



## Clinical trial results:

### Evaluation of immunological effects of the RANKL-inhibitor Denosumab when administered concurrently with PD1-blocking antibodies (Nivolumab, Pembrolizumab) in patients with metastatic malignant melanoma with bone involvement

#### Summary

EudraCT number	2016-001925-15
Trial protocol	DE
Global end of trial date	30 August 2021

#### Results information

Result version number	v1 (current)
This version publication date	22 June 2023
First version publication date	22 June 2023
Summary attachment (see zip file)	Synopsis (BONEMET_Synopsis_CSR_V2.0_2022-10-27_incl.attachment.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	ISS20159321
-----------------------	-------------

##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	DRKS: DRKS00016064

Notes:

##### Sponsors

Sponsor organisation name	Alcedis GmbH
Sponsor organisation address	Winchesterstraße 3, Gießen, Germany, 35394
Public contact	Universitätsklinik für Dermatologie, Johannes Wesling Klinikum Minden, +49 5717904500, ralf.gutzmer@muehlenkreiskliniken.de
Scientific contact	Universitätsklinik für Dermatologie, Johannes Wesling Klinikum Minden, +49 5717904500, ralf.gutzmer@muehlenkreiskliniken.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	26 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 August 2021
Global end of trial reached?	Yes
Global end of trial date	30 August 2021
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

This phase IV study aims to investigate possible immunologic and biologic effects of the concurrent administration of PD-1 blocking antibodies and denosumab as primary endpoint by evaluating peripheral blood mononuclear cells (PBMC, esp. activated T-cells), chemokines, and cytokines (e.g., interferon gamma):

- 1) Dynamic changes in the numbers of central memory, effector memory, and/or effector T-cells in the circulating blood (based on expression of CD45RA, CD45RO, CCR7, CD62L, and TCF-1).
- 2) Dynamic changes in the concentration of cytokines and chemokines present in circulating blood.

Protection of trial subjects:

Patients had to meet the inclusion and exclusion criteria. Pregnant or breast-feeding women are excluded. Women of childbearing potential and male patients with partners of childbearing potential had to use a highly effective form of contraception. There was no preferred enrolment of men or women.

The treatment should be conducted exactly as described in the protocol. Any protocol deviations were reported. criteria for premature treatment discontinuation of study patients were specified in the protocol. The study was conducted in accordance with the 2013 Declaration of Helsinki (Fortaleza, Brazil, 2013). The recommendations of Good Clinical Practice, valid since 17 January 1997, were met.

Background therapy:

Prior therapy with CTLA4-inhibitor or PD1-inhibitor or denosumab for distant metastatic disease as well as any other concurrent medical treatments for metastatic disease such as targeted therapies or chemotherapies was not allowed. Treatments in the adjuvant setting were allowed in case treatment was discontinued at least 4 weeks before inclusion in this study.

All permitted therapies specified in the SmPCs of the used study drugs could be administered during study treatment to assist in the management of pain, infection and other complications of the underlying malignancy. Relevant prior and concomitant medications were documented in the eCRF.

Evidence for comparator:

Since this was a single arm trial, no comparators were used.

Actual start date of recruitment	16 April 2019
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: 17
Worldwide total number of subjects	17
EEA total number of subjects	17

Notes:

<b>Subjects enrolled per age group</b>	
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	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Upon obtaining signed informed consent, screening evaluation were performed to confirm eligibility and to obtain baseline data. Between 16 April 2019 (first patient in) and 18 February 2021 (last patient in), 17 patients were registered by 4 German university clinics.

### Pre-assignment

Screening details:

The investigators selected patients according to the inclusion / exclusion criteria after informing the patient written and orally about the study and after the patient had signed the informed consent. There was no preferred enrolment of men or women. Baseline examinations should be performed within 28 days before study treatment.

### Period 1

Period 1 title	Treatment period (overall study) (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

### Arms

Arm title	PD-1 and denosumab
-----------	--------------------

Arm description:

Patients were treated with nivolumab, either alone or in combination with ipilimumab, or pembrolizumab and denosumab according to the respective SmPCs.

Arm type	Experimental
Investigational medicinal product name	Nivolumab
Investigational medicinal product code	
Other name	Opdivo
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab treatment was performed according to SmPC. At the time of the latest final protocol version (V2.0 dated 25 JUNE 2019), nivolumab was approved for the treatment of metastatic melanoma as monotherapy (either 240 mg every 2 weeks or 480 mg every 4 weeks) or in combination with ipilimumab (1 mg/kg nivolumab + 3 mg/kg ipilimumab every 3 weeks for 4 dose cycles followed by nivolumab monotherapy (either 240 mg every 2 weeks or 480 mg every 4 weeks)).

Investigational medicinal product name	Pembrolizumab
Investigational medicinal product code	
Other name	Keytruda
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Pembrolizumab was used according to the SmPC. At the time of the latest final protocol version (V2.0 dated 25 JUNE 2019), pembrolizumab was approved as monotherapy for patients with metastatic melanoma with either 200 mg pembrolizumab every 3 weeks or 400 mg pembrolizumab every 6 weeks.

Investigational medicinal product name	Ipilimumab
Investigational medicinal product code	
Other name	Yervoy
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

---

Dosage and administration details:

Ipilimumab was administered according to the SmPC. At the time of the latest final protocol version (V2.0 dated 25 JUNE 2019), ipilimumab was approved for the treatment of metastatic melanoma in combination with nivolumab (1 mg/kg nivolumab + 3 mg/kg ipilimumab every 3 weeks for 4 dose cycles followed by nivolumab monotherapy (either 240 mg every 2 weeks or 480 mg every 4 weeks)).

Investigational medicinal product name	Denosumab
Investigational medicinal product code	
Other name	Xgeva
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Denosumab was administered according to the SmPC. At the time of the latest final protocol version (V2.0 dated 25 JUNE 2019), denosumab was applied as a subcutaneous injection of 120 mg every 4 weeks. Supplementation of at least 500 mg calcium and 400 IU vitamin D daily was required for all patients, unless hypercalcaemia was present.

<b>Number of subjects in period 1</b>	PD-1 and denosumab
Started	17
Completed	17

## Baseline characteristics

### Reporting groups

Reporting group title	PD-1 and denosumab
-----------------------	--------------------

Reporting group description:

Patients were treated with nivolumab, either alone or in combination with ipilimumab, or pembrolizumab and denosumab according to the respective SmPCs.

Reporting group values	PD-1 and denosumab	Total	
Number of subjects	17	17	
Age categorical Units: Subjects			
Age continuous			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of screening minus Year of birth.			
Units: years			
median	52		
full range (min-max)	34 to 78	-	
Gender categorical Units: Subjects			
Female	8	8	
Male	9	9	

### Subject analysis sets

Subject analysis set title	ITT
----------------------------	-----

Subject analysis set type	Intention-to-treat
---------------------------	--------------------

Subject analysis set description:

All patients who received at least one treatment administration of PD-1 blocking antibodies and denosumab

Subject analysis set title	mPP
----------------------------	-----

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

Modified per protocol.

Patients who received the study therapy of PD-1 blocking antibody and denosumab at least twice and are evaluable for disease, i.e., have a RECIST staging after baseline or clear medical progression, which makes a staging unnecessary per investigator decision.

Subject analysis set title	PP
----------------------------	----

Subject analysis set type	Per protocol
---------------------------	--------------

Subject analysis set description:

Patients who received the study therapy of PD-1 blocking antibody and denosumab for at least 12 weeks

Reporting group values	ITT	mPP	PP
Number of subjects	17	14	8
Age categorical Units: Subjects			

Age continuous			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of screening minus Year of birth.			
Units: years			
median	52	49.5	51
full range (min-max)	34 to 78	34 to 78	35 to 76
Gender categorical			
Units: Subjects			
Female	8	7	4
Male	9	7	4

## End points

### End points reporting groups

Reporting group title	PD-1 and denosumab
Reporting group description: Patients were treated with nivolumab, either alone or in combination with ipilimumab, or pembrolizumab and denosumab according to the respective SmPCs.	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: All patients who received at least one treatment administration of PD-1 blocking antibodies and denosumab	
Subject analysis set title	mPP
Subject analysis set type	Per protocol
Subject analysis set description: Modified per protocol. Patients who received the study therapy of PD-1 blocking antibody and denosumab at least twice and are evaluable for disease, i.e., have a RECIST staging after baseline or clear medical progression, which makes a staging unnecessary per investigator decision.	
Subject analysis set title	PP
Subject analysis set type	Per protocol
Subject analysis set description: Patients who received the study therapy of PD-1 blocking antibody and denosumab for at least 12 weeks	

### Primary: Dynamic changes in the numbers of central memory T-cells in circulating blood (PBMC)

End point title	Dynamic changes in the numbers of central memory T-cells in circulating blood (PBMC) <sup>[1]</sup>
End point description: 20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).	
End point type	Primary
End point timeframe: From baseline until end of study (= 24 weeks after initiation of therapy)	
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: No statistical analysis was performed due to low sample number	

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[2]</sup>			
Units: % of CD3+				
arithmetic mean (standard deviation)				
baseline	14.44 (± 9.07)			
Week 4	12.19 (± 6.71)			
Week 12	6.59 (± 7.50)			
Week 24	9.07 (± 7.72)			

Notes:

[2] - Number of analyzed patients decreased over time

### Statistical analyses

No statistical analyses for this end point

#### Primary: Dynamic changes in the numbers of activated T-cells in circulating blood (PBMC)

End point title	Dynamic changes in the numbers of activated T-cells in circulating blood (PBMC) <sup>[3]</sup>
-----------------	--

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type	Primary
----------------	---------

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[3] - 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: No statistical analysis was performed due to low sample number

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	13 <sup>[4]</sup>			
Units: % of CD3+				
arithmetic mean (standard deviation)				
baseline	2.93 (± 6.29)			
Week 4	1.58 (± 2.53)			
Week 12	0.32 (± 0.68)			
Week 24	1.3 (± 3.01)			

Notes:

[4] - Number of analyzed patients decreased over time

### Statistical analyses

No statistical analyses for this end point

#### Primary: Dynamic changes in the numbers of cytotoxic T-cells in circulating blood (PBMC)

End point title	Dynamic changes in the numbers of cytotoxic T-cells in circulating blood (PBMC) <sup>[5]</sup>
-----------------	--

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type	Primary
----------------	---------

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[5] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[6]</sup>			
Units: % of CD3+				
arithmetic mean (standard deviation)				
Baseline	31.75 (± 11.01)			
Week 4	35.01 (± 15.84)			
Week 12	51.61 (± 18.09)			
Week 24	57.16 (± 17.71)			

Notes:

[6] - Number of analyzed patients decreased over time

## Statistical analyses

No statistical analyses for this end point

## Primary: Dynamic changes in the numbers of naive T-cells events in circulating blood (PBMC)

End point title	Dynamic changes in the numbers of naive T-cells events in circulating blood (PBMC) <sup>[7]</sup>
-----------------	---

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central central biomarker laboratory (Universität Duisburg/Essen).

End point type	Primary
----------------	---------

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[7] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[8]</sup>			
Units: % of CD3+				
arithmetic mean (standard deviation)				
Baseline	15.5 (± 9.77)			
Week 4	14.52 (± 11.85)			
Week 12	9.42 (± 12.52)			
Week 24	3.95 (± 4.33)			

Notes:

[8] - Number of analyzed patients decreased over time

### Statistical analyses

No statistical analyses for this end point

#### Primary: Dynamic changes in Tcm/Tscm (CD3+ TCF1+) in circulating blood (PMBC)

End point title	Dynamic changes in Tcm/Tscm (CD3+ TCF1+) in circulating blood (PMBC) <sup>[9]</sup>
-----------------	---

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type	Primary
----------------	---------

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[9] - 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: No statistical analysis was performed due to low sample number

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	13 <sup>[10]</sup>			
Units: % of CD3+]				
arithmetic mean (standard deviation)				
Baseline	67.56 (± 24.9)			
Week 4	51.0 (± 25.84)			
Week 12	44.1 (± 29.2)			
Week 24	44.54 (± 30.62)			

Notes:

[10] - Number of analyzed patients decreased over time

### Statistical analyses

No statistical analyses for this end point

#### Primary: Dynamic changes of Interferon-γ in circulating blood (serum)

End point title	Dynamic changes of Interferon-γ in circulating blood
-----------------	--

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type	Primary
----------------	---------

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[11] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[12]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	19.11 (± 24.40)			
Week 4	101.71 (± 143.64)			
Week 12	12.82 (± 8.87)			
Week 24	40.91 (± 65.97)			

Notes:

[12] - Number of analyzed patients decreased over time

## Statistical analyses

No statistical analyses for this end point

## Primary: Dynamic changes of TNF-α in circulating blood (serum)

End point title | Dynamic changes of TNF-α in circulating blood (serum)<sup>[13]</sup>

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type | Primary

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[13] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[14]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	1.56 (± 0.90)			
Week 4	4.33 (± 3.31)			
Week 12	2.37 (± 1.46)			
Week 24	2.31 (± 2.30)			

Notes:

[14] - Number of analyzed patients decreased over time

### Statistical analyses

No statistical analyses for this end point

#### Primary: Dynamic changes of IL-6 in circulating blood (serum)

End point title | Dynamic changes of IL-6 in circulating blood (serum)<sup>[15]</sup>

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type | Primary

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[15] - 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: No statistical analysis was performed due to low sample number

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[16]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	4.54 (± 7.17)			
Week 4	9.60 (± 17.51)			
Week 12	4.64 (± 6.68)			
Week 24	1.66 (± 1.15)			

Notes:

[16] - Number of patients decreased over time

### Statistical analyses

No statistical analyses for this end point

#### Primary: Dynamic changes of IL-8 in circulating blood (serum)

End point title | Dynamic changes of IL-8 in circulating blood (serum)<sup>[17]</sup>

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type | Primary

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[17] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[18]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	68.59 (± 105.60)			
Week 4	110.94 (± 148.97)			
Week 12	53.39 (± 43.95)			
Week 24	49.27 (± 41.50)			

Notes:

[18] - Number of analyzed patients decreased over time

### Statistical analyses

No statistical analyses for this end point

### Primary: Dynamic changes of IL-12/IL-23p40 in circulating blood (serum)

End point title	Dynamic changes of IL-12/IL-23p40 in circulating blood (serum) <sup>[19]</sup>
-----------------	--

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type	Primary
----------------	---------

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[19] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[20]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	154.61 (± 75.42)			
Week 4	317.83 (± 144.13)			
Week 12	160.95 (± 128.06)			
Week 24	146.13 (± 121.70)			

Notes:

[20] - Number of analyzed patients decreased over time

## Statistical analyses

No statistical analyses for this end point

### Primary: Dynamic changes of IL-27 in circulating blood (serum)

End point title | Dynamic changes of IL-27 in circulating blood (serum)<sup>[21]</sup>

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type | Primary

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[21] - 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: No statistical analysis was performed due to low sample number

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[22]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	2263.03 (± 1210.58)			
Week 4	4222.37 (± 2639.11)			
Week 12	2799.77 (± 1424.88)			
Week 24	2405.34 (± 1573.00)			

Notes:

[22] - Number of analyzed patients decreased over time

## Statistical analyses

No statistical analyses for this end point

### Primary: Dynamic changes of IP-10 in circulating blood (serum)

End point title | Dynamic changes of IP-10 in circulating blood (serum)<sup>[23]</sup>

End point description:

20 ml of heparinized blood and 2 x 7,5 ml of blood (preferably using EDTA-tubes and serum separator tubes) for the preparation of plasma and serum, respectively, were obtained from each study patient at baseline and after 4, 12 and 24 weeks of study duration for immunological monitoring. Samples were analyzed in a central biomarker laboratory (Universität Duisburg/Essen).

End point type | Primary

End point timeframe:

From baseline until end of study (= 24 weeks after initiation of therapy)

Notes:

[23] - 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: No statistical analysis was performed due to low sample number

<b>End point values</b>	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14 <sup>[24]</sup>			
Units: pg/ml				
arithmetic mean (standard deviation)				
Baseline	492.73 (± 296.99)			
Week 4	2613.65 (± 1581.41)			
Week 12	1050.06 (± 593.80)			
Week 24	1543.13 (± 1916.20)			

Notes:

[24] - Number of patients decreased over time

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall response rate (ORR) at week 12

End point title Overall response rate (ORR) at week 12

End point description:

Response was assessed according to RECIST 1.1 criteria by the investigator

End point type Secondary

End point timeframe:

12 weeks after start of treatment with concurrent PD-1 and RANKL inhibition

<b>End point values</b>	ITT	mPP	PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	15	13	7	
Units: Patients	2	1	0	

### Statistical analyses

No statistical analyses for this end point

### Secondary: ORR at week 24

End point title ORR at week 24

End point description:

Response was assessed according to RECIST 1.1 criteria by the investigator

End point type Secondary

End point timeframe:

24 weeks after start of treatment with concurrent PD-1 and RANKL inhibition

<b>End point values</b>	ITT	mPP	PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	12	8	
Units: patients	2	1	1	

### Statistical analyses

No statistical analyses for this end point

### Secondary: Response rate of bone metastases

End point title Response rate of bone metastases

End point description:

Best response during the 24 weeks study period was used for determination of response rate of bone metastases (size and number). Response was determined by the investigator according to RECIST 1.1 and by bone scans.

End point type Secondary

End point timeframe:

From start of treatment with concurrent PD-1 and RANKL inhibition up to 24 weeks

<b>End point values</b>	ITT	mPP	PP	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	14	12	8	
Units: Number of Patients	9	8	7	

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From date of first study drug application (for AEs) or from date of informed consent (for SAEs) until regular end (day 169 after start of study treatment) or, in case of premature therapy discontinuation, 30 days after last administration of study drugs

Adverse event reporting additional description:

All AEs including start date, end date, treatment of AE, outcome, relatedness and seriousness had to be recorded in the eCRF.

Relatedness of the AE to study drugs was determined by the investigator.

Due to the definition of the safety population, only SAEs which occurred after start of study treatment are listed.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	NCI CTCAE
-----------------	-----------

Dictionary version	5
--------------------	---

### Reporting groups

Reporting group title	Safety set
-----------------------	------------

Reporting group description:

All patients who received at least one treatment administration = ITT population

Serious adverse events	Safety set		
Total subjects affected by serious adverse events			
subjects affected / exposed	13 / 17 (76.47%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events	1		
General disorders and administration site conditions			
General disorders and administration site conditions - Other, specify: Progressive Disease			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions - Other, specify: Nephritis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions - Other, specify: Immune-related hepatitis			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fever			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchial stricture			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart Failure			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Nervous system disorders - Other, specify: neurological deficits left leg			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Constipation			

subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Gastritis</b>			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Gastrointestinal disorders - Other, specify: immune related ileitis</b>			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Hepatobiliary disorders</b>			
<b>Hepatobiliary disorders - Other, specify: immune related hepatitis</b>			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
<b>Hepatobiliary disorders - Other, specify: autoimmune hepatitis</b>			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Skin and subcutaneous tissue disorders</b>			
<b>Skin and subcutaneous tissue disorders - Other, specify: Panniculitis</b>			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders</b>			
<b>Acute kidney injury</b>			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Renal and urinary disorders - Other, specify: immune related tubulointerstitial nephritis</b>			

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
<b>Endocrine disorders</b>			
Endocrine disorders - Other, specify: Morbus Basedow			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders - Other, specify: autoimmune Thyreoiditis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hypophysitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Musculoskeletal and connective tissue disorders</b>			
Pain in extremity			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
<b>Infections and infestations</b>			
Sepsis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Safety set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 17 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Tumor pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Vascular disorders Lymphedema subjects affected / exposed occurrences (all)  Hot flashes subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1  1 / 17 (5.88%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Fever subjects affected / exposed occurrences (all)  Flu like symptoms subjects affected / exposed occurrences (all)  General disorders and administration site conditions - Other, specify: Sprained right ankle subjects affected / exposed occurrences (all)  General disorders and administration site conditions - Other, specify: decreased sensibility in the subjects affected / exposed occurrences (all)  General disorders and administration site conditions - Other, specify: heartburn subjects affected / exposed occurrences (all)  General disorders and administration site conditions - Other, specify: Cytokine-release Syndrome subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 7  4 / 17 (23.53%) 5  1 / 17 (5.88%) 1  1 / 17 (5.88%) 1  1 / 17 (5.88%) 1  1 / 17 (5.88%) 1  1 / 17 (5.88%) 1		

General disorders and administration site conditions - Other, specify: Cholecystolithiasis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: Sludge in the distal ductus h			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: joint pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: difficulties swallowing			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: Migraine			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: decreased hemaglobin			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: suspicion of immune related h			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: thrombophlebitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: lipase decreased			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		

Pain			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: immune related hepatitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: hordeolum			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: suspicion of immune related p			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: infarct pneumonia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: segmental artery embolisms bi			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: stomatitis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: immune related thyreoditis			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Immune system disorders			
Autoimmune disorder			
subjects affected / exposed	2 / 17 (11.76%)		
occurrences (all)	2		
Immune system disorders - Other, specify: immune-related hepatitis			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Hoarseness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pleural effusion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Sore throat			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Psychiatric disorders			
Restlessness			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	8 / 17 (47.06%)		
occurrences (all)	23		
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 17 (52.94%)		
occurrences (all)	24		
Blood bilirubin increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	3		
CPK increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Creatinine increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Electrocardiogram QT corrected			

interval prolonged subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
GGT increased subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 9		
Lipase increased subjects affected / exposed occurrences (all)	5 / 17 (29.41%) 8		
Lymphocyte count decreased subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 6		
Lymphocyte count increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3		
Serum amylase increased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Injury, poisoning and procedural complications Infusion related reaction subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Cardiac disorders Sinus tachycardia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Sinus bradycardia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Atrial fibrillation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Pericardial effusion subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Chest pain - cardiac			

<p>subjects affected / exposed occurrences (all)</p> <p>Cardiac disorders - Other, specify: tachyarrhythmia absoluta subjects affected / exposed occurrences (all)</p>	<p>1 / 17 (5.88%) 1</p> <p>1 / 17 (5.88%) 1</p>		
<p>Nervous system disorders</p> <p>Headache subjects affected / exposed occurrences (all)</p> <p>Nervous system disorders - Other, specify: worsening of sciatica subjects affected / exposed occurrences (all)</p> <p>Seizure subjects affected / exposed occurrences (all)</p>	<p>1 / 17 (5.88%) 1</p> <p>1 / 17 (5.88%) 1</p> <p>1 / 17 (5.88%) 1</p>		
<p>Blood and lymphatic system disorders</p> <p>Anemia subjects affected / exposed occurrences (all)</p> <p>Blood and lymphatic system disorders - Other, specify: increased CRP subjects affected / exposed occurrences (all)</p> <p>Blood and lymphatic system disorders - Other, specify: increased Alkalische Phosphatase subjects affected / exposed occurrences (all)</p> <p>Blood and lymphatic system disorders - Other, specify: Iron deficiency anemia subjects affected / exposed occurrences (all)</p> <p>Blood and lymphatic system disorders - Other, specify: increased GammaGT subjects affected / exposed occurrences (all)</p>	<p>3 / 17 (17.65%) 7</p> <p>2 / 17 (11.76%) 2</p> <p>2 / 17 (11.76%) 2</p> <p>1 / 17 (5.88%) 1</p> <p>2 / 17 (11.76%) 3</p>		

Blood and lymphatic system disorders - Other, specify: decreased Calcium			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Blood and lymphatic system disorders - Other, specify: Folic acid deficiency			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify: hypoproteinemia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify: increased Lipase			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify: lipase decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify: increased LDH			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify: creatine kinase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Blood and lymphatic system disorders - Other, specify: Thyroid stimulating hormone decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Blood and lymphatic system disorders - Other, specify: Serum amylase decreased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		

Eosinophilia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Blood and lymphatic system disorders - Other, specify: lymphopenia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Blood and lymphatic system disorders - Other, specify: lipaemia subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 5		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Middle ear inflammation subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Eye disorders Blurred vision subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Vision decreased subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Eye disorders - Other, specify: vitreous body clouding left eye subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Eye disorders - Other, specify: mouches volantes subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Abdominal pain			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Colitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 3		
Constipation subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3		
Diarrhea subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 7		
Dry mouth subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 3		
Gastroesophageal reflux disease subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Gastrointestinal disorders - Other, specify: autoimmune colitis subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Nausea subjects affected / exposed occurrences (all)	2 / 17 (11.76%) 2		
Oral pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Stomach pain subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Vomiting subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hepatobiliary disorders Hepatobiliary disorders - Other, specify: Suspected of Hepatitis			

subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Dry skin			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pain of skin			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Rash maculo-papular			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders - Other, specify: Erysipel			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify: Exanthema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify: itching			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders - Other, specify: subcutaneous nodule left Subclavicular			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal and urinary disorders - Other, specify: Enterococcus faecalis			

<p>subjects affected / exposed occurrences (all)</p> <p>Renal and urinary disorders - Other, specify: suspicion of urinary tract infection</p> <p>subjects affected / exposed occurrences (all)</p>	<p>1 / 17 (5.88%) 1</p> <p>1 / 17 (5.88%) 1</p>		
<p>Endocrine disorders</p> <p>Hyperthyroidism</p> <p>subjects affected / exposed occurrences (all)</p> <p>Hypothyroidism</p> <p>subjects affected / exposed occurrences (all)</p> <p>Endocrine disorders - Other, specify: subacute thyroiditis</p> <p>subjects affected / exposed occurrences (all)</p>	<p>1 / 17 (5.88%) 1</p> <p>2 / 17 (11.76%) 3</p> <p>1 / 17 (5.88%) 2</p>		
<p>Musculoskeletal and connective tissue disorders</p> <p>Pain in extremity</p> <p>subjects affected / exposed occurrences (all)</p> <p>Muscle cramp</p> <p>subjects affected / exposed occurrences (all)</p>	<p>1 / 17 (5.88%) 1</p> <p>2 / 17 (11.76%) 2</p>		
<p>Infections and infestations</p> <p>Lip infection</p> <p>subjects affected / exposed occurrences (all)</p> <p>Mucosal infection</p> <p>subjects affected / exposed occurrences (all)</p> <p>Thrush</p> <p>subjects affected / exposed occurrences (all)</p> <p>Urinary tract infection</p>	<p>1 / 17 (5.88%) 1</p> <p>1 / 17 (5.88%) 1</p> <p>1 / 17 (5.88%) 2</p>		

subjects affected / exposed occurrences (all)	4 / 17 (23.53%) 5		
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		
Hypoalbuminemia			
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Hypocalcemia			
subjects affected / exposed occurrences (all)	3 / 17 (17.65%) 5		
Hyponatremia			
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 2		
Hypophosphatemia			
subjects affected / exposed occurrences (all)	1 / 17 (5.88%) 1		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 June 2019	In a first amendment of the study protocol, endpoints were widened to dynamic changes of cells, inclusion and exclusion criteria were adapted to more common medical standards for the addressed indication (e.g., the planned therapy with PD-1 blocking antibodies was opened by including the combination of nivolumab and ipilimumab), the number of clinic visits was adapted to the treatment schedules, and it was clarified that the study represents a hypotheses-generating approach as there was no prespecified hypothesis.

Notes:

---

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported