Clinical trial results:
A randomized phase II study comparing pembrolizumab with methotrexate in elderly, frail or cisplatin-ineligible patients with head and neck cancers

Summary

EudraCT number	2016-001331-12
Trial protocol	DE
Global end of trial date	03 December 2021

Results information

Result version number	v1 (current)
This version publication date	24 February 2023
First version publication date	24 February 2023

Trial information

Trial identification

Sponsor protocol code	AIO-KHT-0115

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03193931
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	AIO-Studien-gGmbH
Sponsor organisation address	Kuno-Fischer-Str. 8, Berlin, Germany,
Public contact	info@aio-studien-ggmbh.de, AIO-Studien-gGmbH, 0049 30814534431, info@aio-studien-ggmbh.de
Scientific contact	info@aio-studien-ggmbh.de, 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	11 July 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2020
Global end of trial reached?	Yes
Global end of trial date	03 December 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess antitumor activity of pembrolizumab in SCCHN

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	02 February 2018
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	Germany: 47
Worldwide total number of subjects	47
EEA total number of subjects	47

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)	14
From 65 to 84 years	30

85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were recruited between Feb 2018 and Dec 2019 at 11 study sites in Germany.
In total, 54 patients were screened, and 48 were randomized. One patient randomized to Arm B was excluded from treatment and from all analysis sets due to violation of in/exclusion criteria prior to treatment start.

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	Arm A - Pembrolizumab

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

200 mg i.v., Q3W for a maximum duration of 24 months or until disease progression, occurrence of non-tolerable toxicity or patient withdrawal of consent.

Arm title	Arm B - Methotrexate

Arm description: -

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

Dosage and administration details:

40 mg i.v., weekly for a maximum duration of 24 months or until disease progression, occurrence of non-tolerable toxicity or patient withdrawal of consent.

Number of subjects in period 1	Arm A - Pembrolizumab	Arm B - Methotrexate
Started	23	24
Completed	3	0
Not completed	20	24
Disease progression	10	8
Patient's wish	-	2

Death	6	6
Investigator decision	3	2
Unacceptable toxicity	-	4
Unrelated medical illness	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	47	47	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65-84 years	30	30	
85 years and over	3	3	
Gender categorical Units: Subjects			
Female	13	13	
Male	34	34	
ECOG status Units: Subjects			
ECOG 0	1	1	
ECOG 1	5	5	
ECOG 2	41	41	
Tumor location Units: Subjects			
Oral cavity	17	17	
Larynx	6	6	
Oropharynx	17	17	
Hypopharynx	7	7	

End points

End points reporting groups

Reporting group title	Arm A - Pembrolizumab
Reporting group description: -	
Reporting group title	Arm B - Methotrexate
Reporting group description: -	

Primary: Overall survival (OS) rate after 1 year

End point title	Overall survival (OS) rate after 1 year
End point description:	
End point type	Primary
End point timeframe:	

Survival status one year after randomization was collected. Randomized subjects for whom survival data at 1 year post randomization was not available (i.e. lost-to-follow-up) were considered dead for the purpose of calculating the primary endpoint.

End point values	Arm A - Pembrolizumab	Arm B - Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Surviving patients				
Pts. alive at 1-year milestone	4	9		
Pts. deceased at 1-year milestone	19	15		

Statistical analyses

Statistical analysis title	Primary endpoint
Comparison groups	Arm A - Pembrolizumab v Arm B - Methotrexate
Number of subjects included in analysis	47
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.123
Method	Chi-squared

Secondary: Failure of strategy rate at 1 year

End point title	Failure of strategy rate at 1 year
End point description:	
End point type	Secondary

End point timeframe:

Failure of strategy rate at 1 year, defined as death, progressive disease (PD), treatment discontinuation or deterioration of the Instrumental Activities of Daily Living (IDAL) score by 2 points [Guigay et al. 2014]

End point values	Arm A - Pembrolizumab	Arm B - Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Patients				
Pts. with failure of strategy	21	24		
Pts. without failure of strategy	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective response rate (ORR)

End point title	Objective response rate (ORR)

End point description:

End point type	Secondary

End point timeframe:

All lesions identified at screening were to be assessed at each scheduled tumor measurement. Tumor assessment was to be performed every 6 weeks until 24 weeks of treatment, thereafter every 12 weeks until progression.

End point values	Arm A - Pembrolizumab	Arm B - Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Patients				
Response (CR or PR)	4	3		
No response	14	14		
Missing values	5	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Subjects who died without a reported prior progression were considered to have progressed on the date of their death. Subjects who did not progress or die were censored on the date of their last evaluable tumor assessment. Subjects who did not have any on-study tumor assessment and did not die were censored on the date they were randomized. Subjects who started any subsequent anticancer therapy without a prior reported progression were censored at the last evaluable tumor assessment prior to or on the date of initiation of the subsequent anticancer therapy.

Results reported here are based on 21 progression events observed in each treatment arm.

End point type	Secondary

End point timeframe:

PFS was defined as the time from randomization to the date of the first documented tumor progression based on investigator assessments (per RECIST 1.1), or death due to any cause.

End point values	Arm A - Pembrolizumab	Arm B - Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Months				
median (confidence interval 95%)	1.84 (1.4 to 4.6)	2.8 (1.4 to 4.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

The data reported here is based on 20 observed events in Arm A and 19 events in Arm B.

End point type	Secondary

End point timeframe:

OS was defined as the time from randomization date to the date of death. A subject who has not died was censored at last known date alive.

End point values	Arm A - Pembrolizumab	Arm B - Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	24		
Units: Months				
median (confidence interval 95%)	6.1 (2.2 to 8.8)	9.8 (2.0 to 15.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of treatment beyond progression

End point title	Duration of treatment beyond progression

End point description:

End point type	Secondary

End point timeframe:

Duration of treatment beyond initial investigator assessed progression

End point values	Arm A - Pembrolizumab	Arm B - Methotrexate		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	9		
Units: Days				
median (confidence interval 95%)	15.5 (1.0 to 28.0)	8.0 (0.0 to 34.0)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from time of signed informed consent until 30 days after last dose of IMP. Serious adverse events were recorded from time of signed informed consent until 90 days after last dose of IMP.

Adverse event reporting additional description:

If the subject initiated new anticancer therapy after last dose of IMP, serious adverse events were recorded for 30 days after the last dose of IMP.

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4.03

Reporting groups

Reporting group title	Arm A - Pembrolizumab
Reporting group description: -	
Reporting group title	Arm B - Methotrexate

Reporting group description: -

Serious adverse events	Arm A - Pembrolizumab	Arm B - Methotrexate	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 22 (54.55%)	15 / 23 (65.22%)	
number of deaths (all causes)	20	19	
number of deaths resulting from adverse events			
Investigations			
Creatinine increased			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations - Other	Additional description: Event specified was Pancytopenia.		
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thromboembolic event			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Stroke			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General disorders and administration site conditions - Other	Additional description: One case of General disorders and administration site conditions - Other was specified as 'weakness, malnutrition', and one as 'clinical detorioration'.		
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death NOS			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal stenosis			

subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral hemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Aspiration			
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspareunia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngeal hemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Bullous dermatitis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchial infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations - Other	Additional description: Events were specified as 'Infection of unclear disease' (Arm A) and 'Suspected systemic infection' (Arm B)-		
subjects affected / exposed	1 / 22 (4.55%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences causally related to treatment / all	0 / 2	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection			

subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	1 / 23 (4.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 22 (4.55%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 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	Arm A - Pembrolizumab	Arm B - Methotrexate	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 22 (100.00%)	23 / 23 (100.00%)	
Investigations			
Lymphocyte count decreased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Neutrophil count decreased			
subjects affected / exposed	0 / 22 (0.00%)	3 / 23 (13.04%)	
occurrences (all)	0	4	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumor pain			
subjects affected / exposed	4 / 22 (18.18%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Blood and lymphatic system disorders			
Anemia			

subjects affected / exposed	3 / 22 (13.64%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
General disorders and administration site conditions			
Edema limbs			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	1	2	
Fatigue			
subjects affected / exposed	6 / 22 (27.27%)	6 / 23 (26.09%)	
occurrences (all)	9	6	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 22 (4.55%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Diarrhea			
subjects affected / exposed	4 / 22 (18.18%)	4 / 23 (17.39%)	
occurrences (all)	4	4	
Dysphagia			
subjects affected / exposed	2 / 22 (9.09%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Mucositis oral			
subjects affected / exposed	2 / 22 (9.09%)	9 / 23 (39.13%)	
occurrences (all)	3	14	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 22 (9.09%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Infections and infestations			
Lip infection			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Lung infection			
subjects affected / exposed	2 / 22 (9.09%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	0 / 22 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	

White blood cell count decreased subjects affected / exposed occurrences (all)	0 / 22 (0.00%) 0	2 / 23 (8.70%) 2	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	0 / 23 (0.00%) 0	
Hypokalemia subjects affected / exposed occurrences (all)	2 / 22 (9.09%) 3	0 / 23 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 June 2017	- Within the statistical methods and sample size section, wordings were corrected and the sample size calculation was added. - Establishment of a DSMB was introduced into the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported