EU Clinical Trials Register

Clinical trial results:
A randomized, open-label, three-arm, multi-center Phase II clinical trial evaluating effect of addition of DCVAC/OvCa to first line standard chemotherapy (carboplatin and paclitaxel) in women with newly diagnosed epithelial ovarian carcinoma

Summary

EudraCT number	2013-001322-26
Trial protocol	DE CZ PL
Global end of trial date	18 November 2021

Results information

Result version number	v1 (current)
This version publication date	13 March 2022
First version publication date	13 March 2022

Trial information

Trial identification

Sponsor protocol code	SOV01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02107937
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SOTIO a.s.
Sponsor organisation address	Jankovcova 1518/2, Prague, Czechia,
Public contact	Clinical Trials SOTIO, SOTIO a.s., +420 224175111, clinicaltrial@sotio.com
Scientific contact	Clinical Trials SOTIO, SOTIO a.s., +420 224175111, clinicaltrial@sotio.com

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	21 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 November 2021
Global end of trial reached?	Yes
Global end of trial date	18 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

PRIMARY OBJECTIVE
To explore the effect of adding DCVAC/OvCa to standard of care (SoC) chemotherapy on progression-free survival (PFS) measured at 2 years after randomization in women with epithelial ovarian cancer who have undergone debulking surgery
SECONDARY OBJECTIVES
• Proportion of patients staying in remission at 6 months after the last dose of first-line chemotherapy
• Proportion of patients staying in remission at 12 months after the last dose of first-line chemotherapy
• Biological progression-free interval (PFIBIO)
• Immunological response
• Proportion of patients requiring second-line chemotherapy
• Time to second-line chemotherapy
• Overall survival (OS)

Protection of trial subjects:

Not applicable

Background therapy:

All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis for patients in treatment groups A and B or within 2 weeks after randomization for patients in treatment group C.

In Part 1, eligible patients were centrally randomized to 3 groups (1:1:1) within 3 weeks after surgery to receive DCVAC/OvCa with SoC chemotherapy (treatment group A), DCVAC/OvCa after SoC chemotherapy (treatment group B), or SoC chemotherapy alone (treatment group C). In Part 2, eligible patients were centrally randomized to 2 groups (2:1) within 3 weeks after surgery to receive DCVAC/OvCa after SoC chemotherapy (treatment group B) or SoC chemotherapy alone (treatment group C). With the exception of safety, the 2 trial parts could not be analysed together. Part 1 is reported here. Part 2 was exploratory and is not reported here.

The number of patients enrolled worldwide had to be increased artificially by 1000 to allow input of safety results due to the fact that with the exception of safety, the 2 trial parts could not be analysed together. Therefore, the safety population includes both Part 1 and Part 2 combined and the number of patients is higher than the actual number of worldwide enrolled patients. The artificial 1000 patients were added to the demographic group of adults (18-64 years).

Evidence for comparator: -

Actual start date of recruitment	07 November 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 1097
Country: Number of subjects enrolled	Poland: 2
Worldwide total number of subjects	1099
EEA total number of subjects	1099

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)	1070
From 65 to 84 years	29
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The number of subjects enrolled was increased artificially by 1000 to allow input of safety results which included both Part 1 and Part 2 patients.

Pre-assignment

Screening details:

Twenty investigational sites participated in the study, of which 3 sites did not initiate any screening process (2 in Poland and 1 in Germany). 15 sites screened at least 1 patient: 11 in the Czech Republic, 2 in Poland and 2 in Germany (no patient has been randomized in Germany).

Period 1

Period 1 title	Part 1 (main trial) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Treatment group A

Arm description:

Parallel DCVAC/OvCa
Patients were to receive up to 10 doses of DCVAC/OvCa (approximately 1x10e7 autologous DCs) with SoC therapy. The first 5 doses were to be administered at 3-week intervals, followed by dosing at 6-week intervals.
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis.

Arm type	Experimental
Investigational medicinal product name	DCVAC/OvCa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

An aliquot of approximately 1×10e7 activated autologous DCs (DCVAC/OvCa) was to be thawed and diluted with 4 mL of pre-cooled saline solution (0.9% NaCl) in an injection syringe to a total volume of 5 mL. DCVAC/OvCa was to be administered subcutaneously to the inguinal and axillary lymph node areas (2.5 mL per injection) within 30 minutes after dilution.

Arm title	Treatment group B

Arm description:

Sequential DCVAC/OvCa
Patients were to receive up to 10 doses of DCVAC/OvCa (approximately 1x10e7 autologous DCs) after SoC therapy. The first 5 doses were to be administered at 3-week intervals, followed by dosing at 6-week intervals.
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis.

Arm type	Experimental
Investigational medicinal product name	DCVAC/OvCa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

An aliquot of approximately 1×10e7 activated autologous DCs (DCVAC/OvCa) was to be thawed and diluted with 4 mL of pre-cooled saline solution (0.9% NaCl) in an injection syringe to a total volume of 5 mL. DCVAC/OvCa was to be administered subcutaneously to the inguinal and axillary lymph node areas (2.5 mL per injection) within 30 minutes after dilution.

Arm title	Treatment group C

Arm description:

Standard of care
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 2 weeks after randomization.

Arm type	Experimental
Investigational medicinal product name	DCVAC/OvCa
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersion for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

An aliquot of approximately 1×10e7 activated autologous DCs (DCVAC/OvCa) was to be thawed and diluted with 4 mL of pre-cooled saline solution (0.9% NaCl) in an injection syringe to a total volume of 5 mL. DCVAC/OvCa was to be administered subcutaneously to the inguinal and axillary lymph node areas (2.5 mL per injection) within 30 minutes after dilution.

Number of subjects in period 1[1]	Treatment group A	Treatment group B	Treatment group C
Started	34	34	31
Completed	28	28	30
Not completed	6	6	1
Consent withdrawn by subject	1	-	-
Physician decision	1	-	-
Treatment not initiated (manufacture failure)	3	2	-
Adverse event, non-fatal	-	1	-
Death	1	1	-
Treatment not initiated	-	-	1
Leukapheresis not initiated	-	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of patients enrolled worldwide had to be increased artificially by 1000 to allow input of safety results due to the fact that with the exception of safety, the 2 trial parts could not be analysed together. Therefore, the safety population includes both Part 1 and Part 2 combined and the number of patients is higher than the actual number of worldwide enrolled patients.

Baseline characteristics

Reporting groups

Reporting group title	Treatment group A

Reporting group description:

Parallel DCVAC/OvCa
Patients were to receive up to 10 doses of DCVAC/OvCa (approximately 1x10e7 autologous DCs) with SoC therapy. The first 5 doses were to be administered at 3-week intervals, followed by dosing at 6-week intervals.
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis.

Reporting group title	Treatment group B

Reporting group description:

Sequential DCVAC/OvCa
Patients were to receive up to 10 doses of DCVAC/OvCa (approximately 1x10e7 autologous DCs) after SoC therapy. The first 5 doses were to be administered at 3-week intervals, followed by dosing at 6-week intervals.
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis.

Reporting group title	Treatment group C

Reporting group description:

Standard of care
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 2 weeks after randomization.

Reporting group values	Treatment group A	Treatment group B	Treatment group C
Number of subjects	34	34	31
Age categorical			
Units: Subjects			
Adults (18-64 years)	23	25	22
From 65-84 years	11	9	9
Gender categorical			
Units: Subjects			
Female	34	34	31
Male	0	0	0

Reporting group values	Total		
Number of subjects	99		
Age categorical			
Units: Subjects			
Adults (18-64 years)	70		
From 65-84 years	29		
Gender categorical			
Units: Subjects			
Female	99		
Male	0		

End points

End points reporting groups

Reporting group title	Treatment group A

Reporting group description:

Parallel DCVAC/OvCa
Patients were to receive up to 10 doses of DCVAC/OvCa (approximately 1x10e7 autologous DCs) with SoC therapy. The first 5 doses were to be administered at 3-week intervals, followed by dosing at 6-week intervals.
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis.

Reporting group title	Treatment group B

Reporting group description:

Sequential DCVAC/OvCa
Patients were to receive up to 10 doses of DCVAC/OvCa (approximately 1x10e7 autologous DCs) after SoC therapy. The first 5 doses were to be administered at 3-week intervals, followed by dosing at 6-week intervals.
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 1 week after leukapheresis.

Reporting group title	Treatment group C

Reporting group description:

Standard of care
All patients were to receive SoC chemotherapy (paclitaxel 175 mg/m2 intravenous over 3 hours followed by carboplatin area under the concentration time curve 5-7 intravenous over 30-60 minutes) given at 3-week intervals (±3 days) for 6 cycles, starting within 2 weeks after randomization.

Primary: Progression-free survival at 2 yrs after randomization (mITT)

End point title	Progression-free survival at 2 yrs after randomization (mITT)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Primary

End point timeframe:

From the time from randomization to documented disease progression or death from any cause, whichever occurs earlier

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: month				
median (confidence interval 95%)	20.3 (15.7 to 1000)	1000 (24.6 to 1000)	21.4 (12.6 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.9483
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2

Notes:

[1] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.0336
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.39
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	0.96

Notes:

[2] - Logrank

Primary: Progression-free survival at 2 yrs after randomization (PP)

End point title	Progression-free survival at 2 yrs after randomization (PP)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Primary

End point timeframe:

From the time from randomization to documented disease progression or death from any cause, whichever occurs earlier

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: month				
median (confidence interval 95%)	20.3 (15.7 to 1000)	1000 (24.6 to 1000)	21.4 (12.6 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group C v Treatment group A
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.8726
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.95

Notes:

[3] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.0081
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.77

Notes:

[4] - Logrank

Secondary: Proportion of patients staying in remission at 6 months after the last dose of first-line SoC (mITT)

End point title	Proportion of patients staying in remission at 6 months after the last dose of first-line SoC (mITT)

End point description:

End point type	Secondary

End point timeframe:

From the last dose of first-line SoC until the last dose of first-line chemotherapy + 6 months

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: percent				
number (not applicable)	80.6	96.6	83.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients staying in remission at 6 months after the last dose of first-line SoC (PP)

End point title	Proportion of patients staying in remission at 6 months after the last dose of first-line SoC (PP)

End point description:

End point type	Secondary

End point timeframe:

From the last dose of first-line SoC until the last dose of first-line chemotherapy + 6 months

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: percent				
number (not applicable)	85.7	100	83.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients staying in remission at 12 months after the last dose of first-line SoC (mITT)

End point title	Proportion of patients staying in remission at 12 months after the last dose of first-line SoC (mITT)

End point description:

End point type	Secondary

End point timeframe:

From the last dose of first-line SoC until the last dose of first-line chemotherapy + 12 months

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: percent				
number (not applicable)	64.5	79.3	56.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients staying in remission at 12 months after the last dose of first-line SoC (PP)

End point title	Proportion of patients staying in remission at 12 months after the last dose of first-line SoC (PP)

End point description:

End point type	Secondary

End point timeframe:

From the last dose of first-line SoC until the last dose of first-line chemotherapy + 12 months

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: percent				
number (not applicable)	67.9	85.2	56.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Biological progression-free interval defined by increasing CA 125 levels (mITT)

End point title	Biological progression-free interval defined by increasing CA 125 levels (mITT)

End point description:
In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary

End point timeframe:
From randomization till progression in CA 125 according to GCIG criteria

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: month				
median (confidence interval 95%)	1000 (1000 to 1000)	1000 (1000 to 1000)	1000 (1000 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.9055
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.16
upper limit	6.31

Notes:

[5] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.3704
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	3.87

Notes:

[6] - Logrank

Secondary: Biological progression-free interval defined by increasing CA 125 levels (PP)

End point title	Biological progression-free interval defined by increasing CA 125 levels (PP)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary

End point timeframe:

From randomization till progression in CA 125 according to GCIG criteria

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: month				
median (confidence interval 95%)	1000 (1000 to 1000)	1000 (1000 to 1000)	1000 (1000 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.9455
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.13
upper limit	6.64

Notes:

[7] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only

Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.3704
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.03
upper limit	3.87

Notes:

[8] - Logrank

Secondary: Immunological response

End point title	Immunological response

End point description:

A significant increase in CD56+ NK cells and a similar trend toward higher percentage of CD8+ T cells was detected in the peripheral blood of patients with low baseline levels of CD8+ from tissue samples in treatment groups A and B compared to patients with low baseline levels of CD8+ from tissue samples in treatment group C. The differences in relative number increases of CD16+/56+ NK cells, HLA-DR+, CD3+ T cells, and CD8+ T cells counts became more significant with time. A significant decrease in relative numbers of CD19+ B cells in patients with low baseline levels of CD8+ from tissue samples in treatment groups A and B compared to patients with low baseline levels of CD8+ from tissue samples in treatment group C was observed.

End point type	Secondary

End point timeframe:

From randomization till week 104 of treatment

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31[9]	29[10]	28[11]	
Units: Not applicable	1000	1000	1000	

Notes:

[9] - 28 patients in the PP population

[10] - 27 patients in the PP population

[11] - 28 patients in the PP population

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients requiring second-line chemotherapy (mITT)

End point title	Proportion of patients requiring second-line chemotherapy (mITT)

End point description:

End point type	Secondary

End point timeframe:
From randomization until the end of survival follow-up

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: percent				
number (not applicable)	64.5	62.1	60.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients requiring second-line chemotherapy (PP)

End point title	Proportion of patients requiring second-line chemotherapy (PP)
End point description:	

End point type	Secondary
End point timeframe:	
From randomization until the first administration of further-line therapy	

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: percent				
number (not applicable)	64.3	59.3	60.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients requiring second-line chemotherapy (ITT)

End point title	Proportion of patients requiring second-line chemotherapy (ITT)
End point description:	

End point type	Secondary
End point timeframe:	
From randomization until the first administration of further-line therapy	

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	32	31	
Units: percent				
number (not applicable)	61.8	56.3	58.1	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to second-line chemotherapy (mITT)

End point title	Time to second-line chemotherapy (mITT)
End point description:	

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary
End point timeframe:	

From randomization until the first administration of further-line therapy

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: month				
median (confidence interval 95%)	24.1 (18.3 to 63.3)	43.9 (32.5 to 1000)	27.4 (20.7 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.5191
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.33

Notes:

[12] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[13]
P-value	= 0.5817
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.6

Notes:

[13] - Logrank

Secondary: Time to second-line chemotherapy (PP)

End point title	Time to second-line chemotherapy (PP)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary

End point timeframe:

From randomization until the end of survival follow-up

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: month				
median (confidence interval 95%)	27.9 (18.3 to 63.3)	51.8 (34.4 to 1000)	27.4 (20.7 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[14]
P-value	= 0.6863
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	2.2

Notes:

[14] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[15]
P-value	= 0.3871
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.46

Notes:

[15] - Logrank

Secondary: Time to second-line chemotherapy (ITT)

End point title	Time to second-line chemotherapy (ITT)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary

End point timeframe:

From randomization until the end of survival follow-up

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	32	31	
Units: month				
median (confidence interval 95%)	24.1 (18.3 to 63.3)	43.9 (32.5 to 1000)	29.0 (21.4 to 1000)	

Statistical analyses

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other[16]
P-value	= 0.7032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.7

Notes:

[16] - Logrank

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[17]
P-value	= 0.4388
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.28
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	2.41

Notes:

[17] - Logrank

Secondary: Overall survival (mITT)

End point title	Overall survival (mITT)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary

End point timeframe:

From randomization till death due to any cause

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	29	30	
Units: month				
median (confidence interval 95%)	1000 (59.0 to 1000)	1000 (69.1 to 1000)	1000 (34.9 to 1000)	

Statistical analyses

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	61
Analysis specification	Pre-specified
Analysis type	other[18]
P-value	= 0.7491
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.86

Notes:

[18] - Logrank

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	other[19]
P-value	= 0.264
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	1.41

Notes:

[19] - Logrank

Secondary: Overall survival (PP)

End point title	Overall survival (PP)
End point description:	

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary
End point timeframe:	

From randomization till death due to any cause

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	28	27	30	
Units: month				
median (confidence interval 95%)	1000 (61.1 to 1000)	1000 (70.4 to 1000)	1000 (34.9 to 1000)	

Statistical analyses

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	other[20]
P-value	= 0.1299
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	1.22

Notes:

[20] - Logrank

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[21]
P-value	= 0.593
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.37
upper limit	1.75

Notes:

[21] - Logrank

Secondary: Overall survival (ITT)

End point title	Overall survival (ITT)

End point description:

In case the value/percentile cannot be estimated due to a low number of events, 1000 is used, meaning Not available.

End point type	Secondary

End point timeframe:

From randomization till death due to any cause

End point values	Treatment group A	Treatment group B	Treatment group C	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	32	31	
Units: month				
median (confidence interval 95%)	1000 (42.9 to 1000)	1000 (65.4 to 1000)	1000 (34.9 to 1000)	

Statistical analyses

Statistical analysis title	Sequential DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group B v Treatment group C
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	other[22]
P-value	= 0.6087
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.39
upper limit	1.73

Notes:

[22] - Logrank

Statistical analysis title	Parallel DCVAC/OvCa vs. SoC only
Comparison groups	Treatment group A v Treatment group C

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	other[23]
P-value	= 0.9739
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.07

Notes:

[23] - Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs were to be reported since subjects´ signature of ICF/study entry until 30 days after the last administration of IMP (arms A and B) or the last dose of SoC first-line chemotherapy (arm C).

Adverse event reporting additional description:

If there was no IMP administration in patient randomized to group A or B and the patient is prematurely discontinued from the study due to any reason (i.e. before the first application of DCVAC/OvCa), the reporting period for AEs/SAEs ends with the date when decision for premature withdrawal from the study was taken.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Safety population

Reporting group description:

The safety (SAF) population consisted of all subjects who received at least one dose of chemotherapy or DCVAC/OvCa. The SAF and mITT populations differ in term of patients in arms A and B. In case patient from arm A or B received at least one dose of chemotherapy but did not initiate DCVAC/OvCa treatment (e.g. DCVAC/OvCa manufacturing failure), the patient is part of the SAF population but not of the mITT population.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	45 / 130 (34.62%)		
number of deaths (all causes)	40		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parathyroid tumour benign			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Drug hypersensitivity				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Breast fibrosis				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea at rest				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Incisional hernia				
subjects affected / exposed	3 / 130 (2.31%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Vaginal cuff dehiscence				

subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Congenital, familial and genetic disorders

Atrial septal defect

subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Cardiac disorders

Atrial fibrillation

subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Nervous system disorders

Ischaemic stroke

subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Blood and lymphatic system disorders

Neutropenia

subjects affected / exposed	8 / 130 (6.15%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			

Anaemia

subjects affected / exposed	8 / 130 (6.15%)			
occurrences causally related to treatment / all	0 / 9			
deaths causally related to treatment / all	0 / 0			

Leukopenia

subjects affected / exposed	3 / 130 (2.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			

Pancytopenia

subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Subileus				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	3 / 130 (2.31%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ascites				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspepsia				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal inflammation				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mechanical ileus				

subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatotoxicity				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Pyelocaliectasis				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Oliguria				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Pain in extremity				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Infected lymphocele				

subjects affected / exposed	4 / 130 (3.08%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	2 / 130 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Anal abscess				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Folliculitis				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Clostridium difficile colitis				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung abscess				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
perirectal a				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative abscess				
subjects affected / exposed	1 / 130 (0.77%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis				

subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Retroperitoneal abscess			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Small intestine gangrene			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolic alkalosis			
subjects affected / exposed	1 / 130 (0.77%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 130 (93.08%)		
Investigations			
Weight decreased			
subjects affected / exposed	10 / 130 (7.69%)		
occurrences (all)	10		
Nervous system disorders			

Neuropathy peripheral			
subjects affected / exposed	15 / 130 (11.54%)		
occurrences (all)	15		
Paraesthesia			
subjects affected / exposed	40 / 130 (30.77%)		
occurrences (all)	45		
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	59 / 130 (45.38%)		
occurrences (all)	109		
Anaemia			
subjects affected / exposed	50 / 130 (38.46%)		
occurrences (all)	73		
Thrombocytopenia			
subjects affected / exposed	36 / 130 (27.69%)		
occurrences (all)	59		
Leukopenia			
subjects affected / exposed	22 / 130 (16.92%)		
occurrences (all)	48		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	18 / 130 (13.85%)		
occurrences (all)	22		
Pyrexia			
subjects affected / exposed	14 / 130 (10.77%)		
occurrences (all)	18		
Pain			
subjects affected / exposed	8 / 130 (6.15%)		
occurrences (all)	8		
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	10 / 130 (7.69%)		
occurrences (all)	14		
Hypersensitivity			
subjects affected / exposed	10 / 130 (7.69%)		
occurrences (all)	14		

Gastrointestinal disorders			
Nausea			
subjects affected / exposed	37 / 130 (28.46%)		
occurrences (all)	58		
Constipation			
subjects affected / exposed	14 / 130 (10.77%)		
occurrences (all)	16		
Abdominal pain			
subjects affected / exposed	8 / 130 (6.15%)		
occurrences (all)	8		
Vomiting			
subjects affected / exposed	13 / 130 (10.00%)		
occurrences (all)	15		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 130 (4.62%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 130 (10.00%)		
occurrences (all)	14		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	7 / 130 (5.38%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	22 / 130 (16.92%)		
occurrences (all)	28		
Pain in extremity			
subjects affected / exposed	9 / 130 (6.92%)		
occurrences (all)	13		
Myalgia			
subjects affected / exposed	6 / 130 (4.62%)		
occurrences (all)	6		
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	11 / 130 (8.46%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	10 / 130 (7.69%)		
occurrences (all)	12		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	11 / 130 (8.46%)		
occurrences (all)	12		
Decreased appetite			
subjects affected / exposed	8 / 130 (6.15%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 August 2013	• Specification of the DCVAC/OvCa application sites (groin and axillary areas) • Specification of SoC chemotherapy toxicity management based on institutional standards or applicable oncology guidelines • Added information regarding the use of historical CT/MRI scans obtained prior to study entry • Specification of pre-treatment assessments of infection
01 November 2013	• Specification of methods of contraception (exclusion criterion 13) • Added justification for the dose of DCVAC/OvCa to be administered • Added definition of slow progressive disease • Added information about the continuation of DCVAC/OvCa administration after disease progression • Specification that not only the medications must be recorded, but also the doses taken/administered • Specification of the exclusion criterion for post-surgery residual disease with lesion(s)>1 cm (exclusion criterion 4) • Specification of procedures for discontinuation • Elimination of blood samples for research and immunology assessment in treatment period 2 • Added information regarding using historical heart and lung X-ray scans obtained prior to study entry
14 February 2014	• Conditional prolongation of screening up to 42 days, under specified conditions • Specification of follow-up including the definition of the EoT visit, efficacy follow-up and survival follow-up • Specification of methods of contraception (exclusion criterion 13) • Change in the AE reporting period (30 days after the EoT visit) • Added condition for patients' replacement • Added calculation of the sample size
16 July 2014	• Change in the study design • Chest X-ray may be replaced by CT of thorax at the investigator's decision • Withdrawal of central reading for the evaluation of patients' eligibility • Specification that pregnant women must pass the EoT visit • Correction in follow-up procedures in Table 1 • Independent blinded radiologist evaluates sensitive analyses of PFS and ORR • This is the last submitted and approved version of this protocol for Germany; the study was locally closed in Germany on 30-Jun-2017, before the Protocol was amended to version 5.0
04 August 2017	• Change of Chief Medical Officer
10 November 2017	• Changing the number of DCVAC/OvCa doses administered to the additional patients enrolled as per Protocol versions 5.1 onwards from up to 10 to up to 15 doses (i.e., all available doses for a patient) • Immunology assessments for additional patients as per Protocol versions 5.1 onwards reduced to TSH testing only, other laboratory tests will not be done (additional patients only)

23 July 2018	• Consolidation of the CZ and PL protocols • Cancellation of interim analyses • Final PFS analysis 2 years after the last patient randomized • Final survival analysis 5 years after randomization of the last patient or when at least 50% of maturity is reached, whichever occurs earlier • Exclusion criterion 7 amended to prevent Protocol violation and/or losing patients from final analysis • Data on OS status and further-line therapy collected for all randomized patients • Tumor assessment – change in wording • Wording adjusted to be in line with the changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Trial Part 1 and trial Part 2 could not be analysed together due to differences in treatment duration, which would introduce bias. As Part 2 is considered to be exploratory, only Part 1 is reported.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34294416