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
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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 met 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 preferrred 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:

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	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Upon obtaining signed informed consent, screening evaluation were performed to confirm eligibilty 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 admninistered 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.

Number of subjects in period 1	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)[1]

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[2]			
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)[3]

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[4]			
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)[5]

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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[6]			
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)[7]

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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[8]			
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)[9]

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[10]			
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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[12]			
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 pover 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)[13]

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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[14]			
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)[15]

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[16]			
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)[17]

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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[18]			
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)[19]

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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[20]			
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)[21]

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[22]			
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)[23]

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

End point values	ITT			
Subject group type	Subject analysis set			
Number of subjects analysed	14[24]			
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

End point values	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

End point values	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

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

subjects affected / exposed	1 / 17 (5.88%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Endocrine disorders			
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		
Musculoskeletal and connective tissue disorders			
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		
Infections and infestations			
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 %

Non-serious adverse events	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	1 / 17 (5.88%)		
occurrences (all)	1		
Vascular disorders			
Lymphedema			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Hot flashes			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	7		
Fever			
subjects affected / exposed	4 / 17 (23.53%)		
occurrences (all)	5		
Flu like symptoms			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: Sprained right ankle			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: decreased sensibility in the			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: heartburn			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
General disorders and administration site conditions - Other, specify: Cytokine-release Syndrome			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	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	1 / 17 (5.88%)		
occurrences (all)	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	1 / 17 (5.88%)		
occurrences (all)	1		
GGT increased			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	9		
Lipase increased			
subjects affected / exposed	5 / 17 (29.41%)		
occurrences (all)	8		
Lymphocyte count decreased			
subjects affected / exposed	3 / 17 (17.65%)		
occurrences (all)	6		
Lymphocyte count increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	3		
Serum amylase increased			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Sinus bradycardia			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Atrial fibrillation			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Pericardial effusion			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Chest pain - cardiac			

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

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

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

subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	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 nodus left Sublavicular			
subjects affected / exposed	1 / 17 (5.88%)		
occurrences (all)	1		
Renal and urinary disorders			
Renal and urinary disorders - Other, specify: Enterococcus faecalis			

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

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