Clinical trial results:
A randomized phase II study of Durvalumab (MEDI4736) and Tremelimumab compared to doxorubicin in patients with advanced or metastatic soft tissue sarcoma.

Summary

EudraCT number	2016-004750-15
Trial protocol	DE
Global end of trial date	12 August 2022

Results information

Result version number	v1 (current)
This version publication date	26 March 2025
First version publication date	26 March 2025

Trial information

Trial identification

Sponsor protocol code	AIO-STS-0415

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03317457
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany, 14057
Public contact	AIO-Studien-gGmbH, AIO-Studien-gGmbH, 0049 30814534431, info@aio-studien-ggmbh.de
Scientific contact	AIO-Studien-gGmbH, AIO-Studien-gGmbH, 0049 30814534431, info@aio-studien-ggmbh.de

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	12 August 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 August 2022
Global end of trial reached?	Yes
Global end of trial date	12 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of tremelimumab and durvalumab (MEDI4736) in comparison to doxorubicin in treatment-naïve soft tissue sarcoma patients

Protection of trial subjects:

This study was planned, analyzed and conducted according to the study protocol and in accordance with the International Conference on Harmonization (ICH) ‚Guideline for Good Clinical Practice E6(R1)', CPMP/ICH/135/95, based on the principles of the Declaration of Helsinki (1964) and its October 1996 amendment (Somerset West, South Africa). The study was duly conducted in compliance with the German Arzneimittelgesetz (AMG; German Drug Law), and the corresponding Directive 2001/20/EC. Subjects were fully informed regarding all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time in language and terms appropriate for the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 April 2018
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	Germany: 103
Worldwide total number of subjects	103
EEA total number of subjects	103

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)	68
From 65 to 84 years	35

85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In total, 118 patients were screened for eligibility for study participation. Of these, 104 were eligible, and 103 were randomized.

Period 1

Period 1 title	Randomization to treatment start
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab + tremelimumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Durvalumab was administered at a fixed dose of 1500 mg Q4W by i.v. infusion.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tremelimumab was administered at a fixed dose of 75 mg Q4W by i.v. infusion.

Arm title	Doxorubicin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin was given at 75 mg/m2 Q3W by i.v. infusion, up to a total of 6 cycles.

Number of subjects in period 1	Durvalumab + tremelimumab	Doxorubicin
Started	53	50
Completed	53	39
Not completed	0	11
No treatment started	-	11

Period 2

Period 2 title	Treatment and Follow-Up
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Durvalumab + tremelimumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Infusion

Dosage and administration details:

Durvalumab was administered at a fixed dose of 1500 mg Q4W by i.v. infusion.

Investigational medicinal product name	Tremelimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Tremelimumab was administered at a fixed dose of 75 mg Q4W by i.v. infusion.

Arm title	Doxorubicin

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Doxorubicin was given at 75 mg/m2 Q3W by i.v. infusion, up to a total of 6 cycles.

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: A considerable number of patients randomized to the control arm did not initiate treatment, while all patients randomized to experimental treatment did. Therefore, a modified intention-to-treat population was defined post-hoc as the relevant patient population for analysis and reporting,

including baseline data. Period 1 reports all randomized patients, while period 2 reports all patients for whom intention to treat persisted after randomizaiton, which is the main patient set for reporting.

Number of subjects in period 2[2]	Durvalumab + tremelimumab	Doxorubicin
Started	53	39
Completed	53	39

Notes:

[2] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A considerable number of patients randomized to the control arm did not initiate treatment, while all patients randomized to experimental treatment did. Therefore, a modified intention-to-treat population was defined post-hoc as the relevant patient population for analysis and reporting, including baseline data. The patient set reported and thus the number of baseline patients is therefore smaller than the number of screened and of randomized patients.

Baseline characteristics

Reporting groups	
Reporting group title	Durvalumab + tremelimumab
Reporting group description: -	
Reporting group title	Doxorubicin
Reporting group description: -	

Reporting group values	Durvalumab + tremelimumab	Doxorubicin	Total
Number of subjects	53	39	92
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	61	62	
inter-quartile range (Q1-Q3)	54 to 68	56 to 67	-
Gender categorical Units: Subjects			
Female	28	22	50
Male	25	17	42

End points

End points reporting groups

Reporting group title	Durvalumab + tremelimumab
Reporting group description: -	
Reporting group title	Doxorubicin
Reporting group description: -	
Reporting group title	Durvalumab + tremelimumab
Reporting group description: -	
Reporting group title	Doxorubicin
Reporting group description: -	

Primary: Overall survival

End point title	Overall survival

End point description:

Censoring rules: If no event was observed, the patient was censored at the day of last contact. If the date of the last contact was not available, the date of the last attended visit was used for the calculation.

End point type	Primary

End point timeframe:

OS was defined as the time in months between the date of randomization and the date of death from any cause.

End point values	Durvalumab + tremelimumab	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	39		
Units: Months				
median (confidence interval 95%)	17.4 (9.1 to 23.5)	12.5 (9.6 to 15.6)		

Statistical analyses

Statistical analysis title	Logrank test of median overall survival
Comparison groups	Durvalumab + tremelimumab v Doxorubicin
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.1829
Method	Logrank

Secondary: Overall response rate

End point title	Overall response rate

End point description:

RECIST was modified so that progressive disease (PD) had to be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment continued between the initial assessment of progression and confirmation for progression. The subsequent imaging was resumed at the pre-specified time point. In case of confirmed pogression, the date of the first imaging with sign of PD (according to RECIST) was counted as an event.

End point type	Secondary

End point timeframe:

Response was assessed as best overall response according to radiologic assessment and modified RECIST criteria

End point values	Durvalumab + tremelimumab	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	39		
Units: Patients				
Complete response	0	1		
Partial response	5	4		
Stable disease	10	12		
Non-CR/Non-PD	1	0		
Progressive disease	39	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Censoring rules: Patients without event were censored at the last evaluable tumor assessment, if available, and on the date of the last contact otherwise. Patients who had started any subsequent anti-cancer therapy without a prior reported progression were censored at the last evaluable tumor assessment prior to the subsequent anti-cancer therapy, if available, and at the date of initiation of the subsequent anti-cancer therapy otherwise.

End point type	Secondary

End point timeframe:

PFS was defined as the time in months between the date of randomization until the date of confirmed PD (based on investigator assessments) or the date of death from any cause (patients who died without a reported progression were considered to have progre

End point values	Durvalumab + tremelimumab	Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53	39		
Units: Months				
median (confidence interval 95%)	2.7 (2.4 to 2.9)	2.8 (2.6 to 4.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were to be reported from signing of informed consent until the first follow-up visit.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	0

Reporting groups

Reporting group title	Durvalumab + tremelimumab
Reporting group description: -	
Reporting group title	Doxorubicin

Reporting group description: -

Serious adverse events	Durvalumab + tremelimumab	Doxorubicin	
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 53 (33.96%)	7 / 39 (17.95%)	
number of deaths (all causes)	37	35	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertension aggravated			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	0 / 53 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever of unknown origin			

subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation			
subjects affected / exposed	0 / 53 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Exacerbation of asthma			
subjects affected / exposed	0 / 53 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 53 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocarditis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cognitive disturbance			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			

subjects affected / exposed	1 / 53 (1.89%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 53 (1.89%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 53 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatitis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 53 (1.89%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myositis			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteolytic lesion			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathologic fracture of femur			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Febrile infection			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 53 (0.00%)	1 / 39 (2.56%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatremia			
subjects affected / exposed	1 / 53 (1.89%)	0 / 39 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Durvalumab + tremelimumab	Doxorubicin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	41 / 53 (77.36%)	28 / 39 (71.79%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	4 / 53 (7.55%)	2 / 39 (5.13%)	
occurrences (all)	5	3	
Vascular disorders			
Hypertension			
subjects affected / exposed	5 / 53 (9.43%)	1 / 39 (2.56%)	
occurrences (all)	9	1	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	13 / 53 (24.53%)	15 / 39 (38.46%)	
occurrences (all)	14	31	
Fever			
subjects affected / exposed	5 / 53 (9.43%)	3 / 39 (7.69%)	
occurrences (all)	5	3	
Edema limbs			
subjects affected / exposed	5 / 53 (9.43%)	1 / 39 (2.56%)	
occurrences (all)	5	1	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	9 / 53 (16.98%)	3 / 39 (7.69%)	
occurrences (all)	12	3	
Dyspnoea			
subjects affected / exposed	6 / 53 (11.32%)	2 / 39 (5.13%)	
occurrences (all)	8	3	
Investigations			
White blood cell decreased			
subjects affected / exposed	2 / 53 (3.77%)	7 / 39 (17.95%)	
occurrences (all)	2	18	
Neutrophil count decreased			
subjects affected / exposed	0 / 53 (0.00%)	7 / 39 (17.95%)	
occurrences (all)	0	18	
Alanine aminotransferase increased			
subjects affected / exposed	5 / 53 (9.43%)	1 / 39 (2.56%)	
occurrences (all)	10	3	
Nervous system disorders			
Dysgeusia			
subjects affected / exposed	4 / 53 (7.55%)	3 / 39 (7.69%)	
occurrences (all)	4	4	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	11 / 53 (20.75%)	9 / 39 (23.08%)	
occurrences (all)	14	11	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	8 / 53 (15.09%)	12 / 39 (30.77%)	
occurrences (all)	8	27	
Vomiting			
subjects affected / exposed	4 / 53 (7.55%)	7 / 39 (17.95%)	
occurrences (all)	4	12	
Abdominal pain			
subjects affected / exposed	7 / 53 (13.21%)	2 / 39 (5.13%)	
occurrences (all)	7	2	
Diarrhea			
subjects affected / exposed	6 / 53 (11.32%)	3 / 39 (7.69%)	
occurrences (all)	9	6	

Mucositis oral			
subjects affected / exposed	3 / 53 (5.66%)	4 / 39 (10.26%)	
occurrences (all)	3	12	
Constipation			
subjects affected / exposed	4 / 53 (7.55%)	2 / 39 (5.13%)	
occurrences (all)	4	4	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	11 / 53 (20.75%)	1 / 39 (2.56%)	
occurrences (all)	15	1	
Alopecia			
subjects affected / exposed	1 / 53 (1.89%)	7 / 39 (17.95%)	
occurrences (all)	1	8	
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	6 / 53 (11.32%)	0 / 39 (0.00%)	
occurrences (all)	6	0	
Hyperthyroidism			
subjects affected / exposed	4 / 53 (7.55%)	1 / 39 (2.56%)	
occurrences (all)	4	1	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	6 / 53 (11.32%)	2 / 39 (5.13%)	
occurrences (all)	10	3	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 53 (3.77%)	4 / 39 (10.26%)	
occurrences (all)	2	5	
Upper respiratory tract infection			
subjects affected / exposed	2 / 53 (3.77%)	3 / 39 (7.69%)	
occurrences (all)	2	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	6 / 53 (11.32%)	1 / 39 (2.56%)	
occurrences (all)	7	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2017	Strategy for evaluation of efficacy endpoints sharpened; Formal corrections, clarifications, and consistency
15 May 2018	Alignment with new information regarding IMPs received from manufacturer, e.g., toxicity management guidelines; Edits and clarifications
12 June 2019	Deletion of olaratumab as possible medication in combination with doxorubicin in the control arm due to revocation of olaratumab's marketing authorization; Shortening of observation period after IMP administration from 2-4 h to 1h; Extension of list of adverse events of special interest
20 April 2020	Edits to align the protocol with updates in the investigator's brochures, mainly relating to toxicity managment guidelines
10 May 2021	Alignment of protocol with IMP manufacturer's update of toxicity managment guidelines
24 June 2021	Alignment of protocol with IMP manufacturer's update of toxicity managment guidelines

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported