Clinical trial results:
A Randomized Multicenter Phase 3 Study of Milademetan Versus Trabectedin in Patients with Dedifferentiated Liposarcoma

Summary

EudraCT number	2021-001394-23
Trial protocol	FR AT PL DE BE IE IT
Global end of trial date	01 March 2023

Results information

Result version number	v1 (current)
This version publication date	03 April 2024
First version publication date	03 April 2024

Trial information

Trial identification

Sponsor protocol code	RAIN-3201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rain Oncology Inc.
Sponsor organisation address	8000 Jarvis Avenue, Suite 204, Newark, United States, 94560
Public contact	Clinical Trial information, Rain Oncology Inc., 1 5109535559, info@rainoncology.com
Scientific contact	Clinical Trial information, Rain Oncology Inc., 1 5109535559, info@rainoncology.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	01 March 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 March 2023
Global end of trial reached?	Yes
Global end of trial date	01 March 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare progression-free survival (PFS) between the milademetan treatment arm and trabectedin control arm, as determined by blinded independent central review (BICR), in patients with unresectable or metastatic dedifferentiated (DD) liposarcoma, with or without a well-differentiated (WD) component, who progressed on 1 or more prior systemic therapies including at least 1 anthracycline-based therapy.

Protection of trial subjects:

This study was to be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki and with other applicable regulatory requirements.
Before the start of the study, the study protocol and/or other relevant documents were approved by the IECs/IRBs/Competent Authorities, in accordance with local legal requirements.
Before each patient was admitted to the study, written informed consent was obtained from the patient according to the regulatory and legal requirements of the participating country. The consent form was signed, dated, and retained by the Investigator or designee (as listed on the Delegation of Authority Log) as part of the study records.
An Independent Data Monitoring Committee (IDMC) reviewed unblinded safety data during the course of the study and made recommendations to the Sponsor as applicable and outlined in the IDMC charter.

Background therapy: -

Evidence for comparator:

Trabectedin was the chosen active control treatment because it has been approved as a second-line therapy by the FDA for patients with liposarcoma (LPS) or leiomyosarcoma who received a prior anthracycline-containing regimen. Trabectedin was approved for LPS based on improved PFS. In this study, the primary endpoint was to compare PFS, as determined by BICR, between patients receiving milademetan versus trabectedin.

Actual start date of recruitment	07 July 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Georgia: 7
Country: Number of subjects enrolled	Hong Kong: 4
Country: Number of subjects enrolled	Korea, Republic of: 10
Country: Number of subjects enrolled	Taiwan: 8
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 61
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Spain: 19

Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 7
Country: Number of subjects enrolled	Italy: 20
Worldwide total number of subjects	175
EEA total number of subjects	73

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	98
From 65 to 84 years	77
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

A total of 200 patients were screened and 175 were randomized across 58 study sites in Austria, Belgium, Canada, France, Georgia, Germany, Hong Kong, Italy, Poland, South Korea, Spain, Taiwan, UK and the US. First patient signed informed consent form: 07 July 2021. First patient randomized/enrolled: 13 July 2021.

Pre-assignment

Screening details:

Male and female patients at least 18 years of age with histologically confirmed DDLPS, with or without a well-differentiated (WD) component, by local pathologic review. They must have received 1 or more systemic cancer therapy regimens, including at least 1 anthracycline-based regimen, and had radiographic progressive disease (per RECIST v1.1).

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Milademetan

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Milademetan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Administered 260 mg QD orally on Days 1 to 3 and Days 15 to 17 of each 28-day cycle

Arm title	Trabectedin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Trabectedin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 1.5 mg/m2 BSA as a 24-hour IV infusion, every 3 weeks (ie, 21-day cycles) through a central venous line

Number of subjects in period 1	Milademetan	Trabectedin
Started	86	89
Completed	0	0
Not completed	86	89
Adverse event, serious fatal	43	30
Consent withdrawn by subject	8	13
Physician decision	1	1
1 d/c study w/reason "progression disease"	-	1
Lost to follow-up	-	2
Ongoing on study when study stopped	34	42

Baseline characteristics

Reporting groups	
Reporting group title	Milademetan
Reporting group description: -	
Reporting group title	Trabectedin
Reporting group description: -	

Reporting group values	Milademetan	Trabectedin	Total
Number of subjects	86	89	175
Age categorical Units: Subjects			
Adults (18-64 years)	51	47	98
From 65-84 years	35	42	77
Gender categorical Units: Subjects			
Female	40	36	76
Male	46	53	99
Tumor status Units: Subjects			
Locally advanced	23	13	36
Metastatic	63	76	139
Number of lines of therapy in metastatic setting Units: Subjects			
Zero	21	26	47
One	38	32	70
Two	14	15	29
Three	7	9	16
Three plus	6	7	13
ECOG PS Units: Subjects			
Zero	45	47	92
One	41	42	83
Number of prior treatments Units: Subjects			
≤ 2	65	65	130
> 2	21	24	45
Race Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	15	12	27
Black or African American	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	1
White	59	63	122
Unknown	11	12	23
Ethnicity Units: Subjects			

Hispanic or Latino	3	6	9
Not Hispanic or Latino	71	72	143
Not reported	12	11	23
Time from initial diagnosis			
Units: year			
arithmetic mean	4.27	4.83	
standard deviation	± 4.301	± 4.102	-
Time from metastatic diagnosis			
Units: year			
arithmetic mean	1.54	1.75	
standard deviation	± 1.523	± 2.112	-

End points

End points reporting groups

Reporting group title	Milademetan
Reporting group description: -	
Reporting group title	Trabectedin
Reporting group description: -	

Primary: Progression Free Survival (PFS) as determined by BICR

End point title	Progression Free Survival (PFS) as determined by BICR

End point description:

The primary efficacy endpoint was to demonstrate whether there was an increase in PFS in patients treated with milademetan versus trabectedin in the ITT population. Tumor response was to be assessed in accordance with RECIST version 1.1 by BICR. The study did not meet its primary endpoint, PFS by BICR.

End point type	Primary

End point timeframe:

PFS=the time from randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause. When 105 BICR assessed PFS events had occurred, the primary PFS analysis was to be performed.

End point values	Milademetan	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[1]	89[2]		
Units: month				
median (confidence interval 95%)	3.6 (2.1 to 4.1)	2.2 (1.9 to 4.2)		

Notes:

[1] - a. Pts with PFS events: 61
b. Pts censored: 25
c. Kaplan-Meier estimate of PFS rate 6 month: 25.7%
[2] - a. Pts with PFS events: 54
b. Pts censored: 35
c. Kaplan-Meier estimate of PFS rate 6 month: 26.5%

Statistical analyses

Statistical analysis title	Statistical analysis for PFS

Statistical analysis description:

2-sided, log-rank test was used to compare milademetan vs trabectedin at a significance value of 0.05. PFS was summarized using Kaplan-Meier. Median event times & corresponding 2-sided 95% CIs were provided. A log-rank test stratified by ECOG (0 versus 1) & number of prior lines of therapy (≤2 vs >2) were used to test the null hypothesis of no difference in the PFS between the 2 treatment groups at a significance level of 0.05.

Comparison groups	Milademetan v Trabectedin

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.53 [4]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.29

Notes:

[3] - The p-value from the stratified log-rank test was 0.53, which indicates there was no statistical difference in BICR PFS between 2 treatment arms.
A stratified Cox proportional hazard model was used to estimate the hazard ratio. Unstratified analysis was also provided as a sensitivity analysis.
[4] - Stratified log-rank test, p-value = 0.53
Stratified Cox proportional hazards model p-value = 0.533

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

To compare the milademetan treatment arm versus the trabectedin control arm for the OS. In the ITT Population, survival data was to be collected throughout the study treatment phase and long-term follow-up. Survival follow-up after patient discontinuation of investigational product was to be conducted approximately every 12 weeks to assess for survival until subject's loss to follow-up or death, or for 24 months following the final dose of study drug, whichever came first.
The study was not powered to address OS as of the cutoff date and the results presented in this report should be understood in this context. There were no statistically significant differences between the study arms in OS. OS was to be followed after the primary PFS analysis, and the final analysis of OS was to be performed 24 months after the last dose; however, the study was prematurely discontinued.

End point type	Secondary

End point timeframe:

OS measured from randomized date to death date by any cause, censored at last date known alive on or prior to the data cutoff date.

End point values	Milademetan	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[5]	89[6]		
Units: month				
median (confidence interval 95%)	9.5 (6.5 to 12.8)	10.2 (8.6 to 99999)		

Notes:

[5] - a. Pts. with death: 44 b. Reason censored: i. ended study not due to death=13 ii. data cut-off=29

[6] - 1.Pt w/death: 31; 2.Reason censored: a.ended study not due to death=21 b.data cut-off=37; "99999"=NE

Statistical analyses

Statistical analysis title	Statistical analysis for OS

Statistical analysis description:

OS was summarized using the Kaplan-Meier method and displayed graphically when appropriate. Median event times and the corresponding 2-sided 95% CIs were provided. The OS rate (proportion of patients

surviving) at various time points (e.g., 3, 6, and 12 months) was calculated using Kaplan-Meier methods.

Comparison groups	Trabectedin v Milademetan
Number of subjects included in analysis	175
Analysis specification	Post-hoc
Analysis type	other[7]
P-value	= 0.308 [8]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	1.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.04

Notes:

[7] - The Kaplan-Meier estimate of OS rate at 6 months was 64.7% (95% CI: 53.3, 73.9) for the Milademetan Arm, and was 71.1% (95% CI: 59.4, 80.0) for the Trabectedin Arm. The OS results using the unstratified Kaplan-Meier and Cox models, the CCDD Population, or the Per Protocol Population reflect those results found in the ITT Population.
[8] - Stratified log-rank test, p-value = 0.308
Stratified Cox proportional hazards model p-value = 0.310

Secondary: Disease Control Rate (DCR)

End point title	Disease Control Rate (DCR)

End point description:

To compare the milademetan treatment arm versus the trabectedin control arm for the DCR (ITT Population) by BICR and Investigator assessment. The DCR for each treatment group was estimated by dividing the number of patients with CR, PR, or SD for at least 16 weeks by the number of patients enrolled in the respective treatment group. Similar analysis as for ORR was to be performed for DCR. There were no statistically significant differences between the study arms in Investigator-assessed DCR.

End point type	Secondary

End point timeframe:

The DCR was to be measured as the percentage of patients who have achieved CR, PR, or SD for at least 16 weeks according to RECIST version 1.1 recorded in the period between first study drug dose and disease progression or death to any cause.

End point values	Milademetan	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[9]	89[10]		
Units: percent				
number (confidence interval 95%)				
By BICR, Patients with disease control	33.7 (23.9 to 44.7)	27.0 (18.1 to 37.4)		
Investigator-assessed, Patients with disease contr	40.7 (30.2 to 51.8)	29.2 (20.1 to 39.8)		

Notes:

[9] - By BICR, Exact 95% CI of DCR (%): 23.9, 44.7
Invgtor-assessed, Exact 95% CI of DCR (%): 30.2, 51.8
[10] - By BICR, Exact 95% CI of DCR (%): 18.1, 37.4
Invgtor-assessed, Exact 95% CI of DCR (%): 20.1, 39.8

Statistical analyses

Statistical analysis title	Difference in DCR By BICR
Comparison groups	Milademetan v Trabectedin
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.332
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in DCR
Point estimate	6.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.8
upper limit	20.4

Statistical analysis title	Difference in DCR for Investigator-assessed
Comparison groups	Milademetan v Trabectedin
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.112
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in DCR
Point estimate	11.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	25.5

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)

End point description:

To compare the milademetan treatment arm versus the trabectedin control arm for the ORR (ITT Population) by BICR and Investigator assessment. The ORR for each treatment group was estimated by dividing the number of patients with confirmed CR or PR by the number of patients enrolled in the respective treatment group. There were no statistically significant differences between the study arms in Investigator-assessed ORR.

End point type	Secondary

End point timeframe:

The ORR was defined as the percentage of patients who achieve a confirmed CR or PR according to RECIST version 1.1 that must be confirmed by a subsequent tumor assessment at least 4 weeks after the initial observed response.

End point values	Milademetan	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[11]	89[12]		
Units: percent				
number (confidence interval 95%)				
By BICR, Patients with an OR	4.7 (1.3 to 11.5)	3.4 (0.7 to 9.5)		
Investigator-assessed, Patients with an OR	10.5 (4.9 to 18.9)	2.2 (0.3 to 7.9)		

Notes:

[11] - By BICR, Exact 95% CI of ORR (%): 1.3, 11.5
Invgtor-assessed, Exact 95% CI of ORR (%): 4.9, 18.9
[12] - By BICR, Exact 95% CI of ORR (%): 0.7, 9.5
Invgtor-assessed, Exact 95% CI of ORR (%): 0.3, 7.9

Statistical analyses

Statistical analysis title	Difference in ORR By BICR
Comparison groups	Trabectedin v Milademetan
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.667
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in ORR
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	7.1

Statistical analysis title	Difference in ORR Investigator-assessed
Comparison groups	Milademetan v Trabectedin
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.026
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in ORR
Point estimate	8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	15.4

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

To compare the milademetan treatment arm versus the trabectedin control arm for the DOR (ITT Population) by BICR and Investigator assessment. The DOR was not evaluable (NE) in either arm.

End point type	Secondary

End point timeframe:

The time from date of first response to date of disease progression or death.DOR was to be summarized by treatment group for the patients who had an ORR.If there were patients that continued to respond, they would be censored at their last tumor assessmen

End point values	Milademetan	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[13]	89[14]		
Units: month				
median (confidence interval 95%)				
DOR By BICR	99999 (99999 to 99999)	99999 (3.5 to 99999)		
DOR By Investigator	5.7 (3.5 to 99999)	6.3 (6.3 to 99999)		

Notes:

[13] - "99999" equals not evaluable (NE)

[14] - "99999" equals NE

Statistical analyses

Statistical analysis title	DOR By BICR
Comparison groups	Milademetan v Trabectedin
Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.317 [15]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	5.83

Notes:

[15] - Unstratified log-rank test, p-value = 0.317
Unstratified Cox proportional hazards model p-value = 0.999

"0" for lower limit equals NE

Statistical analysis title	DOR By Investigator
Comparison groups	Trabectedin v Milademetan

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.484 [16]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	2.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.26
upper limit	50.51

Notes:

[16] - Unstratified log-rank test, p-value = 0.484
Unstratified Cox proportional hazards model p-value = 0.492

Secondary: Progression Free Survival (PFS) as determined by Investigator

End point title	Progression Free Survival (PFS) as determined by Investigator

End point description:

To compare the milademetan treatment arm versus the trabectedin control arm for the PFS (ITT Population) by Investigator assessment. There were no statistically significant differences between the study arms in Investigator-assessed PFS.

End point type	Secondary

End point timeframe:

PFS was defined as the time from randomization to the earliest date of the first objective documentation of radiographic disease progression or death due to any cause.

End point values	Milademetan	Trabectedin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[17]	89[18]		
Units: month				
median (confidence interval 95%)	3.7 (2.1 to 5.4)	2.1 (1.9 to 3.9)		

Notes:

[17] - a. Pts with PFS events: 62
b. Pts censored: 24
c. Kaplan-Meier estimate of PFS rate 6 month: 30.7%
[18] - a. Pts with PFS events: 58
b. Pts censored: 31
c. Kaplan-Meier estimate of PFS rate 6 month: 29.3%

Statistical analyses

Statistical analysis title	Statistical analysis for PFS by Investigator

Statistical analysis description:

The treatment difference in the investigator assessed (IA) PFS was to be assessed w/the product limit estimate of median time to event w/95% CI. Differences between treatment groups were to be examined using a stratified log rank test statistic. A stratified Cox Proportional hazard model was to be used to estimate the hazard ratio. Unstratified log-rank test and Cox model was to be performed as sensitivity analysis. IA PFS was to be displayed using a Kaplan-Meier survival plot.

Comparison groups	Trabectedin v Milademetan

Number of subjects included in analysis	175
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.219 [20]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.15

Notes:

[19] - Interpretation of the PFS by Investigator results was unchanged using the unstratified Kaplan-Meier and Cox models, all observed events, the CCDD Population, or the Per Protocol Population and reflect those found in the ITT Population.

[20] - Stratified Log-rank Test, p-value = 0.219
Stratified Cox Proportional Hazards Model p-value = 0.224

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After signing informed consent but before initiation of study drug, an event was to be entered on the AE CRF if related to protocol-required procedures.After 1st study drug dose, all AEs were to be entered on AE CRF until 30days after last study drug dose

Adverse event reporting additional description:

All AEs were to be followed until resolution or until stable, if possible.The Sponsor may have requested certain AEs be followed beyond the protocol-defined f/u period. Investigator must have reported all SAEs regardless of causality within 24hrs of learning of event.Incidence of SAEs occurring in >1 Patient reported in SAE table. Safety Population

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Milademetan
Reporting group description: -	
Reporting group title	Trabectedin

Reporting group description: -

Serious adverse events	Milademetan	Trabectedin	
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 86 (36.05%)	38 / 79 (48.10%)	
number of deaths (all causes)	44	29	
number of deaths resulting from adverse events	1	5	
Investigations			
Platelet count decreased			
subjects affected / exposed	3 / 86 (3.49%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	14 / 86 (16.28%)	15 / 79 (18.99%)	
occurrences causally related to treatment / all	8 / 16	30 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	8 / 86 (9.30%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	8 / 13	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 86 (0.00%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 86 (0.00%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Small intestinal obstruction			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			

subjects affected / exposed	0 / 86 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal obstruction			
subjects affected / exposed	0 / 86 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Intestinal perforation			
subjects affected / exposed	1 / 86 (1.16%)	0 / 79 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	3 / 86 (3.49%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 86 (0.00%)	5 / 79 (6.33%)	
occurrences causally related to treatment / all	0 / 0	3 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 86 (0.00%)	3 / 79 (3.80%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			

subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
COVID-19 pneumonia			
subjects affected / exposed	0 / 86 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Neutropenic sepsis			
subjects affected / exposed	0 / 86 (0.00%)	1 / 79 (1.27%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Milademetan	Trabectedin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	86 / 86 (100.00%)	77 / 79 (97.47%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	5 / 86 (5.81%)	3 / 79 (3.80%)	
occurrences (all)	7	5	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 86 (2.33%)	3 / 79 (3.80%)	
occurrences (all)	2	3	
Hypertension			

subjects affected / exposed	2 / 86 (2.33%)	2 / 79 (2.53%)	
occurrences (all)	3	2	
Haematoma			
subjects affected / exposed	2 / 86 (2.33%)	0 / 79 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	30 / 86 (34.88%)	24 / 79 (30.38%)	
occurrences (all)	47	42	
Asthenia			
subjects affected / exposed	28 / 86 (32.56%)	18 / 79 (22.78%)	
occurrences (all)	63	32	
Oedema peripheral			
subjects affected / exposed	4 / 86 (4.65%)	9 / 79 (11.39%)	
occurrences (all)	6	11	
Pyrexia			
subjects affected / exposed	3 / 86 (3.49%)	6 / 79 (7.59%)	
occurrences (all)	4	7	
Chills			
subjects affected / exposed	2 / 86 (2.33%)	4 / 79 (5.06%)	
occurrences (all)	2	4	
Mucosal inflammation			
subjects affected / exposed	2 / 86 (2.33%)	4 / 79 (5.06%)	
occurrences (all)	2	4	
Device related thrombosis			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Localised oedema			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	3	
Pain			
subjects affected / exposed	0 / 86 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Respiratory, thoracic and mediastinal disorders			

Rhinorrhoea			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Pulmonary embolism			
subjects affected / exposed	0 / 86 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Pleural effusion			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Hiccups			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Dyspnoea exertional			
subjects affected / exposed	1 / 86 (1.16%)	3 / 79 (3.80%)	
occurrences (all)	1	3	
Productive cough			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	3	
Acute respiratory failure			
subjects affected / exposed	2 / 86 (2.33%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Dyspnoea			
subjects affected / exposed	5 / 86 (5.81%)	9 / 79 (11.39%)	
occurrences (all)	6	11	
Cough			
subjects affected / exposed	5 / 86 (5.81%)	11 / 79 (13.92%)	
occurrences (all)	5	12	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Anxiety			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Insomnia			

subjects affected / exposed	3 / 86 (3.49%)	2 / 79 (2.53%)	
occurrences (all)	3	2	
Investigations			
Platelet count decreased			
subjects affected / exposed	21 / 86 (24.42%)	9 / 79 (11.39%)	
occurrences (all)	58	42	
Blood creatinine increased			
subjects affected / exposed	8 / 86 (9.30%)	7 / 79 (8.86%)	
occurrences (all)	8	11	
White blood cell count decreased			
subjects affected / exposed	12 / 86 (13.95%)	8 / 79 (10.13%)	
occurrences (all)	19	40	
Neutrophil count decreased			
subjects affected / exposed	20 / 86 (23.26%)	15 / 79 (18.99%)	
occurrences (all)	51	58	
Blood alkaline phosphatase increased			
subjects affected / exposed	4 / 86 (4.65%)	12 / 79 (15.19%)	
occurrences (all)	5	20	
Lymphocyte count decreased			
subjects affected / exposed	3 / 86 (3.49%)	5 / 79 (6.33%)	
occurrences (all)	11	12	
Weight decreased			
subjects affected / exposed	3 / 86 (3.49%)	4 / 79 (5.06%)	
occurrences (all)	3	6	
Alanine aminotransferase increased			
subjects affected / exposed	4 / 86 (4.65%)	19 / 79 (24.05%)	
occurrences (all)	8	42	
Blood bilirubin increased			
subjects affected / exposed	4 / 86 (4.65%)	2 / 79 (2.53%)	
occurrences (all)	6	2	
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 86 (2.33%)	12 / 79 (15.19%)	
occurrences (all)	3	25	
Electrocardiogram QT prolonged			

subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	3	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 86 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 86 (0.00%)	4 / 79 (5.06%)	
occurrences (all)	0	4	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 86 (0.00%)	7 / 79 (8.86%)	
occurrences (all)	0	12	
International normalised ratio increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Transaminases increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	5	
Troponin T increased			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	2 / 86 (2.33%)	2 / 79 (2.53%)	
occurrences (all)	2	2	
Nervous system disorders			
Peripheral sensory neuropathy			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Tremor			
subjects affected / exposed	2 / 86 (2.33%)	0 / 79 (0.00%)	
occurrences (all)	4	0	
Taste disorder			
subjects affected / exposed	2 / 86 (2.33%)	0 / 79 (0.00%)	
occurrences (all)	3	0	

Syncope			
subjects affected / exposed	2 / 86 (2.33%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Sciatica			
subjects affected / exposed	2 / 86 (2.33%)	0 / 79 (0.00%)	
occurrences (all)	2	0	
Paraesthesia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	1	
Neuropathy peripheral			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	1	
Dizziness			
subjects affected / exposed	2 / 86 (2.33%)	3 / 79 (3.80%)	
occurrences (all)	2	3	
Headache			
subjects affected / exposed	7 / 86 (8.14%)	3 / 79 (3.80%)	
occurrences (all)	7	4	
Dysgeusia			
subjects affected / exposed	9 / 86 (10.47%)	6 / 79 (7.59%)	
occurrences (all)	12	8	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	35 / 86 (40.70%)	28 / 79 (35.44%)	
occurrences (all)	71	96	
Thrombocytopenia			
subjects affected / exposed	31 / 86 (36.05%)	11 / 79 (13.92%)	
occurrences (all)	137	30	
Neutropenia			
subjects affected / exposed	15 / 86 (17.44%)	13 / 79 (16.46%)	
occurrences (all)	42	28	
Leukopenia			
subjects affected / exposed	3 / 86 (3.49%)	3 / 79 (3.80%)	
occurrences (all)	3	12	
Lymphopenia			

subjects affected / exposed	3 / 86 (3.49%)	2 / 79 (2.53%)	
occurrences (all)	6	2	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	3 / 86 (3.49%)	0 / 79 (0.00%)	
occurrences (all)	4	0	
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	61 / 86 (70.93%)	45 / 79 (56.96%)	
occurrences (all)	118	81	
Vomiting			
subjects affected / exposed	38 / 86 (44.19%)	14 / 79 (17.72%)	
occurrences (all)	64	15	
Diarrhoea			
subjects affected / exposed	24 / 86 (27.91%)	21 / 79 (26.58%)	
occurrences (all)	46	28	
Abdominal pain			
subjects affected / exposed	16 / 86 (18.60%)	9 / 79 (11.39%)	
occurrences (all)	21	15	
Constipation			
subjects affected / exposed	10 / 86 (11.63%)	20 / 79 (25.32%)	
occurrences (all)	15	25	
Dyspepsia			
subjects affected / exposed	6 / 86 (6.98%)	5 / 79 (6.33%)	
occurrences (all)	6	6	
Abdominal distension			
subjects affected / exposed	3 / 86 (3.49%)	3 / 79 (3.80%)	
occurrences (all)	3	3	
Dry mouth			
subjects affected / exposed	3 / 86 (3.49%)	3 / 79 (3.80%)	
occurrences (all)	4	3	
Abdominal pain upper			

subjects affected / exposed	2 / 86 (2.33%)	2 / 79 (2.53%)	
occurrences (all)	4	2	
Dysphagia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	3	
Flatulence			
subjects affected / exposed	2 / 86 (2.33%)	2 / 79 (2.53%)	
occurrences (all)	3	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 86 (1.16%)	3 / 79 (3.80%)	
occurrences (all)	1	4	
Stomatitis			
subjects affected / exposed	1 / 86 (1.16%)	4 / 79 (5.06%)	
occurrences (all)	1	4	
Abdominal discomfort			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Proctalgia			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hepatic cytolysis			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	3	
Cholestasis			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	4	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Alopecia			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	3	1	
Nail disorder			

subjects affected / exposed	3 / 86 (3.49%)	0 / 79 (0.00%)	
occurrences (all)	3	0	
Hyperhidrosis			
subjects affected / exposed	3 / 86 (3.49%)	0 / 79 (0.00%)	
occurrences (all)	4	0	
Dry skin			
subjects affected / exposed	3 / 86 (3.49%)	1 / 79 (1.27%)	
occurrences (all)	3	1	
Renal and urinary disorders			
Proteinuria			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Haematuria			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	3	
Chronic kidney disease			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Acute kidney injury			
subjects affected / exposed	1 / 86 (1.16%)	5 / 79 (6.33%)	
occurrences (all)	1	5	
Dysuria			
subjects affected / exposed	2 / 86 (2.33%)	2 / 79 (2.53%)	
occurrences (all)	2	3	
Musculoskeletal and connective tissue disorders			
Rhabdomyolysis			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	3	
Neck pain			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	5	
Musculoskeletal pain			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	3	
Arthralgia			

subjects affected / exposed	0 / 86 (0.00%)	5 / 79 (6.33%)	
occurrences (all)	0	6	
Myalgia			
subjects affected / exposed	2 / 86 (2.33%)	5 / 79 (6.33%)	
occurrences (all)	2	8	
Muscular weakness			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	1	
Flank pain			
subjects affected / exposed	2 / 86 (2.33%)	1 / 79 (1.27%)	
occurrences (all)	2	1	
Pain in extremity			
subjects affected / exposed	3 / 86 (3.49%)	3 / 79 (3.80%)	
occurrences (all)	3	3	
Back pain			
subjects affected / exposed	5 / 86 (5.81%)	2 / 79 (2.53%)	
occurrences (all)	6	2	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Device related infection			
subjects affected / exposed	0 / 86 (0.00%)	2 / 79 (2.53%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	3	
Urinary tract infection			
subjects affected / exposed	2 / 86 (2.33%)	4 / 79 (5.06%)	
occurrences (all)	3	4	
Oral candidiasis			
subjects affected / exposed	4 / 86 (4.65%)	0 / 79 (0.00%)	
occurrences (all)	4	0	
COVID-19			
subjects affected / exposed	7 / 86 (8.14%)	5 / 79 (6.33%)	
occurrences (all)	7	5	

Metabolism and nutrition disorders			
Hyperphosphataemia			
subjects affected / exposed	1 / 86 (1.16%)	2 / 79 (2.53%)	
occurrences (all)	1	2	
Hyperglycaemia			
subjects affected / exposed	1 / 86 (1.16%)	3 / 79 (3.80%)	
occurrences (all)	1	4	
Hyponatraemia			
subjects affected / exposed	2 / 86 (2.33%)	5 / 79 (6.33%)	
occurrences (all)	2	7	
Hypoalbuminaemia			
subjects affected / exposed	2 / 86 (2.33%)	6 / 79 (7.59%)	
occurrences (all)	2	8	
Hyperkalaemia			
subjects affected / exposed	2 / 86 (2.33%)	4 / 79 (5.06%)	
occurrences (all)	2	4	
Dehydration			
subjects affected / exposed	2 / 86 (2.33%)	4 / 79 (5.06%)	
occurrences (all)	3	5	
Vitamin B12 deficiency			
subjects affected / exposed	3 / 86 (3.49%)	1 / 79 (1.27%)	
occurrences (all)	3	1	
Hypomagnesaemia			
subjects affected / exposed	3 / 86 (3.49%)	3 / 79 (3.80%)	
occurrences (all)	3	3	
Hypokalaemia			
subjects affected / exposed	4 / 86 (4.65%)	5 / 79 (6.33%)	
occurrences (all)	6	6	
Hypophosphataemia			
subjects affected / exposed	5 / 86 (5.81%)	2 / 79 (2.53%)	
occurrences (all)	6	2	
Decreased appetite			
subjects affected / exposed	25 / 86 (29.07%)	17 / 79 (21.52%)	
occurrences (all)	32	22	
Hypocalcaemia			

subjects affected / exposed occurrences (all)	1 / 86 (1.16%) 1	4 / 79 (5.06%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 May 2021	• Made the following updates to the patient selection criteria: o Required documentation of advanced unresectable and/or metastatic disease o Added requirements for anticoagulation medication and antihypertensive medication o Revised the systolic and diastolic parameters • Added criteria for treatment beyond progression
20 May 2021	• Updated milademetan dose modification guidelines to recommend discontinuation for Grade 3 and 4 AEs that do not resolve to Grade 1 within 4 weeks; resumption after Grade 4 nonhematologic AEs must be discussed with the Medical Monitor; required discontinuation for a recurrent Grade 4 event.
18 March 2022	• Changed the definition of DCR from patients who achieve complete response, partial response, or stable disease for at least 8 weeks to patients who achieve this for at least 16 weeks • Changed the definition of TEAEs to account for the possibility of new anticancer therapy starting before 30 days after a patient's last dose of study drug

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported