypertension. The patient who experienced SAE of hypertension discontinued both study treatments and recovered. The patient with hypertensive crisis was PPD had antihypertensive medications increased and no change to treatment with ramucirumab was reported. The patient had not recovered from the event at the time of reporting. Both events were considered to be possibly related to ramucirumab.

One patient (0.2%) in ramucirumab plus paclitaxel cohort had a ramucirumab dose reduction due to hypertension. Refer to Section 10.4.1.3 for additional details.
Additionally, 4 patients (0.7%) had a delay in ramucirumab dose administration due to hypertension: 1 (2.0%) in ramucirumab monotherapy cohort and 3 (0.5%) in ramucirumab plus paclitaxel cohort. Two patients (0.3%), both in ramucirumab plus paclitaxel cohort had ramucirumab dose omitted due to hypertension.

Additional analysis from PRAC

The PRAC had requested Lilly to provide frequency of discontinuation of treatment with ramucirumab due to hypertension. This data is provided as follows:

- One (0.2%) patient in ramucirumab plus paclitaxel cohort discontinued from ramucirumab treatment due to a SAE of hypertension. This event occurred in a PPD patient with cardiac comorbidity. The patient had recovered from this event.

10.4.1.6.2.4. Liver Injury/Failure

Overall, 49 patients (8.1%) experienced liver injury/failure events. These included:

- 4 patients (7.8%) in ramucirumab monotherapy cohort,
- 45 patients (8.2%) in ramucirumab plus paclitaxel cohort. The most frequently reported PTs were:
    - aspartate aminotransferase increased, (12 patients, 2.2%), and
    - blood bilirubin increased (9 patients, 1.6%).

Majority of the events observed were laboratory abnormalities.

Two patients (3.9%) in ramucirumab monotherapy cohort experienced SAEs, 1 (2.0%), each, due to hepatic failure and obstructive cholestatic jaundice. Both these events resulted in a fatal outcome. Both patients were elderly, PPD respectively with hepatic metastases. The patient who developed hepatic failure also had diffuse hepatic metastases and both events were considered to be a result of the progression of underlying disease and not considered to be possibly related to study treatment per physician's assessment. Six patients (1.1%) experienced serious liver injury/failure events in ramucirumab plus paclitaxel cohort, primarily due to jaundice (3 patients, 0.5%). None of these events resulted in a fatal outcome in this cohort.

10.4.1.6.2.5. Infusion-Related Reactions

IRRs are systemic hypersensitivity events occurring in close temporal association with a drug infusion and may present with a variety of clinical symptoms and signs. Table JVDD.10.19 summarises potential immediate HSRs for ramucirumab (narrow events) occurring on the day of ramucirumab administration which represent IRRs. Potential immediate HSRs for ramucirumab (broad events) are available upon request. Immediate HSRs utilised the following SMQs and PT search criteria to collect relevant events (MedDRA Version 24.0). The same PT may be included in one or more SMQ:

- Anaphylactic reaction SMQ,
- Hypersensitivity SMQ,
- Angioedema SMQ,
- PT IRR, and
- PT Cytokine release syndrome.

Overall, there were no potential immediate HSRs in ramucirumab monotherapy cohort. Twenty-one patients (3.5%) experienced potential immediate HSRs (narrow events) in the ramucirumab plus paclitaxel cohort on the day of ramucirumab administration. No patients were reported to have experienced an anaphylactic reaction (narrow) or cytokine release syndrome (PT). The majority of these events occurred only once in each patient, with only 1 patient experiencing multiple IRRs (Table JVDD.10.21). One patient in ramucirumab plus paclitaxel cohort discontinued ramucirumab treatment due to a non-serious event of IRR, from which the patient had recovered.

Additional analysis from PRAC

The PRAC had requested Lilly to provide additional analyses regarding:

- Premedication:
  - whether or not before each administration, and
  - administration after previous infusion related reaction, which drug(s), which doses.

This has been described as follows:

A summary of premedications is presented in Table JVDD.10.9. Overall, 90.3% of patients were reported to have received at least 1 premedication. A total of 68.5% of ramucirumab infusions were recorded with premedications. The highest proportion of premedications were recorded on

the day or day before first ramucirumab infusion (87.1%). Of the 21 patients (3.8%) in the ramucirumab plus paclitaxel cohort who experienced an IRR following ramucirumab infusion, 14 (66.7%) had received premedication (Table JVDD.10.21), predominantly dexamethasone, ranitidine, ondansetron, and chlorpheniramine. A listing of premedications administered within 2 days of infusion at the time and following IRR is available upon request. A total of 18 patients (3.3%) who experienced an IRR received a subsequent ramucirumab infusion, of which 12 patients (66.7%) received premedications on the day or day before the subsequent ramucirumab infusion.

Table JVDD.10.19. Summary of Potential Immediate Hypersensitivity Reactions (Narrow Events) - Based on Events Occurring on the Date of Ramucirumab Administration
Full Analysis Set
I4T-MC-JVDD

Event Category or Term	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Narrow events on the date of ramucirumab administration	0	21 (3.8)	0	21 (3.5)
Anaphylactic reaction (Algorithm)	0	1 (0.2)	0	1 (0.2)
Anaphylactic reaction (Narrow)	0	0	0	0
Hypersensitivity (Narrow)	0	10 (1.8)	0	10 (1.7)
Angioedema (Narrow)	0	2 (0.4)	0	2 (0.3)
Infusion related reaction (PT)	0	11 (2.0)	0	11 (1.8)
Cytokine release syndrome (PT)	0	0	0	0
Specified SMQ narrow and algorithm terms[a]	0	21 (3.8)	0	21 (3.5)
Anaphylactic reaction (Algorithm, not narrow)[b]	0	1 (0.2)	0	1 (0.2)
Anaphylactic reaction (Narrow)	0	0	0	0
Hypersensitivity (Narrow)	0	10 (1.8)	0	10 (1.7)
Rash	0	5 (0.9)	0	5 (0.8)
Periorbital oedema	0	2 (0.4)	0	2 (0.3)
Dermatitis acneiform	0	1 (0.2)	0	1 (0.2)
Perioral dermatitis	0	1 (0.2)	0	1 (0.2)
Rash erythematous	0	1 (0.2)	0	1 (0.2)
Angioedema (Narrow)	0	2 (0.4)	0	2 (0.3)
Periorbital oedema	0	2 (0.4)	0	2 (0.3)
Infusion related reaction (PT)	0	11 (2.0)	0	11 (1.8)
Infusion related reaction	0	11 (2.0)	0	11 (1.8)
Cytokine release syndrome (PT)	0	0	0	0

Abbreviations: Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in specified category; PT = Preferred Term; PTX = paclitaxel; Ram = ramucirumab; SMQ = Standardised MedDRA Query.

a "Specified SMQ Narrow Terms" are the PTs of Infusion-related reaction and Cytokine release syndrome, plus all narrow terms in the Anaphylactic reaction, Angioedema, or Hypersensitivity SMQs.

b Summary line includes all Other Events meeting the timing criterion. Preferred terms are listed only when there are at least 2 events with that PT.

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tirr_narrow.rtf.

Table JVDD.10.20. Premedication Reported as Administered Before Each Ramucirumab Administration
Full Analysis Set
I4T-MC-JVDD

Parameter	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Total number of Ram infusions	**226 (100)**	**4637 (100)**	**46 (100)**	**4909 (100)**
Infusions with premedications	**173 (76.5)**	**3151 (68.0)**	**40 (87.0)**	**3364 (68.5)**
Number of 1st Ram infusions	51 (100)	547 (100)	8 (100)	606 (100)
with premedications on the day or day before	45 (88.2)	476 (87.0)	7 (87.5)	528 (87.1)
Number of 2nd Ram infusions	45 (100)	511 (100)	6 (100)	562 (100)
with premedications on the day or day before	28 (62.2)	258 (50.5)	5 (83.3)	291 (51.8)
Number of subsequent Ram infusions	130 (100)	3579 (100)	32 (100)	3741 (100)
with premedications on the day or day before	100 (76.9)	2416 (67.5)	28 (87.5)	2544 (68.0)

Abbreviations: Mono = monotherapy; N = number of patients in full analysis set; n = number of patients who received medication; PTX = paclitaxel; Ram = ramucirumab.

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpremed_ram.rtf.

Table JVDD.10.21. Premedication Reported to be Used Before and After Potential Immediate Hypersensitivity Reactions (Narrow Events)
Full Analysis Set
I4T-MC-JVDD

Parameter	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Narrow events on the day of Ram administration	**0**	**22 (4.0)**	**0**	**22 (3.6)**
Number of patients with 1 IRR	**0**	**20 (3.7)**	**0**	**20 (3.3)**
Number of patients with multiple IRRs	**0**	**1 (0.2)**	**0**	**1 (0.2)**
Number of Ram infusions resulting in the 1st IRR	0	21 (100)	0	21 (100)
with premedications on the day or day before	0	14 (66.7)	0	14 (66.7)
Number of Ram infusions subsequent[a] to the 1st IRR	0	18 (100)	0	18 (100)
with premedications on the day or day before	0	12 (66.7)	0	12 (66.7)
Number of Ram infusions resulting in the 2nd IRR[b]	0	1 (100)	0	1 (100)
with premedications on the day or day before	0	1 (100)	0	1 (100)

Abbreviations: IRR = infusion-related reaction; Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Number describes only the first subsequent ram infusion after IRR, not all subsequent infusions.

[b] For patients with multiple IRRs.

Final database lock date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/t_irr_prem_n.rtf.

10.4.1.6.3. Clinical Laboratory Evaluation

Summary of clinically significant abnormal laboratory values are available upon request. Analysis of clinical laboratory abnormalities did not reveal any new safety findings and were consistent with the analyses of AE data as discussed in Section 10.4.1.6.

10.5. Other Analyses

10.5.1. Secondary Objective - Subgroup Analyses

The secondary objective of the study was to describe the safety profile in the following subgroups:

- Elderly patients,
- Patients with cardiac comorbidities,
- Patients with hepatic impairment, and
- Patients with renal impairment.

Overview of overall safety data from the first administration to up to 90 days after last ramucirumab administration are reported for these subgroups of patients in Table JVDD.10.22.

For identifying subgroups of interest, sites were asked to identify if patients had certain comorbidities. Sites were asked to explicitly indicate in the eCRF if patients had hepatic impairment, renal impairment, or cardiac comorbidity and capture the related terms in the medical history form. Refer to Section 9.3.1 for a detailed description of how sites identified these subgroups of interest.

Table JVDD.10.22. Summary of Safety in Overall Sample and Subgroups of Interest
Full Analysis Set
I4T-MC-JVDD

Number of Subjects[a]	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram+ Other (N=8) n (%)	Total (N=606) n (%)
Overall safety population	**51 (100)**	**547 (100)**	**8 (100)**	**606 (100)**
Patients with AE[b], overall	49 (96.1)	535 (97.8)	8 (100)	592 (97.7)
Patients with AE[b], related to Ram[c]	15 (29.4)	268 (49.0)	3 (37.5)	286 (47.2)
Patients with SAE[b]	24 (47.1)	220 (40.2)	6 (75.0)	250 (41.3)
Patients with SAE[b], related to Ram[c]	2 (3.9)	39 (7.1)	1 (12.5)	42 (6.9)
Patients who discontinued due to AE				
From any treatment	2 (3.9)	32 (5.9)	0	34 (5.6)
From Ram[d]	2 (3.9)	28 (5.1)	0	30 (5.0)
From PTX[d]	0	29 (5.3)	0	29 (4.8)
Patients who discontinued due to SAE				
From any treatment	7 (13.7)	130 (23.8)	0	137 (22.6)
From Ram[d]	7 (13.7)	68 (12.4)	0	75 (12.4)
From PTX[d]	0	122 (22.3)	0	122 (20.1)
Deaths due to AE[d]	10 (19.6)	67 (12.2)	1 (12.5)	78 (12.9)

Number of Subjects[a]	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram+ Other (N=8) n (%)	Total (N=606) n (%)
Patients ≥ 65 years of age	**33 (100)**	**296 (100)**	**4 (100)**	**333 (100)**
Patients with AE[b], overall	31 (93.9)	290 (98.0)	4 (100)	325 (97.6)
Patients with AE[b], related to Ram[c]	9 (27.3)	157 (53.0)	2 (50.0)	168 (50.5)
Patients with SAE[b]	15 (45)	121 (40.9)	4 (100)	140 (42.0)
Patients with SAE[b], related to Ram[c]	0	24 (8.1)	1 (25.0)	25 (7.5)
Patients who discontinued due to AE				
From any treatment	6 (18.2)	80 (27.0)	0	86 (25.8)
From Ram[d]	6 (18.2)	39 (13.2)	0	45 (13.5)
From PTX[d]	0	76 (25.7)	0	76 (22.8)
Patients who discontinued due to SAE				
From any treatment	1 (3.0)	17 (5.7)	0	18 (5.4)
From Ram[d]	1 (3.0)	15 (5.1)	0	16 (4.8)
From PTX[d]	0	15 (5.1)	0	15 (4.5)
Deaths due to AE[e]	5 (15.2)	36 (12.2)	0	41 (12.3)
Patients ≥75 years of age	**22 (100)**	**111 (100)**	**2 (100)**	**135 (100)**
Patients with AE[b], overall	21 (95.5)	109 (98.2)	2 (100)	132 (97.8)
Patients with AE[b], related to Ram[c]	8 (36.4)	57 (51.4)	0	65 (48.1)
Patients with SAE[b]	8 (36.4)	50 (45.0)	2 (100)	60 (44.4)
Patients with SAE[b], related to Ram[c]	0	9 (8.1)	0	9 (6.7)
Patients who discontinued due to AE				
From any treatment	5 (22.7)	41 (36.9)	0	46 (34.1)
From Ram[d]	5 (22.7)	19 (17.1)	0	24 (17.8)
From PTX[d]	0	38 (34.2)	0	38 (28.1)
Patients who discontinued due to SAE				
From any treatment	1 (4.5)	10 (9.0)	0	11 (8.1)
From Ram[d]	1 (4.5)	8 (7.2)	0	9 (6.7)
From PTX[d]	0	9 (8.1)	0	9 (6.7)
Deaths due to AE[e]	2 (9.1)	12 (10.8)	0	14(10.4)
Patients with any comorbidities of interest[f]	**25 (100)**	**173 (100)**	**5 (100)**	**203 (100)**
Patients with AE[b], overall	24 (96.0)	170 (98.3)	5 (100)	199 (98.0)
Patients with AE[b], related to Ram[c]	7 (28.0)	83 (48.0)	2 (40.0)	92 (45.3)
Patients with SAE[b]	12 (48.0)	84 (48.6)	4 (80.0)	100 (49.3)
Patients with SAE[b], related to Ram[c]	0	15 (8.7)	1 (20.0)	16 (7.9)
Patients who discontinued due to AE				
From any treatment	4 (16.0)	49 (28.3)	0	53 (26.1)
From Ram[d]	4 (16.0)	28 (16.2)	0	32 (15.8)
From PTX[d]	0	47 (27.2)	0	47 (23.2)
Patients who discontinued due to SAE				
From any treatment	1 (4.0)	16 (9.2)	0	17 (8.4)
From Ram[d]	1 (4.0)	14 (8.1)	0	15 (7.4)
From PTX[d]	0	14 (8.1)	0	14 (6.9)
Deaths due to AE[e]	5 (28)	28 (16.2)	0	33 (16.3)

Number of Subjects[a]	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram+ Other (N=8) n (%)	Total (N=606) n (%)
Patients with hepatic impairment	**9 (100)**	**57 (100)**	**2 (100)**	**68 (100)**
Patients with AE[b], overall	8 (88.9)	55 (96.5)	2 (100)	65 (95.6)
Patients with AE[b], related to Ram[c]	4 (44.4)	23 (40.4)	0	27 (39.7)
Patients with SAE[b]	3 (33.3)	29 (50.9)	1 (50.0)	33 (48.5)
Patients with SAE[b], related to Ram[c]	0	5 (8.8)	0	5 (7.4)
Patients who discontinued due to AE				
From any treatment	0	14 (24.6)	0	14 (20.6)
From Ram[d]	0	11 (19.3)	0	11 (16.2)
From PTX[d]	0	14 (24.6)	0	14 (20.6)
Patients who discontinued due to SAE				
From any treatment	0	6 (10.5)	0	6 (8.8)
From Ram[d]	0	5 (8.8)	0	5 (7.4)
From PTX[d]	0	6 (10.5)	0	6 (8.8)
Deaths due to AE[e]	1 (11.1)	14 (24.6)	0	15 (22.1)
Patients with renal impairment	**3 (100)**	**36 (100)**	**0**	**39 (100)**
Patients with AE[b], overall	3 (100)	36 (100)	0	39 (100)
Patients with AE[b], related to Ram[c]	0	20 (55.6)	0	20 (51.3)
Patients with SAE[b]	2 (66.7)	20 (55.6)	0	22 (56.4)
Patients with SAE[b], related to Ram[c]	0	5 (13.9)	0	5 (12.8)
Patients who discontinued due to AE				
From any treatment	0	14 (38.9)	0	14 (35.9)
From Ram[d]	0	8 (22.2)	0	8 (20.5)
From PTX[d]	0	14 (38.9)	0	14 (35.9)
Patients who discontinued due to SAE				
From any treatment	0	4 (11.1)	0	4 (10.3)
From Ram[d]	0	3 (8.3)	0	3 (7.7)
From PTX[d]	0	3 (8.3)	0	3 (7.7)
Deaths due to AE[e]	2 (66.7)	5 (13.9)	0	7 (17.9)
Patients with cardiac condition	**17 (100)**	**117 (100)**	**4 (100)**	**138 (100)**
Patients with AE[b], overall	17 (100.0)	116 (99.1)	4 (100.0)	137 (99.3)
Patients with AE[b], related to Ram[c]	5 (29.4)	59 (50.4)	2 (50.0)	66 (47.8)
Patients with SAE[b]	8 (47.1)	53 (45.3)	4 (100)	65 (47.1)
Patients with SAE[b], related to Ram[c]	0	10 (8.5)	1 (25.0)	11 (8.0)
Patients who discontinued due to AE				
From any treatment	4 (23.5)	35 (29.9)	0	39 (28.3)
From Ram[d]	4 (23.5)	17 (14.5)	0	21 (15.2)
From PTX[d]	0	33 (28.2)	0	33 (23.9)
Patients who discontinued due to SAE				
From any treatment	1 (5.9)	10 (8.5)	0	11 (8.0)
From Ram[d]	1 (5.9)	8 (6.8)	0	9 (6.5)
From PTX[d]	0	9 (7.7)	0	9 (6.5)
Deaths due to AE[e]	3 (17.6)	19 (16.2)	0	22 (15.9)

Abbreviations: AE = adverse event; Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.

[a] Patients may be counted in more than 1 category.

[b] AEs reported between the date of first dose and 90 days after the last dose of ramucirumab.

[c] Relatedness was judged by the treating physician.
[d] Some of the AE lead to discontinuation of both drugs and counted in both totals.
[e] Deaths are also included as serious adverse events and discontinuations due to adverse events.
[f] Patients from any of renal, hepatic or cardiac subgroups.
Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov_age65.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov_age75.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov_como.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov_hepa.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov_renal.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov_cardiac.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taeov.rtf.

10.5.1.1. Elderly Patients

Overall, 333 patients (55.0%) were aged ≥65 years and 135 (22.3%) aged ≥75 years. In general, the safety data were similar in these 2 subgroups. AEs experienced by at least 3% of patients aged ≥65 and ≥75 years on or within 90 days of last ramucirumab dose are summarised in Table JVDD.10.23 and Table JVDD.10.25, respectively. Overall, 42.0% aged ≥65 years and 44.4% aged ≥75 years experienced at least 1 SAE (Table JVDD.10.24 and Table JVDD.10.26, respectively). The most frequently reported AEs in ramucirumab monotherapy cohort were general physical health deterioration (24.2%) and nausea (21.2%), and in ramucirumab plus paclitaxel cohort were fatigue (32.4%) and neutropenia (25.0%).

The AE profile for elderly patients was generally consistent with the overall AE profile for the patient population in this study. The occurrence of ramucirumab discontinuation due to AEs was higher in the elderly population ≥65 years compared to overall population (13.5% vs. 5%) and within the elderly population, the occurrence was slightly higher in patients aged ≥75 years than ≥65 years (17.8% vs. 13.5%). The most common reason for discontinuations of ramucirumab in the elderly ≥65 years old was general physical health deterioration (31%). The occurrence of deaths due to AEs was comparable to the overall patient population.

Table ANN.2.12 and Table ANN.2.13 summarises AESIs experienced by at least 5% of patients aged ≥65 years and ≥75 years, respectively.

The AESI profile of ramucirumab observed in this patient population was consistent with the AESI profile of the overall patient population in this study. Bleeding/haemorrhage events were the most frequently reported AESI in elderly patient population in both ramucirumab monotherapy (3 patients, 9.1%) and ramucirumab plus paclitaxel (65 patients, 22.0%) cohorts. Of these, haematemesis and epistaxis were the only PTs reported in ramucirumab monotherapy cohort, whereas epistaxis (42 patients, 14.2%) and haematemesis, gastrointestinal haemorrhage, and haematuria (4 patients, 1.4% each) were the most frequently reported PTs in ramucirumab plus paclitaxel cohorts. The second most frequently reported AESI in ramucirumab monotherapy cohort was liver injury/failure (2 patients, 6.1%) and in ramucirumab plus paclitaxel cohort was hypertension (31 patients, 10.5%).

Table JVDD.10.23. Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 3% of Patients (Total) Aged ≥65 Years by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=33) n (%)	Ram + PTX (N=296) n (%)	Ram+ Other (N=4) n (%)	Total (N=333) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**31 (93.9)**	**290 (98.0)**	**4 (100)**	**325 (97.6)**
Fatigue	5 (15.2)	96 (32.4)	0	101 (30.3)
Neutropenia	0	74 (25.0)	0	74 (22.2)
Diarrhoea	2 (6.1)	66 (22.3)	0	68 (20.4)
Anaemia	3 (9.1)	62 (20.9)	2 (50.0)	67 (20.1)
Asthenia	5 (15.2)	58 (19.6)	0	63 (18.9)
Nausea	7 (21.2)	54 (18.2)	0	61 (18.3)
Pyrexia	3 (9.1)	48 (16.2)	0	51 (15.3)
Decreased appetite	5 (15.2)	44 (14.9)	0	49 (14.7)
Epistaxis	1 (3.0)	42 (14.2)	1 (25.0)	44 (13.2)
General physical health deterioration	8 (24.2)	32 (10.8)	0	40 (12.0)
Weight decreased	2 (6.1)	35 (11.8)	0	37 (11.1)
Abdominal pain	4 (12.1)	32 (10.8)	0	36 (10.8)
Paraesthesia	1 (3.0)	34 (11.5)	0	35 (10.5)
Constipation	4 (12.1)	26 (8.8)	1 (25.0)	31 (9.3)
Hypertension	1 (3.0)	30 (10.1)	0	31 (9.3)
Oedema peripheral	2 (6.1)	29 (9.8)	0	31 (9.3)
Vomiting	1 (3.0)	30 (10.1)	0	31 (9.3)
Cough	2 (6.1)	24 (8.1)	0	26 (7.8)
Dyspnoea	1 (3.0)	21 (7.1)	0	22 (6.6)
Mucosal inflammation	0	20 (6.8)	0	20 (6.0)
Neuropathy peripheral	1 (3.0)	18 (6.1)	1 (25.0)	20 (6.0)
Platelet count decreased	0	20 (6.8)	0	20 (6.0)
Neutrophil count decreased	0	19 (6.4)	0	19 (5.7)
Dysphagia	1 (3.0)	16 (5.4)	0	17 (5.1)
Ascites	3 (9.1)	13 (4.4)	0	16 (4.8)
Leukopenia	1 (3.0)	15 (5.1)	0	16 (4.8)
Alopecia	0	16 (5.4)	0	16 (4.8)
Stomatitis	2 (6.1)	13 (4.4)	0	15 (4.5)
Thrombocytopenia	1 (3.0)	14 (4.7)	0	15 (4.5)
Abdominal pain upper	2 (6.1)	12 (4.1)	0	14 (4.2)
Malignant neoplasm progression	2 (6.1)	12 (4.1)	0	14 (4.2)
Polyneuropathy	0	14 (4.7)	0	14 (4.2)
Pneumonia	2 (6.1)	11 (3.7)	0	13 (3.9)
Hypokalaemia	1 (3.0)	11 (3.7)	0	12 (3.6)
Neurotoxicity	1 (3.0)	11 (3.7)	0	12 (3.6)
Back pain	0	12 (4.1)	0	12 (3.6)
Urinary tract infection	2 (6.1)	10 (3.4)	0	12 (3.6)
Dysgeusia	0	11 (3.7)	0	11 (3.3)
Proteinuria	1 (3.0)	10 (3.4)	0	11 (3.3)

MedDRA Preferred Term	Ram Mono (N=33) n (%)	Ram + PTX (N=296) n (%)	Ram+ Other (N=4) n (%)	Total (N=333) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**31 (93.9)**	**290 (98.0)**	**4 (100)**	**325 (97.6)**
Intestinal obstruction	0	11 (3.7)	0	11 (3.3)
White blood cell count decreased	0	11 (3.7)	0	11 (3.3)
Arthralgia	0	9 (3.0)	1 (25.0)	10 (3.0)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90_age65.rtf.

Table JVDD.10.24. Serious Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 1% of Patients (Total) Aged ≥65 Years by MedDRA Preferred Term by Decreasing Frequency Full Analysis Set I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=33) n (%)	Ram + PTX (N=296) n (%)	Ram+ Other (N=4) n (%)	Total (N=333) n (%)
Patients with at least 1 SAE on or within 90 days of Ram	**15 (45.5)**	**121 (40.9)**	**4 (100)**	**140 (42.0)**
General physical health deterioration	1 (3.0)	8 (2.7)	0	9 (2.7)
Malignant neoplasm progression	2 (6.1)	7 (2.4)	0	9 (2.7)
Febrile neutropenia	0	8 (2.7)	0	8 (2.4)
Intestinal obstruction	0	8 (2.7)	0	8 (2.4)
Pneumonia	1 (3.0)	6 (2.0)	0	7 (2.1)
Anaemia	1 (3.0)	5 (1.7)	0	6 (1.8)
Ascites	1 (3.0)	5 (1.7)	0	6 (1.8)
Pyrexia	1 (3.0)	5 (1.7)	0	6 (1.8)
Vomiting	0	6 (2.0)	0	6 (1.8)
Haematemesis	2 (6.1)	3 (1.0)	0	5 (1.5)
Pulmonary embolism	0	5 (1.7)	0	5 (1.5)
Respiratory failure	0	5 (1.7)	0	5 (1.5)
Urinary tract infection	1 (3.0)	4 (1.4)	0	5 (1.5)
Abdominal pain	0	4 (1.4)	0	4 (1.2)
Dehydration	1 (3.0)	3 (1.0)	0	4 (1.2)
Dysphagia	1 (3.0)	3 (1.0)	0	4 (1.2)
Gastrointestinal haemorrhage	0	3 (1.0)	1 (25.0)	4 (1.2)
Nausea	0	4 (1.4)	0	4 (1.2)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90_age65.rtf.

Table JVDD.10.25. Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 3% of Patients Aged ≥75 Years by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=22) n (%)	Ram + PTX (N=111) n (%)	Ram+ Other (N=2) n (%)	Total (N=135) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**21 (95.5)**	**109 (98.2)**	**2 (100)**	**132 (97.8)**
Fatigue	5 (22.7)	30 (27.0)	0	35 (25.9)
Diarrhoea	1 (4.5)	27 (24.3)	0	28 (20.7)
Anaemia	1 (4.5)	25 (22.5)	0	26 (19.3)
Asthenia	3 (13.6)	22 (19.8)	0	25 (18.5)
Nausea	5 (22.7)	19 (17.1)	0	24 (17.8)
General physical health deterioration	5 (22.7)	18 (16.2)	0	23 (17.0)
Neutropenia	0	23 (20.7)	0	23 (17.0)
Decreased appetite	5 (22.7)	16 (14.4)	0	21 (15.6)
Epistaxis	1 (4.5)	20 (18.0)	0	21 (15.6
Oedema peripheral	2 (9.1)	14 (12.6)	0	16 (11.9)
Pyrexia	2 (9.1)	14 (12.6)	0	16 (11.9)
Constipation	3 (13.6)	11 (9.9)	0	14 (10.4)
Weight decreased	2 (9.1)	12 (10.8)	0	14 (10.4)
Abdominal pain	2 (9.1)	10 (9.0)	0	12 (8.9)
Hypertension	1 (4.5)	10 (9.0)	0	11 (8.1)
Cough	2 (9.1)	8 (7.2)	0	10 (7.4)
Dyspnoea	0	10 (9.0)	0	10 (7.4)
Paraesthesia	1 (4.5)	9 (8.1)	0	10 (7.4)
Stomatitis	2 (9.1)	8 (7.2)	0	10 (7.4)
Mucosal inflammation	0	10 (9.0)	0	10 (7.4)
Neuropathy peripheral	0	9 (8.1)	0	9 (6.7)
Abdominal pain upper	2 (9.1)	6 (5.4)	0	8 (5.9)
Dysphagia	1 (4.5)	7 (6.3)	0	8 (5.9)
Vomiting	0	8 (7.2)	0	8 (5.9)
Thrombocytopenia	1 (4.5)	7 (6.3)	0	8 (5.9)
Neutrophil count decreased	0	8 (7.2)	0	8 (5.9)
Platelet count decreased	0	8 (7.2)	0	8 (5.9)
Ascites	2 (9.1)	5 (4.5)	0	7 (5.2)
Febrile neutropenia	0	7 (6.3)	0	7 (5.2)
Leukopenia	1 (4.5)	6 (5.4)	0	7 (5.2)
Neurotoxicity	1 (4.5)	5 (4.5)	0	6 (4.4)
Polyneuropathy	0	6 (5.4)	0	6 (4.4)
Dysgeusia	0	5 (4.5)	0	5 (3.7)
Alopecia	0	5 (4.5)	0	5 (3.7)
Depression	1 (4.5)	3 (2.7)	0	4 (3.0)
Oedema	0	4 (3.6)	0	4 (3.0)
Aspartate aminotransferase increased	0	4 (3.6)	0	4 (3.0)
Blood bilirubin increased	0	4 (3.6)	0	4 (3.0)
White blood cell count decreased	0	4 (3.6)	0	4 (3.0)

MedDRA Preferred Term	Ram Mono (N=22) n (%)	Ram + PTX (N=111) n (%)	Ram+ Other (N=2) n (%)	Total (N=135) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**21 (95.5)**	**109 (98.2)**	**2 (100)**	**132 (97.8)**
Bronchitis	1 (4.5)	3 (2.7)	0	4 (3.0)
Pneumonia	1 (4.5)	3 (2.7)	0	4 (3.0)
Urinary tract infection	2 (9.1)	2 (1.8)	0	4 (3.0)
Hypokalaemia	1 (4.5)	3 (2.7)	0	4 (3.0)
Hypotension	1 (4.5)	3 (2.7)	0	4 (3.0)
Myalgia	0	4 (3.6)	0	4 (3.0)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.
Final database cut-off date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90_age75.rtf.

Table JVDD.10.26. Serious Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 1% of Patients (Total) Aged ≥75 Years by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=22) n (%)	Ram + PTX (N=111) n (%)	Ram+ Other (N=2) n (%)	Total (N=135) n (%)
Patients with at least 1 SAE on or within 90 days of Ram	**8 (36.4)**	**50 (45.0)**	**2 (100)**	**60 (44.4)**
Febrile neutropenia	0	6 (5.4)	0	6 (4.4)
Dysphagia	1 (4.5)	3 (2.7)	0	4 (3.0)
Anaemia	0	3 (2.7)	0	3 (2.2)
Dehydration	1 (4.5)	2 (1.8)	0	3 (2.2)
Respiratory failure	0	3 (2.7)	0	3 (2.2)
Abdominal pain	0	2 (1.8)	0	2 (1.5)
Ascites	0	2 (1.8)	0	2 (1.5)
Vomiting	0	2 (1.8)	0	2 (1.5)
Bronchitis	1 (4.5)	1 (0.9)	0	2 (1.5)
Pneumonia	0	2 (1.8)	0	2 (1.5)
General physical health deterioration	0	2 (1.8)	0	2 (1.5)
Pyrexia	1 (4.5)	1 (0.9)	0	2 (1.5)
Malignant neoplasm progression	0	2 (1.8)	0	2 (1.5)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.
Final database cut-off date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90_age75.rtf.

10.5.1.2. Patients with Cardiac Comorbidities

Overall, 138 patients (22.8%) enrolled had cardiac comorbidities. Of these, 137 patients (99.3%) experienced at least 1 AE (Table JVDD.10.27) and 65 patients (47.1%) experienced at least 1 SAE (Table JVDD.10.28) on or within 90 days of last ramucirumab dose. The most frequently reported AEs in ramucirumab monotherapy cohort were general physical health deterioration and decreased appetite (5 patients, 29.4% each), and in ramucirumab plus paclitaxel cohort were fatigue and neutropenia (28 patients, 23.9%, each). None of the SAEs were reported to have occurred in more than 1 patient in ramucirumab monotherapy cohort. The most frequently reported SAEs in ramucirumab plus paclitaxel cohort were general physical health deterioration (7 patients, 6.0%) and febrile neutropenia (5 patients, 4.3%).

The AE profile for patients with cardiac comorbidities was generally consistent with the overall AE profile for the patient population in this study. The occurrence of discontinuations of ramucirumab due to AEs are higher in this patient population compared to overall population (15.2% vs. 5%). The most common reason for discontinuations of ramucirumab in patients with cardiac comorbidity was general health condition worsened (4 patients, 19%). The occurrence of deaths due to AEs were comparable to the overall patient population. Three deaths (2.2%) were reported due to cardiac-related AEs including cardiac failure, cardiopulmonary failure and myocardial infarction; the relatedness to study treatment were not reported.

Table ANN.2.14 summarises AESIs experienced by at least 5% of patients with cardiac comorbidities. The AESI profile of ramucirumab observed in this patient population was consistent with the AESI profile of the overall patient population in this study, with a higher incidence as compared with the overall patient population (45.7% vs. 39.9%).

In the ramucirumab monotherapy cohort, the most frequently reported AESIs were liver injury/failure (3 patients, 17.6%) and hypertension (2 patients, 11.8%). In ramucirumab plus paclitaxel cohort, the most frequently reported AESIs were bleeding/haemorrhage events (32 patients, 27.4%) and hypertension (10 patients, 8.5%). Epistaxis (20 patients, 17.1%) was the most frequently reported PT in this cohort.

Table JVDD.10.27. Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 3% of Patients (Total) with Cardiac Comorbidities by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=17) n (%)	Ram + PTX (N=117) n (%)	Ram+ Other (N=4) n (%)	Total (N=138) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**17 (100)**	**116 (99.1)**	**4 (100)**	**137 (99.3)**
Fatigue	4 (23.5)	28 (23.9)	0	32 (23.2)
Diarrhoea	2 (11.8)	27 (23.1)	0	29 (21.0)
Neutropenia	0	28 (23.9)	0	28 (20.3)
Anaemia	0	24 (20.5)	2 (50.0)	26 (18.8)

MedDRA Preferred Term	Ram Mono (N=17) n (%)	Ram + PTX (N=117) n (%)	Ram+ Other (N=4) n (%)	Total (N=138) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**17 (100)**	**116 (99.1)**	**4 (100)**	**137 (99.3)**
Nausea	4 (23.5)	19 (16.2)	0	23 (16.7)
Asthenia	4 (23.5)	19 (16.2)	0	23 (16.7)
General physical health deterioration	5 (29.4)	18 (15.4)	0	23 (16.7)
Epistaxis	1 (5.9)	20 (17.1)	1 (25.0)	22 (15.9)
Decreased appetite	5 (29.4)	16 (13.7)	0	21 (15.2)
Pyrexia	2 (11.8)	16 (13.7)	0	18 (13.0)
Paraesthesia	1 (5.9)	15 (12.8)	0	16 (11.6)
Weight decreased	1 (5.9)	13 (11.1)	0	14 (10.1)
Abdominal pain	2 (11.8)	11 (9.4)	0	13 (9.4)
Constipation	2 (11.8)	10 (8.5)	1 (25.0)	13 (9.4)
Polyneuropathy	1 (5.9)	12 (10.3)	0	13 (9.4)
Hypertension	2 (11.8)	10 (8.5)	0	12 (8.7)
Vomiting	1 (5.9)	11 (9.4)	0	12 (8.7)
Cough	2 (11.8)	9 (7.7)	0	11 (8.0)
Dyspnoea	1 (5.9)	10 (8.5)	0	11 (8.0)
Oedema peripheral	0	10 (8.5)	0	10 (7.2)
Neutrophil count decreased	0	8 (6.8)	0	8 (5.8)
Platelet count decreased	0	8 (6.8)	0	8 (5.8)
White blood cell count decreased	0	8 (6.8)	0	8 (5.8)
Hypokalaemia	1 (5.9)	6 (5.1)	0	7 (5.1)
Stomatitis	1 (5.9)	6 (5.1)	0	7 (5.1)
Leukopenia	0	7 (6.0)	0	7 (5.1)
Neuropathy peripheral	0	6 (5.1)	1 (25.0)	7 (5.1)
Arthralgia	0	6 (5.1)	1 (25.0)	7 (5.1)
Malignant neoplasm progression	1 (5.9)	6 (5.1)	0	7 (5.1)
Abdominal pain upper	3 (17.6)	3 (2.6)	0	6 (4.3)
Febrile neutropenia	0	6 (5.1)	0	6 (4.3)
Gastrooesophageal reflux disease	0	6 (5.1)	0	6 (4.3)
Peripheral sensory neuropathy	0	6 (5.1)	0	6 (4.3)
Ascites	1 (5.9)	4 (3.4)	0	5 (3.6)
Dysphagia	0	5 (4.3)	0	5 (3.6)
Pleural effusion	1 (5.9)	3 (2.6)	1 (25.0)	5 (3.6)
Hypocalcaemia	0	5 (4.3)	0	5 (3.6)
Pneumonia	0	5 (4.3)	0	5 (3.6)
Urinary tract infection	1 (5.9)	4 (3.4)	0	5 (3.6)
Back pain	0	5 (4.3)	0	5 (3.6)
Alopecia	0	5 (4.3)	0	5 (3.6)
Mucosal inflammation	0	5 (4.3)	0	5 (3.6)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90_card.rtf.

Table JVDD.10.28. Serious Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 1% of Patients (Total) with Cardiac Comorbidities by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=17) n (%)	Ram + PTX (N=117) n (%)	Ram+ Other (N=4) n (%)	Total (N=138) n (%)
Patients with at least 1 SAE on or within 90 days of Ram	**8 (47.1)**	**53 (45.3)**	**42 (100)**	**65 (47.1)**
General physical health deterioration	1 (5.9)	7 (6.0)	0	8 (5.8)
Febrile neutropenia	0	5 (4.3)	0	5 (3.6)
Anaemia	0	4 (3.4)	0	4 (2.9)
Gastrointestinal haemorrhage	0	3 (2.6)	1 (25.0)	4 (2.9)
Malignant neoplasm progression	1 (5.9)	3 (2.6)	0	4 (2.9)
Vomiting	0	4 (3.4)	0	4 (2.9)
Dehydration	1 (5.9)	2 (1.7)	0	3 (2.2)
Haematemesis	0	3 (2.6)	0	3 (2.2)
Intestinal obstruction	0	3 (2.6)	0	3 (2.2)
Nausea	0	3 (2.6)	0	3 (2.2)
Pleural effusion	1 (5.9)	1 (0.9)	1 (25.0)	3 (2.2)
Pneumonia	0	3 (2.6)	0	3 (2.2)
Urinary tract infection	1 (5.9)	2 (1.7)	0	3 (2.2)
Abdominal pain upper	1 (5.9)	1 (0.9)	0	2 (1.4)
Dysphagia	0	2 (1.7)	0	2 (1.4)
Dyspnoea	0	2 (1.7)	0	2 (1.4)
Pulmonary embolism	0	2 (1.7)	0	2 (1.4)
Malignant pleural effusion	0	2 (1.7)	0	2 (1.4)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.
Final database cut-off date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90_card.rtf.

10.5.1.3. Patients with Hepatic Impairment

Overall, 68 patients (11.2%) enrolled had a hepatic impairment. Of these, 65 patients (95.6%) were reported to have experienced at least 1 AE (Table JVDD.10.29) and 33 patients (48.5%) experienced at least 1 SAE (Table JVDD.10.30) on or within 90 days of last ramucirumab dose. The most frequently reported AEs in ramucirumab monotherapy cohort were nausea (3 patients, 33.3%) and abdominal pain, fatigue, ascites, general physical health deterioration, and vomiting (2 patients, 22.2% each), and in ramucirumab plus paclitaxel cohort were neutropenia (17 patients, 29.8%) and fatigue (16 patients, 28.1%). None of the SAEs were reported to have occurred in more than 1 patient in ramucirumab monotherapy cohort. The most frequently reported SAEs in ramucirumab plus paclitaxel cohort were malignant neoplasm progression (4 patients, 7.0%) and ascites, general physical health deterioration and urinary tract infection (3 patients, 5.3% each).

The AE profile for patients with hepatic impairment was generally consistent with the overall AE profile for the patient population in this study. Discontinuation of ramucirumab treatment due to AEs was higher in this patient population compared to overall population (16.2% vs. 5.0%). No discontinuations of ramucirumab due to AEs occurred in the monotherapy subgroup. Of the 11 patients in ramucirumab plus paclitaxel cohort that discontinued ramucirumab due to AEs, each AE was reported once and none of these AEs were associated with the liver. The occurrence of SAEs and deaths due to AEs are higher in patients with hepatic impairment than the overall patient population (48.5% vs. 41.3% and 22.1% vs. 12.9%, respectively). The most frequent deaths due to AEs were due to progression of disease or general physical health deterioration as per the reported terms (40%). One death was reported due to hepatic failure. This patient also had diffuse hepatic metastases. This event was considered to be possibly related to progression of underlying disease and not due to ramucirumab treatment. Overall, the number of patients in this subgroup is small therefore increased variability in the data is not unexpected.

Table ANN.2.15. summarises AESIs experienced by at least 5% of patients with hepatic impairment. The AESI profile of ramucirumab observed in this patient population was consistent with the AESI profile of the overall patient population in this study. In ramucirumab monotherapy cohort, the most frequently reported AESI was liver injury/failure (2 patients, 22.2%), with 1 (11.1%), each, who experienced blood bilirubin increased and hepatic failure. In ramucirumab plus paclitaxel cohort, the most frequently reported AESIs were bleeding/haemorrhage events (11 patients, 19.3%) and liver injury/failure and venous thromboembolic events (4 patients, 7.0% each). Epistaxis (6 patients, 10.5%) was the most frequently reported PT in this cohort.

Table JVDD.10.29. Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 3% of Patients (Total) with Hepatic Impairment by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=9) n (%)	Ram + PTX (N=57) n (%)	Ram+ Other (N=2) n (%)	Total (N=68) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**8 (88.9)**	**55 (96.5)**	**2 (100)**	**65 (95.6)**
Fatigue	2 (22.2)	16 (28.1)	0	18 (26.5)
Neutropenia	0	17 (29.8)	0	17 (25.0)
Asthenia	1 (11.1)	12 (21.1)	0	13 (19.1)
Abdominal pain	2 (22.2)	11 (19.3)	0	13 (19.1)
Nausea	3 (33.3)	10 (17.5)	0	13 (19.1)
Diarrhoea	0	12 (21.1)	0	12 (17.6)
Pyrexia	1 (11.1)	9 (15.8)	0	10 (14.7)
Ascites	2 (22.2)	6 (10.5)	0	8 (11.8)
Anaemia	1 (11.1)	7 (12.3)	0	8 (11.8)
General physical health deterioration	2 (22.2)	5 (8.8)	0	7 (10.3)
Neuropathy peripheral	1 (11.1)	6 (10.5)	0	7 (10.3)
Weight decreased	0	7 (12.3)	0	7 (10.3)

MedDRA Preferred Term	Ram Mono (N=9) n (%)	Ram + PTX (N=57) n (%)	Ram+ Other (N=2) n (%)	Total (N=68) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**8 (88.9)**	**55 (96.5)**	**2 (100)**	**65 (95.6)**
Decreased appetite	0	7 (12.3)	0	7 (10.3)
Vomiting	2 (22.2)	5 (8.8)	0	7 (10.3)
Constipation	1 (11.1)	4 (7.0)	1 (50.0)	6 (8.8)
Dyspnoea	1 (11.1)	5 (8.8)	0	6 (8.8)
Epistaxis	0	6 (10.5)	0	6 (8.8)
Oedema peripheral	1 (11.1)	5 (8.8)	0	6 (8.8)
Pleural effusion	1 (11.1)	3 (5.3)	1 (50.0)	5 (7.4)
Abdominal pain upper	1 (11.1)	2 (3.5)	1 (50.0)	4 (5.9)
Back pain	1 (11.1)	3 (5.3)	0	4 (5.9)
Dysphagia	0	4 (7.0)	0	4 (5.9)
Hypokalaemia	0	4 (7.0)	0	4 (5.9)
Leukopenia	0	4 (7.0)	0	4 (5.9)
Malignant neoplasm progression	0	4 (7.0)	0	4 (5.9)
Polyneuropathy	1 (11.1)	3 (5.3)	0	4 (5.9)
Thrombocytopenia	0	4 (7.0)	0	4 (5.9)
Urinary tract infection	0	4 (7.0)	0	4 (5.9)
Pneumonia	1 (11.1)	2 (3.5)	0	3 (4.4)
Mucosal inflammation	0	3 (5.3)	0	3 (4.4)
Urinary retention	1 (11.1)	1 (1.8)	1 (50.0)	3 (4.4)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90_hep.rtf.

Table JVDD.10.30. Serious Adverse Events on or within 90 Days of Ramucirumab Treatment Experienced by at least 2% of Patients (Total) with Hepatic Impairment by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=9) n (%)	Ram + PTX (N=57) n (%)	Ram+ Other (N=2) n (%)	Total (N=68) n (%)
Patients with at least 1 SAE on or within 90 days of Ram	**3 (33.3)**	**29 (50.9)**	**1 (50.0)**	**33 (48.5)**
Ascites	1 (11.1)	3 (5.3)	0	4 (5.9)
Malignant neoplasm progression	0	4 (7.0)	0	4 (5.9)
General physical health deterioration	0	3 (5.3)	0	3 (4.4)
Pleural effusion	0	2 (3.5)	1 (50.0)	3 (4.4)
Pneumonia	1 (11.1)	2 (3.5)	0	3 (4.4)
Urinary tract infection	0	3 (5.3)	0	3 (4.4)
Gastrointestinal haemorrhage	0	2 (3.5)	0	2 (2.9)
Ileus	0	2 (3.5)	0	2 (2.9)

MedDRA Preferred Term	Ram Mono (N=9) n (%)	Ram + PTX (N=57) n (%)	Ram+ Other (N=2) n (%)	Total (N=68) n (%)
Patients with at least 1 SAE on or within 90 days of Ram	**3 (33.3)**	**29 (50.9)**	**1 (50.0)**	**33 (48.5)**
Device related infection	1 (11.1)	1 (1.8)	0	2 (2.9)
Pulmonary embolism	0	2 (3.5)	0	2 (2.9)
Pyrexia	0	2 (3.5)	0	2 (2.9)
Febrile neutropenia	0	2 (3.5)	0	2 (2.9)
Device dislocation	0	2 (3.5)	0	2 (2.9)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90_hep.rtf.

10.5.1.4. Patients with Renal Impairment

Overall, 39 patients (6.4%) enrolled had a renal impairment; all of them experienced at least 1 AE (Table JVDD.10.31) and 22 patients (56.4%) experienced at least 1 SAE (Table JVDD.10.32) on or within 90 days of last ramucirumab dose. Asthenia was the only AE reported in more than 1 patient in ramucirumab monotherapy cohort. The most frequently reported AEs in ramucirumab plus paclitaxel cohort were anaemia (8 patients, 22.2%) and diarrhoea, nausea, and weight decreased (7 patients, 19.4% each). Two patients (66.7%) experienced SAEs in ramucirumab monotherapy cohort: 1 (33.3%), each due to multiple organ dysfunction syndrome and malignant neoplasm progression. The most frequently reported SAEs in ramucirumab plus paclitaxel cohort were abdominal pain, anaemia, ileus and pneumonia (2 patients, 5.6% each).

The AE profile for patients with renal impairment is generally consistent with the overall AE profile for the patient population in this study. The occurrence of discontinuations due to AEs for ramucirumab are higher in this patient subgroup (20.5% [8/39 patients] vs. 5%). One (0.2%) patient discontinued ramucirumab treatment due to a non-serious event of proteinuria, from which the patient had recovered; relatedness to study treatment was not reported. Of the 8 patients who discontinued ramucirumab due to AEs, the majority (62.5% [5/8 patients]) were likely due to underlying disease (general health deterioration, weight decreased, ileus and intestinal obstruction). The occurrence of deaths due to AEs are comparable with the overall patient population, none of which were associated with renal events. Overall, due to limited number of patients in this subgroup, increased variability in the data is not unexpected.

Table ANN.2.16 summarises AESIs experienced by at least 5% of patients with renal impairment. The AESI profile of ramucirumab observed in this patient population was consistent with the AESI profile of the overall patient population in this study.

The most frequently reported AESIs in ramucirumab plus paclitaxel cohort were bleeding/haemorrhage events (6 patients, 16.7%) and hypertension (4 patients, 11.1%). Epistaxis (3 patients, 8.3%) was the most frequently reported bleeding/haemorrhage event.

Table JVDD.10.31. Adverse Events on or within 90 Days of Ramucirumab Treatment Experienced by at least 3% of Patients (Total) with Renal Impairment by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=3) n (%)	Ram + PTX (N=36) n (%)	Ram+ Other (N=0) n (%)	Total (N=39) n (%)
Patients with at least 1 AE on or within 90 days of Ram	**3 (100)**	**36 (100)**	**0**	**39 (100)**
Anaemia	0	8 (22.2)	0	8 (20.5)
Asthenia	2 (66.7)	5 (13.9)	0	7 (17.9)
Diarrhoea	0	7 (19.4)	0	7 (17.9)
Nausea	0	7 (19.4)	0	7 (17.9)
Weight decreased	0	7 (19.4)	0	7 (17.9)
Abdominal pain	0	6 (16.7)	0	6 (15.4)
Neutropenia	0	6 (16.7)	0	6 (15.4)
Paraesthesia	0	6 (16.7)	0	6 (15.4)
Pyrexia	0	6 (16.7)	0	6 (15.4)
Fatigue	0	5 (13.9)	0	5 (12.8)
General physical health deterioration	0	5 (13.9)	0	5 (12.8)
Polyneuropathy	0	5 (13.9)	0	5 (12.8)
Vomiting	0	5 (13.9)	0	5 (12.8)
Constipation	0	3 (8.3)	0	3 (7.7)
Dysphagia	0	3 (8.3)	0	3 (7.7)
Dyspnoea	0	3 (8.3)	0	3 (7.7)
Epistaxis	0	3 (8.3)	0	3 (7.7)
Leukopenia	0	3 (8.3)	0	3 (7.7)
Pneumonia	0	3 (8.3)	0	3 (7.7)
Urinary tract infection	0	3 (8.3)	0	3 (7.7)
Ascites	0	2 (5.6)	0	2 (5.1)
Decubitus ulcer	0	2 (5.6)	0	2 (5.1)
Ileus	0	2 (5.6)	0	2 (5.1)
Mucosal inflammation	0	2 (5.6)	0	2 (5.1)
Neutrophil count decreased	0	2 (5.6)	0	2 (5.1)
Oedema peripheral	0	2 (5.6)	0	2 (5.1)
Proteinuria	0	2 (5.6)	0	2 (5.1)
Stomatitis	0	2 (5.6)	0	2 (5.1)

Abbreviations: AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90_renal.rtf.

Table JVDD.10.32. Serious Adverse Events on or within 90 days of Ramucirumab Treatment Experienced by at least 5% of Patients (Total) with Renal Impairment by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=3) n (%)	Ram + PTX (N=36) n (%)	Ram+ Other (N=0) n (%)	Total (N=39) n (%)
Patients with at least 1 SAE on or within 90 days of Ram	**2 (66.7)**	**20 (55.6)**	**0**	**22 (56.4)**
Abdominal pain	0	2 (5.6)	0	2 (5.1)
Ileus	0	2 (5.6)	0	2 (5.1)
Pneumonia	0	2 (5.6)	0	2 (5.1)
Anaemia	0	2 (5.6)	0	2 (5.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab; SAE = serious adverse event.
Final database cut-off date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90_renal.rtf.

10.5.2. Effectiveness

10.5.2.1. Overall Survival

Overall, the median OS for patients in this study was 7.2 months (95% CI: 6.5, 7.9). The median OS in ramucirumab monotherapy and ramucirumab plus paclitaxel cohorts were 3.6 months (95% CI: 2.7, 4.3) and 7.6 months (95% CI: 7.0, 8.4), respectively (Table JVDD.10.33). Figure JVDD.10.2 presents the KM plot for OS from ramucirumab treatment initiation to up to 12 months.

10.5.2.2. Real-World Progression-free Survival

Overall, the median rwPFS for patients in this study was 3.8 months (95% CI: 3.3, 4.2). The median rwPFS in ramucirumab monotherapy and ramucirumab plus paclitaxel cohorts were 1.9 months (95% CI: 1.4, 2.2) and 4.0 months (95% CI: 3.8, 4.5), respectively (Table JVDD.10.33). Figure JVDD.10.3 presents the KM plot for rwPFS from ramucirumab treatment initiation.

10.5.2.3. Real-World Best Overall Response

Overall, tumour response was not available for 103 patients (17.0%): 16 (31.4%) in ramucirumab monotherapy cohort and 85 (15.5%) in ramucirumab plus paclitaxel cohort, and not evaluable in 4 patients (0.7%) in ramucirumab plus paclitaxel cohort. None of the patients in ramucirumab monotherapy cohort had a record of CR or PR and 8 patients (1.5%) had a CR and 54 (9.9%) had a PR in ramucirumab plus paclitaxel cohort. Four patients (7.8%) in ramucirumab monotherapy cohort and 165 patients (30.2%) in ramucirumab plus paclitaxel cohort demonstrated SD as their best response to therapy (Table JVDD.10.33). The effectiveness analyses that rely on the

evaluation of response, such as rwPFS and rwBOR should be interpreted with caution (refer to Section 11.2 for additional details).

Table JVDD.10.33. Summary of Efficacy Parameters (OS, rwPFS, and rwBOR)

Efficacy Parameters	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total (N=606)
Overall survival (OS)				
Number of deaths, n (%)	40 (78.4)	350 (64.0)	7 (87.5)	397 (65.5)
Number of patients censored, n (%)	11 (21.6)	197 (36.0)	1 (12.5)	209 (34.5)
Alive	9 (17.6)	185 (33.8)	1 (12.5)	195 (32.2)
Lost to follow-up	2 (3.9)	12 (2.2)	0	14 (2.3)
Median OS in months (95% CI)	3.6 (2.7, 4.3)	7.6 (7.0, 8.4)	3.9 (0.8, 11.5)	7.2 (6.5, 7.9)
Real-world progression-free survival (rwPFS)				
Number of events, n (%)	46 (90.2)	475 (86.8)	7 (87.5)	528 (87.1)
Death without PD	11 (21.6)	92 (16.8)	3 (37.5)	106 (17.5)
PD	35 (68.6)	383 (70.0)	4 (50.0)	422 (69.6)
Number of patients censored, n (%)	5 (9.8)	72 (13.2)	1 (12.5)	78 (12.9)
Alive without PD	5 (9.8)	72 (13.2)	1 (12.5)	78 (12.9)
Median rwPFS in months (95% CI)	1.9 (1.4, 2.2)	4.0 (3.8, 4.5)	3.3 (0.8, 11.5)	3.8 (3.3, 4.2)
Real-world best overall response (rwBOR)[a]				
Complete response (CR), n (%)	0	8 (1.5)	0	8 (1.3)
Partial response (PR), n (%)	0	54 (9.9)	0	54 (8.9)
Stable disease (SD), n (%)	4 (7.8)	165 (30.2)	2 (25.0)	171 (28.2)
Progressive disease (PD), n (%)	31 (60.8)	231 (42.2)	4 (50.0)	266 (43.9)
Non-evaluable	0	4 (0.7)	0	4 (0.7)
Not available	16 (31.4)	85 (15.5)	2 (25.0)	103 (17.0)
Real-world overall response rate (CR + PR), n (%)	0	62 (11.3)	0	62 (10.2)
Real-world disease control rate (CR+PR+SD), n (%)	4 (7.8)	227 (41.5)	2 (25.0)	233 (38.5)

Abbreviations: CI = Confidence Interval; N = number of patients in Full analysis set; n = number of patients in the specified category.

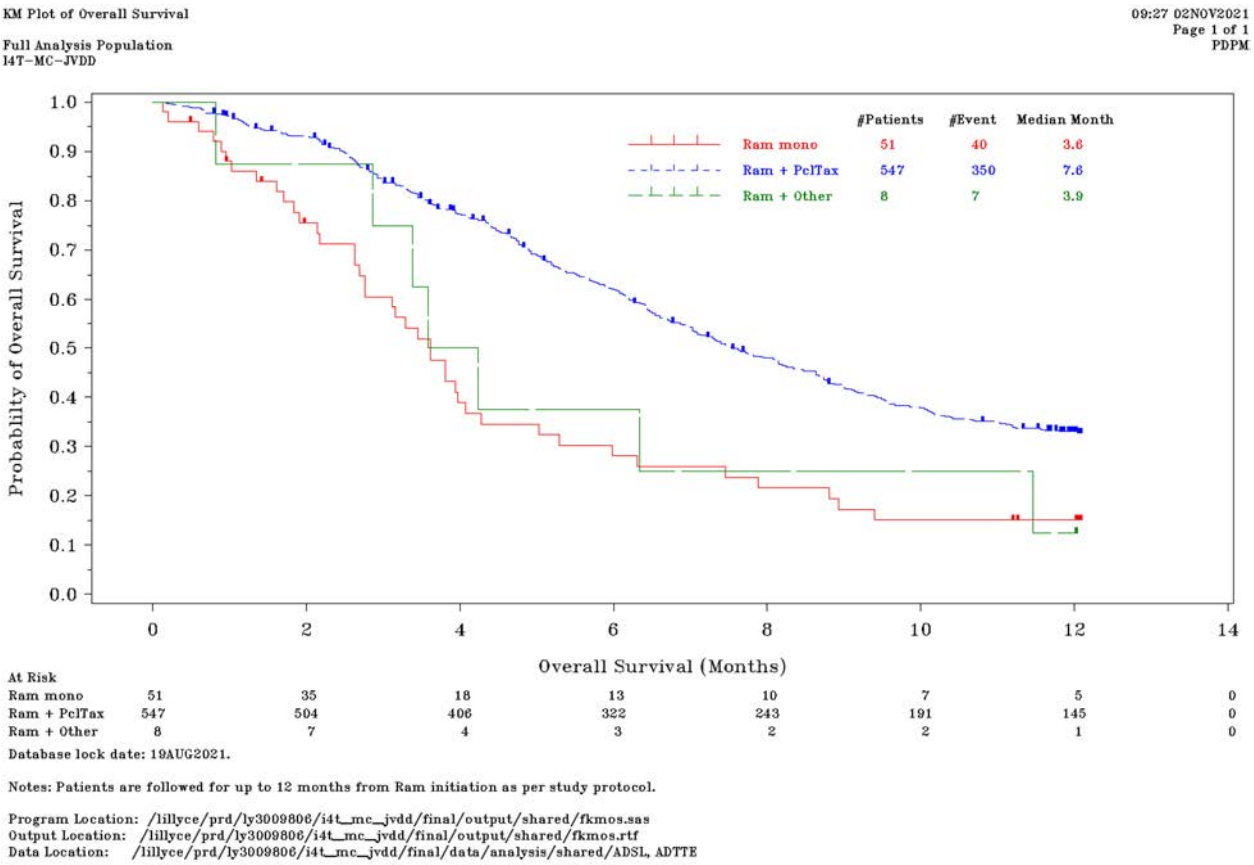
a Tumour response was determined by the physician based on normal clinical practice.

Notes: Patients are followed for up to 12 months from Ram initiation as per study protocol. Quartiles, OS rates, rwPFS rates, along with 95% CIs, were estimated using the Kaplan-Meier method. Corresponding 95% CIs were estimated using the methods of Brookmeyer and Crowley, and Greenwood, respectively.

Both clinical or radiological progression based on physician assessment were included in rwPFS derivation.

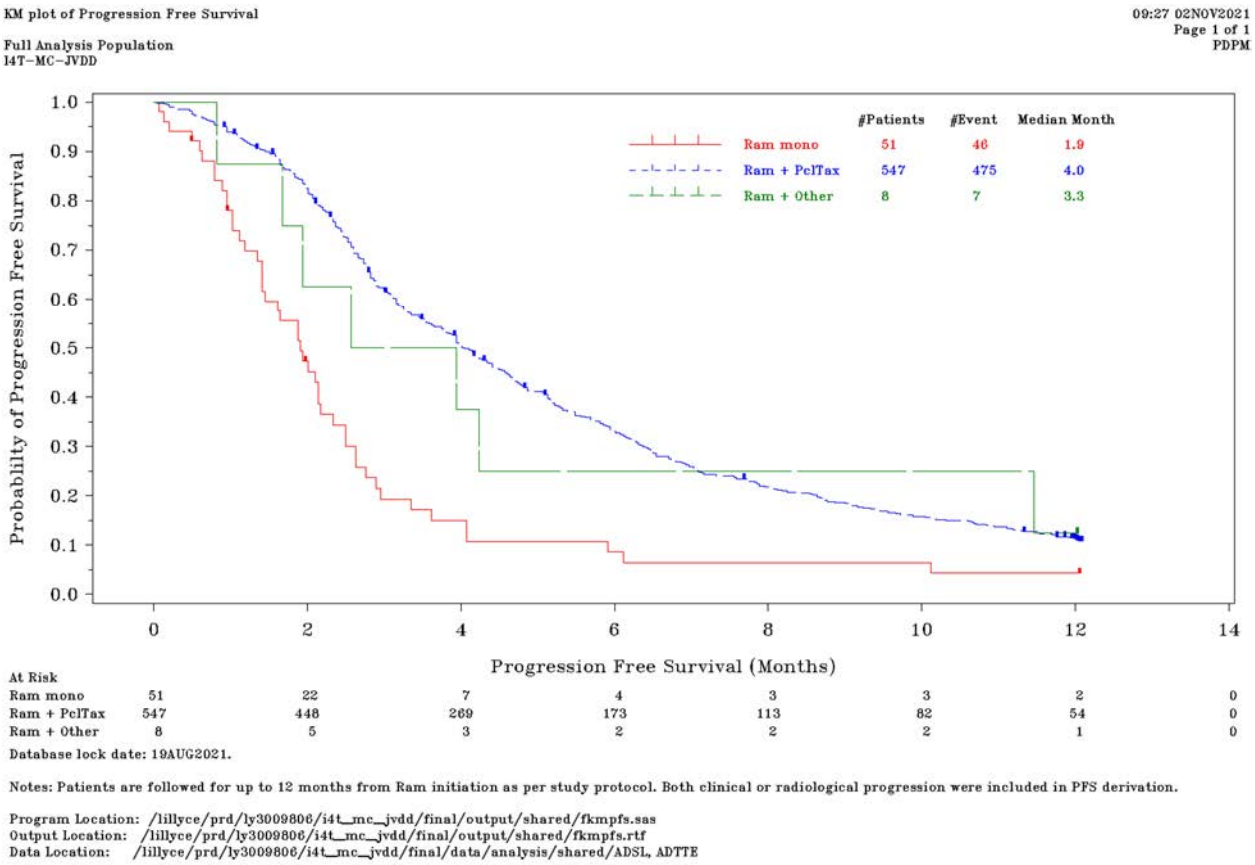
Progressive Disease is counted when best response over treatment was either clinical or radiological progression.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tos.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpfs.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tbor.rtf.



Abbreviations: KM = Kaplan-Meier; PclTax = paclitaxel; Ram = ramucirumab.

Figure JVDD.10.2. KM plot of overall survival, Full Analysis Set, I4T-MC-JVDD.



Abbreviations: KM = Kaplan-Meier; PclTax = paclitaxel; Ram = ramucirumab.

Figure JVDD.10.3. KM plot of progression-free survival, Full Analysis Set, I4T-MC-JVDD.

10.5.3. Postdiscontinuation Therapy

Table JVDD.10.34 summarises postdiscontinuation anticancer therapies received by patients in this study. Overall, postdiscontinuation anticancer therapy were recorded for 183 patients (30.2%): 11 (21.6%) in ramucirumab monotherapy cohort and 171 (31.3%) in ramucirumab plus paclitaxel cohort.

The frequently used classes of postdiscontinuation anticancer therapy received by at least 2% of the patients were

- topoisomerase I inhibitor (eg, irinotecan; 131 patients, 21.6%),
- fluoropyrimidine (121 patients, 20.0%),
- immunotherapy (21 patients, 3.5%), and
- platinum (13 patients, 2.1%).

The frequently used postdiscontinuation anticancer medications received by at least 2% of the patients were

- calcium folinate; fluorouracil; irinotecan hydrochloride (66 patients, 10.9%),
- irinotecan (61 patients, 10.1%),
- fluorouracil (36 patients, 5.9%), and
- nivolumab and tipiracil hydrochloride; trifluridine (13 patients, 2.1%, each).

Table JVDD.10.34. Summary of Postdiscontinuation Anticancer Therapy
Full Analysis Set
I4T-MC-JVDD

Class of postdiscontinuation medication	Ram Mono (N=51) n (%)	Ram + PTX (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Patients with at least 1 postdiscontinuation medication	**11 (21.6)**	**171 (31.3)**	**1 (12.5)**	**183 (30.2)**
Postdiscontinuation anticancer therapy classes				
Platinum	1 (2.0)	12 (2.2)	0	13 (2.1)
Fluoropyrimidine	7 (13.7)	113 (20.7	1 (12.5)	121 (20.0)
Topoisomerase I inhibitor (eg, irinotecan)	8 (15.7)	122 (22.3)	1 (12.5)	131 (21.6)
Immunotherapy	0	21 (3.8)	0	21 (3.5)
Taxane	2 (3.9)	5 (0.9)	0	7 (1.2)
Anthracycline	0	1 (0.2)	0	1 (0.2)
Anti-angiogenic	1 (2.0)	5 (0.9)	0	6 (1.0)
Investigational	1 (2.0)	2 (0.4)	0	3 (0.5)
HER2-targeted agent	0	3 (0.5)	0	3 (0.5)
Topoisomerase II inhibitor	0	2 (0.4)	0	2 (0.3)
Antifolate	0	1 (0.2)	0	1 (0.2)
Tyrosine kinase inhibitor	0	1 (0.2)	0	1 (0.2)
Postdiscontinuation anticancer therapy medications[a] (n>3 patients [total])				
Calcium folinate; fluorouracil; irinotecan hydrochloride	2 (3.9)	63 (11.5)	1 (12.5)	66 (10.9)
Irinotecan	5 (9.8)	56 (10.2)	0	61 (10.1)
Fluorouracil	3 (5.9)	33 (6.0)	0	36 (5.9)
Nivolumab	0	13 (2.4)	0	13 (2.1)
Tipiracil hydrochloride; trifluridine	0	13 (2.4)	0	13 (2.1)
Pembrolizumab	0	7 (1.3)	0	7 (1.2)
Ramucirumab	1 (2.0)	5 (0.9)	0	6 (1.0)
Paclitaxel	1 (2.0)	4 (0.7)	0	5 (0.8)
Capecitabine; oxaliplatin	1 (2.0)	2 (0.4)	0	3 (0.5)
Cisplatin	0	3 (0.5)	0	3 (0.5)
Investigational drug	1 (2.0)	2 (0.4)	0	3 (0.5)
Irinotecan hydrochloride	0	3 (0.5)	0	3 (0.5)
Oxaliplatin	0	3 (0.5)	0	3 (0.5)
Trastuzumab	0	3 (0.5)	0	3 (0.5)

Abbreviations: HER2 = human epidermal growth factor receptor 2; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Sites could enter combination of drugs as a single record or multiple records.

Based on MedDRA preferred terms, where applicable.
Final database lock date: 19 August 2021.
Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpost_class.rtf;
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpost_therapy.rtf.

10.5.4. Healthcare Resource Utilisation

Table ANN.2.17 presents a summary of hospitalisation on or within 90 days of last ramucirumab dose. Overall, 282 patients (46.5%) were hospitalised; 25 (49.0%) in ramucirumab monotherapy cohort and 251 (45.9%) in ramucirumab plus paclitaxel cohort. The primary reason for hospitalisation was AE (37.5%), followed by primary study condition (7.4%) and others (3.6%). The most frequently experienced AEs leading to hospitalisation were malignant neoplasm progression (3.0%), and intestinal obstruction and pneumonia (2.1%, each).

Of those who were hospitalised due to an AE, the majority of patients (70.5%) were hospitalised only once. The median total days of hospitalisation due to AEs was 14 days (range: 3 to 71 days) for patients in ramucirumab monotherapy cohort and 11 days (range: 1 to 76 days) for patients in ramucirumab plus paclitaxel cohort.

10.5.5. Supportive Care

Patients were provided best supportive care, including concomitant medications, transfusions, and procedures (Table ANN.2.18).

Concomitant medications

A total of 98.0% patients, each in ramucirumab monotherapy cohort and ramucirumab plus paclitaxel cohort received at least 1 concomitant medication. Overall, the most frequently used classes of concomitant medication in at least 20% of patients were

- gastric acid suppressants (49.2%),
- analgesics (47.7%),
- antihypertensives or diuretics (45.4%)
- antiemetics (36.5%),
- antimicrobial agents (27.7%), and
- corticosteroids (23.6%).

Transfusions

A total of 13.7% patients in ramucirumab monotherapy cohort and 11.7% patients in ramucirumab plus paclitaxel cohort underwent a transfusion. Overall, patients underwent transfusion mainly with

- packed red blood cells (10.6%),
- whole blood (1.7%), and
- platelets (0.5%).

Selected concomitant procedures

Selected concomitant procedures were reported for 13.7% of patients in ramucirumab monotherapy cohort and 10.4% in ramucirumab plus paclitaxel cohort. These procedures were abdominal cavity drainage (6.8%), radiotherapy (2.6%) and gastrointestinal tube insertion (1.7%) in the overall patient population.

11. Discussion

11.1. Key results

Study JVDD was designed to characterise the safety profile and effectiveness of ramucirumab in patients with gastric cancer under real-world disease conditions.

Overall, 606 eligible patients were enrolled and assigned cohorts according to the regimen reported at first ramucirumab treatment administration: 51 in ramucirumab monotherapy cohort, 547 in ramucirumab plus paclitaxel cohort and 8 in ramucirumab plus other treatment cohort.

Overall safety analysis

The real-world use of ramucirumab is generally aligned with the recommended dosage and schedule of ramucirumab per label: 8 mg/kg every 2 weeks either as a single agent or in combination with weekly paclitaxel. Over 90% of patients were planned to receive ramucirumab infusion once every 14 days. The median duration of ramucirumab treatment was 8 weeks (IQR: 4.0 to 10.6) as monotherapy and 15 weeks (IQR: 8.4 to 26.7) in combination with paclitaxel.

The occurrence of AEs/SAEs that occurred during the 30-day follow-up period was similar to data reported within the 90-day follow-up period, suggesting the 30-day follow-up period frequently used in reporting clinical trials is a sufficient length of time to capture safety information for ramucirumab.

The safety profile observed in this study was generally consistent with the established safety profile of ramucirumab in the clinical settings for this patient population and no new safety concerns or notable findings were identified. Review of available safety data for elderly patients and patients with cardiac, hepatic and renal co-morbidities did not identify any new safety findings. Therefore, ramucirumab as a monotherapy or in combination with paclitaxel has a similar safety profile in patients with gastric cancer in the real-world setting to that established in clinical trial settings.

Safety profile in subgroups of interest

Safety profile in elderly patients

In Study JVDD, approximately 55.0% of patients were aged ≥65 years and 22.3% were ≥75 years. Review of the available safety data for these patients did not indicate any new safety findings or an increased occurrence of AEs/SAEs. The safety profile observed was generally consistent with the expected safety profile of this patient population. The occurrence of ramucirumab discontinuation due to AEs was higher in the elderly population ≥65 years compared to overall population (13.5% vs. 5%), with general physical health deterioration (31%) as the most frequently reported reason for discontinuation. The AESI profile of ramucirumab observed in elderly population in this study was consistent with the AESI profile of the overall patient population in this study.

Safety profile in patients with cardiac, renal, and hepatic comorbidities

It has been reported in the literature that the prevalence of cardiac comorbidity among gastric cancer patients ranged from 7.8% (CHF) to 28.0% (including cardiac arrhythmias: 13.5%; CHF: 8.2%; and angina: 6.4%).[3-5] The percentage of patients with cardiac comorbidities in Study JVDD (22.8%) was within the range of patients in real-world settings.

The prevalence of hepatic and renal impairment increases with age, but patients with these impairments were expected to represent a small subset of the overall study sample. Considering the expected median age of the study patients and the disease prevalence reported in the real-world setting,[6-8] it was estimated that the prevalence in both subgroups would be at least 5%. In Study JVDD, the proportion of patients with hepatic or renal impairment was 11.2% and 6.4%, respectively.

Following review of available safety data, there were no new safety findings in patients with comorbidities of interest. The safety profile in these subgroups was generally consistent with that expected in the patient population of advanced gastric cancer patients treated with ramucirumab. The increased occurrence of discontinuations from ramucirumab treatment due to AEs compared with the overall patient population in each subgroup was mainly related to progression of underlying disease and/or general health deterioration. The AESI profile observed in the subgroups of interest was overall consistent with the patient population in this study.

Effectiveness analysis of ramucirumab

The median OS for patients in ramucirumab monotherapy and ramucirumab plus paclitaxel cohorts were 3.6 months (95% CI: 2.7, 4.3) and 7.6 months (95% CI: 7.0, 8.4), respectively and the median rwPFS were 1.9 months (95% CI: 1.4, 2.2) and 4.0 months (95% CI: 3.8, 4.5), respectively. The median OS and rwPFS observed in this study were as expected in patients of advanced age, with multiple comorbidities and metastasis and were in line with the results from the Phase 3 trials of ramucirumab either as single-agent (REGARD) or in combination with paclitaxel (RAINBOW) in patients with gastric cancer receiving second-line therapy, (5.2 and 9.6 months for OS and 2.1 and 4.4 months for PFS in Studies REGARD and RAINBOW, respectively).[1,2] Considering, only 2 patients in this study were of Asian race, the OS and rwPFS observed for patients in ramucirumab plus paclitaxel cohort in this study were more in line with the OS (8.5 months) and PFS (4.2 months) data observed in non-East Asian patient population belonging to Region 1 (comprising of Europe including Israel, Australia, and the United States) and Region 2 (comprising of Argentina, Brazil, Chile, and Mexico) of the RAINBOW trial.[9] Real-world best overall response should be interpreted with caution due to the limitations of response evaluation in the real-world setting. Refer to Section 11.3 for additional details.

Response to additional data requested by PRAC

Based on the PRAC review of Study JVDD PASS protocol version 2.0, the PRAC requested specific analyses from the MAH. These analyses have been discussed in the following sections throughout Section 10.

Type of Analyses	Section No.
Premedication - whether or not before each administration, - administration after previous infusion related reaction, which drug(s), which doses.	Section 10.4.1.6.2.5
Frequency of dose reductions of ramucirumab due to hypertension	Section 10.4.1.3
Frequency of discontinuation of treatment with ramucirumab due to hypertension	Section 10.4.1.6.2.3
Frequency of gastrointestinal perforation and fistula	Section 10.4.1.6.2.2

11.2. Limitations

As a non-interventional, observational study, JVDD has both advantages, as a reflection of real-world experience and also limitations. The medical information that is being collected is based on the data reported in patient's medical chart and was not collected for research purposes. Although the accuracy and completeness of the information entered into the database primarily depended on the reporting physician, the database was built to minimise illogical data entries, and consistency checks were performed between different pieces of data whenever possible. Unlike use of retrospective data from registries, prospective data collection allows for systematic and more comprehensive data collection. Adverse events like for example hypertension and proteinuria that lack signs and symptoms in the early stages and are only detected by routine laboratory monitoring may be underestimated in this real-world setting.[10] Of note in this study the overall total occurrence of AESIs of hypertension and proteinuria were 10.9% and 3% respectively. In clinical trials of ramucirumab in combination with paclitaxel in the gastric cancer setting, hypertension and proteinuria are reported at higher incidences of >25% and >15%, respectively.

Recruitment of patients was dependent on reimbursement and market uptake in a specific country. The majority of the patients were enrolled from Italy (45.7%), Germany (24.8%) and Spain (11.7%). Analyses by geographic region (i.e., Europe vs. North America) were not conducted due to limited number of patients enrolled from North America (4%).

In this study, follow up was planned for up to 12 months. This was mostly sufficient for patients with this indication, but 35 patients had continued ramucirumab treatment beyond 12 months. Therefore, not all information had been captured in this setting. To incorporate the incomplete information into analysis, survival methodology that censors incomplete observations at the last available date was used for calculation of the duration of treatment, rwPFS and OS.

Considering this was an observational study, infusions were not always accurately captured in eCRF. Moreover, duration of treatments was not always aligned with the number of infusions

based on the planned treatment regimen, hence, the final data may have missing infusions and should be interpreted with caution.

The data on dose adjustment should be interpreted with caution as dose adjustments were done as per routine clinical practice and may have not been consistently reported in the eCRF by all the investigators.

Clinical trials often utilise RECIST evaluation for assessing tumour response; however, in the real-world settings, best overall response was determined based on the treating physician's assessment of disease burden change as documented during routine clinical practice. Also, the frequency of re-evaluations was not defined in the study protocol and was performed as per routine clinical practice, which could be less frequent than in clinical trial setting. Additionally, the frequency of screening of response assessment in real world settings are potentially driven by patients presenting symptoms unlike in clinical trials where there is a predefined schedule. Moreover, frequency of screening may also vary between countries and clinical practices. This could potentially have led to fewer detection of responses in this study and overestimation of the time to progression.

11.3. Interpretation

Study JVDD's study design reflects real-life clinical management of patients with advanced/metastatic gastric cancer.

Analysis of final results from this study indicate that the safety profile of ramucirumab as a single agent or in combination with paclitaxel was generally consistent with the established safety profile of ramucirumab in the clinical settings for the overall patient population. No new safety concerns or notable findings were identified.

There was no evidence to indicate that ramucirumab-treated patients aged 65 years or older in the real-world setting were at increased risk of AEs compared to patients younger than 65 years in Phase 3 clinical trials in gastric cancer. There were no new safety findings in any of the subgroups of interest. The safety profile of patients in subgroups of interest was generally consistent with that expected in the patient population of advanced gastric cancer patients treated with ramucirumab. It was noted that a higher incidence of discontinuations of ramucirumab due to AEs occurred in all subgroups compared to the overall study population.

This study enrolled a sizeable population of patients who were elderly with lower or reduced performance status and comorbidities, which was reflective of the real-world patient characteristics. These factors may have reflected in the overall safety and effectiveness outcome, including OS.

11.4. Generalisability

Randomized clinical trials often employ excessive or overly restrictive eligibility criteria and are not broadly representative of real-world patients, and this may jeopardize the external validity of randomized clinical trials. In Study JVDD, no restrictions with regard to baseline demographic and clinical characteristics (such as age, comorbidities, performance status) were applied and the

observed characteristics of the study population were reflective of the epidemiology of gastric cancer. For example, there was a sizeable population of elderly patients and the prevalence of comorbidities of special interest were generally consistent with data reported by previous epidemiological studies in gastric cancer. This would allow for making inferences about the typical population of patients with gastric cancer eligible for ramucirumab treatment.

Geography and the selection of sites may affect generalisability. This study enrolled patients from 8 countries in Europe and the US. This covered a broad geography with a broad variety of treatment, diagnosis, and safety follow up practices. However, the study findings are based on a predominantly White (97.4%) cohort and may not be generalisable to other racial/ethnic groups.

Since the initial marketing authorisation application submission and consequent approval for gastric cancer, multiple large Phase 3 clinical studies for additional tumours have been completed, including advanced or metastatic non-small cell lung cancer, metastatic colorectal cancer, metastatic breast cancer, and hepatocellular carcinoma. In the 9 completed Phase 3 studies (REGARD, RAINBOW, REVEL, ROSE, REACH, RAISE, REACH-2, RAINFALL, and RELAY), 3489 patients (safety population) have been treated with ramucirumab, either as a single agent or in combination with antineoplastic agents (Table ANN.2.19). Although only a limited number of ramucirumab-treated patients with cardiac comorbidities have been studied due to the inclusion/exclusion criteria, the data available from these trials represent a sizable number of patients who fall within some subgroups of interest, such as elderly patients and patients with hepatic or renal impairment.

Of the 3489 patients treated with ramucirumab in completed Phase 3 clinical trials, 1246 patients (35.7%) were ≥65 years old. Study JVDD enrolled 333 patients (55%) of age 65 years and older, 138 patients (22.8%) with cardiac comorbidities, 68 patients (11.2%) with hepatic impairment and 39 patients (6.4%) with renal impairment.

Treatment decisions were at the discretion of the treating physicians allowing to assess safety in real-world conditions while not being restricted or guided by a specific protocol.

12. Other information

Not applicable.

13. Conclusions

- In patients with advanced gastric cancer, the observed safety profile of ramucirumab administered as monotherapy or in combination with paclitaxel, in the real-world setting was manageable and consistent with the established safety profile of ramucirumab identified from clinical trials in this patient population.
- No new safety concerns or notable findings were observed in the overall population or in the subgroups of interest including elderly patients, patients with cardiac comorbidities, hepatic impairment, or renal impairment.
- In this study conducted in a real-world setting, the effectiveness of ramucirumab treatment as monotherapy or in combination with paclitaxel is in line with what has been observed in clinical trials, in the light of a sizeable population of elderly patients with lower or reduced performance status and comorbidities.

Overall, results of this study indicate that the benefit-risk profile of ramucirumab remains positive in the real-world setting.

14. References

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Annex 1. List of Standalone Documents

No.	Document Reference No	Date	Title
1.	NA	NA	Principal investigator and site information
2.	NA	NA	Listing of clinically significant abnormal lab values
3.	NA	NA	Potential immediate HSRs for ramucirumab (broad events)
4.	NA	NA	Listing of premedications administered within 2 days of infusion at the time and following IRR (narrow events)

Annex 2. Additional Information

Relevant data tables applicable for this study are presented below in addition to the main body of the report. Additional tables are available on request.

Table ANN.2.1. Patients with Identified Inclusion Criteria Deviation
Informed Consent Population
Study I4T-MC-JVDD

Criteria	Ram mono (N=51)	Ram + PclTax (N=548)	Ram + Other (N=8)	Total (N=611)
Any Inclusion or Exclusion criteria	2 (3.9)	17 (3.1)	0	23 (3.8)
Not meeting Inclusion criteria				
1. Disease has progressed after prior chemotherapy	0	1 (0.2)	0	1 (0.2)
2. Patients who have initiated Ramucirumab				4 (0.7)
3. IC signed (delay)	0	1 (0.2)	0	1 (0.2)
Exclusion criteria fulfilled				
4. Patients received more than 1 line of chemo	2 (3.9)	4 (0.7)	0	6 (1.0)
5. Participating in investigational study	0	10 (1.8)	0	10 (1.6)
Other				
Patients were enrolled during enrollment hold	0	1 (0.2)	0	1 (0.2)
Among Patients excluded from analysis (critical deviation or No Ram)	0	1 (0.2)	0	5 (0.8)
Not meeting Inclusion criteria				
2. Patients who have initiated Ramucirumab				4 (0.7)
Exclusion criteria fulfilled				
4. Patients received more than 1 line of chemo	0	1 (0.2)	0	1 (0.2)
Patients included in the analysis	51 (100.0)	547 (99.8)	8 (100.0)	606 (99.2)

Database lock date: 19AUG2021.
Note:Patients may be counted in multiple rows.
Denominators are based on the total number of patients in the database
Abbreviations: N = number of subjects in population; n = number of subjects in the specified category.
Patients with IDs PPD were not present in ADSL but recorded in the 'patient tracker' which are not included in this table.

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Table ANN.2.2. Summary of Paclitaxel Disposition
Full Analysis Set
I4T-MC-JVDD

	Ram + PclTax (N=547) n (%)	Total (N=547) n (%)
Treated with Paclitaxel	547 (100.0)	547 (100.0)
Paclitaxel Disposition		
Continuing*a	17 (3.1)	17 (3.1)
Discontinued*a	530 (96.9)	530 (96.9)
Reason for Paclitaxel Discontinuation		
ADVERSE EVENT*b	117 (21.4)	117 (21.4)
DEATH	62 (11.3)	62 (11.3)
LOST TO FOLLOW UP	8 (1.5)	8 (1.5)
OTHER	13 (2.4)	13 (2.4)
PHYSICIAN DECISION	46 (8.4)	46 (8.4)
PROGRESSIVE DISEASE	267 (48.8)	267 (48.8)
WITHDRAWAL BY SUBJECT	17 (3.1)	17 (3.1)

Database lock date: 19AUG2021.
*a at the end of 12 months follow up.
*b Discontinuation due to death where primary reason for death is "Adverse Event" is not included.

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Table ANN.2.3. Non-Anticancer Medications Taken by at least 5% of Patients within 14 Days Prior to Ramucirumab Infusion
Full Analysis Set
I4T-MC-JVDD

Prior (non-anticancer) medications	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Subjects with >=1 Medication	39 (76.5)	360 (65.8)	6 (75.0)	405 (66.8)
DEXAMETHASONE	21 (41.2)	262 (47.9)	6 (75.0)	289 (47.7)
RANITIDINE HYDROCHLORIDE	3 (5.9)	129 (23.6)	0	132 (21.8)
ONDANSETRON	5 (9.8)	121 (22.1)	2 (25.0)	128 (21.1)
RANITIDINE	9 (17.6)	118 (21.6)	0	127 (21.0)
CHLORPHENAMINE	6 (11.8)	75 (13.7)	0	81 (13.4)
CHLORPHENAMINE MALEATE	0	66 (12.1)	0	66 (10.9)
METOCLOPRAMIDE	1 (2.0)	62 (11.3)	0	63 (10.4)
DIMETINDENE MALEATE	8 (15.7)	36 (6.6)	0	44 (7.3)
CLEMASTINE FUMARATE	2 (3.9)	41 (7.5)	0	43 (7.1)
DEXAMETHASONE SODIUM PHOSPHATE	1 (2.0)	40 (7.3)	0	41 (6.8)
GRANISETRON	0	40 (7.3)	0	40 (6.6)
DIPHENHYDRAMINE HYDROCHLORIDE	6 (11.8)	26 (4.8)	3 (37.5)	35 (5.8)
DIPHENHYDRAMINE	1 (2.0)	33 (6.0)	0	34 (5.6)
PALONOSETRON HYDROCHLORIDE	0	26 (4.8)	2 (25.0)	28 (4.6)
PARACETAMOL	2 (3.9)	26 (4.8)	0	28 (4.6)
CLEMASTINE	3 (5.9)	22 (4.0)	2 (25.0)	27 (4.5)
GRANISETRON HYDROCHLORIDE	1 (2.0)	22 (4.0)	0	23 (3.8)
DEXCHLORPHENIRAMINE	1 (2.0)	19 (3.5)	0	20 (3.3)
HYDROCORTISONE	0	15 (2.7)	0	15 (2.5)
PREDNISONE	1 (2.0)	13 (2.4)	0	14 (2.3)
FAMOTIDINE	0	13 (2.4)	0	13 (2.1)
PALONOSETRON	0	10 (1.8)	2 (25.0)	12 (2.0)

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MedDRA Version 24.0, CTCAE Version V4.0

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Non-anticancer medications taken within 14 days prior to Ram page 2 of 4
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Prior (non-anticancer) medications	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
METHYLPREDNISOLONE SODIUM SUCCINATE	1 (2.0)	10 (1.8)	0	11 (1.8)
PANTOPRAZOLE	0	10 (1.8)	0	10 (1.7)
PANTOPRAZOLE SODIUM SESQUIHYDRATE	1 (2.0)	9 (1.6)	0	10 (1.7)
METHYLPREDNISOLONE	0	9 (1.6)	0	9 (1.5)
CIMETIDINE	1 (2.0)	5 (0.9)	0	6 (1.0)
DEXCHLORPHENIRAMINE MALEATE	1 (2.0)	5 (0.9)	0	6 (1.0)
CETIRIZINE HYDROCHLORIDE	0	5 (0.9)	0	5 (0.8)
TROPISETRON HYDROCHLORIDE	0	5 (0.9)	0	5 (0.8)
ALIZAPRIDE HYDROCHLORIDE	0	4 (0.7)	0	4 (0.7)
APREPITANT	0	4 (0.7)	0	4 (0.7)
CETIRIZINE	0	4 (0.7)	0	4 (0.7)
OMEPRAZOLE	1 (2.0)	3 (0.5)	0	4 (0.7)
DIMETINDENE	1 (2.0)	2 (0.4)	0	3 (0.5)
LEVOCETIRIZINE DIHYDROCHLORIDE	0	3 (0.5)	0	3 (0.5)
ONDANSETRON HYDROCHLORIDE	3 (5.9)	0	0	3 (0.5)
SODIUM CHLORIDE	0	3 (0.5)	0	3 (0.5)
ALIZAPRIDE	0	2 (0.4)	0	2 (0.3)
CEFUROXIME	0	2 (0.4)	0	2 (0.3)
RIVAROXABAN	0	2 (0.4)	0	2 (0.3)
ACETYLSALICYLIC ACID	0	1 (0.2)	0	1 (0.2)
AMLODIPINE	0	1 (0.2)	0	1 (0.2)
AMOXICILLIN;CLAVULANATE POTASSIUM	0	1 (0.2)	0	1 (0.2)
ATROPINE	0	0	1 (12.5)	1 (0.2)
BETAMETHASONE SODIUM PHOSPHATE	0	1 (0.2)	0	1 (0.2)

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Based on MedDRA preferred terms where applicable
MedDRA Version 24.0, CTCAE Version V4.0

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Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADCM
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/observed/shared/cutoff/CM

Non-anticancer medications taken within 14 days prior to Ram page 3 of 4
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Prior (non-anticancer) medications	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
BETAMETHASONE VALERATE;FUSIDIC ACID	0	1 (0.2)	0	1 (0.2)
BILASTINE	0	1 (0.2)	0	1 (0.2)
CALCIUM CHLORIDE DIHYDRATE;MAGNESIUM CHLORIDE;POTA	0	1 (0.2)	0	1 (0.2)
CALCIUM;COLECALCIFEROL	0	1 (0.2)	0	1 (0.2)
CLOPIDOGREL BISULFATE	0	1 (0.2)	0	1 (0.2)
DALTEPARIN SODIUM	0	0	1 (12.5)	1 (0.2)
DARBEPOETIN ALFA	0	1 (0.2)	0	1 (0.2)
DOMPERIDONE	0	1 (0.2)	0	1 (0.2)
ENOXAPARIN	0	1 (0.2)	0	1 (0.2)
ERTAPENEM SODIUM	1 (2.0)	0	0	1 (0.2)
ESOMEPRAZOLE	0	1 (0.2)	0	1 (0.2)
FENTANYL CITRATE	0	1 (0.2)	0	1 (0.2)
FERRIC SODIUM GLUCONATE COMPLEX	0	1 (0.2)	0	1 (0.2)
FOSAPREPITANT	0	1 (0.2)	0	1 (0.2)
FUROSEMIDE	0	1 (0.2)	0	1 (0.2)
HERBAL REMEDIES WITH ESTROGEN-LIKE ACTIVITY	0	1 (0.2)	0	1 (0.2)
HYDROXYZINE	1 (2.0)	0	0	1 (0.2)
MEROPENEM	0	1 (0.2)	0	1 (0.2)
METAMIZOLE SODIUM	0	1 (0.2)	0	1 (0.2)
METFORMIN	0	1 (0.2)	0	1 (0.2)
METOCLOPRAMIDE HYDROCHLORIDE	0	1 (0.2)	0	1 (0.2)
MIRTAZAPINE	0	1 (0.2)	0	1 (0.2)
NADROPARIN CALCIUM	0	1 (0.2)	0	1 (0.2)
NALOXONE HYDROCHLORIDE;OXYCODONE HYDROCHLORIDE	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Based on MedDRA preferred terms where applicable
MedDRA Version 24.0, CTCAE Version V4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tpricm.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpricm.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADCM
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/observed/shared/cutoff/CM

Non-anticancer medications taken within 14 days prior to Ram
Full analysis set
I4T-MC-JVDD

Prior (non-anticancer) medications	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
NITRENDIPINE	0	1 (0.2)	0	1 (0.2)
OMEPRAZOLE SODIUM	0	1 (0.2)	0	1 (0.2)
PHLOROGLUCINOL;TRIMETHYLPHLOROGLUCINOL	0	1 (0.2)	0	1 (0.2)
POTASSIUM CHLORIDE	0	1 (0.2)	0	1 (0.2)
PREDNISOLONE SODIUM SUCCINATE	0	1 (0.2)	0	1 (0.2)
PROCHLORPERAZINE	0	1 (0.2)	0	1 (0.2)
PROMETHAZINE	0	1 (0.2)	0	1 (0.2)
SACCHARATED IRON OXIDE	0	1 (0.2)	0	1 (0.2)
SEROTONIN (5HT3) ANTAGONISTS	0	1 (0.2)	0	1 (0.2)
SODIUM CITRATE;SODIUM LAURYL SULFOACETATE;SORBITOL	0	1 (0.2)	0	1 (0.2)
SOLUTIONS AFFECTING THE ELECTROLYTE BALANCE	0	1 (0.2)	0	1 (0.2)
SPIRONOLACTONE	0	1 (0.2)	0	1 (0.2)
TELMISARTAN	0	1 (0.2)	0	1 (0.2)
ZOLEDRONIC ACID	0	1 (0.2)	0	1 (0.2)
ZOLEDRONIC ACID MONOHYDRATE	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Based on MedDRA preferred terms where applicable
MedDRA Version 24.0, CTCAE Version V4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tpricm.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tpricm.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADCM
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/observed/shared/cutoff/CM

Table ANN.2.4. Summary of Drug Adjustment for Ramucirumab
Full Analysis Set
I4T-MC-JVDD

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Patients with at least one Dose Adjustment n(%)	13	(25.5)	319	(58.3)	4	(50.0)	336	(55.4)
Number of Patients with Dose Reduction	4	(7.8)	55	(10.1)	0		59	(9.7)
Patients with 1 dose reduction	4	(7.8)	43	(7.9)	0		47	(7.8)
Patients with 2 dose reductions	0		11	(2.0)	0		11	(1.8)
Patients with >=3 dose reductions	0		1	(0.2)	0		1	(0.2)
Reasons leading to dose reduction								
ADVERSE EVENT	4	(7.8)	54	(9.9)	0		58	(9.6)
Abdominal pain	0		1	(0.2)	0		1	(0.2)
Abdominal pain upper	0		1	(0.2)	0		1	(0.2)
Anaemia	0		2	(0.4)	0		2	(0.3)
Asthenia	1	(2.0)	6	(1.1)	0		7	(1.2)
Blood creatinine increased	0		1	(0.2)	0		1	(0.2)
Cachexia	0		1	(0.2)	0		1	(0.2)
Decreased appetite	0		1	(0.2)	0		1	(0.2)
Epistaxis	0		3	(0.5)	0		3	(0.5)
Fatigue	0		4	(0.7)	0		4	(0.7)
General physical health deterioration	0		1	(0.2)	0		1	(0.2)
Hypertension	0		1	(0.2)	0		1	(0.2)
Hypokalaemia	0		1	(0.2)	0		1	(0.2)
Leukopenia	0		1	(0.2)	0		1	(0.2)
Mucosal inflammation	0		1	(0.2)	0		1	(0.2)
Neuropathy peripheral	0		1	(0.2)	0		1	(0.2)
Neutropenia	0		7	(1.3)	0		7	(1.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 2 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Neutrophil count decreased	0		1	(0.2)	0		1	(0.2)
Platelet count decreased	0		1	(0.2)	0		1	(0.2)
Proteinuria	1	(2.0)	1	(0.2)	0		2	(0.3)
Pulmonary embolism	0		1	(0.2)	0		1	(0.2)
Stomatitis	0		1	(0.2)	0		1	(0.2)
Weight decreased	2	(3.9)	16	(2.9)	0		18	(3.0)
Weight increased	0		2	(0.4)	0		2	(0.3)
White blood cell count decreased	0		1	(0.2)	0		1	(0.2)
Number of Patients with Dose Delay	8	(15.7)	196	(35.8)	3	(37.5)	207	(34.2)
Patients with 1 dose delay	6	(11.8)	123	(22.5)	3	(37.5)	132	(21.8)
Patients with 2 dose delays	2	(3.9)	46	(8.4)	0		48	(7.9)
Patients with >=3 dose delays	0		27	(4.9)	0		27	(4.5)
Reasons leading to dose delay								
ADVERSE EVENT	6	(11.8)	133	(24.3)	1	(12.5)	140	(23.1)
Abdominal pain	0		1	(0.2)	0		1	(0.2)
Alanine aminotransferase increased	1	(2.0)	0		0		1	(0.2)
Anaemia	1	(2.0)	1	(0.2)	0		2	(0.3)
Anal abscess	0		1	(0.2)	0		1	(0.2)
Antineutrophil cytoplasmic antibody decreased	0		1	(0.2)	0		1	(0.2)
Anxiety	0		1	(0.2)	0		1	(0.2)
Asthenia	0		3	(0.5)	0		3	(0.5)
Back pain	0		1	(0.2)	0		1	(0.2)
Bone pain	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 3 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Bronchitis	0		1	(0.2)	0		1	(0.2)
C-reactive protein increased	0		1	(0.2)	0		1	(0.2)
COVID-19	0		1	(0.2)	0		1	(0.2)
Cheilitis	0		1	(0.2)	0		1	(0.2)
Chills	0		1	(0.2)	0		1	(0.2)
Cholangitis	0		1	(0.2)	0		1	(0.2)
Cholecystitis	0		1	(0.2)	0		1	(0.2)
Chronic obstructive pulmonary disease	0		1	(0.2)	0		1	(0.2)
Cough	0		4	(0.7)	0		4	(0.7)
Cystitis	0		1	(0.2)	0		1	(0.2)
Deep vein thrombosis	0		1	(0.2)	0		1	(0.2)
Dehydration	1	(2.0)	0		0		1	(0.2)
Device malfunction	0		1	(0.2)	0		1	(0.2)
Device related infection	0		1	(0.2)	0		1	(0.2)
Diarrhoea	0		6	(1.1)	0		6	(1.0)
Dizziness	0		1	(0.2)	0		1	(0.2)
Dysphagia	0		2	(0.4)	0		2	(0.3)
Dyspnoea	0		1	(0.2)	0		1	(0.2)
Enterobacter test positive	0		1	(0.2)	0		1	(0.2)
Epistaxis	0		1	(0.2)	0		1	(0.2)
Erysipelas	0		1	(0.2)	0		1	(0.2)
Fatigue	0		1	(0.2)	0		1	(0.2)
Febrile neutropenia	0		1	(0.2)	0		1	(0.2)
Femur fracture	0		1	(0.2)	0		1	(0.2)
Fistula	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 4 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Gastrointestinal disorder	0		1	(0.2)	0		1	(0.2)
General physical health deterioration	1	(2.0)	1	(0.2)	0		2	(0.3)
Hepatitis B reactivation	0		1	(0.2)	0		1	(0.2)
Hypertension	1	(2.0)	3	(0.5)	0		4	(0.7)
Hypertransaminasaemia	0		3	(0.5)	0		3	(0.5)
Hypotension	0		1	(0.2)	0		1	(0.2)
Hypotonia	0		1	(0.2)	0		1	(0.2)
Ileus	0		2	(0.4)	0		2	(0.3)
Infection	0		1	(0.2)	0		1	(0.2)
Influenza	0		1	(0.2)	0		1	(0.2)
Influenza like illness	0		1	(0.2)	0		1	(0.2)
Infusion related reaction	0		1	(0.2)	0		1	(0.2)
Injury	0		1	(0.2)	0		1	(0.2)
Intestinal obstruction	0		1	(0.2)	0		1	(0.2)
Leukopenia	0		2	(0.4)	0		2	(0.3)
Lymphoedema	0		1	(0.2)	0		1	(0.2)
Metastases to bone	0		1	(0.2)	0		1	(0.2)
Mucosal inflammation	0		1	(0.2)	0		1	(0.2)
Nasopharyngitis	0		1	(0.2)	0		1	(0.2)
Nausea	0		2	(0.4)	0		2	(0.3)
Neuropathy peripheral	0		1	(0.2)	0		1	(0.2)
Neurotoxicity	0		1	(0.2)	0		1	(0.2)
Neutropenia	0		37	(6.8)	0		37	(6.1)
Neutrophil count decreased	0		12	(2.2)	0		12	(2.0)
Oedema peripheral	0		2	(0.4)	0		2	(0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 5 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Oliguria	0		1	(0.2)	0		1	(0.2)
Onycholysis	0		1	(0.2)	0		1	(0.2)
Oral candidiasis	0		1	(0.2)	0		1	(0.2)
Paraesthesia	0		1	(0.2)	0		1	(0.2)
Peripheral sensory neuropathy	0		1	(0.2)	0		1	(0.2)
Platelet count decreased	0		4	(0.7)	0		4	(0.7)
Pleural effusion	0		1	(0.2)	0		1	(0.2)
Pneumonia	1	(2.0)	4	(0.7)	0		5	(0.8)
Pneumonitis	0		2	(0.4)	0		2	(0.3)
Pneumothorax	0		1	(0.2)	0		1	(0.2)
Polyneuropathy	0		1	(0.2)	0		1	(0.2)
Post procedural complication	0		1	(0.2)	0		1	(0.2)
Proteinuria	0		1	(0.2)	0		1	(0.2)
Pulmonary embolism	0		2	(0.4)	0		2	(0.3)
Pyrexia	0		7	(1.3)	0		7	(1.2)
Radius fracture	0		1	(0.2)	0		1	(0.2)
Respiratory tract infection	0		1	(0.2)	0		1	(0.2)
Sepsis	0		1	(0.2)	0		1	(0.2)
Stoma site pain	0		1	(0.2)	0		1	(0.2)
Stomatitis	0		2	(0.4)	0		2	(0.3)
Thrombocytopenia	0		2	(0.4)	0		2	(0.3)
Tooth abscess	0		1	(0.2)	0		1	(0.2)
Tooth infection	0		1	(0.2)	0		1	(0.2)
Urinary tract infection	0		3	(0.5)	0		3	(0.5)
Viral infection	0		0		1	(12.5)	1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 6 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Viral upper respiratory tract infection	0		2	(0.4)	0		2	(0.3)
Vomiting	0		3	(0.5)	0		3	(0.5)
White blood cell count decreased	0		2	(0.4)	0		2	(0.3)
SCHEDULING CONFLICT	2	(3.9)	91	(16.6)	2	(25.0)	95	(15.7)
Number of Patients with Dose Omission	4	(7.8)	173	(31.6)	2	(25.0)	179	(29.5)
Patients with 1 dose Omitted	4	(7.8)	122	(22.3)	1	(12.5)	127	(21.0)
Patients with 2 dose Omitted	0		35	(6.4)	0		35	(5.8)
Patients with >=3 dose Omitted	0		16	(2.9)	1	(12.5)	17	(2.8)
Reasons leading to dose omitted								
ADVERSE EVENT	3	(5.9)	137	(25.0)	1	(12.5)	141	(23.3)
Abdominal pain	0		2	(0.4)	0		2	(0.3)
Anaemia	0		3	(0.5)	0		3	(0.5)
Anal abscess	0		1	(0.2)	0		1	(0.2)
Anorectal disorder	0		1	(0.2)	0		1	(0.2)
Aortic aneurysm	0		1	(0.2)	0		1	(0.2)
Ascites	0		1	(0.2)	0		1	(0.2)
Asthenia	0		3	(0.5)	0		3	(0.5)
Bronchitis	1	(2.0)	0		0		1	(0.2)
Cataract	0		1	(0.2)	0		1	(0.2)
Cellulitis	0		1	(0.2)	0		1	(0.2)
Cerebral ischaemia	0		1	(0.2)	0		1	(0.2)
Colitis ulcerative	0		1	(0.2)	0		1	(0.2)
Cough	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 7 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Cystitis	0		1	(0.2)	0		1	(0.2)
Decreased appetite	0		1	(0.2)	0		1	(0.2)
Dehydration	0		1	(0.2)	0		1	(0.2)
Device related infection	0		1	(0.2)	0		1	(0.2)
Diarrhoea	0		5	(0.9)	0		5	(0.8)
Diarrhoea haemorrhagic	0		1	(0.2)	0		1	(0.2)
Disease progression	1	(2.0)	0		0		1	(0.2)
Drug hypersensitivity	0		1	(0.2)	0		1	(0.2)
Dysphagia	0		1	(0.2)	0		1	(0.2)
Dyspnoea	0		2	(0.4)	0		2	(0.3)
Ejection fraction decreased	0		1	(0.2)	0		1	(0.2)
Epistaxis	0		6	(1.1)	0		6	(1.0)
Fall	0		1	(0.2)	0		1	(0.2)
Fatigue	0		3	(0.5)	0		3	(0.5)
Fistula	0		1	(0.2)	0		1	(0.2)
Gastric haemorrhage	0		1	(0.2)	0		1	(0.2)
Gastric perforation	0		1	(0.2)	0		1	(0.2)
General physical health deterioration	0		9	(1.6)	0		9	(1.5)
Haematoma	0		0		1	(12.5)	1	(0.2)
Haematuria	0		1	(0.2)	0		1	(0.2)
Haemoptysis	0		1	(0.2)	0		1	(0.2)
Haemorrhoidal haemorrhage	0		1	(0.2)	0		1	(0.2)
Herpes simplex	0		1	(0.2)	0		1	(0.2)
Hypersensitivity	0		1	(0.2)	0		1	(0.2)
Hypertension	0		2	(0.4)	0		2	(0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 8 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Influenza	0		1	(0.2)	0		1	(0.2)
Influenza like illness	0		1	(0.2)	0		1	(0.2)
Infusion related reaction	0		1	(0.2)	0		1	(0.2)
Intermenstrual bleeding	0		1	(0.2)	0		1	(0.2)
Intestinal obstruction	0		4	(0.7)	0		4	(0.7)
Karnofsky scale worsened	0		1	(0.2)	0		1	(0.2)
Leukopenia	0		3	(0.5)	0		3	(0.5)
Malignant neoplasm progression	0		3	(0.5)	0		3	(0.5)
Mucosal inflammation	0		4	(0.7)	0		4	(0.7)
Nasopharyngitis	1	(2.0)	0		0		1	(0.2)
Nausea	0		1	(0.2)	0		1	(0.2)
Neuropathy peripheral	0		1	(0.2)	0		1	(0.2)
Neutropenia	0		33	(6.0)	0		33	(5.4)
Neutrophil count decreased	0		11	(2.0)	0		11	(1.8)
Oedema	0		1	(0.2)	0		1	(0.2)
Oedema peripheral	0		1	(0.2)	0		1	(0.2)
Oral disorder	0		1	(0.2)	0		1	(0.2)
Osteonecrosis of jaw	0		0		1	(12.5)	1	(0.2)
Pericardial effusion	0		1	(0.2)	0		1	(0.2)
Periodontal disease	0		1	(0.2)	0		1	(0.2)
Peritonitis bacterial	0		1	(0.2)	0		1	(0.2)
Platelet count decreased	0		4	(0.7)	0		4	(0.7)
Pneumonia	0		1	(0.2)	0		1	(0.2)
Proteinuria	0		9	(1.6)	0		9	(1.5)
Pulmonary oedema	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Ramucirumab - 2 page 9 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Pyrexia	0		3	(0.5)	0		3	(0.5)
Respiratory tract infection	1	(2.0)	1	(0.2)	0		2	(0.3)
Skin ulcer	0		1	(0.2)	0		1	(0.2)
Stoma site pain	0		1	(0.2)	0		1	(0.2)
Thrombocytopenia	0		3	(0.5)	0		3	(0.5)
Thrombosis	0		1	(0.2)	0		1	(0.2)
Tooth abscess	0		1	(0.2)	0		1	(0.2)
Toothache	0		1	(0.2)	0		1	(0.2)
Urinary tract infection	0		2	(0.4)	0		2	(0.3)
Urinary tract infection bacterial	0		1	(0.2)	0		1	(0.2)
Vomiting	0		1	(0.2)	0		1	(0.2)
Weight decreased	0		1	(0.2)	0		1	(0.2)
White blood cell count decreased	0		1	(0.2)	0		1	(0.2)
SCHEDULING CONFLICT	0		8	(1.5)	1	(12.5)	9	(1.5)
TREATMENT AVAILABILITY	1	(2.0)	6	(1.1)	0		7	(1.2)
OTHER	0		39	(7.1)	1	(12.5)	40	(6.6)
Number of Patients with Dose Increase	0		0		0		0	

Database lock date: 19AUG2021.
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Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjram1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjram1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Table ANN.2.5. Summary of Drug Adjustment for Paclitaxel
Full Analysis Set
I4T-MC-JVDD

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Patients with at least one Dose Adjustment n(%)	0		371	(67.8)	0		371	(61.2)
Number of Patients with Dose Reduction	0		181	(33.1)	0		181	(29.9)
Patients with 1 dose reduction	0		123	(22.5)	0		123	(20.3)
Patients with 2 dose reductions	0		46	(8.4)	0		46	(7.6)
Patients with >=3 dose reductions	0		12	(2.2)	0		12	(2.0)
Reasons leading to dose reduction								
ADVERSE EVENT	0		178	(32.5)	0		178	(29.4)
Abdominal pain upper	0		2	(0.4)	0		2	(0.3)
Agranulocytosis	0		1	(0.2)	0		1	(0.2)
Anaemia	0		10	(1.8)	0		10	(1.7)
Arthralgia	0		1	(0.2)	0		1	(0.2)
Asthenia	0		12	(2.2)	0		12	(2.0)
Blood bilirubin increased	0		1	(0.2)	0		1	(0.2)
Cachexia	0		1	(0.2)	0		1	(0.2)
Cerebral ischaemia	0		1	(0.2)	0		1	(0.2)
Chest pain	0		1	(0.2)	0		1	(0.2)
Chills	0		1	(0.2)	0		1	(0.2)
Decreased appetite	0		2	(0.4)	0		2	(0.3)
Diarrhoea	0		7	(1.3)	0		7	(1.2)
Dysaesthesia	0		1	(0.2)	0		1	(0.2)
Dysgeusia	0		1	(0.2)	0		1	(0.2)
Dysphagia	0		2	(0.4)	0		2	(0.3)
Fatigue	0		12	(2.2)	0		12	(2.0)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Paclitaxel - 2 page 2 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Febrile neutropenia	0		2	(0.4)	0		2	(0.3)
Gastric haemorrhage	0		1	(0.2)	0		1	(0.2)
General physical health deterioration	0		4	(0.7)	0		4	(0.7)
Haematemesis	0		1	(0.2)	0		1	(0.2)
Hepatotoxicity	0		2	(0.4)	0		2	(0.3)
Hypertransaminasaemia	0		2	(0.4)	0		2	(0.3)
Hypokalaemia	0		1	(0.2)	0		1	(0.2)
Influenza	0		2	(0.4)	0		2	(0.3)
Infusion related reaction	0		1	(0.2)	0		1	(0.2)
Insomnia	0		1	(0.2)	0		1	(0.2)
Leukopenia	0		3	(0.5)	0		3	(0.5)
Lymphocyte count decreased	0		1	(0.2)	0		1	(0.2)
Mucosal inflammation	0		5	(0.9)	0		5	(0.8)
Nausea	0		2	(0.4)	0		2	(0.3)
Neuropathy peripheral	0		13	(2.4)	0		13	(2.1)
Neurotoxicity	0		2	(0.4)	0		2	(0.3)
Neutropenia	0		37	(6.8)	0		37	(6.1)
Neutrophil count decreased	0		8	(1.5)	0		8	(1.3)
Oedema peripheral	0		1	(0.2)	0		1	(0.2)
Palmar-plantar erythrodysaesthesia syndrome	0		1	(0.2)	0		1	(0.2)
Paraesthesia	0		19	(3.5)	0		19	(3.1)
Peripheral sensory neuropathy	0		4	(0.7)	0		4	(0.7)
Platelet count decreased	0		2	(0.4)	0		2	(0.3)
Polyneuropathy	0		9	(1.6)	0		9	(1.5)
Respiratory tract infection	0		1	(0.2)	0		1	(0.2)

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Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Paclitaxel - 2 page 3 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Stomatitis	0		5	(0.9)	0		5	(0.8)
Thrombocytopenia	0		2	(0.4)	0		2	(0.3)
Tooth abscess	0		1	(0.2)	0		1	(0.2)
Vomiting	0		2	(0.4)	0		2	(0.3)
Weight decreased	0		14	(2.6)	0		14	(2.3)
Weight increased	0		1	(0.2)	0		1	(0.2)
White blood cell count decreased	0		5	(0.9)	0		5	(0.8)
Number of Patients with Dose Delay	0		189	(34.6)	0		189	(31.2)
Patients with 1 dose delay	0		122	(22.3)	0		122	(20.1)
Patients with 2 dose delays	0		42	(7.7)	0		42	(6.9)
Patients with >=3 dose delays	0		25	(4.6)	0		25	(4.1)
Reasons leading to dose delay								
ADVERSE EVENT	0		130	(23.8)	0		130	(21.5)
Abdominal pain	0		1	(0.2)	0		1	(0.2)
Anaemia	0		3	(0.5)	0		3	(0.5)
Antineutrophil cytoplasmic antibody decreased	0		1	(0.2)	0		1	(0.2)
Anxiety	0		1	(0.2)	0		1	(0.2)
Asthenia	0		1	(0.2)	0		1	(0.2)
Back pain	0		1	(0.2)	0		1	(0.2)
Blood bilirubin increased	0		1	(0.2)	0		1	(0.2)
Bone pain	0		1	(0.2)	0		1	(0.2)
Bronchitis	0		1	(0.2)	0		1	(0.2)
C-reactive protein increased	0		1	(0.2)	0		1	(0.2)

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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

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Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
COVID-19	0		1	(0.2)	0		1	(0.2)
Cerebral ischaemia	0		1	(0.2)	0		1	(0.2)
Cheilitis	0		1	(0.2)	0		1	(0.2)
Chills	0		1	(0.2)	0		1	(0.2)
Cholangitis	0		1	(0.2)	0		1	(0.2)
Chronic obstructive pulmonary disease	0		1	(0.2)	0		1	(0.2)
Constipation	0		1	(0.2)	0		1	(0.2)
Cough	0		4	(0.7)	0		4	(0.7)
Cystitis	0		1	(0.2)	0		1	(0.2)
Deep vein thrombosis	0		1	(0.2)	0		1	(0.2)
Device dislocation	0		1	(0.2)	0		1	(0.2)
Device malfunction	0		1	(0.2)	0		1	(0.2)
Device related infection	0		2	(0.4)	0		2	(0.3)
Diarrhoea	0		4	(0.7)	0		4	(0.7)
Dizziness	0		1	(0.2)	0		1	(0.2)
Dysphagia	0		2	(0.4)	0		2	(0.3)
Dysphonia	0		1	(0.2)	0		1	(0.2)
Dyspnoea	0		1	(0.2)	0		1	(0.2)
Enterobacter test positive	0		1	(0.2)	0		1	(0.2)
Epistaxis	0		1	(0.2)	0		1	(0.2)
Erysipelas	0		1	(0.2)	0		1	(0.2)
Fatigue	0		1	(0.2)	0		1	(0.2)
Fistula	0		1	(0.2)	0		1	(0.2)
Gastrointestinal disorder	0		1	(0.2)	0		1	(0.2)
General physical health deterioration	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
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Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

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Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Hepatitis B reactivation	0		1	(0.2)	0		1	(0.2)
Hypertension	0		1	(0.2)	0		1	(0.2)
Hypertransaminasaemia	0		3	(0.5)	0		3	(0.5)
Hypotonia	0		1	(0.2)	0		1	(0.2)
Ileus	0		2	(0.4)	0		2	(0.3)
Infection	0		1	(0.2)	0		1	(0.2)
Influenza	0		1	(0.2)	0		1	(0.2)
Influenza like illness	0		1	(0.2)	0		1	(0.2)
Infusion related reaction	0		1	(0.2)	0		1	(0.2)
Injury	0		1	(0.2)	0		1	(0.2)
Intestinal obstruction	0		1	(0.2)	0		1	(0.2)
Leukopenia	0		1	(0.2)	0		1	(0.2)
Lymphoedema	0		1	(0.2)	0		1	(0.2)
Mucosal inflammation	0		2	(0.4)	0		2	(0.3)
Nasopharyngitis	0		1	(0.2)	0		1	(0.2)
Nausea	0		2	(0.4)	0		2	(0.3)
Neuropathy peripheral	0		1	(0.2)	0		1	(0.2)
Neurotoxicity	0		1	(0.2)	0		1	(0.2)
Neutropenia	0		43	(7.9)	0		43	(7.1)
Neutrophil count decreased	0		11	(2.0)	0		11	(1.8)
Oedema peripheral	0		1	(0.2)	0		1	(0.2)
Onycholysis	0		1	(0.2)	0		1	(0.2)
Oral candidiasis	0		1	(0.2)	0		1	(0.2)
Paraesthesia	0		1	(0.2)	0		1	(0.2)
Periodontal disease	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

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Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Paclitaxel - 2 page 6 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Platelet count decreased	0		4	(0.7)	0		4	(0.7)
Pleural effusion	0		1	(0.2)	0		1	(0.2)
Pneumonia	0		4	(0.7)	0		4	(0.7)
Pneumonitis	0		3	(0.5)	0		3	(0.5)
Pneumothorax	0		1	(0.2)	0		1	(0.2)
Proteinuria	0		1	(0.2)	0		1	(0.2)
Pulmonary embolism	0		1	(0.2)	0		1	(0.2)
Pyrexia	0		8	(1.5)	0		8	(1.3)
Respiratory tract infection	0		3	(0.5)	0		3	(0.5)
Sepsis	0		2	(0.4)	0		2	(0.3)
Stoma site pain	0		1	(0.2)	0		1	(0.2)
Stomatitis	0		2	(0.4)	0		2	(0.3)
Thrombocytopenia	0		1	(0.2)	0		1	(0.2)
Tooth abscess	0		1	(0.2)	0		1	(0.2)
Tooth infection	0		1	(0.2)	0		1	(0.2)
Upper respiratory tract infection	0		1	(0.2)	0		1	(0.2)
Urinary tract infection	0		1	(0.2)	0		1	(0.2)
Viral upper respiratory tract infection	0		2	(0.4)	0		2	(0.3)
Vomiting	0		2	(0.4)	0		2	(0.3)
White blood cell count decreased	0		2	(0.4)	0		2	(0.3)
SCHEDULING CONFLICT	0		88	(16.1)	0		88	(14.5)
Number of Patients with Dose Omission	0		218	(39.9)	0		218	(36.0)
Patients with 1 dose Omitted	0		148	(27.1)	0		148	(24.4)
Patients with 2 dose Omitted	0		39	(7.1)	0		39	(6.4)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Paclitaxel - 2 page 7 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Patients with >=3 dose Omitted	0		31	(5.7)	0		31	(5.1)
Reasons leading to dose omitted								
ADVERSE EVENT	0		132	(24.1)	0		132	(21.8)
Abdominal pain	0		1	(0.2)	0		1	(0.2)
Abdominal pain upper	0		1	(0.2)	0		1	(0.2)
Anaemia	0		7	(1.3)	0		7	(1.2)
Anal abscess	0		1	(0.2)	0		1	(0.2)
Aortic aneurysm	0		1	(0.2)	0		1	(0.2)
Asthenia	0		4	(0.7)	0		4	(0.7)
Back pain	0		1	(0.2)	0		1	(0.2)
Blood bilirubin increased	0		1	(0.2)	0		1	(0.2)
C-reactive protein increased	0		1	(0.2)	0		1	(0.2)
Cellulitis	0		1	(0.2)	0		1	(0.2)
Chills	0		1	(0.2)	0		1	(0.2)
Cholestasis	0		1	(0.2)	0		1	(0.2)
Condition aggravated	0		1	(0.2)	0		1	(0.2)
Cough	0		1	(0.2)	0		1	(0.2)
Dehydration	0		1	(0.2)	0		1	(0.2)
Dermal cyst	0		1	(0.2)	0		1	(0.2)
Device dislocation	0		1	(0.2)	0		1	(0.2)
Device related infection	0		2	(0.4)	0		2	(0.3)
Diarrhoea	0		5	(0.9)	0		5	(0.8)
Dysphagia	0		1	(0.2)	0		1	(0.2)
Dyspnoea	0		2	(0.4)	0		2	(0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Paclitaxel - 2 page 8 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Fall	0		1	(0.2)	0		1	(0.2)
Fatigue	0		6	(1.1)	0		6	(1.0)
Gastric perforation	0		1	(0.2)	0		1	(0.2)
General physical health deterioration	0		4	(0.7)	0		4	(0.7)
Gingival bleeding	0		1	(0.2)	0		1	(0.2)
Headache	0		1	(0.2)	0		1	(0.2)
Hepatotoxicity	0		1	(0.2)	0		1	(0.2)
Herpes simplex	0		1	(0.2)	0		1	(0.2)
Hypertransaminasaemia	0		3	(0.5)	0		3	(0.5)
Influenza	0		2	(0.4)	0		2	(0.3)
Influenza like illness	0		2	(0.4)	0		2	(0.3)
Intestinal obstruction	0		3	(0.5)	0		3	(0.5)
Karnofsky scale worsened	0		1	(0.2)	0		1	(0.2)
Leukocytosis	0		1	(0.2)	0		1	(0.2)
Leukopenia	0		2	(0.4)	0		2	(0.3)
Malignant neoplasm progression	0		1	(0.2)	0		1	(0.2)
Mucosal inflammation	0		3	(0.5)	0		3	(0.5)
Nausea	0		2	(0.4)	0		2	(0.3)
Neuropathy peripheral	0		8	(1.5)	0		8	(1.3)
Neurotoxicity	0		1	(0.2)	0		1	(0.2)
Neutropenia	0		26	(4.8)	0		26	(4.3)
Neutrophil count decreased	0		11	(2.0)	0		11	(1.8)
Pain in extremity	0		2	(0.4)	0		2	(0.3)
Paraesthesia	0		6	(1.1)	0		6	(1.0)
Pericardial effusion	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Summary of Drug Adjustment for Paclitaxel - 2 page 9 of 9
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Parameter	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Total (N=606) n	(%)
Peripheral sensory neuropathy	0		2	(0.4)	0		2	(0.3)
Peritonitis bacterial	0		1	(0.2)	0		1	(0.2)
Platelet count decreased	0		7	(1.3)	0		7	(1.2)
Pneumonia	0		1	(0.2)	0		1	(0.2)
Polyneuropathy	0		6	(1.1)	0		6	(1.0)
Post procedural complication	0		1	(0.2)	0		1	(0.2)
Productive cough	0		1	(0.2)	0		1	(0.2)
Proteinuria	0		1	(0.2)	0		1	(0.2)
Pyrexia	0		8	(1.5)	0		8	(1.3)
Respiratory tract infection	0		1	(0.2)	0		1	(0.2)
Stoma site inflammation	0		1	(0.2)	0		1	(0.2)
Thrombocytopenia	0		2	(0.4)	0		2	(0.3)
Tooth abscess	0		1	(0.2)	0		1	(0.2)
Toothache	0		1	(0.2)	0		1	(0.2)
Urinary tract infection	0		3	(0.5)	0		3	(0.5)
Vomiting	0		1	(0.2)	0		1	(0.2)
White blood cell count decreased	0		3	(0.5)	0		3	(0.5)
SCHEDULING CONFLICT	0		9	(1.6)	0		9	(1.5)
TREATMENT AVAILABILITY	0		1	(0.2)	0		1	(0.2)
OTHER	0		26	(4.8)	0		26	(4.3)
Number of Patients with Dose Increase	0		0		0		0	

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category.
Note: Dose interruption or dose delay with missing or 0 dose are considered dose omission.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/texadjpac1.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/texadjpac1.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/adsl, adexsum

Table ANN.2.6. Summary of Deaths
Full Analysis Set
I4T-MC-JVDD

		Ram mono (N=51) n(%)	Ram + PclTax (N=547) n(%)	Ram + Other (N=8) n(%)	Overall (N=606) n(%)
All Deaths	Total	40 (78.4)	350 (64.0)	7 (87.5)	397 (65.5)
Deaths on Ram or within 30 days of last Ram dose	Total	15 (29.4)	75 (13.7)	2 (25.0)	92 (15.2)
Reason for death*	Adverse Events	4 (7.8)	19 (3.5)	0	23 (3.8)
	Anaemia	1 (2.0)	0	0	1 (0.2)
	Candida Pneumonia	0	1 (0.2)	0	1 (0.2)
	Cardiac Failure	0	1 (0.2)	0	1 (0.2)
	Coma	0	1 (0.2)	0	1 (0.2)
	Device Related Sepsis	0	1 (0.2)	0	1 (0.2)
	Gastric Perforation	0	2 (0.4)	0	2 (0.3)
	Gastrointestinal Haemorrhage	0	2 (0.4)	0	2 (0.3)
	Hepatic Failure	1 (2.0)	0	0	1 (0.2)
	Hypotension	0	1 (0.2)	0	1 (0.2)
	Intestinal Perforation	0	1 (0.2)	0	1 (0.2)
	Jaundice Cholestatic	1 (2.0)	0	0	1 (0.2)
	Malignant Neoplasm Progression	0	1 (0.2)	0	1 (0.2)
	Myocardial Infarction	0	1 (0.2)	0	1 (0.2)
	Peritonitis	0	1 (0.2)	0	1 (0.2)
	Pneumocystis Jirovecii Pneumonia	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tdeath.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Summary of Deaths
Full analysis set
I4T-MC-JVDD

		Ram mono (N=51) n(%)	Ram + PclTax (N=547) n(%)	Ram + Other (N=8) n(%)	Overall (N=606) n(%)
Reason for death*	Pneumonia	0	1 (0.2)	0	1 (0.2)
	Pneumonia Aspiration	0	1 (0.2)	0	1 (0.2)
	Renal Failure	0	1 (0.2)	0	1 (0.2)
	Sepsis	0	1 (0.2)	0	1 (0.2)
	Septic Shock	0	1 (0.2)	0	1 (0.2)
	Small Intestinal Perforation	1 (2.0)	0	0	1 (0.2)
	Adverse Events Related To Study Treatment	1 (2.0)	6 (1.1)	0	7 (1.2)
	Gastric Perforation	0	2 (0.4)	0	2 (0.3)
	Gastrointestinal Haemorrhage	0	1 (0.2)	0	1 (0.2)
	Intestinal Perforation	0	1 (0.2)	0	1 (0.2)
	Myocardial Infarction	0	1 (0.2)	0	1 (0.2)
	Pneumocystis Jirovecii Pneumonia	0	1 (0.2)	0	1 (0.2)
	Small Intestinal Perforation	1 (2.0)	0	0	1 (0.2)
	Study Disease	11 (21.6)	56 (10.2)	2 (25.0)	69 (11.4)
Deaths on Ram or within 90 days of last Ram dose	Total	32 (62.7)	223 (40.8)	4 (50.0)	259 (42.7)
Reason for death*	Adverse Events	5 (9.8)	28 (5.1)	0	33 (5.4)
	Anaemia	1 (2.0)	0	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tdeath.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Summary of Deaths
Full analysis set
I4T-MC-JVDD

		Ram mono (N=51) n(%)	Ram + PclTax (N=547) n(%)	Ram + Other (N=8) n(%)	Overall (N=606) n(%)
Reason for death*	Cachexia	0	1 (0.2)	0	1 (0.2)
	Candida Pneumonia	0	1 (0.2)	0	1 (0.2)
	Cardiac Failure	0	1 (0.2)	0	1 (0.2)
	Coma	0	1 (0.2)	0	1 (0.2)
	Device Related Sepsis	0	1 (0.2)	0	1 (0.2)
	Gastric Perforation	0	2 (0.4)	0	2 (0.3)
	Gastrointestinal Haemorrhage	0	3 (0.5)	0	3 (0.5)
	General Physical Health Deterioration	0	2 (0.4)	0	2 (0.3)
	Hepatic Failure	1 (2.0)	0	0	1 (0.2)
	Hypotension	0	1 (0.2)	0	1 (0.2)
	Intestinal Perforation	0	1 (0.2)	0	1 (0.2)
	Jaundice Cholestatic	1 (2.0)	0	0	1 (0.2)
	Malignant Neoplasm Progression	0	4 (0.7)	0	4 (0.7)
	Mechanical Ileus	0	1 (0.2)	0	1 (0.2)
	Multiple Organ Dysfunction Syndrome	1 (2.0)	0	0	1 (0.2)
	Myocardial Infarction	0	1 (0.2)	0	1 (0.2)
	Oesophageal Perforation	0	1 (0.2)	0	1 (0.2)
	Peritonitis	0	1 (0.2)	0	1 (0.2)
	Pneumocystis Jirovecii Pneumonia	0	1 (0.2)	0	1 (0.2)
	Pneumonia	0	1 (0.2)	0	1 (0.2)
	Pneumonia Aspiration	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tdeath.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Summary of Deaths
Full analysis set
I4T-MC-JVDD

		Ram mono (N=51) n(%)	Ram + PclTax (N=547) n(%)	Ram + Other (N=8) n(%)	Overall (N=606) n(%)
Reason for death*	Renal Failure	0	1 (0.2)	0	1 (0.2)
	Sepsis	0	1 (0.2)	0	1 (0.2)
	Septic Shock	0	1 (0.2)	0	1 (0.2)
	Small Intestinal Perforation	1 (2.0)	0	0	1 (0.2)
	Adverse Events Related To Study Treatment	1 (2.0)	7 (1.3)	0	8 (1.3)
	Gastric Perforation	0	2 (0.4)	0	2 (0.3)
	Gastrointestinal Haemorrhage	0	1 (0.2)	0	1 (0.2)
	Intestinal Perforation	0	1 (0.2)	0	1 (0.2)
	Myocardial Infarction	0	1 (0.2)	0	1 (0.2)
	Oesophageal Perforation	0	1 (0.2)	0	1 (0.2)
	Pneumocystis Jirovecii Pneumonia	0	1 (0.2)	0	1 (0.2)
	Small Intestinal Perforation	1 (2.0)	0	0	1 (0.2)
	Death	0	1 (0.2)	0	1 (0.2)
	Study Disease	27 (52.9)	194 (35.5)	4 (50.0)	225 (37.1)
Deaths between 30 and 90 days of last Ram dose	Total	17 (33.3)	148 (27.1)	2 (25.0)	167 (27.6)
Reason for death*	Adverse Events	1 (2.0)	9 (1.6)	0	10 (1.7)
	Cachexia	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tdeath.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Summary of Deaths
Full analysis set
I4T-MC-JVDD

		Ram mono (N=51) n(%)	Ram + PclTax (N=547) n(%)	Ram + Other (N=8) n(%)	Overall (N=606) n(%)
Reason for death*	Gastrointestinal Haemorrhage	0	1 (0.2)	0	1 (0.2)
	General Physical Health Deterioration	0	2 (0.4)	0	2 (0.3)
	Malignant Neoplasm Progression	0	3 (0.5)	0	3 (0.5)
	Mechanical Ileus	0	1 (0.2)	0	1 (0.2)
	Multiple Organ Dysfunction Syndrome	1 (2.0)	0	0	1 (0.2)
	Oesophageal Perforation	0	1 (0.2)	0	1 (0.2)
	Adverse Events Related To Study Treatment	0	1 (0.2)	0	1 (0.2)
	Oesophageal Perforation	0	1 (0.2)	0	1 (0.2)
	Death	0	1 (0.2)	0	1 (0.2)
	Study Disease	16 (31.4)	138 (25.2)	2 (25.0)	156 (25.7)
Deaths after 90 days of last Ram dose	Total	8 (15.7)	127 (23.2)	3 (37.5)	138 (22.8)
Reason for death*	Adverse Events	0	2 (0.4)	0	2 (0.3)
	Acute Kidney Injury	0	1 (0.2)	0	1 (0.2)
	Death	0	1 (0.2)	0	1 (0.2)
	Death	0	2 (0.4)	0	2 (0.3)
	Study Disease	8 (15.7)	123 (22.5)	3 (37.5)	134 (22.1)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tdeath.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tdeath.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Table ANN.2.7. Serious Adverse Events on or within 90 days of Ramucirumab Preferred Term by Decreasing Frequency within System Organ Class Full Analysis Set I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Subjects with >=1 SAE on or within 90 days of Ram	24 (47.1)	220 (40.2)	6 (75.0)	250 (41.3)
Gastrointestinal disorders	11 (21.6)	96 (17.6)	2 (25.0)	109 (18.0)
Abdominal pain	1 (2.0)	14 (2.6)	0	15 (2.5)
Intestinal obstruction	0	15 (2.7)	0	15 (2.5)
Ascites	1 (2.0)	9 (1.6)	0	10 (1.7)
Vomiting	1 (2.0)	9 (1.6)	0	10 (1.7)
Dysphagia	1 (2.0)	5 (0.9)	1 (12.5)	7 (1.2)
Gastrointestinal haemorrhage	0	6 (1.1)	1 (12.5)	7 (1.2)
Haematemesis	2 (3.9)	5 (0.9)	0	7 (1.2)
Ileus	1 (2.0)	6 (1.1)	0	7 (1.2)
Nausea	0	7 (1.3)	0	7 (1.2)
Abdominal pain upper	2 (3.9)	3 (0.5)	0	5 (0.8)
Constipation	0	4 (0.7)	0	4 (0.7)
Diarrhoea	0	3 (0.5)	0	3 (0.5)
Gastric haemorrhage	0	3 (0.5)	0	3 (0.5)
Gastric perforation	0	3 (0.5)	0	3 (0.5)
Intestinal perforation	0	2 (0.4)	0	2 (0.3)
Obstruction gastric	1 (2.0)	1 (0.2)	0	2 (0.3)
Subileus	0	2 (0.4)	0	2 (0.3)
Abdominal distension	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

c

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Abdominal hernia	0	1 (0.2)	0	1 (0.2)
Anal fistula	0	1 (0.2)	0	1 (0.2)
Biliary ascites	0	1 (0.2)	0	1 (0.2)
Colitis	0	1 (0.2)	0	1 (0.2)
Colitis ischaemic	0	0	1 (12.5)	1 (0.2)
Enteritis	1 (2.0)	0	0	1 (0.2)
Faecaloma	0	1 (0.2)	0	1 (0.2)
Gastric ulcer perforation	0	1 (0.2)	0	1 (0.2)
Gastrooesophageal reflux disease	0	1 (0.2)	0	1 (0.2)
Haemorrhoidal haemorrhage	0	1 (0.2)	0	1 (0.2)
Ileus paralytic	0	1 (0.2)	0	1 (0.2)
Inguinal hernia	0	1 (0.2)	0	1 (0.2)
Mechanical ileus	0	1 (0.2)	0	1 (0.2)
Melaena	0	1 (0.2)	0	1 (0.2)
Oesophageal haemorrhage	0	1 (0.2)	0	1 (0.2)
Oesophageal perforation	0	1 (0.2)	0	1 (0.2)
Pneumoperitoneum	0	1 (0.2)	0	1 (0.2)
Small intestinal obstruction	0	1 (0.2)	0	1 (0.2)
Small intestinal perforation	1 (2.0)	0	0	1 (0.2)
Stomatitis	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

c

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Upper gastrointestinal haemorrhage	0	1 (0.2)	0	1 (0.2)
Infections and infestations	6 (11.8)	45 (8.2)	3 (37.5)	54 (8.9)
Pneumonia	1 (2.0)	12 (2.2)	0	13 (2.1)
Urinary tract infection	1 (2.0)	6 (1.1)	0	7 (1.2)
Device related infection	2 (3.9)	4 (0.7)	0	6 (1.0)
Sepsis	0	4 (0.7)	1 (12.5)	5 (0.8)
Infection	0	3 (0.5)	0	3 (0.5)
Bronchitis	1 (2.0)	1 (0.2)	0	2 (0.3)
Peritonitis bacterial	1 (2.0)	1 (0.2)	0	2 (0.3)
Abdominal abscess	0	1 (0.2)	0	1 (0.2)
Anorectal infection	0	1 (0.2)	0	1 (0.2)
Biliary sepsis	0	1 (0.2)	0	1 (0.2)
Candida pneumonia	0	1 (0.2)	0	1 (0.2)
Cellulitis	0	1 (0.2)	0	1 (0.2)
Clostridial infection	1 (2.0)	0	0	1 (0.2)
Device related sepsis	0	1 (0.2)	0	1 (0.2)
Endocarditis	0	0	1 (12.5)	1 (0.2)
Gastroenteritis	0	0	1 (12.5)	1 (0.2)
Meningitis	0	1 (0.2)	0	1 (0.2)
Paronychia	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

c

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Peritonitis	0	1 (0.2)	0	1 (0.2)
Pneumocystis jirovecii pneumonia	0	1 (0.2)	0	1 (0.2)
Septic shock	0	1 (0.2)	0	1 (0.2)
Splenic abscess	0	1 (0.2)	0	1 (0.2)
Staphylococcal infection	0	0	1 (12.5)	1 (0.2)
Stoma site abscess	0	1 (0.2)	0	1 (0.2)
Urinary tract infection bacterial	0	1 (0.2)	0	1 (0.2)
Vascular device infection	0	1 (0.2)	0	1 (0.2)
Viral infection	0	1 (0.2)	0	1 (0.2)
Viral upper respiratory tract infection	0	1 (0.2)	0	1 (0.2)
Wound abscess	0	1 (0.2)	0	1 (0.2)
General disorders and administration site conditions	5 (9.8)	37 (6.8)	0	42 (6.9)
General physical health deterioration	1 (2.0)	16 (2.9)	0	17 (2.8)
Pyrexia	1 (2.0)	8 (1.5)	0	9 (1.5)
Chest pain	0	3 (0.5)	0	3 (0.5)
Asthenia	0	2 (0.4)	0	2 (0.3)
Condition aggravated	0	2 (0.4)	0	2 (0.3)
Fatigue	0	2 (0.4)	0	2 (0.3)
Multiple organ dysfunction syndrome	1 (2.0)	1 (0.2)	0	2 (0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Disease progression	1 (2.0)	0	0	1 (0.2)
Implant site dehiscence	0	1 (0.2)	0	1 (0.2)
Mucosal haemorrhage	0	1 (0.2)	0	1 (0.2)
Mucosal inflammation	0	1 (0.2)	0	1 (0.2)
Oedema peripheral	0	1 (0.2)	0	1 (0.2)
Pain	0	1 (0.2)	0	1 (0.2)
Systemic inflammatory response syndrome	1 (2.0)	0	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (9.8)	35 (6.4)	1 (12.5)	41 (6.8)
Malignant neoplasm progression	4 (7.8)	27 (4.9)	1 (12.5)	32 (5.3)
Malignant pleural effusion	0	3 (0.5)	0	3 (0.5)
Metastases to meninges	0	2 (0.4)	0	2 (0.3)
Metastases to central nervous system	0	1 (0.2)	0	1 (0.2)
Metastases to liver	1 (2.0)	0	0	1 (0.2)
Metastases to peritoneum	0	1 (0.2)	0	1 (0.2)
Tumour haemorrhage	0	1 (0.2)	0	1 (0.2)
Tumour pain	0	1 (0.2)	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	1 (2.0)	29 (5.3)	1 (12.5)	31 (5.1)
Dyspnoea	0	7 (1.3)	0	7 (1.2)
Pulmonary embolism	0	7 (1.3)	0	7 (1.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Pleural effusion	1 (2.0)	4 (0.7)	1 (12.5)	6 (1.0)
Respiratory failure	0	5 (0.9)	0	5 (0.8)
Chronic obstructive pulmonary disease	0	2 (0.4)	0	2 (0.3)
Pneumonia aspiration	0	2 (0.4)	0	2 (0.3)
Epistaxis	0	1 (0.2)	0	1 (0.2)
Pneumonitis	0	1 (0.2)	0	1 (0.2)
Pneumothorax	0	1 (0.2)	0	1 (0.2)
Pulmonary oedema	0	1 (0.2)	0	1 (0.2)
Blood and lymphatic system disorders	1 (2.0)	20 (3.7)	0	21 (3.5)
Anaemia	1 (2.0)	7 (1.3)	0	8 (1.3)
Febrile neutropenia	0	8 (1.5)	0	8 (1.3)
Neutropenia	0	4 (0.7)	0	4 (0.7)
Leukopenia	0	1 (0.2)	0	1 (0.2)
Metabolism and nutrition disorders	3 (5.9)	9 (1.6)	0	12 (2.0)
Dehydration	1 (2.0)	4 (0.7)	0	5 (0.8)
Cachexia	1 (2.0)	1 (0.2)	0	2 (0.3)
Alkalosis	0	1 (0.2)	0	1 (0.2)
Hypocalcaemia	0	1 (0.2)	0	1 (0.2)
Hypoglycaemia	0	1 (0.2)	0	1 (0.2)
Hypokalaemia	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
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MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Malnutrition	1 (2.0)	0	0	1 (0.2)
Hepatobiliary disorders	3 (5.9)	8 (1.5)	0	11 (1.8)
Jaundice	0	3 (0.5)	0	3 (0.5)
Cholangitis	1 (2.0)	1 (0.2)	0	2 (0.3)
Biliary obstruction	0	1 (0.2)	0	1 (0.2)
Cholecystitis	0	1 (0.2)	0	1 (0.2)
Cholecystitis acute	0	1 (0.2)	0	1 (0.2)
Cholestasis	0	1 (0.2)	0	1 (0.2)
Hepatic failure	1 (2.0)	0	0	1 (0.2)
Jaundice cholestatic	1 (2.0)	0	0	1 (0.2)
Renal and urinary disorders	1 (2.0)	7 (1.3)	1 (12.5)	9 (1.5)
Hydronephrosis	1 (2.0)	3 (0.5)	0	4 (0.7)
Acute kidney injury	0	2 (0.4)	0	2 (0.3)
Renal failure	0	2 (0.4)	0	2 (0.3)
Urinary retention	0	0	1 (12.5)	1 (0.2)
Injury, poisoning and procedural complications	1 (2.0)	7 (1.3)	0	8 (1.3)
Fall	0	2 (0.4)	0	2 (0.3)
Femur fracture	1 (2.0)	1 (0.2)	0	2 (0.3)
Femoral neck fracture	0	1 (0.2)	0	1 (0.2)
Post procedural complication	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Procedural complication	0	1 (0.2)	0	1 (0.2)
Procedural pain	0	1 (0.2)	0	1 (0.2)
Cardiac disorders	0	6 (1.1)	1 (12.5)	7 (1.2)
Pericardial effusion	0	2 (0.4)	0	2 (0.3)
Acute myocardial infarction	0	0	1 (12.5)	1 (0.2)
Atrial fibrillation	0	1 (0.2)	0	1 (0.2)
Cardiac failure	0	1 (0.2)	0	1 (0.2)
Cardiopulmonary failure	0	1 (0.2)	0	1 (0.2)
Myocardial infarction	0	1 (0.2)	0	1 (0.2)
Vascular disorders	0	6 (1.1)	1 (12.5)	7 (1.2)
Hypotension	0	1 (0.2)	1 (12.5)	2 (0.3)
Aortic aneurysm	0	1 (0.2)	0	1 (0.2)
Hypertension	0	1 (0.2)	0	1 (0.2)
Hypertensive crisis	0	1 (0.2)	0	1 (0.2)
Shock haemorrhagic	0	1 (0.2)	0	1 (0.2)
Thrombosis	0	1 (0.2)	0	1 (0.2)
Nervous system disorders	0	6 (1.1)	0	6 (1.0)
Cerebral ischaemia	0	2 (0.4)	0	2 (0.3)
Cerebrovascular accident	0	1 (0.2)	0	1 (0.2)
Coma	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Serious Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Epilepsy	0	1 (0.2)	0	1 (0.2)
Posterior reversible encephalopathy syndrome	0	1 (0.2)	0	1 (0.2)
Product issues	0	6 (1.1)	0	6 (1.0)
Device dislocation	0	4 (0.7)	0	4 (0.7)
Device malfunction	0	2 (0.4)	0	2 (0.3)
Investigations	0	4 (0.7)	0	4 (0.7)
Neutrophil count decreased	0	2 (0.4)	0	2 (0.3)
Blood bilirubin increased	0	1 (0.2)	0	1 (0.2)
Intestinal transit time decreased	0	1 (0.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (2.0)	3 (0.5)	0	4 (0.7)
Back pain	1 (2.0)	2 (0.4)	0	3 (0.5)
Musculoskeletal chest pain	0	1 (0.2)	0	1 (0.2)
Psychiatric disorders	0	2 (0.4)	0	2 (0.3)
Anxiety	0	1 (0.2)	0	1 (0.2)
Confusional state	0	1 (0.2)	0	1 (0.2)
Congenital, familial and genetic disorders	0	1 (0.2)	0	1 (0.2)
Pyloric stenosis	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*SAE from initiation of Ram until up to 90 days after last dose of Ram.

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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Table ANN.2.8. Summary of AEs Leading to Ramucirumab Discontinuation by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

MedDRA Preferred Term	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total[b] (N=606)
Patients who discontinued ramucirumab due to AE[a]	**7 (13.7)**	**68 (12.4)**	**0**	**75 (12.4)**
General physical health deterioration	4 (7.8)	14 (2.6)	0	18 (3.0)
Asthenia	0	2 (0.4)	0	2 (0.3)
Cerebral Ischaemia	0	2 (0.4)	0	2 (0.3)
Decreased appetite	1 (0.2)	1 (0.2)	0	2 (0.3)
Epistaxis	0	1 (0.2)	0	2 (0.3)
Haematemesis	0	2 (0.4)	0	2 (0.3)
Ileus	0	2 (0.4)	0	2 (0.3)
Intestinal Obstruction	0	2 (0.4)	0	2 (0.3)
Malignant Neoplasm Progression	0	2 (0.4)	0	2 (0.3)
Peripheral Sensory Neuropathy	0	2 (0.4)	0	2 (0.3)
Proteinuria	0	2 (0.4)	0	2 (0.3)
Abdominal Abscess	0	1 (0.2)	0	1 (0.2)
Abdominal Hernia	0	1 (0.2)	0	1 (0.2)
Abdominal Pain Upper	0	1 (0.2)	0	1 (0.2)
Anaemia	0	1 (0.2)	0	1 (0.2)
Atrial fibrillation	0	1 (0.2)	0	1 (0.2)
Blood Bilirubin Increased	0	1 (0.2)	0	1 (0.2)
Bronchitis	0	1 (0.2)	0	1 (0.2)
Cachexia	0	1 (0.2)	0	1 (0.2)
Dehydration	0	1 (0.2)	0	1 (0.2)
Disease progression	1 (0.2)	0	0	1 (0.2)
Drug Hypersensitivity	0	1 (0.2)	0	1 (0.2)
Fatigue	0	1 (0.2)	0	1 (0.2)
Febrile neutropenia	0	1 (0.2)	0	1 (0.2)
Fistula	0	1 (0.2)	0	1 (0.2)
Gastric haemorrhage	0	1 (0.2)	0	1 (0.2)
Gastric perforation	0	1 (0.2)	0	1 (0.2)
Gastric ulcer perforation	0	1 (0.2)	0	1 (0.2)
Haematuria	0	1 (0.2)	0	1 (0.2)
Haemorrhage	0	1 (0.2)	0	1 (0.2)
Hypertension	0	1 (0.2)	0	1 (0.2)
Impaired healing	0	1 (0.2)	0	1 (0.2)
Implant Site Dehiscence	0	1 (0.2)	0	1 (0.2)
Infusion Related Reaction	0	1 (0.2)	0	1 (0.2)
Jaundice cholestatic	1 (0.2)	0	0	1 (0.2)
Leukopenia	0	1 (0.2)	0	1 (0.2)
Metastases To Central Nervous System	0	1 (0.2)	0	1 (0.2)
Nausea	0	1 (0.2)	0	1 (0.2)
Oesophageal Perforation	0	1 (0.2)	0	1 (0.2)
Pericardial Effusion	0	1 (0.2)	0	1 (0.2)

MedDRA Preferred Term	Ram Mono (N=51)	Ram + PTX (N=547)	Ram + Other (N=8)	Total[b] (N=606)
Platelet Count Decreased	0	1 (0.2)	0	1 (0.2)
Pneumonia Aspiration	0	1 (0.2)	0	1 (0.2)
Pneumothorax	0	1 (0.2)	0	1 (0.2)
Pulmonary Embolism	0	1 (0.2)	0	1 (0.2)
Thrombocytopenia	0	1 (0.2)	0	1 (0.2)
Tumour Haemorrhage	0	1 (0.2)	0	1 (0.2)
Venous Thrombosis	0	1 (0.2)	0	1 (0.2)
Weight Decreased	0	1 (0.2)	0	1 (0.2)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in Full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Patients may be counted in more than 1 category.

[b] Includes patients in the ramucirumab plus other cohort.

Final database lock date: 19 August 2021.

Sources: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_ser_ram.rtf.

Table ANN.2.9. Adverse Events Leading to Paclitaxel Discontinuation
Full Analysis Set
I4T-MC-JVDD

Serious Event Preferred Term*	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Total Number of Subjects who Discontinued Paclitaxel due to AE	0		122	(22.3)	0		122	(20.1)
Non-Serious Adverse Events	0		93	(17.0)	0		93	(15.3)
General physical health deterioration	0		12	(2.2)	0		12	(2.0)
Neuropathy peripheral	0		10	(1.8)	0		10	(1.7)
Polyneuropathy	0		9	(1.6)	0		9	(1.5)
Neurotoxicity	0		7	(1.3)	0		7	(1.2)
Paraesthesia	0		6	(1.1)	0		6	(1.0)
Peripheral sensory neuropathy	0		6	(1.1)	0		6	(1.0)
Thrombocytopenia	0		4	(0.7)	0		4	(0.7)
Neutropenia	0		3	(0.5)	0		3	(0.5)
Asthenia	0		2	(0.4)	0		2	(0.3)
Fatigue	0		2	(0.4)	0		2	(0.3)
Infusion related reaction	0		2	(0.4)	0		2	(0.3)
Platelet count decreased	0		2	(0.4)	0		2	(0.3)
Abdominal abscess	0		1	(0.2)	0		1	(0.2)
Abdominal pain	0		1	(0.2)	0		1	(0.2)
Abdominal pain upper	0		1	(0.2)	0		1	(0.2)
Ageusia	0		1	(0.2)	0		1	(0.2)
Anaemia	0		1	(0.2)	0		1	(0.2)
Atrial fibrillation	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_ser_pac.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_ser_pac.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events Leading to Paclitaxel Discontinuation page 2 of 4
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Serious Event Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Bronchitis	0	1 (0.2)	0	1 (0.2)
Cachexia	0	1 (0.2)	0	1 (0.2)
Confusional state	0	1 (0.2)	0	1 (0.2)
Cough	0	1 (0.2)	0	1 (0.2)
Decreased appetite	0	1 (0.2)	0	1 (0.2)
Diarrhoea	0	1 (0.2)	0	1 (0.2)
Drug hypersensitivity	0	1 (0.2)	0	1 (0.2)
Dyspnoea	0	1 (0.2)	0	1 (0.2)
Haemorrhage	0	1 (0.2)	0	1 (0.2)
Hypersensitivity	0	1 (0.2)	0	1 (0.2)
Hypertransaminasaemia	0	1 (0.2)	0	1 (0.2)
Leukopenia	0	1 (0.2)	0	1 (0.2)
Malignant neoplasm progression	0	1 (0.2)	0	1 (0.2)
Mucosal inflammation	0	1 (0.2)	0	1 (0.2)
Nausea	0	1 (0.2)	0	1 (0.2)
Pain in extremity	0	1 (0.2)	0	1 (0.2)
Palmar-plantar erythrodysaesthesia syndrome	0	1 (0.2)	0	1 (0.2)
Pleural effusion	0	1 (0.2)	0	1 (0.2)
Proteinuria	0	1 (0.2)	0	1 (0.2)
Pulmonary embolism	0	1 (0.2)	0	1 (0.2)
Venous thrombosis	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_ser_pac.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_ser_pac.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events Leading to Paclitaxel Discontinuation page 3 of 4
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Serious Event Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Weight decreased	0	1 (0.2)	0	1 (0.2)
Serious Adverse Events	0	29 (5.3)	0	29 (4.8)
Febrile neutropenia	0	2 (0.4)	0	2 (0.3)
Haematemesis	0	2 (0.4)	0	2 (0.3)
Ileus	0	2 (0.4)	0	2 (0.3)
Abdominal hernia	0	1 (0.2)	0	1 (0.2)
Anaemia	0	1 (0.2)	0	1 (0.2)
Asthenia	0	1 (0.2)	0	1 (0.2)
Blood bilirubin increased	0	1 (0.2)	0	1 (0.2)
Cerebral ischaemia	0	1 (0.2)	0	1 (0.2)
Cholestasis	0	1 (0.2)	0	1 (0.2)
Dehydration	0	1 (0.2)	0	1 (0.2)
Gastric haemorrhage	0	1 (0.2)	0	1 (0.2)
Gastric perforation	0	1 (0.2)	0	1 (0.2)
Gastric ulcer perforation	0	1 (0.2)	0	1 (0.2)
General physical health deterioration	0	1 (0.2)	0	1 (0.2)
Hypertension	0	1 (0.2)	0	1 (0.2)
Implant site dehiscence	0	1 (0.2)	0	1 (0.2)
Intestinal obstruction	0	1 (0.2)	0	1 (0.2)
Malignant neoplasm progression	0	1 (0.2)	0	1 (0.2)
Metastases to central nervous system	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_ser_pac.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_ser_pac.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events Leading to Paclitaxel Discontinuation page 4 of 4
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Serious Event Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Oesophageal perforation	0	1 (0.2)	0	1 (0.2)
Pericardial effusion	0	1 (0.2)	0	1 (0.2)
Pneumonia aspiration	0	1 (0.2)	0	1 (0.2)
Pneumothorax	0	1 (0.2)	0	1 (0.2)
Splenic abscess	0	1 (0.2)	0	1 (0.2)
Tumour haemorrhage	0	1 (0.2)	0	1 (0.2)
Urinary tract infection bacterial	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events;
MedDRA = Medical Dictionary for Regulatory Activities.
*Subjects may be counted in more than one category.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_ser_pac.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_ser_pac.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Table ANN.2.10. Adverse Events on or within 90 Days of Ramucirumab Preferred Term by Decreasing Frequency within System Organ Class Full Analysis Set I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Subjects with >=1 AE on Ram +90 days	49 (96.1)	535 (97.8)	8 (100.0)	592 (97.7)
General disorders and administration site conditions	28 (54.9)	370 (67.6)	1 (12.5)	399 (65.8)
Fatigue	7 (13.7)	155 (28.3)	1 (12.5)	163 (26.9)
Asthenia	9 (17.6)	102 (18.6)	0	111 (18.3)
Pyrexia	4 (7.8)	95 (17.4)	0	99 (16.3)
General physical health deterioration	9 (17.6)	55 (10.1)	0	64 (10.6)
Oedema peripheral	4 (7.8)	47 (8.6)	0	51 (8.4)
Mucosal inflammation	0	37 (6.8)	0	37 (6.1)
Oedema	1 (2.0)	10 (1.8)	0	11 (1.8)
Chest pain	0	10 (1.8)	0	10 (1.7)
Pain	1 (2.0)	9 (1.6)	0	10 (1.7)
Influenza like illness	0	6 (1.1)	0	6 (1.0)
Chills	0	5 (0.9)	0	5 (0.8)
Impaired healing	0	4 (0.7)	0	4 (0.7)
Condition aggravated	0	3 (0.5)	0	3 (0.5)
Catheter site erythema	1 (2.0)	1 (0.2)	0	2 (0.3)
Disease progression	1 (2.0)	1 (0.2)	0	2 (0.3)
Multiple organ dysfunction syndrome	1 (2.0)	1 (0.2)	0	2 (0.3)
Non-cardiac chest pain	0	2 (0.4)	0	2 (0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Peripheral swelling	0	2 (0.4)	0	2 (0.3)
Catheter site pain	0	1 (0.2)	0	1 (0.2)
Chest discomfort	0	1 (0.2)	0	1 (0.2)
Gait disturbance	0	1 (0.2)	0	1 (0.2)
Generalised oedema	0	1 (0.2)	0	1 (0.2)
Gravitational oedema	0	1 (0.2)	0	1 (0.2)
Hyperpyrexia	1 (2.0)	0	0	1 (0.2)
Hypothermia	0	1 (0.2)	0	1 (0.2)
Implant site dehiscence	0	1 (0.2)	0	1 (0.2)
Implant site inflammation	0	1 (0.2)	0	1 (0.2)
Infusion site extravasation	0	1 (0.2)	0	1 (0.2)
Infusion site inflammation	0	1 (0.2)	0	1 (0.2)
Injection site pain	1 (2.0)	0	0	1 (0.2)
Localised oedema	0	1 (0.2)	0	1 (0.2)
Malaise	0	1 (0.2)	0	1 (0.2)
Medical device site inflammation	0	1 (0.2)	0	1 (0.2)
Mucosal haemorrhage	0	1 (0.2)	0	1 (0.2)
Nodule	0	1 (0.2)	0	1 (0.2)
Swelling face	0	1 (0.2)	0	1 (0.2)
Systemic inflammatory response syndrome	1 (2.0)	0	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Temperature regulation disorder	0	1 (0.2)	0	1 (0.2)
Gastrointestinal disorders	26 (51.0)	360 (65.8)	5 (62.5)	391 (64.5)
Nausea	11 (21.6)	116 (21.2)	2 (25.0)	129 (21.3)
Diarrhoea	3 (5.9)	121 (22.1)	1 (12.5)	125 (20.6)
Abdominal pain	6 (11.8)	83 (15.2)	0	89 (14.7)
Vomiting	7 (13.7)	69 (12.6)	0	76 (12.5)
Constipation	6 (11.8)	57 (10.4)	3 (37.5)	66 (10.9)
Dysphagia	1 (2.0)	34 (6.2)	2 (25.0)	37 (6.1)
Abdominal pain upper	4 (7.8)	30 (5.5)	1 (12.5)	35 (5.8)
Ascites	5 (9.8)	29 (5.3)	0	34 (5.6)
Stomatitis	2 (3.9)	30 (5.5)	1 (12.5)	33 (5.4)
Intestinal obstruction	0	20 (3.7)	0	20 (3.3)
Dyspepsia	0	16 (2.9)	0	16 (2.6)
Gastrooesophageal reflux disease	1 (2.0)	13 (2.4)	0	14 (2.3)
Gastrointestinal haemorrhage	1 (2.0)	8 (1.5)	1 (12.5)	10 (1.7)
Haematemesis	2 (3.9)	8 (1.5)	0	10 (1.7)
Haemorrhoids	0	8 (1.5)	0	8 (1.3)
Ileus	1 (2.0)	6 (1.1)	0	7 (1.2)
Flatulence	0	6 (1.1)	0	6 (1.0)
Gingival bleeding	0	6 (1.1)	0	6 (1.0)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Toothache	0	5 (0.9)	0	5 (0.8)
Abdominal distension	1 (2.0)	3 (0.5)	0	4 (0.7)
Gastric haemorrhage	0	4 (0.7)	0	4 (0.7)
Abdominal pain lower	1 (2.0)	2 (0.4)	0	3 (0.5)
Colitis	0	3 (0.5)	0	3 (0.5)
Gastric perforation	0	3 (0.5)	0	3 (0.5)
Haemorrhoidal haemorrhage	0	3 (0.5)	0	3 (0.5)
Oesophageal stenosis	0	3 (0.5)	0	3 (0.5)
Subileus	0	3 (0.5)	0	3 (0.5)
Dry mouth	0	2 (0.4)	0	2 (0.3)
Enteritis	1 (2.0)	1 (0.2)	0	2 (0.3)
Gastritis	0	2 (0.4)	0	2 (0.3)
Gingival pain	0	2 (0.4)	0	2 (0.3)
Impaired gastric emptying	0	2 (0.4)	0	2 (0.3)
Intestinal perforation	0	2 (0.4)	0	2 (0.3)
Melaena	0	2 (0.4)	0	2 (0.3)
Obstruction gastric	1 (2.0)	1 (0.2)	0	2 (0.3)
Odynophagia	0	2 (0.4)	0	2 (0.3)
Periodontal disease	0	2 (0.4)	0	2 (0.3)
Abdominal discomfort	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Abdominal hernia	0	1 (0.2)	0	1 (0.2)
Anal fistula	0	1 (0.2)	0	1 (0.2)
Anal haemorrhage	0	1 (0.2)	0	1 (0.2)
Anorectal disorder	0	1 (0.2)	0	1 (0.2)
Biliary ascites	0	1 (0.2)	0	1 (0.2)
Bowel movement irregularity	0	1 (0.2)	0	1 (0.2)
Cheilitis	0	1 (0.2)	0	1 (0.2)
Colitis ischaemic	0	0	1 (12.5)	1 (0.2)
Colitis ulcerative	0	1 (0.2)	0	1 (0.2)
Diarrhoea haemorrhagic	0	1 (0.2)	0	1 (0.2)
Dumping syndrome	0	1 (0.2)	0	1 (0.2)
Epigastric discomfort	0	1 (0.2)	0	1 (0.2)
Faecaloma	0	1 (0.2)	0	1 (0.2)
Gastric ulcer perforation	0	1 (0.2)	0	1 (0.2)
Gastrointestinal disorder	0	1 (0.2)	0	1 (0.2)
Gastrointestinal fistula	0	1 (0.2)	0	1 (0.2)
Gastrointestinal mucosal disorder	0	1 (0.2)	0	1 (0.2)
Gastrointestinal pain	0	1 (0.2)	0	1 (0.2)
Haematochezia	0	1 (0.2)	0	1 (0.2)
Ileus paralytic	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Inguinal hernia	0	1 (0.2)	0	1 (0.2)
Lip haemorrhage	0	0	1 (12.5)	1 (0.2)
Loose tooth	0	1 (0.2)	0	1 (0.2)
Mechanical ileus	0	1 (0.2)	0	1 (0.2)
Noninfective gingivitis	0	1 (0.2)	0	1 (0.2)
Oesophageal haemorrhage	0	1 (0.2)	0	1 (0.2)
Oesophageal perforation	0	1 (0.2)	0	1 (0.2)
Oesophagitis	0	1 (0.2)	0	1 (0.2)
Oral disorder	0	1 (0.2)	0	1 (0.2)
Pneumoperitoneum	0	1 (0.2)	0	1 (0.2)
Rectal haemorrhage	0	1 (0.2)	0	1 (0.2)
Salivary hypersecretion	0	1 (0.2)	0	1 (0.2)
Small intestinal obstruction	0	1 (0.2)	0	1 (0.2)
Small intestinal perforation	1 (2.0)	0	0	1 (0.2)
Tooth disorder	0	1 (0.2)	0	1 (0.2)
Umbilical hernia	0	1 (0.2)	0	1 (0.2)
Upper gastrointestinal haemorrhage	0	1 (0.2)	0	1 (0.2)
Blood and lymphatic system disorders	8 (15.7)	229 (41.9)	2 (25.0)	239 (39.4)
Neutropenia	0	129 (23.6)	0	129 (21.3)
Anaemia	6 (11.8)	105 (19.2)	2 (25.0)	113 (18.6)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Leukopenia	1 (2.0)	27 (4.9)	0	28 (4.6)
Thrombocytopenia	1 (2.0)	21 (3.8)	0	22 (3.6)
Febrile neutropenia	0	9 (1.6)	0	9 (1.5)
Leukocytosis	1 (2.0)	4 (0.7)	0	5 (0.8)
Iron deficiency anaemia	0	2 (0.4)	0	2 (0.3)
Agranulocytosis	0	1 (0.2)	0	1 (0.2)
Cytopenia	0	1 (0.2)	0	1 (0.2)
Lymphadenopathy	0	1 (0.2)	0	1 (0.2)
Lymphatic obstruction	0	1 (0.2)	0	1 (0.2)
Nervous system disorders	7 (13.7)	207 (37.8)	3 (37.5)	217 (35.8)
Paraesthesia	1 (2.0)	72 (13.2)	0	73 (12.0)
Neuropathy peripheral	1 (2.0)	39 (7.1)	1 (12.5)	41 (6.8)
Polyneuropathy	2 (3.9)	25 (4.6)	1 (12.5)	28 (4.6)
Headache	2 (3.9)	16 (2.9)	1 (12.5)	19 (3.1)
Neurotoxicity	1 (2.0)	18 (3.3)	0	19 (3.1)
Dysgeusia	0	17 (3.1)	0	17 (2.8)
Peripheral sensory neuropathy	0	16 (2.9)	0	16 (2.6)
Dizziness	1 (2.0)	9 (1.6)	0	10 (1.7)
Syncope	0	5 (0.9)	0	5 (0.8)
Dysaesthesia	0	4 (0.7)	0	4 (0.7)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
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N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Tremor	0	3 (0.5)	0	3 (0.5)
Balance disorder	0	2 (0.4)	0	2 (0.3)
Cerebral ischaemia	0	2 (0.4)	0	2 (0.3)
Epilepsy	0	2 (0.4)	0	2 (0.3)
Peripheral motor neuropathy	0	2 (0.4)	0	2 (0.3)
Presyncope	0	2 (0.4)	0	2 (0.3)
Restless legs syndrome	0	2 (0.4)	0	2 (0.3)
Sciatica	0	2 (0.4)	0	2 (0.3)
Seizure	0	2 (0.4)	0	2 (0.3)
Ageusia	0	1 (0.2)	0	1 (0.2)
Cerebrovascular accident	0	1 (0.2)	0	1 (0.2)
Coma	0	1 (0.2)	0	1 (0.2)
Depressed level of consciousness	0	1 (0.2)	0	1 (0.2)
Essential tremor	0	1 (0.2)	0	1 (0.2)
Hepatic encephalopathy	0	1 (0.2)	0	1 (0.2)
Hypoaesthesia	0	1 (0.2)	0	1 (0.2)
Myoclonus	0	1 (0.2)	0	1 (0.2)
Posterior reversible encephalopathy syndrome	0	1 (0.2)	0	1 (0.2)
Somnolence	0	1 (0.2)	0	1 (0.2)
Taste disorder	0	1 (0.2)	0	1 (0.2)

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N=4 (Ram + Other), N=185(Overall)
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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Respiratory, thoracic and mediastinal disorders	7 (13.7)	168 (30.7)	3 (37.5)	178 (29.4)
Epistaxis	1 (2.0)	77 (14.1)	1 (12.5)	79 (13.0)
Cough	2 (3.9)	42 (7.7)	1 (12.5)	45 (7.4)
Dyspnoea	2 (3.9)	37 (6.8)	0	39 (6.4)
Pleural effusion	2 (3.9)	13 (2.4)	1 (12.5)	16 (2.6)
Pulmonary embolism	0	9 (1.6)	0	9 (1.5)
Dysphonia	0	6 (1.1)	0	6 (1.0)
Respiratory failure	0	5 (0.9)	0	5 (0.8)
Dyspnoea exertional	2 (3.9)	2 (0.4)	0	4 (0.7)
Hiccups	0	3 (0.5)	0	3 (0.5)
Nasal inflammation	0	3 (0.5)	0	3 (0.5)
Oropharyngeal pain	0	3 (0.5)	0	3 (0.5)
Pneumonitis	0	3 (0.5)	0	3 (0.5)
Rhinorrhoea	0	3 (0.5)	0	3 (0.5)
Chronic obstructive pulmonary disease	0	2 (0.4)	0	2 (0.3)
Haemoptysis	0	2 (0.4)	0	2 (0.3)
Pneumonia aspiration	0	2 (0.4)	0	2 (0.3)
Productive cough	0	2 (0.4)	0	2 (0.3)
Hypoventilation	0	1 (0.2)	0	1 (0.2)
Hypoxia	1 (2.0)	0	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Laryngeal inflammation	0	1 (0.2)	0	1 (0.2)
Pleuritic pain	0	1 (0.2)	0	1 (0.2)
Pneumothorax	0	1 (0.2)	0	1 (0.2)
Pulmonary congestion	1 (2.0)	0	0	1 (0.2)
Pulmonary oedema	0	1 (0.2)	0	1 (0.2)
Rhinitis allergic	0	1 (0.2)	0	1 (0.2)
Sputum discoloured	0	1 (0.2)	0	1 (0.2)
Investigations	10 (19.6)	160 (29.3)	0	170 (28.1)
Weight decreased	4 (7.8)	72 (13.2)	0	76 (12.5)
Neutrophil count decreased	0	31 (5.7)	0	31 (5.1)
Platelet count decreased	0	29 (5.3)	0	29 (4.8)
White blood cell count decreased	0	17 (3.1)	0	17 (2.8)
C-reactive protein increased	1 (2.0)	13 (2.4)	0	14 (2.3)
Aspartate aminotransferase increased	1 (2.0)	12 (2.2)	0	13 (2.1)
Blood bilirubin increased	1 (2.0)	9 (1.6)	0	10 (1.7)
Weight increased	1 (2.0)	9 (1.6)	0	10 (1.7)
Blood creatinine increased	1 (2.0)	8 (1.5)	0	9 (1.5)
Alanine aminotransferase increased	1 (2.0)	7 (1.3)	0	8 (1.3)
Blood alkaline phosphatase increased	0	8 (1.5)	0	8 (1.3)
Gamma-glutamyltransferase increased	0	6 (1.1)	0	6 (1.0)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Haemoglobin decreased	0	6 (1.1)	0	6 (1.0)
Lymphocyte count decreased	0	5 (0.9)	0	5 (0.8)
Transaminases increased	0	3 (0.5)	0	3 (0.5)
Blood calcium decreased	0	2 (0.4)	0	2 (0.3)
Antineutrophil cytoplasmic antibody decreased	0	1 (0.2)	0	1 (0.2)
Blood glucose increased	0	1 (0.2)	0	1 (0.2)
Blood iron decreased	0	1 (0.2)	0	1 (0.2)
Blood pressure increased	0	1 (0.2)	0	1 (0.2)
Carcinoembryonic antigen increased	0	1 (0.2)	0	1 (0.2)
Ejection fraction decreased	0	1 (0.2)	0	1 (0.2)
Enterobacter test positive	0	1 (0.2)	0	1 (0.2)
Haematocrit decreased	1 (2.0)	0	0	1 (0.2)
Intestinal transit time decreased	0	1 (0.2)	0	1 (0.2)
Intra-abdominal pressure increased	0	1 (0.2)	0	1 (0.2)
Karnofsky scale worsened	0	1 (0.2)	0	1 (0.2)
Neutrophil count increased	1 (2.0)	0	0	1 (0.2)
Infections and infestations	9 (17.6)	112 (20.5)	4 (50.0)	125 (20.6)
Pneumonia	2 (3.9)	19 (3.5)	0	21 (3.5)
Urinary tract infection	2 (3.9)	17 (3.1)	1 (12.5)	20 (3.3)
Device related infection	2 (3.9)	9 (1.6)	0	11 (1.8)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Nasopharyngitis	1 (2.0)	6 (1.1)	0	7 (1.2)
Bronchitis	1 (2.0)	5 (0.9)	0	6 (1.0)
Respiratory tract infection	1 (2.0)	5 (0.9)	0	6 (1.0)
Sepsis	0	5 (0.9)	1 (12.5)	6 (1.0)
Infection	1 (2.0)	4 (0.7)	0	5 (0.8)
Influenza	0	5 (0.9)	0	5 (0.8)
Paronychia	0	4 (0.7)	0	4 (0.7)
Viral infection	0	3 (0.5)	1 (12.5)	4 (0.7)
Cystitis	0	3 (0.5)	0	3 (0.5)
Herpes zoster	0	3 (0.5)	0	3 (0.5)
Peritonitis bacterial	1 (2.0)	2 (0.4)	0	3 (0.5)
Vascular device infection	0	3 (0.5)	0	3 (0.5)
Abdominal abscess	0	2 (0.4)	0	2 (0.3)
Anal abscess	0	2 (0.4)	0	2 (0.3)
Gastroenteritis	0	1 (0.2)	1 (12.5)	2 (0.3)
Oral candidiasis	0	1 (0.2)	1 (12.5)	2 (0.3)
Postoperative wound infection	1 (2.0)	1 (0.2)	0	2 (0.3)
Rhinitis	0	2 (0.4)	0	2 (0.3)
Sinusitis	0	2 (0.4)	0	2 (0.3)
Tooth abscess	0	2 (0.4)	0	2 (0.3)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Tooth infection	0	2 (0.4)	0	2 (0.3)
Upper respiratory tract infection	0	2 (0.4)	0	2 (0.3)
Urinary tract infection bacterial	0	2 (0.4)	0	2 (0.3)
Viral upper respiratory tract infection	0	2 (0.4)	0	2 (0.3)
Anorectal infection	0	1 (0.2)	0	1 (0.2)
Bacteraemia	0	1 (0.2)	0	1 (0.2)
Bacteroides bacteraemia	0	1 (0.2)	0	1 (0.2)
Biliary sepsis	0	1 (0.2)	0	1 (0.2)
COVID-19	0	1 (0.2)	0	1 (0.2)
Candida infection	0	1 (0.2)	0	1 (0.2)
Candida pneumonia	0	1 (0.2)	0	1 (0.2)
Cellulitis	0	1 (0.2)	0	1 (0.2)
Clostridial infection	1 (2.0)	0	0	1 (0.2)
Clostridium bacteraemia	0	1 (0.2)	0	1 (0.2)
Conjunctivitis	0	1 (0.2)	0	1 (0.2)
Device related sepsis	0	1 (0.2)	0	1 (0.2)
Dysentery	0	1 (0.2)	0	1 (0.2)
Endocarditis	0	0	1 (12.5)	1 (0.2)
Erysipelas	0	1 (0.2)	0	1 (0.2)
Escherichia bacteraemia	0	1 (0.2)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Escherichia infection	0	1 (0.2)	0	1 (0.2)
Febrile infection	0	1 (0.2)	0	1 (0.2)
Folliculitis	0	1 (0.2)	0	1 (0.2)
Fungal skin infection	0	1 (0.2)	0	1 (0.2)
Furuncle	0	1 (0.2)	0	1 (0.2)
Gastroenteritis norovirus	0	1 (0.2)	0	1 (0.2)
Gastroenteritis viral	0	1 (0.2)	0	1 (0.2)
Gastrointestinal bacterial infection	0	1 (0.2)	0	1 (0.2)
Gingivitis	0	1 (0.2)	0	1 (0.2)
Hepatitis B reactivation	0	1 (0.2)	0	1 (0.2)
Herpes simplex	0	1 (0.2)	0	1 (0.2)
Lower respiratory tract infection	0	1 (0.2)	0	1 (0.2)
Meningitis	0	1 (0.2)	0	1 (0.2)
Oesophageal candidiasis	0	1 (0.2)	0	1 (0.2)
Oral fungal infection	0	1 (0.2)	0	1 (0.2)
Oral herpes	0	1 (0.2)	0	1 (0.2)
Peritonitis	0	1 (0.2)	0	1 (0.2)
Pharyngitis	0	1 (0.2)	0	1 (0.2)
Pneumocystis jirovecii pneumonia	0	1 (0.2)	0	1 (0.2)
Pulpitis dental	0	1 (0.2)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Septic shock	0	1 (0.2)	0	1 (0.2)
Splenic abscess	0	1 (0.2)	0	1 (0.2)
Staphylococcal infection	0	0	1 (12.5)	1 (0.2)
Stenotrophomonas infection	1 (2.0)	0	0	1 (0.2)
Stoma site abscess	0	1 (0.2)	0	1 (0.2)
Wound abscess	0	1 (0.2)	0	1 (0.2)
Metabolism and nutrition disorders	10 (19.6)	112 (20.5)	1 (12.5)	123 (20.3)
Decreased appetite	5 (9.8)	69 (12.6)	0	74 (12.2)
Hypokalaemia	1 (2.0)	19 (3.5)	0	20 (3.3)
Hypocalcaemia	0	13 (2.4)	0	13 (2.1)
Dehydration	3 (5.9)	8 (1.5)	1 (12.5)	12 (2.0)
Cachexia	1 (2.0)	7 (1.3)	0	8 (1.3)
Hypoalbuminaemia	0	5 (0.9)	0	5 (0.8)
Hypomagnesaemia	1 (2.0)	3 (0.5)	0	4 (0.7)
Malnutrition	2 (3.9)	2 (0.4)	0	4 (0.7)
Hyperglycaemia	0	3 (0.5)	0	3 (0.5)
Hyperuricaemia	0	3 (0.5)	0	3 (0.5)
Hypercalcaemia	0	2 (0.4)	0	2 (0.3)
Hypoglycaemia	0	2 (0.4)	0	2 (0.3)
Hyponatraemia	1 (2.0)	1 (0.2)	0	2 (0.3)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Hypophosphataemia	0	2 (0.4)	0	2 (0.3)
Alkalosis	0	1 (0.2)	0	1 (0.2)
Hyperkalaemia	0	1 (0.2)	0	1 (0.2)
Hypernatraemia	0	1 (0.2)	0	1 (0.2)
Hypovolaemia	0	1 (0.2)	0	1 (0.2)
Iron deficiency	0	1 (0.2)	0	1 (0.2)
Vitamin D deficiency	0	1 (0.2)	0	1 (0.2)
Vascular disorders	7 (13.7)	89 (16.3)	2 (25.0)	98 (16.2)
Hypertension	4 (7.8)	60 (11.0)	0	64 (10.6)
Hypotension	1 (2.0)	8 (1.5)	1 (12.5)	10 (1.7)
Deep vein thrombosis	1 (2.0)	3 (0.5)	0	4 (0.7)
Haematoma	0	2 (0.4)	1 (12.5)	3 (0.5)
Lymphoedema	0	3 (0.5)	0	3 (0.5)
Haemorrhage	0	2 (0.4)	0	2 (0.3)
Hypertensive crisis	0	2 (0.4)	0	2 (0.3)
Thrombosis	0	2 (0.4)	0	2 (0.3)
Venous thrombosis	0	2 (0.4)	0	2 (0.3)
Aortic aneurysm	0	1 (0.2)	0	1 (0.2)
Axillary vein thrombosis	0	1 (0.2)	0	1 (0.2)
Circulatory collapse	0	1 (0.2)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Hot flush	0	1 (0.2)	0	1 (0.2)
Microangiopathy	0	1 (0.2)	0	1 (0.2)
Peripheral vascular disorder	0	1 (0.2)	0	1 (0.2)
Peripheral venous disease	1 (2.0)	0	0	1 (0.2)
Shock haemorrhagic	0	1 (0.2)	0	1 (0.2)
Thrombophlebitis	0	1 (0.2)	0	1 (0.2)
Varicose vein	1 (2.0)	0	0	1 (0.2)
Vascular compression	0	1 (0.2)	0	1 (0.2)
Venous thrombosis limb	0	1 (0.2)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	5 (9.8)	83 (15.2)	3 (37.5)	91 (15.0)
Back pain	1 (2.0)	25 (4.6)	0	26 (4.3)
Arthralgia	0	18 (3.3)	1 (12.5)	19 (3.1)
Pain in extremity	0	14 (2.6)	0	14 (2.3)
Myalgia	1 (2.0)	12 (2.2)	0	13 (2.1)
Bone pain	1 (2.0)	8 (1.5)	0	9 (1.5)
Neck pain	1 (2.0)	5 (0.9)	0	6 (1.0)
Musculoskeletal chest pain	0	5 (0.9)	0	5 (0.8)
Osteoarthritis	2 (3.9)	2 (0.4)	0	4 (0.7)
Muscle spasms	0	3 (0.5)	0	3 (0.5)
Musculoskeletal pain	0	3 (0.5)	0	3 (0.5)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
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N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Arthritis	0	2 (0.4)	0	2 (0.3)
Fistula	0	2 (0.4)	0	2 (0.3)
Musculoskeletal stiffness	0	1 (0.2)	1 (12.5)	2 (0.3)
Joint swelling	0	1 (0.2)	0	1 (0.2)
Mobility decreased	0	1 (0.2)	0	1 (0.2)
Muscle contracture	0	1 (0.2)	0	1 (0.2)
Myalgia intercostal	0	1 (0.2)	0	1 (0.2)
Osteonecrosis of jaw	0	0	1 (12.5)	1 (0.2)
Skin and subcutaneous tissue disorders	1 (2.0)	74 (13.5)	0	75 (12.4)
Alopecia	0	33 (6.0)	0	33 (5.4)
Rash	0	10 (1.8)	0	10 (1.7)
Dry skin	0	5 (0.9)	0	5 (0.8)
Onycholysis	0	5 (0.9)	0	5 (0.8)
Nail disorder	0	4 (0.7)	0	4 (0.7)
Palmar-plantar erythrodysaesthesia syndrome	0	4 (0.7)	0	4 (0.7)
Decubitus ulcer	0	3 (0.5)	0	3 (0.5)
Pruritus	0	3 (0.5)	0	3 (0.5)
Dermatitis acneiform	0	2 (0.4)	0	2 (0.3)
Erythema	0	2 (0.4)	0	2 (0.3)
Nail discolouration	0	2 (0.4)	0	2 (0.3)

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N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

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Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Nail pigmentation	0	2 (0.4)	0	2 (0.3)
Rash maculo-papular	0	2 (0.4)	0	2 (0.3)
Skin lesion	0	2 (0.4)	0	2 (0.3)
Skin ulcer	0	2 (0.4)	0	2 (0.3)
Urticaria	0	2 (0.4)	0	2 (0.3)
Blister	0	1 (0.2)	0	1 (0.2)
Dermal cyst	0	1 (0.2)	0	1 (0.2)
Eczema	0	1 (0.2)	0	1 (0.2)
Hidradenitis	0	1 (0.2)	0	1 (0.2)
Intertrigo	1 (2.0)	0	0	1 (0.2)
Nail toxicity	0	1 (0.2)	0	1 (0.2)
Onychoclasis	0	1 (0.2)	0	1 (0.2)
Perioral dermatitis	0	1 (0.2)	0	1 (0.2)
Rash erythematous	0	1 (0.2)	0	1 (0.2)
Rash pruritic	0	1 (0.2)	0	1 (0.2)
Scar pain	0	1 (0.2)	0	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5 (9.8)	57 (10.4)	2 (25.0)	64 (10.6)
Malignant neoplasm progression	4 (7.8)	40 (7.3)	1 (12.5)	45 (7.4)
Tumour pain	0	6 (1.1)	0	6 (1.0)

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MedDRA Version 24.0;

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Cancer pain	0	5 (0.9)	0	5 (0.8)
Malignant pleural effusion	0	4 (0.7)	0	4 (0.7)
Metastases to liver	1 (2.0)	1 (0.2)	0	2 (0.3)
Metastases to meninges	0	2 (0.4)	0	2 (0.3)
Metastases to peritoneum	0	2 (0.4)	0	2 (0.3)
Tumour haemorrhage	0	1 (0.2)	1 (12.5)	2 (0.3)
Metastases to adrenals	0	1 (0.2)	0	1 (0.2)
Metastases to bone	0	1 (0.2)	0	1 (0.2)
Metastases to central nervous system	0	1 (0.2)	0	1 (0.2)
Pleural neoplasm	0	1 (0.2)	0	1 (0.2)
Renal and urinary disorders	4 (7.8)	45 (8.2)	1 (12.5)	50 (8.3)
Proteinuria	1 (2.0)	17 (3.1)	0	18 (3.0)
Haematuria	0	6 (1.1)	0	6 (1.0)
Dysuria	0	5 (0.9)	0	5 (0.8)
Hydronephrosis	1 (2.0)	4 (0.7)	0	5 (0.8)
Renal failure	1 (2.0)	3 (0.5)	0	4 (0.7)
Urinary retention	1 (2.0)	2 (0.4)	1 (12.5)	4 (0.7)
Acute kidney injury	0	3 (0.5)	0	3 (0.5)
Pollakiuria	0	3 (0.5)	0	3 (0.5)
Leukocyturia	0	2 (0.4)	0	2 (0.3)

Database lock date: 19AUG2021.
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Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Polyuria	0	2 (0.4)	0	2 (0.3)
Anuria	0	1 (0.2)	0	1 (0.2)
Incontinence	0	1 (0.2)	0	1 (0.2)
Nocturia	0	1 (0.2)	0	1 (0.2)
Oliguria	0	1 (0.2)	0	1 (0.2)
Strangury	0	1 (0.2)	0	1 (0.2)
Urge incontinence	0	1 (0.2)	0	1 (0.2)
Urinary tract disorder	0	1 (0.2)	0	1 (0.2)
Injury, poisoning and procedural complications	1 (2.0)	40 (7.3)	1 (12.5)	42 (6.9)
Infusion related reaction	0	14 (2.6)	0	14 (2.3)
Fall	0	9 (1.6)	1 (12.5)	10 (1.7)
Femur fracture	1 (2.0)	1 (0.2)	0	2 (0.3)
Gastrointestinal stoma complication	0	2 (0.4)	0	2 (0.3)
Limb injury	0	2 (0.4)	0	2 (0.3)
Anastomotic complication	0	1 (0.2)	0	1 (0.2)
Bone contusion	0	1 (0.2)	0	1 (0.2)
Femoral neck fracture	0	1 (0.2)	0	1 (0.2)
Head injury	0	1 (0.2)	0	1 (0.2)
Injury	0	1 (0.2)	0	1 (0.2)
Muscle strain	0	1 (0.2)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Post procedural complication	0	1 (0.2)	0	1 (0.2)
Procedural complication	0	1 (0.2)	0	1 (0.2)
Procedural pain	0	1 (0.2)	0	1 (0.2)
Radius fracture	0	1 (0.2)	0	1 (0.2)
Recall phenomenon	0	1 (0.2)	0	1 (0.2)
Skin wound	0	1 (0.2)	0	1 (0.2)
Stoma site extravasation	0	1 (0.2)	0	1 (0.2)
Stoma site inflammation	0	1 (0.2)	0	1 (0.2)
Stoma site pain	0	1 (0.2)	0	1 (0.2)
Tendon rupture	0	1 (0.2)	0	1 (0.2)
Thoracic vertebral fracture	0	1 (0.2)	0	1 (0.2)
Wound	0	1 (0.2)	0	1 (0.2)
Hepatobiliary disorders	3 (5.9)	27 (4.9)	0	30 (5.0)
Hypertransaminasaemia	0	8 (1.5)	0	8 (1.3)
Hepatotoxicity	0	4 (0.7)	0	4 (0.7)
Jaundice	0	4 (0.7)	0	4 (0.7)
Biliary obstruction	0	2 (0.4)	0	2 (0.3)
Cholangitis	1 (2.0)	1 (0.2)	0	2 (0.3)
Hepatic failure	1 (2.0)	1 (0.2)	0	2 (0.3)
Acute hepatic failure	0	1 (0.2)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Cholecystitis	0	1 (0.2)	0	1 (0.2)
Cholecystitis acute	0	1 (0.2)	0	1 (0.2)
Cholestasis	0	1 (0.2)	0	1 (0.2)
Haemobilia	0	1 (0.2)	0	1 (0.2)
Hepatitis	0	1 (0.2)	0	1 (0.2)
Hyperbilirubinaemia	0	1 (0.2)	0	1 (0.2)
Jaundice cholestatic	1 (2.0)	0	0	1 (0.2)
Ocular icterus	0	1 (0.2)	0	1 (0.2)
Psychiatric disorders	3 (5.9)	22 (4.0)	0	25 (4.1)
Insomnia	0	10 (1.8)	0	10 (1.7)
Depression	1 (2.0)	6 (1.1)	0	7 (1.2)
Sleep disorder	0	3 (0.5)	0	3 (0.5)
Anxiety	0	2 (0.4)	0	2 (0.3)
Confusional state	0	2 (0.4)	0	2 (0.3)
Apathy	1 (2.0)	0	0	1 (0.2)
Nervousness	0	1 (0.2)	0	1 (0.2)
Restlessness	1 (2.0)	0	0	1 (0.2)
Suicidal ideation	1 (2.0)	0	0	1 (0.2)
Cardiac disorders	4 (7.8)	16 (2.9)	1 (12.5)	21 (3.5)
Atrial fibrillation	2 (3.9)	3 (0.5)	0	5 (0.8)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Tachycardia	0	4 (0.7)	0	4 (0.7)
Pericardial effusion	0	3 (0.5)	0	3 (0.5)
Sinus tachycardia	1 (2.0)	2 (0.4)	0	3 (0.5)
Acute myocardial infarction	0	0	1 (12.5)	1 (0.2)
Angina pectoris	1 (2.0)	0	0	1 (0.2)
Cardiac failure	0	1 (0.2)	0	1 (0.2)
Cardiac valve disease	0	1 (0.2)	0	1 (0.2)
Cardiopulmonary failure	0	1 (0.2)	0	1 (0.2)
Left ventricular dysfunction	0	0	1 (12.5)	1 (0.2)
Myocardial infarction	0	1 (0.2)	0	1 (0.2)
Sinus node dysfunction	1 (2.0)	0	0	1 (0.2)
Eye disorders	0	14 (2.6)	0	14 (2.3)
Diplopia	0	2 (0.4)	0	2 (0.3)
Ocular discomfort	0	2 (0.4)	0	2 (0.3)
Periorbital oedema	0	2 (0.4)	0	2 (0.3)
Blepharitis	0	1 (0.2)	0	1 (0.2)
Cataract	0	1 (0.2)	0	1 (0.2)
Conjunctival haemorrhage	0	1 (0.2)	0	1 (0.2)
Eye haemorrhage	0	1 (0.2)	0	1 (0.2)
Eye swelling	0	1 (0.2)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Keratitis	0	1 (0.2)	0	1 (0.2)
Lacrimation increased	0	1 (0.2)	0	1 (0.2)
Retinopathy	0	1 (0.2)	0	1 (0.2)
Product issues	1 (2.0)	11 (2.0)	0	12 (2.0)
Device dislocation	0	6 (1.1)	0	6 (1.0)
Device malfunction	0	3 (0.5)	0	3 (0.5)
Device occlusion	0	2 (0.4)	0	2 (0.3)
Thrombosis in device	1 (2.0)	0	0	1 (0.2)
Ear and labyrinth disorders	1 (2.0)	9 (1.6)	0	10 (1.7)
Vertigo	1 (2.0)	5 (0.9)	0	6 (1.0)
Tinnitus	0	3 (0.5)	0	3 (0.5)
Vertigo positional	0	1 (0.2)	0	1 (0.2)
Reproductive system and breast disorders	0	9 (1.6)	0	9 (1.5)
Pelvic pain	0	2 (0.4)	0	2 (0.3)
Benign prostatic hyperplasia*a	0	1 (0.3)	0	1 (0.2)
Erectile dysfunction*a	0	1 (0.3)	0	1 (0.2)
Genital tract inflammation	0	1 (0.2)	0	1 (0.2)
Intermenstrual bleeding*b	0	1 (0.6)	0	1 (0.5)
Oedema genital	0	1 (0.2)	0	1 (0.2)
Spermatocele*a	0	1 (0.3)	0	1 (0.2)

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Adverse Events on or within 90 days of Ram
Preferred Term (by Decreasing Frequency) within System Organ Class
Full analysis set
I4T-MC-JVDD

System Organ Class Preferred Term*	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Overall (N=606) n (%)
Testicular pain*a	0	1 (0.3)	0	1 (0.2)
Vaginal discharge*b	0	1 (0.6)	0	1 (0.5)
Immune system disorders	0	3 (0.5)	0	3 (0.5)
Contrast media reaction	0	1 (0.2)	0	1 (0.2)
Drug hypersensitivity	0	1 (0.2)	0	1 (0.2)
Hypersensitivity	0	1 (0.2)	0	1 (0.2)
Endocrine disorders	1 (2.0)	1 (0.2)	0	2 (0.3)
Hypothyroidism	1 (2.0)	1 (0.2)	0	2 (0.3)
Congenital, familial and genetic disorders	0	1 (0.2)	0	1 (0.2)
Pyloric stenosis	0	1 (0.2)	0	1 (0.2)
Social circumstances	0	1 (0.2)	0	1 (0.2)
Limb prosthesis user	0	1 (0.2)	0	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
*a - Denominator adjusted because gender-specific event for males: N=35 (Ram mono),N=382 (Ram + PclTax)
N=4 (Ram + Other), N=421(Overall)
*b - Denominator adjusted because gender-specific event for females: N=16 (Ram mono),N=165 (Ram + PclTax)
N=4 (Ram + Other), N=185(Overall)
MedDRA Version 24.0;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tae_soc90.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tae_soc90.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Table ANN.2.11. Overview of Adverse Events with Relationship
Full Analysis Set
I4T-MC-JVDD

	Ram mono (N=51)		Ram + PclTax (N=547)		Ram + Other (N=8)		Overall (N=606)	
Preferred Term*a	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with >=1 AE within 30 days of Ram*b	49	(96.1)	531	(97.1)	8	(100.0)	588	(97.0)
Related to anti-cancer Treatment*c	14	(27.5)	412	(75.3)	5	(62.5)	431	(71.1)
Related to ramucirumab*d	14	(27.5)	267	(48.8)	2	(25.0)	283	(46.7)
Related to other drug*d	0		391	(71.5)	5	(62.5)	396	(65.3)
Subjects with >=1 AE within 90 days of Ram*b	49	(96.1)	535	(97.8)	8	(100.0)	592	(97.7)
Related to anti-cancer Treatment*c	15	(29.4)	415	(75.9)	6	(75.0)	436	(71.9)
Related to ramucirumab*d	15	(29.4)	268	(49.0)	3	(37.5)	286	(47.2)
Related to other drug*d	0		395	(72.2)	6	(75.0)	401	(66.2)
Subjects with >=1 AE after 90 days of Ram	0		12	(2.2)	0		12	(2.0)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Overview of Adverse Events with relationship
Full analysis set
I4T-MC-JVDD

Preferred Term*a	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Related to anti-cancer Treatment*c	0		3	(0.5)	0		3	(0.5)
Related to ramucirumab*d	0		2	(0.4)	0		2	(0.3)
Related to other drug*d	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Overview of Adverse Events with relationship
Full analysis set
I4T-MC-JVDD

Preferred Term*a	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Subjects with >=1 SAE on Ram +30 days*b	22	(43.1)	197	(36.0)	5	(62.5)	224	(37.0)
Related to anti-cancer Treatment*c	2	(3.9)	59	(10.8)	2	(25.0)	63	(10.4)
Related to ramucirumab*d	2	(3.9)	39	(7.1)	1	(12.5)	42	(6.9)
Related to other drug*d	0		37	(6.8)	1	(12.5)	38	(6.3)
Subjects with >=1 SAE on Ram +90 days*b	24	(47.1)	220	(40.2)	6	(75.0)	250	(41.3)
Related to anti-cancer Treatment*c	2	(3.9)	62	(11.3)	3	(37.5)	67	(11.1)
Related to ramucirumab*d	2	(3.9)	39	(7.1)	1	(12.5)	42	(6.9)
Related to other drug*d	0		40	(7.3)	2	(25.0)	42	(6.9)
Subjects with >=1 SAE after 90 days post Ram	0		6	(1.1)	0		6	(1.0)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Overview of Adverse Events with relationship
Full analysis set
I4T-MC-JVDD

Preferred Term*a	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Related to anti-cancer Treatment*c	0		2	(0.4)	0		2	(0.3)
Related to ramucirumab*d	0		1	(0.2)	0		1	(0.2)
Related to other drug*d	0		1	(0.2)	0		1	(0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Overview of Adverse Events with relationship
Full analysis set
I4T-MC-JVDD

Preferred Term*a	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Subjects who discontinued Ram due to AE	7	(13.7)	68	(12.4)	0		75	(12.4)
Related to anti-cancer Treatment*c	1	(2.0)	30	(5.5)	0		31	(5.1)
Related to ramucirumab*d	1	(2.0)	24	(4.4)	0		25	(4.1)
Related to other drug*d	0		16	(2.9)	0		16	(2.6)
Subjects who discontinued Ram due to SAE	2	(3.9)	28	(5.1)	0		30	(5.0)
Related to anti-cancer Treatment*c	0		11	(2.0)	0		11	(1.8)
Related to ramucirumab*d	0		9	(1.6)	0		9	(1.5)
Related to other drug*d	0		5	(0.9)	0		5	(0.8)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Overview of Adverse Events with relationship
Full analysis set
I4T-MC-JVDD

Preferred Term*a	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Subjects who died due to AE on study treatment*e	4	(7.8)	23	(4.2)	0		27	(4.5)
Related to anti-cancer Treatment*c	1	(2.0)	7	(1.3)	0		8	(1.3)
Related to ramucirumab*d	1	(2.0)	7	(1.3)	0		8	(1.3)
Related to other drug*d	0		2	(0.4)	0		2	(0.3)
Subjects who died due to AE within 30 days of Ram*e	7	(13.7)	55	(10.1)	1	(12.5)	63	(10.4)
Related to anti-cancer Treatment*c	1	(2.0)	8	(1.5)	0		9	(1.5)
Related to ramucirumab*d	1	(2.0)	8	(1.5)	0		9	(1.5)
Related to other drug*d	0		2	(0.4)	0		2	(0.3)
Subjects who died due to AE within 90 days of Ram*e	10	(19.6)	67	(12.2)	1	(12.5)	78	(12.9)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Overview of Adverse Events with relationship
Full analysis set
I4T-MC-JVDD

Preferred Term*a	Ram mono (N=51) n	(%)	Ram + PclTax (N=547) n	(%)	Ram + Other (N=8) n	(%)	Overall (N=606) n	(%)
Related to anti-cancer Treatment*c	1	(2.0)	8	(1.5)	0		9	(1.5)
Related to ramucirumab*d	1	(2.0)	8	(1.5)	0		9	(1.5)
Related to other drug*d	0		2	(0.4)	0		2	(0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in Full analysis set; n = number of subjects in the specified category;
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities;
AE = Adverse Event; SAE = Serious Adverse Event.
*a - Subjects may be counted in more than one category.
*b - Adverse events observed from 1st dose of Ram till 30 or 90 days after last dose.
*c - Includes events that were considered related to treatment as judged by the treating physician.
*d - Related to ramucirumab/other drug if recorded as 'yes' or 'unknown'.

MedDRA Version 24.0; CTCAE Version 4.0

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/taerel.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taerel.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADAE

Table ANN.2.12. Adverse Events of Special Interest Experienced by at least 5% of Patients (Total) Aged ≥65 Years by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=33)	Ram + PTX (N=296)	Ram + Other (N=4)	Total[b] (N=333)
Patients with any AESIs within 90 days of last Ram dose	**8 (24.2)**	**121 (40.9)**	**2 (50.0)**	**131 (39.3)**
Bleeding/haemorrhage events	**3 (9.1)**	**65 (22.0)**	**2 (50.0)**	**70 (21.0)**
Epistaxis	1 (3.0)	42 (14.2)	1 (25.0)	44 (13.2)
Gastrointestinal haemorrhage events	2 (6.1)	14 (4.7)	1 (25.0)	17 (5.1)
Haematemesis	2 (6.1)	4 (1.4)	0	6 (1.8)
Gastrointestinal haemorrhage	0	4 (1.4)	1 (25.0)	5 (1.5)
Haemorrhoidal haemorrhage	0	2 (0.7)	0	2 (0.6)
Melaena	0	2 (0.7)	0	2 (0.6)
Oesophageal haemorrhage	0	1 (0.3)	0	1 (0.3)
Rectal haemorrhage	0	1 (0.3)	0	1 (0.3)
Upper gastrointestinal haemorrhage	0	1 (0.3)	0	1 (0.3)
Haematuria	0	4 (1.4)	0	4 (1.2)
Intermenstrual bleeding[a]	0	1 (1.3)	0	1 (1.1)
Gingival bleeding	0	2 (0.7)	0	2 (0.6)
Haemoptysis	0	2 (0.7)	0	2 (0.6)
Tumour haemorrhage	0	1 (0.3)	1 (25.0)	2 (0.6)
Eye haemorrhage	0	1 (0.3)	0	1 (0.3)
Haematoma	0	1 (0.3)	0	1 (0.3)
Haemobilia	0	1 (0.3)	0	1 (0.3)
Lip haemorrhage	0	0	1 (25.0)	1 (0.3)
Shock haemorrhagic	0	1 (0.3)	0	1 (0.3)
Hypertension	**1 (3.0)**	**31 (10.5)**	**0**	**32 (9.6)**
Hypertension	1	30 (10.1)	0	31 (9.3)
Hypertensive crisis	0	2 (0.7)	0	2 (0.6)
Liver injury/failure	**2 (6.1)**	**24 (8.1)**	**0**	**26 (7.8)**
Aspartate aminotransferase increased	0	8 (2.7)	0	8 (2.4)
Blood bilirubin increased	0	6 (2.0)	0	6 (1.8)
Alanine aminotransferase increased	0	4 (1.4)	0	4 (1.2)
Hypertransaminasaemia	0	4 (1.4)	0	4 (1.2)
Jaundice	0	4 (1.4)	0	4 (1.2)
Gamma-glutamyltransferase increased	0	3 (1.0)	0	3 (0.9)
Biliary ascites	0	1 (0.3)	0	1 (0.3)
Hepatic encephalopathy	0	1 (0.3)	0	1 (0.3)
Hepatic failure	1 (3.0)	0	0	1 (0.3)
Hepatitis	0	1 (0.3)	0	1 (0.3)
Hepatotoxicity	0	1 (0.3)	0	1 (0.3)
Hyperbilirubinaemia	0	1 (0.3)	0	1 (0.3)
Jaundice cholestatic	1 (3.0)	0	0	1 (0.3)
Transaminases increased	0	1 (0.3)	0	1 (0.3)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Denominator adjusted because gender-specific event for females: N = 8 (Ram mono), N = 79 (Ram + PTX), N = 1 (Ram + Other), N = 88 (Overall).

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_age65.rtf.

Table ANN.2.13. Adverse Events of Special Interest Experienced by at least 5% of Patients (Total) Aged ≥75 Years by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=22)	Ram + PTX (N=111)	Ram + Other (N=2)	Total[b] (N=135)
Patients with any AESIs on or within 90 days of Ram	**6 (27.3)**	**48 (43.2)**	**0**	**54 (40.0)**
Bleeding/haemorrhage events	**2 (9.1)**	**28 (25.2)**	**0**	**30 (22.2)**
Epistaxis	1 (4.5)	20 (18.0)	0	21 (15.6)
Gastrointestinal haemorrhage events	1 (4.5)	3 (2.7)	0	4 (3.0)
Haemorrhoidal haemorrhage	0	2 (1.8)	0	2 (1.5)
Gastrointestinal haemorrhage	0	1 (0.9)	0	1 (0.7)
Haematemesis	1 (4.5)	0	0	1 (0.7)
Intermenstrual bleeding[a]	0	1 (3.3)	0	1 (2.8)
Conjunctival haemorrhage	0	1 (0.9)	0	1 (0.7)
Haemobilia	0	1 (0.9)	0	1 (0.7)
Haematuria	0	1 (0.9)	0	1 (0.7)
Shock haemorrhagic	0	1 (0.9)	0	1 (0.7)
Tumour haemorrhage	0	1 (0.9)	0	1 (0.7)
Hypertension	**1 (4.5)**	**11 (9.9)**	**0**	**12 (8.9)**
Hypertension	1 (4.5)	10 (9.0)	0	11 (8.1)
Hypertensive crisis	0	2 (1.8)	0	2 (1.5)
Liver injury/failure	**2 (9.1)**	**10 (9.0)**	**0**	**12 (8.9)**
Aspartate aminotransferase increased	0	4 (3.6)	0	4 (3.0)
Blood bilirubin increased	0	4 (3.6)	0	4 (3.0)
Alanine aminotransferase increased	0	2 (1.8)	0	2 (1.5)
Gamma-glutamyltransferase increased	0	2 (1.8)	0	2 (1.5)
Hepatic failure	1 (4.5)	0	0	1 (0.7)
Hepatotoxicity	0	1 (0.9)	0	1 (0.7)
Hyperbilirubinaemia	0	1 (0.9)	0	1 (0.7)
Jaundice	0	1 (0.9)	0	1 (0.7)
Jaundice cholestatic	1 (4.5)	0	0	1 (0.7)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Denominator adjusted because gender-specific event for females: N = 5 (Ram mono), N = 30 (Ram + PTX), N = 1 (Ram + Other), N = 36 (Overall).

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_age75.rtf.

Table ANN.2.14. Adverse Events of Special Interest Experienced by at least 5% of Patients (Total) with Cardiac Comorbidities by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=17)	Ram + PTX (N=117)	Ram + Other (N=4)	Total[b] (N=138)
Patients with any AESIs on or within 90 days of Ram	**6 (35.3)**	**55 (47.0)**	**2 (50.0)**	**63 (45.7)**
Bleeding/haemorrhage events	**1 (5.9)**	**32 (27.4)**	**2 (50.0)**	**35 (25.4)**
Epistaxis	1 (5.9)	20 (17.1)	1 (25.0)	22 (15.9)
Gastrointestinal haemorrhage events	0	7 (6.0)	1 (25.0)	8 (5.8)
Gastrointestinal haemorrhage	0	3 (2.6)	1 (25.0)	4 (2.9)
Haematemesis	0	3 (2.6)	0	3 (2.2)
Upper gastrointestinal haemorrhage	0	1 (0.9)	0	1 (0.7)
Gingival bleeding	0	2 (1.7)	0	2 (1.4)
Tumour haemorrhage	0	1 (0.9)	1 (25.0)	2 (1.4)
Haematoma	0	1 (0.9)	0	1 (0.7)
Haematuria	0	1 (0.9)	0	1 (0.7)
Lip haemorrhage	0	0	1 (25.0)	1 (0.7)
Mucosal haemorrhage	0	1 (0.9)	0	1 (0.7)
Shock haemorrhagic	0	1 (0.9)	0	1 (0.7)
Hypertension	**2 (11.8)**	**10 (8.5)**	**0**	**12 (8.7)**
Hypertension	2 (11.8)	10 (8.5)	0	12 (8.7)
Hypertensive crisis	0	1 (0.9)	0	1 (0.7)
Liver injury/failure	**3 (17.6)**	**9 (7.7)**	**0**	**12 (8.7)**
Aspartate aminotransferase increased	0	4 (3.4)	0	4 (2.9)
Blood bilirubin increased	1 (5.9)	3 (2.6)	0	4 (2.9)
Alanine aminotransferase increased	0	2 (1.7)	0	2 (1.4)
Gamma-glutamyltransferase increased	0	1 (0.9)	0	1 (0.7)
Hepatic failure	1 (5.9)	0	0	1 (0.7)
Hepatotoxicity	0	1 (0.9)	0	1 (0.7)
Hyperbilirubinaemia	0	1 (0.9)	0	1 (0.7)
Jaundice	0	1 (0.9)	0	1 (0.7)
Jaundice cholestatic	1 (5.9)	0	0	1 (0.7)
Venous thromboembolic events	**1 (5.9)**	**7 (6.0)**	**0**	**8 (5.8)**
Pulmonary embolism	0	3 (2.6)	0	3 (2.2)
Axillary vein thrombosis	0	1 (0.9)	0	1 (0.7)
Deep vein thrombosis	0	1 (0.9)	0	1 (0.7)
Thrombophlebitis	0	1 (0.9)	0	1 (0.7)
Thrombosis in device	1 (5.9)	0	0	1 (0.7)
Venous thrombosis	0	1 (0.9)	0	1 (0.7)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_card.rtf.

Table ANN.2.15. Adverse Events of Special Interest Experienced by at least 5% of Patients (Total) with Hepatic Impairment by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=9)	Ram + PTX (N=57)	Ram + Other (N=2)	Total[b] (N=68)
Patients with any AESIs on or within 90 days of Ram	**3 (33.3)**	**19 (33.3)**	**0**	**22 (32.4)**
Bleeding/haemorrhage events	**1 (11.1)**	**11 (19.3)**	**0**	**12 (17.6)**
Epistaxis	0	6 (10.5)	0	6 (8.8)
Gastrointestinal haemorrhage events	1 (11.1)	3 (5.3)	0	4 (5.9)
Gastrointestinal haemorrhage	0	2 (3.5)	0	2 (2.9)
Anal haemorrhage	0	1 (1.8)	0	1 (1.5)
Haematemesis	1	0	0	1 (1.5)
Intermenstrual bleeding[a]	0	1 (6.3)	0	1 (5.9)
Gingival bleeding	0	1 (1.8)	0	1 (1.5)
Liver injury/failure	**2 (22.2)**	**4 (7.0)**	**0**	**6 (8.8)**
Alanine aminotransferase increased	0	1 (1.8)	0	1 (1.5)
Aspartate aminotransferase increased	0	1 (1.8)	0	1 (1.5)
Biliary ascites	0	1 (1.8)	0	1 (1.5)
Blood bilirubin increased	1 (11.1)	0	0	1 (1.5)
Hepatic encephalopathy	0	1 (1.8)	0	1 (1.5)
Hepatic failure	1 (11.1)	0	0	1 (1.5)
Hepatotoxicity	0	1 (1.8)	0	1 (1.5)
Venous thromboembolic events	**0**	**4 (7.0)**	**0**	**4 (5.9)**
Pulmonary embolism	0	2 (3.5)	0	2 (2.9)
Deep vein thrombosis	0	1 (1.8)	0	1 (1.5)
Thrombosis	0	1 (1.8)	0	1 (1.5)
Venous thrombosis limb	0	1 (1.8)	0	1 (1.5)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

[a] Denominator adjusted because gender-specific event for females: N = 0 (Ram mono), N = 16 (Ram + PTX), N = 1 (Ram + Other), N = 17 (Overall).

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_hepa.rtf.

Table ANN.2.16. Adverse Events of Special Interest Experienced by at least 5% of Patients (Total) with Renal Impairment by MedDRA Preferred Term by Decreasing Frequency
Full Analysis Set
I4T-MC-JVDD

AESI Term MedDRA Preferred Term	Ram Mono (N=3)	Ram + PTX (N=36)	Ram + Other (N=0)	Total[b] (N=39)
Patients with any AESIs on or within 90 days of Ram	**0**	**14 (38.9)**	**0**	**14 (35.9)**
Bleeding/haemorrhage events	**0**	**6 (16.7)**	**0**	**6 (15.4)**
Epistaxis	0	3 (8.3)	0	3 (7.7)
Gastrointestinal haemorrhage events	0	1 (2.8)	0	1 (2.6)
Anal haemorrhage	0	1 (2.8)	0	1 (2.6)
Shock haemorrhage	0	1 (2.8)	0	1 (2.6)
Haematoma	0	1 (2.8)	0	1 (2.6)
Hypertension	**0**	**4 (11.1)**	**0**	**4 (10.3)**
Hypertension	0	4 (11.1)	0	4 (10.3)
Arterial thromboembolic events	**0**	**2 (5.6)**	**0**	**2 (5.1)**
Cerebral ischaemia	0	1 (2.8)	0	1 (2.6)
Myocardial infarction	0	1 (2.8)	0	1 (2.6)
Proteinuria	**0**	**2 (5.6)**	**0**	**2 (5.1)**
Proteinuria	0	2 (5.6)	0	2 (5.1)

Abbreviations: AESI = adverse events of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 24.0); Mono = monotherapy; N = number of patients in full analysis set; n = number of patients in the specified category; PTX = paclitaxel; Ram = ramucirumab.

Final database cut-off date: 19 August 2021.

Source: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/taesi90_renal.rtf.

Table ANN.2.17. Summary of Hospitalisation
Full Analysis Set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Patients Hospitalized	25 (49.0)	251 (45.9)	6 (75.0)	282 (46.5)
Reasons *a				
Primary Study Condition	6 (11.8)	39 (7.1)	0 (0.0)	45 (7.4)
Other	2 (3.9)	20 (3.7)	0 (0.0)	22 (3.6)
Adverse Event	19 (37.3)	202 (36.9)	6 (75.0)	227 (37.5)
Malignant Neoplasm Progression	1 (2.0)	16 (2.9)	1 (12.5)	18 (3.0)
Intestinal Obstruction	0 (0.0)	13 (2.4)	0 (0.0)	13 (2.1)
Pneumonia	1 (2.0)	12 (2.2)	0 (0.0)	13 (2.1)
Abdominal Pain	0 (0.0)	10 (1.8)	0 (0.0)	10 (1.7)
General Physical Health Deterioration	0 (0.0)	10 (1.8)	0 (0.0)	10 (1.7)
Dyspnoea	0 (0.0)	8 (1.5)	0 (0.0)	8 (1.3)
Haematemesis	2 (3.9)	6 (1.1)	0 (0.0)	8 (1.3)
Anaemia	0 (0.0)	7 (1.3)	0 (0.0)	7 (1.2)
Ascites	2 (3.9)	5 (0.9)	0 (0.0)	7 (1.2)
Febrile Neutropenia	0 (0.0)	7 (1.3)	0 (0.0)	7 (1.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
*d - Hospitalization Duration relative to Exposure = Duration of Hospitalization / Duration of Therapy.
Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Pulmonary Embolism	0 (0.0)	7 (1.3)	0 (0.0)	7 (1.2)
Dysphagia	1 (2.0)	4 (0.7)	1 (12.5)	6 (1.0)
Gastrointestinal Haemorrhage	0 (0.0)	5 (0.9)	1 (12.5)	6 (1.0)
Pyrexia	1 (2.0)	5 (0.9)	0 (0.0)	6 (1.0)
Urinary Tract Infection	1 (2.0)	5 (0.9)	0 (0.0)	6 (1.0)
Device Related Infection	2 (3.9)	3 (0.5)	0 (0.0)	5 (0.8)
Ileus	1 (2.0)	4 (0.7)	0 (0.0)	5 (0.8)
Pleural Effusion	1 (2.0)	3 (0.5)	1 (12.5)	5 (0.8)
Vomiting	1 (2.0)	4 (0.7)	0 (0.0)	5 (0.8)
Abdominal Pain Upper	2 (3.9)	2 (0.4)	0 (0.0)	4 (0.7)
Hydronephrosis	1 (2.0)	3 (0.5)	0 (0.0)	4 (0.7)
Nausea	0 (0.0)	4 (0.7)	0 (0.0)	4 (0.7)
Sepsis	0 (0.0)	3 (0.5)	1 (12.5)	4 (0.7)
Chest Pain	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Constipation	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Dehydration	1 (2.0)	2 (0.4)	0 (0.0)	3 (0.5)

Database lock date: 19AUG2021.
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Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Device Dislocation	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Diarrhoea	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Gastric Haemorrhage	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Gastric Perforation	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Jaundice	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Missing PT	0 (0.0)	3 (0.5)	0 (0.0)	3 (0.5)
Back Pain	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Cachexia	1 (2.0)	1 (0.2)	0 (0.0)	2 (0.3)
Cholangitis	1 (2.0)	1 (0.2)	0 (0.0)	2 (0.3)
Chronic Obstructive Pulmonary Disease	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Condition Aggravated	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Device Malfunction	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Intestinal Perforation	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Malignant Pleural Effusion	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Melaena	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Metastases To Meninges	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
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*a - Reasons for admission could be multiple.
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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Neutropenia	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Pericardial Effusion	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Renal Failure	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Respiratory Failure	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Small Intestinal Perforation	1 (2.0)	1 (0.2)	0 (0.0)	2 (0.3)
Subileus	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Urinary Tract Infection Bacterial	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.3)
Abdominal Abscess	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Abdominal Hernia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Acute Kidney Injury	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Alkalosis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Anal Fistula	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Anorectal Infection	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Anxiety	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Aortic Aneurysm	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Asthenia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
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SD = Standard deviation;
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Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Atrial Fibrillation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Biliary Ascites	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Biliary Obstruction	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Blood Bilirubin Increased	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Bronchitis	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)
Candida Pneumonia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cardiac Failure	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cellulitis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cerebral Ischaemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Cholestasis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Clostridial Infection	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)
Colitis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Confusional State	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Dysentery	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Dyspnoea, Bronchitis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
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Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Enteritis	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)
Faecaloma	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Fall	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Femoral Neck Fracture	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Femur Fracture	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (12.5)	1 (0.2)
Gastrooesophageal Reflux Disease	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Haematuria	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Hypertension	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Hypertensive Crisis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Hypocalcaemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Hypokalaemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Hypotension	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Ileus Paralytic	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Impaired Gastric Emptying, Impaired Gastric Emptying	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Infection	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
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Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Intestinal Obstruction, Ascites	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Jaundice Cholestatic	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)
Leukopenia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Malnutrition	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)
Mechanical Ileus	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Metastases To Central Nervous System	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Mucosal Haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Mucosal Inflammation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Multiple Organ Dysfunction Syndrome	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)
Myocardial Infarction	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Obstruction Gastric	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Oesophageal Haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Oesophageal Perforation	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Pain	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Paronychia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Peritonitis Bacterial	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
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Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Pneumocystis Jirovecii Pneumonia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Pneumoperitoneum	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Pneumothorax	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Post Procedural Complication	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Posterior Reversible Encephalopathy Syndrome	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Procedural Complication	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Procedural Pain	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Pulmonary Oedema	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Pyloric Stenosis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Radius Fracture	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Small Intestinal Obstruction	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Splenic Abscess	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Staphylococcal Infection	0 (0.0)	0 (0.0)	1 (12.5)	1 (0.2)
Stoma Site Abscess	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Stomatitis	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Systemic Inflammatory Response Syndrome	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.2)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
*d - Hospitalization Duration relative to Exposure = Duration of Hospitalization / Duration of Therapy.
Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Tumour Haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Tumour Pain	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Upper Gastrointestinal Haemorrhage	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Vascular Device Infection	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Viral Infection	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Viral Upper Respiratory Tract Infection	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Vomiting, Vomiting	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Wound Abscess	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)
Missing Reason	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Type of Health Care Services	0 (0.0)	0 (0.0)	0 (0.0)	
EMERGENCY ROOM	1 (2.0)	19 (3.5)	0 (0.0)	20 (3.3)
HOSPITAL	18 (35.3)	177 (32.4)	6 (75.0)	201 (33.2)
INTENSIVE CARE UNIT	2 (3.9)	2 (0.4)	0 (0.0)	4 (0.7)
ONCOLOGY WARD	5 (9.8)	56 (10.2)	0 (0.0)	61 (10.1)
OTHER CARE FACILITY	2 (3.9)	10 (1.8)	0 (0.0)	12 (2.0)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
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AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
*d - Hospitalization Duration relative to Exposure = Duration of Hospitalization / Duration of Therapy.
Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Total Duration of Hospitalization				
N	25	232	5	262
Mean (SD)	19.8(15.70)	14.7(13.09)	24.8(13.75)	15.4(13.47)
Median	16.0	11.0	26.0	11.0
Q1 - Q3	10.0 - 24.0	5.0 - 21.0	20.0 - 36.0	6.0 - 21.0
Min - Max	3.0 - 71.0	1.0 - 76.0	4.0 - 38.0	1.0 - 76.0
Number of Hospitalizations due to AE				
1	12 (23.5)	144 (26.3)	4 (50.0)	160 (26.4)
2	4 (7.8)	34 (6.2)	2 (25.0)	40 (6.6)
3	1 (2.0)	20 (3.7)	0 (0.0)	21 (3.5)
>3	2 (3.9)	4 (0.7)	0 (0.0)	6 (1.0)
Total Duration of hospitalization due to AEs (for patients who were hospitalized for AEs) (days) *b *c				
N	19	189	5	213

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
*d - Hospitalization Duration relative to Exposure = Duration of Hospitalization / Duration of Therapy.
Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Summary of Hospitalization
Full analysis set
I4T-MC-JVDD

	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Mean (SD)	17.3(13.46)	15.3(13.69)	24.8(13.75)	15.7(13.70)
Median	14.0	11.0	26.0	11.0
Q1 - Q3	6.0 - 24.0	5.0 - 22.0	20.0 - 36.0	6.0 - 22.0
Min - Max	3.0 - 57.0	1.0 - 76.0	4.0 - 38.0	1.0 - 76.0
Total Duration of hospitalization due to AEs relative to duration of therapy (for patients who were hospitalized for AEs) *d				
N	19	187	5	211
Mean (SD)	0.4(0.39)	0.2(0.36)	0.5(0.36)	0.3(0.37)
Median	0.3	0.1	0.6	0.1
Q1 - Q3	0.1 - 0.7	0.0 - 0.3	0.2 - 0.7	0.0 - 0.3
Min - Max	0.0 - 1.3	0.0 - 2.8	0.1 - 1.0	0.0 - 2.8

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in safety population;
n = number of subjects in the specified category;
AE = Adverse Event;
SD = Standard deviation;
*a - Reasons for admission could be multiple.
*b - No imputation when end date of hospitalization is missing.
*c - Total duration is the sum of durations of all hospitalizations.
*d - Hospitalization Duration relative to Exposure = Duration of Hospitalization / Duration of Therapy.
Note: The table only summarizes hospitalization within 90 days of study treatment discontinuation.

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tho.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tho.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADHO

Table ANN.2.18. Supportive Care: Selected Concomitant Medications, Transfusions, and Procedures
Full Analysis Set
I4T-MC-JVDD

Class of Concomitant Medication	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Subjects with >=1 Medication	50 (98.0)	536 (98.0)	8 (100.0)	594 (98.0)
Gastric acid suppressants	22 (43.1)	271 (49.5)	5 (62.5)	298 (49.2)
proton pump inhibitors	20 (39.2)	249 (45.5)	5 (62.5)	274 (45.2)
H2 antagonists	2 (3.9)	32 (5.9)	0	34 (5.6)
antacids / protectants	2 (3.9)	31 (5.7)	1 (12.5)	34 (5.6)
Antidiarrheals	3 (5.9)	49 (9.0)	3 (37.5)	55 (9.1)
Antiemetics	14 (27.5)	203 (37.1)	4 (50.0)	221 (36.5)
propulsives	7 (13.7)	119 (21.8)	1 (12.5)	127 (21.0)
5HT3 antagonists	8 (15.7)	103 (18.8)	4 (50.0)	115 (19.0)
phenothiazines or antipsychotics	3 (5.9)	30 (5.5)	1 (12.5)	34 (5.6)
NK1 antagonists	0	4 (0.7)	0	4 (0.7)
alkaloids	0	2 (0.4)	0	2 (0.3)
Corticosteroids	2 (3.9)	141 (25.8)	0	143 (23.6)
Analgesics	31 (60.8)	253 (46.3)	5 (62.5)	289 (47.7)
opioids	15 (29.4)	178 (32.5)	3 (37.5)	196 (32.3)
non-steroidal anti-inflammatory drugs (NSAIDs)	17 (33.3)	85 (15.5)	2 (25.0)	104 (17.2)
paracetamol	5 (9.8)	96 (17.6)	2 (25.0)	103 (17.0)
other analgesics	6 (11.8)	41 (7.5)	0	47 (7.8)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in population; n = number of subjects in the specified category;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsupcare.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsupcare.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADCM, ADPR
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/observed/shared/cutoff/CM, PR

Supportive Care: Selected Concomitant Medications, Transfusions, and Procedures page 2 of 3
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Class of Concomitant Medication	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Antihypertensives or diuretics	24 (47.1)	247 (45.2)	4 (50.0)	275 (45.4)
antihypertensives	15 (29.4)	182 (33.3)	3 (37.5)	200 (33.0)
diuretics	15 (29.4)	117 (21.4)	1 (12.5)	133 (21.9)
Anticoagulants	9 (17.6)	96 (17.6)	3 (37.5)	108 (17.8)
low molecular weight heparin	5 (9.8)	70 (12.8)	1 (12.5)	76 (12.5)
other anticoagulants	4 (7.8)	30 (5.5)	2 (25.0)	36 (5.9)
Antiplatelets	8 (15.7)	44 (8.0)	2 (25.0)	54 (8.9)
acetylsalicylic acid	7 (13.7)	36 (6.6)	2 (25.0)	45 (7.4)
other antiplatelets	1 (2.0)	10 (1.8)	0	11 (1.8)
Nutritional support	7 (13.7)	67 (12.2)	5 (62.5)	79 (13.0)
parenteral nutrition	4 (7.8)	34 (6.2)	2 (25.0)	40 (6.6)
enteral nutrition	1 (2.0)	31 (5.7)	2 (25.0)	34 (5.6)
appetite stimulant	3 (5.9)	9 (1.6)	2 (25.0)	14 (2.3)
H1 Antagonists	0	35 (6.4)	0	35 (5.8)
Antimicrobial agents	10 (19.6)	153 (28.0)	5 (62.5)	168 (27.7)
antibiotics	10 (19.6)	139 (25.4)	4 (50.0)	153 (25.2)
antifungals	0	25 (4.6)	2 (25.0)	27 (4.5)
G-CSF	0	63 (11.5)	2 (25.0)	65 (10.7)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in population; n = number of subjects in the specified category;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsupcare.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsupcare.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADCM, ADPR
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/observed/shared/cutoff/CM, PR

Supportive Care: Selected Concomitant Medications, Transfusions, and Procedures page 3 of 3
Full analysis set 09:27 02NOV2021
I4T-MC-JVDD PDPM

Class of Concomitant Medication	Ram mono (N=51) n (%)	Ram + PclTax (N=547) n (%)	Ram + Other (N=8) n (%)	Total (N=606) n (%)
Bone-Modifying Agents	7 (13.7)	29 (5.3)	1 (12.5)	37 (6.1)
Erythropoiesis-Stimulating Agents (Esas)	1 (2.0)	26 (4.8)	0	27 (4.5)
Any transfusion	7 (13.7)	64 (11.7)	3 (37.5)	74 (12.2)
packed red blood cells	6 (11.8)	56 (10.2)	2 (25.0)	64 (10.6)
whole blood	2 (3.9)	7 (1.3)	1 (12.5)	10 (1.7)
platelets	1 (2.0)	2 (0.4)	0	3 (0.5)
Concomitant procedures	7 (13.7)	57 (10.4)	1 (12.5)	65 (10.7)
Abdominal cavity drainage	6 (11.8)	34 (6.2)	1 (12.5)	41 (6.8)
RADIOTHERAPY	2 (3.9)	14 (2.6)	0	16 (2.6)
Gastrointestinal tube insertion	1 (2.0)	9 (1.6)	0	10 (1.7)

Database lock date: 19AUG2021.
Abbreviations: N = number of subjects in population; n = number of subjects in the specified category;

Program Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/programs/primary/tfl/tsupcare.sas
Output Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/output/shared/tsupcare.rtf
Data Location: /lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/analysis/shared/ADSL, ADCM, ADPR
/lillyce/prd/ly3009806/i4t_mc_jvdd/final/data/observed/shared/cutoff/CM, PR

Table ANN.2.19. Summary of Elderly Population in Completed Phase 3 Studies

	Number of Patients (%)	
Study	**Ramucirumab**	**Placebo**
REGARD (N)	236	115
<65 years	152 (64.4)	69 (60.0)
≥65 years and <75 years	59 (25.0)	31 (27.0)
≥75 years and <85 years	24 (10.2)	14 (12.2)
>85 years	1 (0.4)	1 (0.9)
RAINBOW (N)	327	329
<65 years	205 (62.7)	207 (62.9)
≥65 years and <75 years	101 (30.9)	105 (31.9)
≥75 years and <85 years	21 (6.4)	17 (5.2)
>85 years	0	0
REVEL (N)	627	618
<65 years	390 (62.2)	404 (65.4)
≥65 years and <75 years	192 (30.6)	175 (28.3)
≥75 years and <85 years	44 (7.0)	38 (6.1)
>85 years	1 (0.2)	1 (0.2)
ROSE (N)	752	382
<65 years	625 (83.1)	322 (84.3)
≥65 years and <75 years	116 (15.4)	57 (14.9)
≥75 years and <85 years	11 (1.5)	3 (0.8)
>85 years	0	0
REACH (N)	277	276
<65 years	145 (52.3)	154 (55.8)
≥65 years and <75 years	83 (30.0)	79 (28.6)
≥75 years and <85 years	46 (16.6)	42 (15.2)
>85 years	3 (1.1)	2 (0.4)
RAISE (N)	529	528
<65 years	320 (60.5)	316 (59.8)
≥65 years and <75 years	158 (29.9)	171 (32.4)
≥75 years and <85 years	51 (9.6)	39 (7.4)
>85 years	0	2 (0.4)
REACH-2 (N)	197	95
<65 years	102 (51.8)	49 (51.6)
≥65 years and <75 years	58 (29.4)	35 (36.8)
≥75 years and <85 years	35 (17.8)	10 (10.5)
>85 years	2 (1.0)	1 (1.1)
RAINFALL (N)	323	315
<65 years	202 (62.5)	199 (63.2)
≥65 years and <75 years	101 (31.3)	91 (28.9)
≥75 years and <85 years	19 (5.9)	24 (7.6)
>85 years	1 (0.3)	1 (0.3)
RELAY (N)	221	225
<65 years	102 (46.2)	114 (50.7)
≥65 years and <75 years	90 (40.7)	82 (36.4)
≥75 years and <85 years	28 (12.7)	28 (12.4)
>85 years	1 (0.5)	1 (0.4)

Abbreviation: N = number of patients in the safety population.
Sources: prd/ly3009806/integrations/idb/programs_stat/crc_2ndline/tfl_output/rmp/tage_ramph3.rtf;
prd\ly3009806\rmpdec2018\output\t_2_REACH-2.rtf;
RELAY 2.7.4 Summary of Clinical Safety Table 2.7.4.4.