Clinical trial results:
Lurbinectedin Monotherapy in Patients with Progressive Malignant Pleural Mesothelioma. A Multicenter, Single-arm Phase II Trial

Summary

EudraCT number	2017-001016-11
Trial protocol	IT
Global end of trial date	22 March 2021

Results information

Result version number	v1 (current)
This version publication date	28 September 2022
First version publication date	28 September 2022

Trial information

Trial identification

Sponsor protocol code	SAKK17/16

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03213301
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Swiss Group for Clinical Cancer Research (SAKK)
Sponsor organisation address	Effingerstrasse 33, Bern, Switzerland, 3008
Public contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31 508 41 51, sakkcc@sakk.ch
Scientific contact	Head Regulatory Affairs, Swiss Group for Clinical Cancer Research (SAKK), +41 31 508 41 51, sakkcc@sakk.ch

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	11 June 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 March 2021
Global end of trial reached?	Yes
Global end of trial date	22 March 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess efficacy and safety of lurbinectedin monotherapy in patients with progressive malignant mesothelioma

Protection of trial subjects:

Protection of trial subjects was ensured by Safety Monitoring, i.e. assessment of adverse events, serious adverse events, adverse drug reactions, and the continous assessment of laboratory values and vital signs.

Background therapy:

All patients received standard antiemetic prophylaxis 30 minutes before each lurbinectedin treatment infusion, as follows: (i) Corticosteroids (dexamethasone i.v. at least 8 mg or equivalent; if institutional standard antiemetic dose is higher, institutional dose is allowed), (ii) Serotonin (5-HT3) antagonists (ondansetron at least 8 mg i.v. or equivalent).
If necessary, during treatment and in addition to the above, the duration of treatment with 5-HT3 antagonists and/or dexamethasone could be extended. Additional antiemetic agents (with the exception of aprepitant or equivalents) could be administered as appropriate.

Evidence for comparator:

N/A; single arm study

Actual start date of recruitment	06 October 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 17
Country: Number of subjects enrolled	Switzerland: 25
Worldwide total number of subjects	42
EEA total number of subjects	17

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	10
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment phase started September 28th, 2017 and was completed October 25th, 2018 after recruitment of 42 out of 39 planned patients. Twenty-five patients were enrolled at six sites in Switzerland and 17 patients at three sites in Italy.

Pre-assignment

Screening details:

Eligibility criteria of a patient were checked by the investigator. Once a patient fullfils all inclusion criteria and not any of the exclusion criteria, he/she was enrolled.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Lurbinectedin - Treatment arm

Arm description:

Lurbinectedin, 3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient’s withdrawal of consent.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	
Other name	Zepsyre, Zepzelca, PM01183
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w)

Number of subjects in period 1	Lurbinectedin - Treatment arm
Started	42
Completed	42

Period 2

Period 2 title	Treatment
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Lurbinectedin - Treatment arm

Arm description:

Lurbinectedin, 3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.
After treatment discontinuation patients were followed up for up to two years.

Arm type	Experimental
Investigational medicinal product name	Lurbinectedin
Investigational medicinal product code	
Other name	Zepsyre, Zepzelca, PM01183
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w)

Number of subjects in period 2	Lurbinectedin - Treatment arm
Started	42
Completed	0
Not completed	42
Physician decision	2
Consent withdrawn by subject	7
Treatment delay >6 weeks	1
Progressive disease	32

Baseline characteristics

Reporting groups	
Reporting group title	Lurbinectedin - Treatment arm

Reporting group description:

Lurbinectedin, 3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient's withdrawal of consent.

Reporting group values	Lurbinectedin - Treatment arm	Total	
Number of subjects	42	42	
Age categorical Units: Subjects			
Adults (18-64 years)	10	10	
From 65-84 years	32	32	
Gender categorical Units: Subjects			
Female	7	7	
Male	35	35	

End points

End points reporting groups

Reporting group title	Lurbinectedin - Treatment arm

Reporting group description:

Lurbinectedin, 3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient’s withdrawal of consent.

Reporting group title	Lurbinectedin - Treatment arm

Reporting group description:

Lurbinectedin, 3.2 mg/m2 by intravenous infusion on day one every three weeks (q3w) until disease progression, unacceptable toxicity or patient’s withdrawal of consent.
After treatment discontinuation patients were followed up for up to two years.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

Defined as all patients who received at least one dose of trial treatment, excluding patients with major eligibility violations.

Subject analysis set title	PPS
Subject analysis set type	Per protocol

Subject analysis set description:

Defined as a subset of patients of the FAS population excluding patients with major protocol violations.

Subject analysis set title	FAS | Subgroup Immunotherapy - Prior Immunotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in FAS receiving prior immunotherapy.

Subject analysis set title	FAS | Subgroup Immunotherapy - No Prior Immunotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in FAS receiving no prior immunotherapy.

Subject analysis set title	PPS | Subgroup Immunotherapy - Prior Immunotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in PPS receiving prior immunotherapy.

Subject analysis set title	PPS | Subgroup Immunotherapy - No prior Immunotherapy
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in PPS receiving no prior immunotherapy.

Subject analysis set title	FAS | Subgroup Histological type - Epithelioid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in FAS with histological type at initial diagnosis = Epithelioid

Subject analysis set title	FAS | Subgroup Histological type - Non-Epithelioid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in FAS with histological type at initial diagnosis = Non-epithelioid

Subject analysis set title	PPS | Subgroup Histological type - Epithelioid
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subgroup of patients in PPS with histological type at initial diagnosis = Epithelioid

Subject analysis set title	PPS | Subgroup Histological type - Non-epithelioid

Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in PPS with histological type at initial diagnosis = Non-epithelioid	
Subject analysis set title	FAS | Subgroup Prior PT-Pemetrexed - <6 months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in FAS with prior platinum-pemetrexed chemotherapy in <6 months	
Subject analysis set title	FAS | Subgroup Prior PT-Pemetrexed - ≥6 months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in FAS with prior platinum-pemetrexed chemotherapy in ≥6 months	
Subject analysis set title	PPS | Subgroup Prior PT-Pemetrexed - <6 months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in PPS with prior platinum-pemetrexed chemotherapy in <6 months	
Subject analysis set title	PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in PPS with prior platinum-pemetrexed chemotherapy in ≥6 months	
Subject analysis set title	FAS | Subgroup Subsequent treatment received
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in FAS starting subsequent systemic further treatment.	
Subject analysis set title	FAS | Subgroup Subsequent treatment not received
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in FAS not starting subsequent systemic further treatment.	
Subject analysis set title	PPS | Subgroup Subsequent treatment received
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in PPS starting subsequent systemic further treatment.	
Subject analysis set title	PPS | Subgroup Subsequent treatment not received
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subgroup of patients in PPS not starting subsequent systemic further treatment.	

Primary: PE || Progression-free survival (PFS) at 12 weeks

End point title	PE || Progression-free survival (PFS) at 12 weeks[1]

End point description:

PFS is defined as time from registration to one of the following events, whichever occurs first: (i) Relapse or progression according to the modified RECIST criteria for malignant pleural mesothelioma (ii) Death due to any cause. Patients not experiencing an event will be censored at the date of last evaluable tumor assessment before starting a subsequent treatment, if any.

p-value for FAS = 0.015; p-value for PPS = 0.024

End point type	Primary

End point timeframe:

PFS at 12 +/- 2 weeks.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: This was a single arm study, no comparison groups were available. However, the null hypothesis was rejected as the lower of the 90%CI of the primary endpoint calculated using the

uniformly minimum variance unbiased estimator (UMVUE) was over 35% (null hypothesis).

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: % patients with PFS				
number (confidence interval 90%)	52.4 (38.7 to 63.6)	51.6 (37.5 to 62.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Progression-free survival

End point title	SE || Progression-free survival
End point description:	
Kaplan-Meier analysis. Number of events 39/42 (FAS) and 38/41 (PPS), respectively.	
End point type	Secondary
End point timeframe:	
From registration until death or progressive disease (PD).	

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: Progression-free survival (months)				
median (confidence interval 95%)	4.1 (2.6 to 5.5)	3.4 (2.6 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Objective Response

End point title	SE || Objective Response
End point description:	
CR - Complete response; PR - Partial response	
End point type	Secondary
End point timeframe:	
From registration until CR or PR.	

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: % patients with CR or PR				
number (confidence interval 95%)	4.8 (0.6 to 16.2)	4.9 (0.6 to 16.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Disease control (DC) at 12 weeks

End point title	SE || Disease control (DC) at 12 weeks

End point description:

Disease control defined as CR (complete response), PR (partial response) or SD (stable disease) at week 12.
(FAS: CR=1; PR=1; SD=20); (FAS: CR=1; PR=1; SD=19)

End point type	Secondary

End point timeframe:

At 12 weeks.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: % patients with DC				
number (confidence interval 95%)	52.4 (36.4 to 68.0)	51.2 (35.1 to 67.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Duration of disease control

End point title	SE || Duration of disease control

End point description:

Kaplan-Meier analysis of duration of DC.
(FAS: 20 events [1 death, 19 PD]), (PPS: 20 events [1 death, 19 PD])

End point type	Secondary

End point timeframe:

From registration until death or progressive disease.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20[2]	20[3]		
Units: Duration of DC (months)				
number (confidence interval 95%)	6.6 (5.2 to 7.4)	6.6 (5.2 to 7.4)		

Notes:

[2] - 20 patients with DC at 12 weeks.

[3] - 20 patients with DC at 12 weeks.

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Overall survival (OS)

End point title	SE || Overall survival (OS)

End point description:

Median follow-up time =32.8 months (95%CI: 28.5 – 39.0).
(FAS 36/42 events [deaths]); (FAS 35/41 events [deaths])

End point type	Secondary

End point timeframe:

From registration until death.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: OS (months)				
median (confidence interval 95%)	11.5 (8.8 to 13.9)	11.9 (8.5 to 14.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Overall survival - OS at fixed timepoints

End point title	SE || Overall survival - OS at fixed timepoints

End point description:

Estimates of OS rate at 3, 6, 9 and 12 months.

End point type	Secondary

End point timeframe:

At 3, 6, 9, 12 months.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: % patients				
number (confidence interval 95%)				
3 months	95.2 (82.3 to 98.8)	95.1 (85.2 to 98.4)		
6 months	73.8 (57.7 to 84.6)	73.2 (59.8 to 82.7)		
9 months	64.3 (47.9 to 76.7)	63.4 (49.7 to 74.3)		
12 months	47.6 (32.1 to 61.6)	48.8 (35.5 to 60.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: SE || Time to treatment failure (TTF)

End point title	SE || Time to treatment failure (TTF)

End point description:

Kaplan-Meier Analysis of time to treatment failure from registration.
(FAS: 42 events; PPS: 41 events)

End point type	Secondary

End point timeframe:

From registration until end of treatment due to any reason.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: Time to treatment failure (months)				
median (confidence interval 95%)	2.5 (0.9 to 3.6)	2.3 (0.9 to 3.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: PE || Progression-free survival (PFS) at 12 weeks - Subgroup analyses

End point title	PE || Progression-free survival (PFS) at 12 weeks - Subgroup analyses

End point description:

PFS as defined before. Subgroup analyses.

End point type	Other pre-specified

End point timeframe:

PFS at 12 +/- 2 weeks.

End point values	FAS | Subgroup Immunotherapy - Prior Immunotherapy	FAS | Subgroup Immunotherapy - No Prior Immunotherapy	PPS | Subgroup Immunotherapy - Prior Immunotherapy	PPS | Subgroup Immunotherapy - No prior Immunotherapy
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	32	9	32
Units: % patients with PFS				
number (confidence interval 95%)	70 (32.9 to 89.2)	61.4 (42.1 to 75.9)	66.7 (28.2 to 87.8)	61.4 (42.1 to 75.9)

End point values	FAS | Subgroup Histological type - Epithelioid	FAS | Subgroup Histological type - Non-Epithelioid	PPS | Subgroup Histological type - Epithelioid	PPS | Subgroup Histological type - Non-epithelioid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	9	33	8
Units: % patients with PFS				
number (confidence interval 95%)	63.6 (44.9 to 77.5)	62.5 (22.9 to 86.1)	63.6 (44.9 to 77.5)	57.1 (17.2 to 83.7)

End point values	FAS | Subgroup Prior PT-Pemetrexed - <6 months	FAS | Subgroup Prior PT-Pemetrexed - ≥6 months	PPS | Subgroup Prior PT-Pemetrexed - <6 months	PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	28	11	27
Units: % patients with PFS				
number (confidence interval 95%)	53.8 (24.8 to 76.0)	67.9 (47.3 to 81.8)	53.8 (24.8 to 76.0)	66.7 (45.7 to 81.1)

Statistical analyses

Statistical analysis title	Subgroup analysis Immunotherapy (FAS)

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

Comparison groups	FAS | Subgroup Immunotherapy - Prior Immunotherapy v FAS | Subgroup Immunotherapy - No Prior Immunotherapy
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.628
Method	Logrank

Statistical analysis title	Subgroup analysis Immunotherapy (PPS)

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

Comparison groups	PPS | Subgroup Immunotherapy - Prior Immunotherapy v PPS | Subgroup Immunotherapy - No prior Immunotherapy
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.775
Method	Logrank

Statistical analysis title	Subgroup analysis Histological type (FAS)

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

Comparison groups	FAS | Subgroup Histological type - Epithelioid v FAS | Subgroup Histological type - Non-Epithelioid
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.952
Method	Logrank

Statistical analysis title	Subgroup analysis Histological type (PPS)

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

Comparison groups	PPS | Subgroup Histological type - Epithelioid v PPS | Subgroup Histological type - Non-epithelioid
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.744
Method	Logrank

Statistical analysis title	Subgroup analysis Prior Pt-Pemetrexed (FAS)

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

Comparison groups	FAS | Subgroup Prior PT-Pemetrexed - <6 months v FAS | Subgroup Prior PT-Pemetrexed - ≥6 months
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.381
Method	Logrank

Statistical analysis title	Subgroup analysis Prior Pt-Pemetrexed (PPS)

Statistical analysis description:

The 12-week PFS rate between categories were compared using the Kaplan-Meier estimator at 12 weeks.

Comparison groups	PPS | Subgroup Prior PT-Pemetrexed - <6 months v PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.428
Method	Logrank

Other pre-specified: PE || Progression-free survival (PFS) at 12 weeks	
End point title	PE || Progression-free survival (PFS) at 12 weeks

End point description:

PFS as defined before. Using Kaplan Meier Estimator.

End point type	Other pre-specified

End point timeframe:

At 12 weeks.

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: % patients with PFS				
number (confidence interval 90%)	63.5 (49.7 to 74.4)	62.5 (48.6 to 73.7)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: SE || Progression-free survival - PFS at fixed timepoints	
End point title	SE || Progression-free survival - PFS at fixed timepoints
End point description: Kaplan-Meier analysis.	
End point type	Other pre-specified
End point timeframe: At 3, 6, 9, 12 months.	

End point values	FAS	PPS		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	42	41		
Units: % patietnts with PFS				
number (confidence interval 95%)				
3 months	58.4 (41.8 to 71.7)	57.3 (43.4 to 69.0)		
6 months	30.5 (17.1 to 44.9)	31.3 (19.6 to 43.6)		
9 months	12.7 (4.7 to 24.9)	13.0 (5.8 to 23.3)		
12 months	3.4 (0.3 to 14.1)	3.5 (0.5 to 12.0)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: SE || Progression-free survival - Subgroup analyses	
End point title	SE || Progression-free survival - Subgroup analyses
End point description: Kaplan-Meier analysis for subgroups.	
End point type	Other pre-specified
End point timeframe: From registration until death or progressive disease (PD).	

End point values	FAS | Subgroup Immunotherapy - Prior Immunotherapy	FAS | Subgroup Immunotherapy - No Prior Immunotherapy	PPS | Subgroup Immunotherapy - Prior Immunotherapy	PPS | Subgroup Immunotherapy - No prior Immunotherapy
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	32	9	32
Units: Progression-free survival (months)				

number (confidence interval 95%)	3.2 (1.4 to 5.8)	4.1 (2.3 to 6.4)	3.2 (1.4 to 5.8)	4.1 (2.3 to 6.4)

End point values	FAS | Subgroup Histological type - Epithelioid	FAS | Subgroup Histological type - Non-Epithelioid	PPS | Subgroup Histological type - Epithelioid	PPS | Subgroup Histological type - Non-epithelioid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	9	33	8
Units: Progression-free survival (months)				
number (confidence interval 95%)	4.1 (2.5 to 6.4)	3.7 (1.1 to 5.5)	4.1 (2.5 to 6.4)	3.2 (1.1 to 5.5)

End point values	FAS | Subgroup Prior PT-Pemetrexed - <6 months	FAS | Subgroup Prior PT-Pemetrexed - ≥6 months	PPS | Subgroup Prior PT-Pemetrexed - <6 months	PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	28	14	27
Units: Progression-free survival (months)				
number (confidence interval 95%)	3.0 (1.3 to 5.5)	4.3 (2.6 to 6.6)	3.0 (1.3 to 5.5)	4.4 (2.5 to 6.6)

Statistical analyses

Statistical analysis title	Subgroup analysis Immunotherapy (FAS)
Statistical analysis description:	
Comparisons of PFS between subgroups were investigated using the log rank test.	
Comparison groups	FAS | Subgroup Immunotherapy - Prior Immunotherapy v FAS | Subgroup Immunotherapy - No Prior Immunotherapy
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.508
Method	Logrank

Statistical analysis title	Subgroup analysis Immunotherapy (PPS)
Statistical analysis description:	
Comparisons of PFS between subgroups were investigated using the log rank test.	
Comparison groups	PPS | Subgroup Immunotherapy - Prior Immunotherapy v PPS | Subgroup Immunotherapy - No prior Immunotherapy

Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.555
Method	Logrank

Statistical analysis title	Subgroup analysis Histological type (FAS)
Statistical analysis description:	
Comparisons of PFS between subgroups were investigated using the log rank test.	
Comparison groups	FAS | Subgroup Histological type - Epithelioid v FAS | Subgroup Histological type - Non-Epithelioid
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.986
Method	Logrank

Statistical analysis title	Subgroup analysis Histological type (PPS)
Statistical analysis description:	
Comparisons of PFS between subgroups were investigated using the log rank test.	
Comparison groups	PPS | Subgroup Histological type - Epithelioid v PPS | Subgroup Histological type - Non-epithelioid
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.916
Method	Logrank

Statistical analysis title	Subgroup analysis Prior Pt-Pemetrexed (FAS)
Statistical analysis description:	
Comparisons of PFS between subgroups were investigated using the log rank test.	
Comparison groups	FAS | Subgroup Prior PT-Pemetrexed - <6 months v FAS | Subgroup Prior PT-Pemetrexed - ≥6 months
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.402
Method	Logrank

Statistical analysis title	Subgroup analysis Prior Pt-Pemetrexed (PPS)
Statistical analysis description:	
Comparisons of PFS between subgroups were investigated using the log rank test.	

Comparison groups	PPS | Subgroup Prior PT-Pemetrexed - <6 months v PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.387
Method	Logrank

Other pre-specified: SE \|\| Overall survival - Subgroup analyses

End point title	SE || Overall survival - Subgroup analyses
End point description: Kaplan-Meier analyses for subgroups.	
End point type	Other pre-specified
End point timeframe: From registration until death.	

End point values	FAS | Subgroup Immunotherapy - Prior Immunotherapy	FAS | Subgroup Immunotherapy - No Prior Immunotherapy	PPS | Subgroup Immunotherapy - Prior Immunotherapy	PPS | Subgroup Immunotherapy - No prior Immunotherapy
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10	32	9	32
Units: Overall survival (months)				
median (confidence interval 95%)	10.8 (2.5 to 13.3)	12.0 (8.1 to 22.4)	11.1 (2.5 to 14.7)	12.0 (8.1 to 22.4)

End point values	FAS | Subgroup Histological type - Epithelioid	FAS | Subgroup Histological type - Non-Epithelioid	PPS | Subgroup Histological type - Epithelioid	PPS | Subgroup Histological type - Non-epithelioid
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	33	9	33	8
Units: Overall survival (months)				
median (confidence interval 95%)	12.4 (8.1 to 15.5)	10.0 (2.9 to 30.9)	12.4 (8.1 to 15.5)	9.8 (2.9 to 30.9)

End point values	FAS | Subgroup Prior PT-Pemetrexed - <6 months	FAS | Subgroup Prior PT-Pemetrexed - ≥6 months	PPS | Subgroup Prior PT-Pemetrexed - <6 months	PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	14	28	14	27

Units: Overall survival (months)				
median (confidence interval 95%)	8.8 (3.2 to 11.1)	14.2 (10.0 to 22.4)	8.8 (3.2 to 11.1)	14.7 (8.8 to 22.5)

Statistical analyses

Statistical analysis title	Subgroup analysis Immunotherapy (FAS)
Statistical analysis description:	
Comparisons of OS between subgroups were investigated using the log rank test.	
Comparison groups	FAS | Subgroup Immunotherapy - Prior Immunotherapy v FAS | Subgroup Immunotherapy - No Prior Immunotherapy
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.063
Method	Logrank

Statistical analysis title	Subgroup analysis Immunotherapy (PPS)
Statistical analysis description:	
Comparisons of OS between subgroups were investigated using the log rank test.	
Comparison groups	PPS | Subgroup Immunotherapy - Prior Immunotherapy v PPS | Subgroup Immunotherapy - No prior Immunotherapy
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.075
Method	Logrank

Statistical analysis title	Subgroup analysis Histological type (FAS)
Statistical analysis description:	
Comparisons of OS between subgroups were investigated using the log rank test.	
Comparison groups	FAS | Subgroup Histological type - Non-Epithelioid v FAS | Subgroup Histological type - Epithelioid
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.385
Method	Logrank

Statistical analysis title	Subgroup analysis Histological type (PPS)
Statistical analysis description:	
Comparisons of OS between subgroups were investigated using the log rank test.	

Comparison groups	PPS | Subgroup Histological type - Epithelioid v PPS | Subgroup Histological type - Non-epithelioid
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.478
Method	Logrank

Statistical analysis title	Subgroup analysis Prior Pt-Pemetrexed (FAS)
Statistical analysis description:	
Comparisons of OS between subgroups were investigated using the log rank test.	
Comparison groups	FAS | Subgroup Prior PT-Pemetrexed - <6 months v FAS | Subgroup Prior PT-Pemetrexed - ≥6 months
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Logrank

Statistical analysis title	Subgroup analysis Prior Pt-Pemetrexed (PPS)
Statistical analysis description:	
Comparisons of OS between subgroups were investigated using the log rank test.	
Comparison groups	PPS | Subgroup Prior PT-Pemetrexed - <6 months v PPS | Subgroup Prior PT-Pemetrexed - ≥6 months
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.003
Method	Logrank

Other pre-specified: SE || Overall survival - Subgroup analysis Subsequent treatment

End point title	SE || Overall survival - Subgroup analysis Subsequent treatment
End point description:	
Subgroup analysis for patients starting further systemic treatment.	
End point type	Other pre-specified
End point timeframe:	
From registration until death.	

End point values	FAS | Subgroup Subsequent treatment received	FAS | Subgroup Subsequent treatment not received	PPS | Subgroup Subsequent treatment received	PPS | Subgroup Subsequent treatment not received
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	14	28	13
Units: Number of patients	28	14	28	13

Statistical analyses

Statistical analysis title	Hazard ratio (OS / Subsequent treatment) - FAS
Statistical analysis description:	
Effect of systemic subsequent treatment on OS.	
Comparison groups	FAS | Subgroup Subsequent treatment received v FAS | Subgroup Subsequent treatment not received
Number of subjects included in analysis	42
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.699
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.851
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.375
upper limit	1.931

Statistical analysis title	Hazard ratio (OS / Subsequent treatment) - PPS
Statistical analysis description:	
Effect of systemic subsequent treatment on OS.	
Comparison groups	PPS | Subgroup Subsequent treatment received v PPS | Subgroup Subsequent treatment not received
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.84
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.917
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.396
upper limit	2.123

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From registration up to 30 days after last dose of study medication or until the start of a new antitumor therapy, whichever occured first.

Adverse event reporting additional description:

Recording during the follow-up period, except for new malignancies or congenital abnormalities, only for events with possible relationship to the study drug.
Safety was assessed with the safety set, defined as all patients who took at least one dose of the trial treatment after registration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Safety analysis set

Reporting group description:

Safety set, defined as all patients who took at least one dose of the trial treatment after registration.

Serious adverse events	Safety analysis set		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 42 (21.43%)		
number of deaths (all causes)	36		
number of deaths resulting from adverse events	0		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Platelet count decreased			
subjects affected / exposed	1 / 42 (2.38%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Fatigue				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Vomiting				
subjects affected / exposed	2 / 42 (4.76%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Cholangitis				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infection				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Subdiaphragmatic abscess	Additional description: Sub-diaphragmatic fluid collection			
subjects affected / exposed	1 / 42 (2.38%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Safety analysis set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 42 (100.00%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	14 / 42 (33.33%)		
occurrences (all)	24		
Weight decreased			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Alanine aminotransferase increased			
subjects affected / exposed	10 / 42 (23.81%)		
occurrences (all)	12		
Blood bilirubin increased			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	4		
Blood creatinine increased			
subjects affected / exposed	4 / 42 (9.52%)		
occurrences (all)	5		
Gamma-glutamyltransferase increased			
subjects affected / exposed	6 / 42 (14.29%)		
occurrences (all)	8		
Lymphocyte count decreased			
subjects affected / exposed	23 / 42 (54.76%)		
occurrences (all)	23		
Blood urea increased			
subjects affected / exposed	5 / 42 (11.90%)		
occurrences (all)	6		
White blood cell count decreased			
subjects affected / exposed	12 / 42 (28.57%)		
occurrences (all)	17		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	3 / 42 (7.14%)		
occurrences (all)	3		
Vascular disorders			

Hypertension subjects affected / exposed occurrences (all) Superficial vein thrombosis subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 10 3 / 42 (7.14%) 3		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	3 / 42 (7.14%) 3 3 / 42 (7.14%) 6		
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	18 / 42 (42.86%) 26 6 / 42 (14.29%) 10		
General disorders and administration site conditions Oedema peripheral subjects affected / exposed occurrences (all) Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Non-cardiac chest pain subjects affected / exposed occurrences (all)	4 / 42 (9.52%) 4 32 / 42 (76.19%) 38 5 / 42 (11.90%) 10 7 / 42 (16.67%) 8		
Gastrointestinal disorders Abdominal pain			

subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dysphagia subjects affected / exposed occurrences (all) Stomatitis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 6 12 / 42 (28.57%) 21 5 / 42 (11.90%) 7 3 / 42 (7.14%) 5 3 / 42 (7.14%) 3 25 / 42 (59.52%) 36 11 / 42 (26.19%) 12		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 11 / 42 (26.19%) 13 12 / 42 (28.57%) 15		
Psychiatric disorders Insomnia subjects affected / exposed occurrences (all)	 3 / 42 (7.14%) 3		
Renal and urinary disorders Chronic kidney disease subjects affected / exposed occurrences (all)	 10 / 42 (23.81%) 10		
Musculoskeletal and connective tissue disorders			

Muscular weakness subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 6		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	14 / 42 (33.33%) 16		
Hyperkalaemia subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 6		
Hypoalbuminaemia subjects affected / exposed occurrences (all)	6 / 42 (14.29%) 7		
Hypomagnesaemia subjects affected / exposed occurrences (all)	5 / 42 (11.90%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

n/a

Notes: