Clinical trial results:
A Phase II Randomized, Double-Blind Trial of Immunotherapy with Nivolumab or Nivolumab plus Ipilimumab versus Double-Placebo Control as a Post-Surgical/Post-Radiation Treatment for Stage IV Melanoma with No Evidence of Disease

Summary

EudraCT number	2014-001167-12
Trial protocol	DE AT
Global end of trial date	27 June 2021

Results information

Result version number	v1 (current)
This version publication date	29 September 2022
First version publication date	29 September 2022
Summary attachment (see zip file)	Immuned_Synpsos (IMMUNED_Synopsis CSR_V1.0_2022-06-20_incl. attachments.pdf)

Trial information

Trial identification

Sponsor protocol code	IMMUNED

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02523313
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospital Essen
Sponsor organisation address	Hufelandstraße 55, Essen, Germany, 45147
Public contact	Departement of Dermatology, University Hospital Essen, 0049 2017234342, dirk.schadendorf@uk-essen.de
Scientific contact	Departement of Dermatology, University Hospital Essen, 0049 2017234342, dirk.schadendorf@uk-essen.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	10 June 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 June 2021
Global end of trial reached?	Yes
Global end of trial date	27 June 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to estimate the efficacy of adjuvant immunotherapy with nivolumab alone or in combination with ipilimumab therapy in stage IV melanoma patients with no evidence of disease, i.e. the primary endpoint is recurrence-free survival (RFS).

Protection of trial subjects:

The treatment should be conducted exactly as described in the protocol. Any protocol deviations were reported. The recommendations of Good Clinical Practice (ICH-GCP: International Conference on Harmonisation - Good Clinical Practice), valid since 17.1.1997, were observed.
The selection of patients occurred through the investigator according to the inclusion and exclusion criteria after informing the patient orally and in writing about the study and after the patient has signed the informed consent. There was no preferred enrolment of men or women within this study. However, pregnant or lactating female patients were excluded from study participation.
Women of childbearing potential and male patients with partners of childbearing potential had to use a highly effective form ofcontraception according to Clinical Trials Facilitation Group.

Background therapy:

Relevant prior and concomitant medications were documented in the eCRF.
Any immunosuppressive therapy given within the past 30 days prior to study drug administration (excluding physiologic steroid hormone replacement) was not permitted.
Prior radiotherapy had to be completed at least two weeks prior to study drug administration.

Evidence for comparator:

Eligible patients were randomly assigned to one of the three treatment groups (1:1:1) using a central, interactive, online system. Both experimental treatment groups – i.e., nivolumab alone (arm A) and nivolumab plus ipilimumab (arm B) – were compared with a double-matching placebo group (arm C).
Patients in arm A received nivolumab (3 mg/kg) plus ipilimumab-placebo (nivolumab montherapy).
Patients in arm B received nivolumab (1 mg/kg) and ipilimumab (3 mg/kg) (nivolumab-ipilimumab-combination therapy)
Patients in arm C received nivolumab-placebo and ipilimumab-placebo (double placebo control)

Actual start date of recruitment	01 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 167
Worldwide total number of subjects	167
EEA total number of subjects	167

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)	123
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

After written informed consent, eligibility was confirmed and baseline data were obtained. Patients were randomzed 1 : 1 : 1 into the arms. Block randomization was used (block length of six) stratified according to PD-L1 status, site of metastasis, and trial site. Randomization period was from 02 SEP 2015 and 20 NOV 2018. Active German sites: 20

Pre-assignment

Screening details:

Selection of patients occurred by the investigators according to the inclusion / exclusion criteria. Baseline examinations should be performed within 3 weeks before first dose of study treatment.

Pre-assignment period milestones

Number of subjects started	237[1]
Intermediate milestone: Number of subjects	Randomization: 167
Number of subjects completed	167

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 7
Reason: Number of subjects	patient's wish: 1
Reason: Number of subjects	not matching eligibility criteria: 62

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The screening period was defined as pre-assignment period. 237 patients were screened, but only 167 patients were randomized into the 3 study arms.

Period 1

Period 1 title	Induction phase (12 weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer

Blinding implementation details:

The Sponsor, subjects, investigator and site staff were blinded to the study drug administered. matching Nivolumab and Ipilimumab-Placebos were used. In order to protect the blind in Arm B, the 1mg/kg Nivolumab administered in weeks 1, 4, 7 and 10 should be diluted to the same volume as 3 mg/kg Nivolumab-placebo prepared on weeks 3, 5, 9, 11. In general, all placebo infusions were diluted to the same volume of the corresponding study drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Nivolumab-monotherapy (plus Placebo) given as adjuvant therapy after surgery or radiation therapy: Patients received Nivolumab 3 mg/kg every 2 weeks for up to 12 weeks (+ Ipilimumab-Placebo on weeks 1, 4, 7 and 10 and Nivolumab-Placebo on weeks 4 and 10).
Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject’s treatment assignment to determine the appropriate subsequent treatment.

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 was applied at a dose of 3 mg/kg given as IV infusion every 2 weeks (q2wx6): weeks 1, 3, 5, 7, 9, 11 during induction phase

Investigational medicinal product name	Nivolumab-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab-Placebo was administered at week 4 and 10 during induction phase.

Investigational medicinal product name	Ipilimumab-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab-Placebo was administered at weeks 1, 4, 7 and 10 during induction phase.

Arm title	Arm B

Arm description:

Nivolumab + ipilimumab combination therapy given as adjuvant therapy after surgery or radiation therapy:
Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg) were applied as IV infusion every 3 weeks for 4 doses. Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject’s treatment assignment to determine the appropriate subsequent treatment.

Arm type	Active comparator
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 was applied at a dose of 1 mg/kg given as IV infusion every 3 weeks for 4 doses: weeks 1, 4, 7, 10 of induction phase.

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 (3 mg/kg) was administered as an IV infusion on the same day as the Nivolumab infusion every 3 weeks for 4 doses: weeks 1, 4, 7, 10 of induction phase.

Investigational medicinal product name	Nivolumab-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Nivolumab-Placebo was administered on weeks 3, 5, 9 and 11.

Arm title	Arm C

Arm description:

Double placebo control given as adjuvant therapy after surgery or radiation therapy.
Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment.
Patients in Arm C had a cross-over option: In case of documented recurrence of disease in the eCRF (confirmed via tumor assessment using radiologic imaging), subjects in Arm C could receive Nivolumab 3mg/kg monotherapy every 2 weeks until subsequent progression or for up to 1 year, whichever occurs first.

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

Dosage and administration details:

Nivolumab-Placebo was administered on weeks 1, 3, 4, 5, 7, 9, 10, 11 during induction phase.

Investigational medicinal product name	Ipilimumab-Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Ipilimumab-Placebo was administered at weeks 1, 4, 7 and 10 during induction phase.

Number of subjects in period 1	Arm A	Arm B	Arm C
Started	59	56	52
Completed	56	55	51
Not completed	3	1	1
Consent withdrawn by subject	3	1	1

Period 2

Period 2 title	Maintenance Phase (40 weeks)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

Nivoluman-Placebo was diluted to the same volume as 3 mg/kg Nivolumab.

Arms

Are arms mutually exclusive?	Yes

Arm title	Arm A

Arm description:

Nivolumab-Monotherapy as maintenance for up to 40 weeks or until recurrence of disease.

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 was applied at a dose of 3 mg/kg IV every 2 weeks for up to 40 weeks or until recurrence of disease, whichever occurred first.

Arm title	Arm B

Arm description:

Nivolumab-Monotherapy as maintenance for up to 40 weeks or until recurrence of disease.

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 was applied at a dose of 3 mg/kg IV every 2 weeks for up to 40 weeks or until recurrence of disease, whichever occurred first.

Arm title	Arm C

Arm description:

Nivolumab-Placebo as maintenance for up to 40 weeks or until recurrence of disease.

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

Dosage and administration details:

Nivolumab-Placebo was administered as IV infusion every 2 weeks for up to 40 weeks or occurrence of relapse/progress, whichever occurred first.

Number of subjects in period 2	Arm A	Arm B	Arm C
Started	56	55	51
Completed	21	11	10
Not completed	35	44	41
Consent withdrawn by subject	-	-	1
patient's wish	1	1	1

unknown	-	1	-
Adverse event, non-fatal	7	34	2
Relapse / Progress	25	7	36
Protocol deviation	2	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Arm A
Reporting group description:	
Nivolumab-monotherapy (plus Placebo) given as adjuvant therapy after surgery or radiation therapy: Patients received Nivolumab 3 mg/kg every 2 weeks for up to 12 weeks (+ Ipilimumab-Placebo on weeks 1, 4, 7 and 10 and Nivolumab-Placebo on weeks 4 and 10). Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment.	
Reporting group title	Arm B
Reporting group description:	
Nivolumab + ipilimumab combination therapy given as adjuvant therapy after surgery or radiation therapy: Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg) were applied as IV infusion every 3 weeks for 4 doses. Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment.	
Reporting group title	Arm C
Reporting group description:	
Double placebo control given as adjuvant therapy after surgery or radiation therapy. Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment. Patients in Arm C had a cross-over option: In case of documented recurrence of disease in the eCRF (confirmed via tumor assessment using radiologic imaging), subjects in Arm C could receive Nivolumab 3mg/kg monotherapy every 2 weeks until subsequent progression or for up to 1 year, whichever occurs first.	

Reporting group values	Arm A	Arm B	Arm C
Number of subjects	59	56	52
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of randomization minus Year of birth.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	43	45	35
From 65-84 years	16	11	17
85 years and over	0	0	0
Age continuous			
Units: years			
median	57.0	52.0	58.5
inter-quartile range (Q1-Q3)	48.0 to 65.0	44.5 to 59.0	46.0 to 65.5
Gender categorical			
Units: Subjects			
Female	28	25	19
Male	31	31	33

Reporting group values	Total		

Number of subjects	167		
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of randomization minus Year of birth.			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	123		
From 65-84 years	44		
85 years and over	0		
Age continuous			
Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical			
Units: Subjects			
Female	72		
Male	95		

Subject analysis sets

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

Subject analysis set description:

All patients who gave their informed consent and who were randomized.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients from the ITT population who received at least one single infusion of investigational agent and who did not have major disqualifying protocol violations.
Definition of major disqualifying protocol violations:
Patients with documented stage I-III melanoma as per AJCC staging / Documented/confirmed disease at baseline / The last intervention demonstrating that the subject is free of disease is more than 13 weeks before the first infusion / Incomplete baseline staging (missing CT chest or CT abdomen, pelvis or CT/MRT head) / Prior therapy with CTLA4 or PD1 antibodies / Subjects with uveal or mucosal melanoma.
Disqualifying protocol violatiosn during study:
Subjects who receive anti-cancer therapy other than study treatment while on study therapy / Subjects treated differently than as randomized (subjects who received the wrong treatment or who discontinued prematurely due to protocol violation)

Reporting group values	Intent-to-treat-set	Safety set	
Number of subjects	167	162	
Age categorical			
Patients aged 18 years or older could be enrolled. There was no maximum age limit. Age was calculated as Year of randomization minus Year of birth.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	

Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	123	119	
From 65-84 years	44	43	
85 years and over	0	0	
Age continuous			
Units: years			
median	55.0		
inter-quartile range (Q1-Q3)	46.0 to 65.0		
Gender categorical			
Units: Subjects			
Female	72	68	
Male	95	94	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Nivolumab-monotherapy (plus Placebo) given as adjuvant therapy after surgery or radiation therapy:
Patients received Nivolumab 3 mg/kg every 2 weeks for up to 12 weeks (+ Ipilimumab-Placebo on weeks 1, 4, 7 and 10 and Nivolumab-Placebo on weeks 4 and 10).
Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment.

Reporting group title	Arm B

Reporting group description:

Nivolumab + ipilimumab combination therapy given as adjuvant therapy after surgery or radiation therapy:
Nivolumab (1 mg/kg) and Ipilimumab (3 mg/kg) were applied as IV infusion every 3 weeks for 4 doses.
Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment.

Reporting group title	Arm C

Reporting group description:

Double placebo control given as adjuvant therapy after surgery or radiation therapy.
Upon recurrence of disease and treatment discontinuation of each subject, investigators were unblinded to each subject's treatment assignment to determine the appropriate subsequent treatment.
Patients in Arm C had a cross-over option: In case of documented recurrence of disease in the eCRF (confirmed via tumor assessment using radiologic imaging), subjects in Arm C could receive Nivolumab 3mg/kg monotherapy every 2 weeks until subsequent progression or for up to 1 year, whichever occurs first.

Reporting group title	Arm A

Reporting group description:

Nivolumab-Monotherapy as maintenance for up to 40 weeks or until recurrence of disease.

Reporting group title	Arm B

Reporting group description:

Nivolumab-Monotherapy as maintenance for up to 40 weeks or until recurrence of disease.

Reporting group title	Arm C

Reporting group description:

Nivolumab-Placebo as maintenance for up to 40 weeks or until recurrence of disease.

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

Subject analysis set description:

All patients who gave their informed consent and who were randomized.

Subject analysis set title	Safety set
Subject analysis set type	Safety analysis

Subject analysis set description:

All patients from the ITT population who received at least one single infusion of investigational agent and who did not have major disqualifying protocol violations.
Definition of major disqualifying protocol violations:
Patients with documented stage I-III melanoma as per AJCC staging / Documented/confirmed disease at baseline / The last intervention demonstrating that the subject is free of disease is more than 13 weeks before the first infusion / Incomplete baseline staging (missing CT chest or CT abdomen, pelvis or CT/MRT head) / Prior therapy with CTLA4 or PD1 antibodies / Subjects with uveal or mucosal melanoma.
Disqualifying protocol violatiosn during study:
Subjects who receive anti-cancer therapy other than study treatment while on study therapy / Subjects treated differently than as randomized (subjects who received the wrong treatment or who discontinued prematurely due to protocol violation)

Primary: Recurrence-free survival (RFS)

End point title	Recurrence-free survival (RFS)

End point description:

Since this study included patients with NED and investigated the adjuvant use of immunotherapy, RFS replaced progression-free survival as normally used in stage IV disease (the definitions of both surrogate endpoints are congruent).
Tumor assessments using CT or MRI scans and classification of the response by the investigator according to RECIST v1.1 were performed at the beginning every 12 weeks during study treatment. During follow-up period, tumor assessment was performed every 3 months for the first 2 years after last infusion of study medication, therafter every 6 months. If recurrence/progression of disease was suspected for any reason at or between the 12-weekly evaluation visits, radiological confirmation was necessary.

End point type	Primary

End point timeframe:

Time from randomization until first recurrence (local or distant metastasis), new primary melanoma or death from any cause, whichever occurred first. Patients without recurrence and patients who did not die were censored at the date of last contact.

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: months				
median (confidence interval 95%)	12.3 (5.30 to 23.85)	9999 (24.97 to 9999999999)	6.3 (3.26 to 9.61)	

Statistical analyses

Statistical analysis title	Hazard ratio for disease recurrence /Arm A - Arm C
Comparison groups	Arm A v Arm C
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0236
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.36
upper limit	1

Statistical analysis title	Hazard ratio for disease recurrence /Arm B - Arm C
Comparison groups	Arm B v Arm C

Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.25
Confidence interval	
level	Other: 97.5 %
sides	2-sided
lower limit	0.13
upper limit	0.48

Primary: 1-year RFS rate

End point title	1-year RFS rate

End point description:

Proportion of patients being alive or with unknown survival status and without recurrence (local or distant metastasis) or new primary melanoma or not known to show recurrence 12 months after randomization, derived by Kaplan-Meier.

End point type	Primary

End point timeframe:

12 months after date of randomization

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: percent				
number (confidence interval 95%)	51.7 (37.98 to 63.83)	75.3 (61.10 to 84.88)	32.2 (19.81 to 45.32)	

Statistical analyses

Statistical analysis title	1 year RFS rate Arm A vs. Arm C
Comparison groups	Arm A v Arm C
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0506
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.6034

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1

Statistical analysis title	1 year RFS rate Arm B vs. Arm C
Comparison groups	Arm B v Arm C
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.273
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.52

Primary: 2-year RFS rate

End point title	2-year RFS rate

End point description:

Proportion of patients being alive or with unknown survival status and without recurrence (local or distant metastasis) or new primary melanoma or not known to show recurrence 24 months after randomization, derived by Kaplan-Meier.

End point type	Primary

End point timeframe:

24 months after date of randomization

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: percent				
number (confidence interval 95%)	36.9 (24.46 to 49.46)	66.5 (51.58 to 77.81)	15.0 (6.68 to 26.56)	

Statistical analyses

Statistical analysis title	2 year RFS rate Arm A vs. Arm C
Comparison groups	Arm A v Arm C
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0141
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.5677
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.89

Statistical analysis title	2 year RFS rate Arm B vs. Arm C
Comparison groups	Arm B v Arm C
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.2436
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	0.43

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as time from randomization until date of death. OS for patients who have not died were censored at the date of last contact.
19 patients of double-placebo arm C switched to arm A. The rank preserving structural failure time model (RPSFTM) was used to adjust survival time for treatment switching after disease progression from arm C to Nivolumab (Arm A) group. RPSFT estimates the survival time gained or lost by receiving active treatment. RPSFT splits the survival time in time off and on treatment and estimates the treatment effect (Ψ) using g-estimation (grid search from -1.0 to 1.0 with an interval of 0.001) (Here: Ψ = -0.00005, hence the factor is 1, i.e. there is no effect). Time to event for crossover patients were re-calculated based on the optimal Ψ. The method relies on the assumption that the only difference between randomized groups is the treatment received and the treatment effect is the same for all patients regardless of when treatment is received.

End point type	Secondary

End point timeframe:

From date of randomization until end of study (= 2 years after last patient off treatment).

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: months				
median (confidence interval 95%)	999999 (999999 to 999999)	999999 (999999 to 999999)	999999 (38.59 to 999999)	

Statistical analyses

No statistical analyses for this end point

Secondary: 1-year OS rate

End point title	1-year OS rate

End point description:

Proportion of patients being alive 12 months after randomization, derived by Kaplan-Meier.

End point type	Secondary

End point timeframe:

12 months after date of randomization

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: percent				
number (confidence interval 95%)	92.2 (80.44 to 96.98)	95.7 (84.02 to 98.92)	93.9 (82.31 to 98.00)	

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year OS rate

End point title	2-year OS rate

End point description:

Proportion of patients being alive 24 months after randomization, derived by Kaplan-Meier.

End point type	Secondary

End point timeframe:

24 months after date of randomization

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: percent				
number (confidence interval 95%)	81.7 (67.81 to 90.07)	91.2 (78.16 to 96.60)	87.3 (73.87 to 94.10)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to recurrence (TTR)

End point title	Time to recurrence (TTR)

End point description:

TTR of a patient was defined as the time from randomization until disease recurrence (local or distant metastasis) or melanoma-related death. TTR for patients without recurrence or melanoma-related death were censored at the date of last contact. TTR replaced here consistently time to progression (TTP) as normally used in stage IV disease.

End point type	Secondary

End point timeframe:

From date of randomization until end of study (= defined as 2 years after last patient off treatment)

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: months				
median (confidence interval 95%)	15.2 (5.30 to 33.26)	999999 (24.97 to 999999)	6.3 (4.87 to 9.61)	

Statistical analyses

Statistical analysis title	HR (arm A vs. double placebo (Arm C))

Statistical analysis description:

Risk of disease recurrence (local or distant metastasis) or melanoma-related death

Comparison groups	Arm A v Arm C

Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0137
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.9

Statistical analysis title	HR (arm B vs. double placebo (Arm C))
Statistical analysis description:	
Risk of disease recurrence (local or distant metastasis) or melanoma-related death	
Comparison groups	Arm A v Arm C
Number of subjects included in analysis	111
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.45

Secondary: 1-year TTR rate

End point title	1-year TTR rate
End point description:	
Proportion of patients alive without disease recurrence (local or distant metastasis) 12 months after randomization, derived by Kaplan-Meier.	
End point type	Secondary
End point timeframe:	
12 months after date of randomization	

End point values	Arm A	Arm B	Arm C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59	56	52	
Units: percent				
number (confidence interval 95%)	55.2 (41.25 to 67.09)	75.3 (61.10 to 84.88)	32.2 (19.81 to 45.32)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression/recurrence free survival 2 (PRFS2)

End point title	Progression/recurrence free survival 2 (PRFS2)[1]

End point description:

For crossover patients (arm C into arm A) the PRFS2 was defined as time from randomization until the earliest of the following:
- date of first disease progression per RECIST 1.1 or new primary melanoma beyond the initial unresectable disease recurrence,
- date of second recurrence in patients without evidence of disease after surgery of a resectable first recurrence or
- death.
For patients who remained alive and whose disease has not recurred, or disease has recurred but subsequent disease progression or recurrence has not occurred, PRFS2 was censored on the date of last contact.

End point type	Secondary

End point timeframe:

From date of randomization until end of study (= 2 years after last patient off study treatment)

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Progression/recurrence free survival 2 is only calculated for crossover patients. Crossover was only allowed for patients randomized to arm C (double placebo arm). Therefore only results for arm C patients are presented.

End point values	Arm C			
Subject group type	Reporting group			
Number of subjects analysed	19[2]			
Units: month				
median (confidence interval 95%)	999999 (21.18 to 999999)			

Notes:

[2] - 19 patients of 52 patients randomized into arm C crossed over.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All AEs that occurred from the patient's written consent until 90 days after discontinuation of study treatment were reported, except in cases where a study participant had started a new anti-neoplastic therapy.

Adverse event reporting additional description:

Any SAE occurring after the start of a new anti-neoplastic therapy that was suspected to be related to study treatment by the investigator had to be reported.
AEs associated with the disease under study or its relapse or progression did not have to be reported, because recurrence/progression was assessed as outcome da

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Safety set_Arm A

Reporting group description:

All patients of the ITT set who received at least one single infusion of investigational agent.

Reporting group title	Safety set_Arm B

Reporting group description: -

Reporting group title	Safety set_Arm C

Reporting group description: -

Serious adverse events	Safety set_Arm A	Safety set_Arm B	Safety set_Arm C
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 56 (33.93%)	36 / 55 (65.45%)	16 / 51 (31.37%)
number of deaths (all causes)	13	7	16
number of deaths resulting from adverse events	0	0	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Autoimmune disorder			

subjects affected / exposed	1 / 56 (1.79%)	8 / 55 (14.55%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	1 / 1	8 / 8	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	0 / 56 (0.00%)	4 / 55 (7.27%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	2 / 56 (3.57%)	4 / 55 (7.27%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	3 / 3	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune-mediated hepatitis			
subjects affected / exposed	0 / 56 (0.00%)	4 / 55 (7.27%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Safety set_Arm A	Safety set_Arm B	Safety set_Arm C
Total subjects affected by non-serious adverse events			
subjects affected / exposed	53 / 56 (94.64%)	55 / 55 (100.00%)	46 / 51 (90.20%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Basal cell carcinoma			
subjects affected / exposed	2 / 56 (3.57%)	0 / 55 (0.00%)	3 / 51 (5.88%)
occurrences (all)	2	0	3
Melanocytic naevus			
subjects affected / exposed	1 / 56 (1.79%)	3 / 55 (5.45%)	1 / 51 (1.96%)
occurrences (all)	2	3	1
Vascular disorders			
Flushing			
subjects affected / exposed	3 / 56 (5.36%)	1 / 55 (1.82%)	0 / 51 (0.00%)
occurrences (all)	3	1	0
Hypertension			
subjects affected / exposed	3 / 56 (5.36%)	2 / 55 (3.64%)	6 / 51 (11.76%)
occurrences (all)	4	2	7
Lymphoedema			
subjects affected / exposed	4 / 56 (7.14%)	1 / 55 (1.82%)	2 / 51 (3.92%)
occurrences (all)	5	1	2
General disorders and administration site conditions			
Chills			
subjects affected / exposed	3 / 56 (5.36%)	8 / 55 (14.55%)	2 / 51 (3.92%)
occurrences (all)	3	9	2
Fatigue			
subjects affected / exposed	16 / 56 (28.57%)	25 / 55 (45.45%)	14 / 51 (27.45%)
occurrences (all)	19	28	16
Influenza like illness			
subjects affected / exposed	15 / 56 (26.79%)	10 / 55 (18.18%)	4 / 51 (7.84%)
occurrences (all)	18	13	5
Oedema peripheral			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Pain			
subjects affected / exposed	4 / 56 (7.14%)	4 / 55 (7.27%)	4 / 51 (7.84%)
occurrences (all)	5	5	4
Pyrexia			
subjects affected / exposed	9 / 56 (16.07%)	11 / 55 (20.00%)	1 / 51 (1.96%)
occurrences (all)	11	13	1
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	13 / 56 (23.21%)	7 / 55 (12.73%)	10 / 51 (19.61%)
occurrences (all)	14	8	10
Dyspnoea			
subjects affected / exposed	3 / 56 (5.36%)	4 / 55 (7.27%)	3 / 51 (5.88%)
occurrences (all)	4	5	3
Oropharyngeal pain			
subjects affected / exposed	1 / 56 (1.79%)	4 / 55 (7.27%)	3 / 51 (5.88%)
occurrences (all)	1	4	3
Pneumonitis			
subjects affected / exposed	0 / 56 (0.00%)	5 / 55 (9.09%)	0 / 51 (0.00%)
occurrences (all)	0	5	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	3 / 56 (5.36%)	2 / 55 (3.64%)	1 / 51 (1.96%)
occurrences (all)	3	2	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	6 / 56 (10.71%)	22 / 55 (40.00%)	2 / 51 (3.92%)
occurrences (all)	6	24	2
Amylase increased			
subjects affected / exposed	8 / 56 (14.29%)	9 / 55 (16.36%)	5 / 51 (9.80%)
occurrences (all)	11	9	6
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 56 (5.36%)	6 / 55 (10.91%)	1 / 51 (1.96%)
occurrences (all)	3	6	1
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 56 (1.79%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences (all)	1	4	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	3 / 56 (5.36%)	0 / 55 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
C-reactive protein increased			
subjects affected / exposed	3 / 56 (5.36%)	0 / 55 (0.00%)	1 / 51 (1.96%)
occurrences (all)	3	0	1
Gamma-glutamyltransferase			

increased			
subjects affected / exposed	5 / 56 (8.93%)	9 / 55 (16.36%)	1 / 51 (1.96%)
occurrences (all)	5	9	1
Lipase increased			
subjects affected / exposed	9 / 56 (16.07%)	15 / 55 (27.27%)	7 / 51 (13.73%)
occurrences (all)	14	19	11
Lymphocyte count decreased			
subjects affected / exposed	2 / 56 (3.57%)	4 / 55 (7.27%)	5 / 51 (9.80%)
occurrences (all)	2	4	9
Tri-iodothyronine free decreased			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Weight decreased			
subjects affected / exposed	3 / 56 (5.36%)	1 / 55 (1.82%)	1 / 51 (1.96%)
occurrences (all)	3	1	1
White blood cell count decreased			
subjects affected / exposed	2 / 56 (3.57%)	2 / 55 (3.64%)	3 / 51 (5.88%)
occurrences (all)	2	2	6
Cardiac disorders			
Sinus tachycardia			
subjects affected / exposed	1 / 56 (1.79%)	4 / 55 (7.27%)	3 / 51 (5.88%)
occurrences (all)	1	4	3
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 56 (5.36%)	3 / 55 (5.45%)	2 / 51 (3.92%)
occurrences (all)	4	3	2
Headache			
subjects affected / exposed	14 / 56 (25.00%)	11 / 55 (20.00%)	11 / 51 (21.57%)
occurrences (all)	18	11	18
Paraesthesia			
subjects affected / exposed	3 / 56 (5.36%)	4 / 55 (7.27%)	2 / 51 (3.92%)
occurrences (all)	4	4	2
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	4 / 56 (7.14%)	3 / 55 (5.45%)	4 / 51 (7.84%)
occurrences (all)	4	3	4
Eye disorders			
Vision blurred			
subjects affected / exposed	0 / 56 (0.00%)	4 / 55 (7.27%)	1 / 51 (1.96%)
occurrences (all)	0	4	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 56 (16.07%)	5 / 55 (9.09%)	6 / 51 (11.76%)
occurrences (all)	9	5	7
Abdominal pain upper			
subjects affected / exposed	2 / 56 (3.57%)	3 / 55 (5.45%)	3 / 51 (5.88%)
occurrences (all)	2	3	3
Constipation			
subjects affected / exposed	3 / 56 (5.36%)	2 / 55 (3.64%)	1 / 51 (1.96%)
occurrences (all)	3	2	1
Diarrhoea			
subjects affected / exposed	15 / 56 (26.79%)	17 / 55 (30.91%)	4 / 51 (7.84%)
occurrences (all)	19	20	4
Gastritis			
subjects affected / exposed	1 / 56 (1.79%)	4 / 55 (7.27%)	0 / 51 (0.00%)
occurrences (all)	1	4	0
Nausea			
subjects affected / exposed	9 / 56 (16.07%)	12 / 55 (21.82%)	6 / 51 (11.76%)
occurrences (all)	15	15	10
Vomiting			
subjects affected / exposed	5 / 56 (8.93%)	3 / 55 (5.45%)	2 / 51 (3.92%)
occurrences (all)	7	4	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	2 / 56 (3.57%)	5 / 55 (9.09%)	1 / 51 (1.96%)
occurrences (all)	2	6	1
Dry skin			
subjects affected / exposed	6 / 56 (10.71%)	2 / 55 (3.64%)	2 / 51 (3.92%)
occurrences (all)	6	3	2
Hyperhidrosis			

subjects affected / exposed	0 / 56 (0.00%)	7 / 55 (12.73%)	1 / 51 (1.96%)
occurrences (all)	0	7	1
Night sweats			
subjects affected / exposed	1 / 56 (1.79%)	3 / 55 (5.45%)	1 / 51 (1.96%)
occurrences (all)	1	3	1
Pruritus			
subjects affected / exposed	8 / 56 (14.29%)	14 / 55 (25.45%)	4 / 51 (7.84%)
occurrences (all)	8	19	5
Rash			
subjects affected / exposed	2 / 56 (3.57%)	6 / 55 (10.91%)	0 / 51 (0.00%)
occurrences (all)	2	6	0
Rash maculo-papular			
subjects affected / exposed	4 / 56 (7.14%)	15 / 55 (27.27%)	0 / 51 (0.00%)
occurrences (all)	4	17	0
Pash pustular			
subjects affected / exposed	3 / 56 (5.36%)	0 / 55 (0.00%)	0 / 51 (0.00%)
occurrences (all)	3	0	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	6 / 56 (10.71%)	19 / 55 (34.55%)	1 / 51 (1.96%)
occurrences (all)	6	19	1
Hypothyroidism			
subjects affected / exposed	8 / 56 (14.29%)	11 / 55 (20.00%)	1 / 51 (1.96%)
occurrences (all)	10	12	1
Thyroiditis			
subjects affected / exposed	0 / 56 (0.00%)	4 / 55 (7.27%)	0 / 51 (0.00%)
occurrences (all)	0	4	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 56 (19.64%)	7 / 55 (12.73%)	4 / 51 (7.84%)
occurrences (all)	11	8	5
Back pain			
subjects affected / exposed	8 / 56 (14.29%)	6 / 55 (10.91%)	5 / 51 (9.80%)
occurrences (all)	11	6	6
Bone pain			

subjects affected / exposed	2 / 56 (3.57%)	4 / 55 (7.27%)	4 / 51 (7.84%)
occurrences (all)	2	5	4
Hyperglycaemia			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	0 / 51 (0.00%)
occurrences (all)	0	3	0
Joint range of motion decreased			
subjects affected / exposed	0 / 56 (0.00%)	3 / 55 (5.45%)	1 / 51 (1.96%)
occurrences (all)	0	3	1
Musculoskeletal chest pain			
subjects affected / exposed	0 / 56 (0.00%)	4 / 55 (7.27%)	0 / 51 (0.00%)
occurrences (all)	0	4	0
Myalgia			
subjects affected / exposed	4 / 56 (7.14%)	4 / 55 (7.27%)	1 / 51 (1.96%)
occurrences (all)	4	4	1
Pain in extremitiy			
subjects affected / exposed	7 / 56 (12.50%)	10 / 55 (18.18%)	5 / 51 (9.80%)
occurrences (all)	8	10	5
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 56 (3.57%)	3 / 55 (5.45%)	1 / 51 (1.96%)
occurrences (all)	2	4	1
Nasopharyngitis			
subjects affected / exposed	7 / 56 (12.50%)	7 / 55 (12.73%)	6 / 51 (11.76%)
occurrences (all)	10	8	8
Rhinitis			
subjects affected / exposed	1 / 56 (1.79%)	4 / 55 (7.27%)	1 / 51 (1.96%)
occurrences (all)	2	4	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 56 (1.79%)	6 / 55 (10.91%)	1 / 51 (1.96%)
occurrences (all)	1	6	1
Hyperuricaemia			
subjects affected / exposed	3 / 56 (5.36%)	2 / 55 (3.64%)	1 / 51 (1.96%)
occurrences (all)	3	2	1
Hypokalaemia			

subjects affected / exposed occurrences (all)	1 / 56 (1.79%) 2	5 / 55 (9.09%) 5	0 / 51 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2018	Recruitment period was extended by three months, and the number of planned patients was adapted according to a new calculation based on recent findings from study CA209-238.
05 September 2019	Amendment included an extension of the follow-up period (after the treatment period of approx. one year, all patients are followed-up for a maximum of 5 years or until end of study, i.e. 24 months after end of treatment of last patient), an addition of two more secondary objectives (TTR, PFS2/RFS2 for crossover patients of arm C), further explanations on AE reporting, and statistical adaptions.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported