Clinical trial results:
A Phase 2, Open-label, Multicenter Study to Evaluate the Safety and Clinical Activity of Durvalumab in Combination with Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (R-CHOP) or with Lenalidomide plus R-CHOP (R2-CHOP) in Subjects With Previously Untreated, High-Risk Diffuse Large B-Cell Lymphoma

Summary

EudraCT number	2015-005173-20
Trial protocol	AT DK EE SK PL
Global end of trial date	24 April 2022

Results information

Result version number	v1 (current)
This version publication date	10 May 2023
First version publication date	10 May 2023

Trial information

Trial identification

Sponsor protocol code	MEDI4736-DLBCL-001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bristol-Myers Squibb
Sponsor organisation address	Chaussée de la Hulpe 185, Brussels, Belgium, 1170
Public contact	EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com
Scientific contact	Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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	09 November 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 April 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to explore the clinical activity of durvalumab (MEDI4736) in combination with R-CHOP or R2-CHOP followed by durvalumab consolidation therapy in previously untreated subjects diagnosed with high-risk DLBCL.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 February 2017
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	United States: 22
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Austria: 15
Worldwide total number of subjects	46
EEA total number of subjects	23

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)	24

From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

46 participants were enrolled and treated.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	DUR + R-CHOP

Arm description:

Participants receive Induction Therapy (21-day cycles): Durvalumab 1125 mg intravenously (IV) on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5). Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

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

Dosage and administration details:

Administered at 1.4 mg/m2 BSA (recommended capping at 2 mg absolute dose) on Day 1 of each 21-day cycle for 6-8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Prednisone / Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Oral solution
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

a 100 mg

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 50 mg/m2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 375 mg/m2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 750 mg/m2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Durvalumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1125 and 1500 mg administered intravenously (IV)

Arm title	DUR + R2-CHOP

Arm description:

Participants receive Induction Therapy (21-day cycles): Cycle 1 - induction therapy of durvalumab in combination with R-CHOP (as described in DUR + R-CHOP arm). Starting at cycle 2 - Durvalumab 1125 mg IV on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R2-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5; daily oral lenalidomide 15 mg from Day 1 to 14) from the cycle following COO determination until end of induction therapy (Cycle 6 or Cycle 8) or starting Cycle 1 if ABC subtype is identified prior to C1D1. Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

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

Dosage and administration details:

1125 and 1500 mg administered intravenously (IV)

Investigational medicinal product name	Rituximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 375 mg/m2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Cyclophosphamide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 750 mg/m2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 50 mg/m2 BSA on Day 1 of each 21-day cycle for 6 to 8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Vincristine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administered at 1.4 mg/m2 BSA (recommended capping at 2 mg absolute dose) on Day 1 of each 21-day cycle for 6-8 cycles as part of the R-CHOP treatment regimen.

Investigational medicinal product name	Prednisone / Prednisolone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Oral use

Dosage and administration details:

a 100 mg

Investigational medicinal product name	Lenalidomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion, Oral solution
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

15 mg

Number of subjects in period 1	DUR + R-CHOP	DUR + R2-CHOP
Started	43	3
Completed Induction Treatment	31	3
Completed Consolidation Treatment	14	2
Completed	14	2
Not completed	29	1
Adverse event, serious fatal	1	-
Consent withdrawn by subject	6	-
Adverse event, non-fatal	9	-
Other reasons	4	-
Progressive disease	9	1

Baseline characteristics

Reporting groups	
Reporting group title	DUR + R-CHOP
Reporting group description:	
Participants receive Induction Therapy (21-day cycles): Durvalumab 1125 mg intravenously (IV) on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5). Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.	
Reporting group title	DUR + R2-CHOP
Reporting group description:	
Participants receive Induction Therapy (21-day cycles): Cycle 1 - induction therapy of durvalumab in combination with R-CHOP (as described in DUR + R-CHOP arm). Starting at cycle 2 - Durvalumab 1125 mg IV on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R2-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5; daily oral lenalidomide 15 mg from Day 1 to 14) from the cycle following COO determination until end of induction therapy (Cycle 6 or Cycle 8) or starting Cycle 1 if ABC subtype is identified prior to C1D1. Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.	

Reporting group values	DUR + R-CHOP	DUR + R2-CHOP	Total
Number of subjects	43	3	46
Age Categorical Units: participants			
<65 years	23	1	24
>=65 years	20	2	22
Age Continuous Units: years			
arithmetic mean	61.1	67.7	
standard deviation	± 12.77	± 8.62	-
Sex: Female, Male Units: participants			
Female	17	1	18
Male	26	2	28
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	43	3	46
Unknown or Not Reported	0	0	0
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	42	3	45
Not Colected or Reported	0	0	0
Other	1	0	1
Eastern Cooperative Oncology Group			
ECOG performance status is used by doctors and researchers to assess how a participant's disease is			

progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. - 0 = Fully Active (most favorable status); - 1 = Restricted activity but ambulatory; - 2 = Ambulatory but unable to carry out work activities; - 3 = Limited Self-Care; - 4 = Completely Disabled, No self-care (least favorable status)			
Units: Subjects			
0 = Fully Active	16	2	18
1 = Restricted activity but ambulatory	19	0	19
2 = Ambulatory but unable to work	8	1	9
3 = Limited Self-Care	0	0	0
4 = Completely Disabled, No self-care	0	0	0
Ann Arbor Stage at Diagnosis			
The criteria for Clinical Stage (Ann Arbor staging) are as below: - I: involvement of a single nodal region. - II: involvement of 2 or more lymph node regions on the same side of the diaphragm. - III: involvement of lymph node regions on both sides of the diaphragm. - IV: disseminated involvement of 1 or more extra-lymphatic sites with or without associated lymph node involvement.			
Units: Subjects			
Stage I	0	0	0
Stage II	0	0	0
Stage III	9	2	11
Stage IV	34	1	35
Presence of Bulky Disease (Baseline)			
Bulky disease refers to the size of the tumor.			
Units: Subjects			
Yes = tumor diameter >= 7.0 cm	21	2	23
No = tumor diameter < 7.0 cm	22	1	23
International Prognostic Index (IPSS) Score			
The IPI assesses risk of central nervous system disease according to the following scale: - 0-1: Low risk - 2: Low-Intermediate risk - 3: High-Intermediate risk - 4-5: High risk			
Units: Subjects			
0-1: Low risk	0	0	0
2: Low-Intermediate risk	9	0	9
3: High-Intermediate risk	21	0	21
4-5: High risk	9	2	11
Missing	4	1	5

Subject analysis sets

Subject analysis set title	High Group for CD8 Density
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their CD8 density evaluation was above threshold,defined as the median of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for CD8 Density
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their CD8 density evaluation was below threshold,defined as the median of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Subject analysis set title	High Group for PDL1 % of total cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PDL1 % of total cell evaluation was above threshold,defined as the median of 13.8% found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for PDL1 % of total cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PDL1 % of total cell evaluation was below threshold,defined as the median of 13.8% found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Subject analysis set title	High Group for PDL1 % of tumor cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PD-1 % of tumor cell evaluation was above threshold,defined as the median of 6.2% found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for PDL1 % of tumor cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PDL1 % of tumor cell evaluation was below threshold,defined as the median of 6.2% found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Subject analysis set title	High Group for RNA IFN Gamma Score
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had RNA IFN Gamma Score calculated based on a biopsy sample collected before treatment on this protocol. The result of their RNA IFN Gamma Score was above threshold,defined as the median of 3.28 found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for RNA IFN Gamma Score
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had RNA IFN Gamma Score calculated based on a biopsy sample collected before treatment on this protocol. The result of their RNA IFN Gamma Score was below threshold,defined as the median of 3.28 found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Reporting group values	High Group for CD8 Density	Low Group for CD8 Density	High Group for PDL1 % of total cells
Number of subjects	15	11	20
Age Categorical Units: participants			
<65 years			
>=65 years			
Age Continuous Units: years			
arithmetic mean	67	64	75
standard deviation	±	±	±
Sex: Female, Male Units: participants			
Female			
Male			

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Not Colected or Reported Other			
Eastern Cooperative Oncology Group			
ECOG performance status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. - 0 = Fully Active (most favorable status); - 1 = Restricted activity but ambulatory; - 2 = Ambulatory but unable to carry out work activities; - 3 = Limited Self-Care; - 4 = Completely Disabled, No self-care (least favorable status)			
Units: Subjects			
0 = Fully Active 1 = Restricted activity but ambulatory 2 = Ambulatory but unable to work 3 = Limited Self-Care 4 = Completely Disabled, No self-care			
Ann Arbor Stage at Diagnosis			
The criteria for Clinical Stage (Ann Arbor staging) are as below: - I: involvement of a single nodal region. - II: involvement of 2 or more lymph node regions on the same side of the diaphragm. - III: involvement of lymph node regions on both sides of the diaphragm. - IV: disseminated involvement of 1 or more extra-lymphatic sites with or without associated lymph node involvement.			
Units: Subjects			
Stage I Stage II Stage III Stage IV			
Presence of Bulky Disease (Baseline)			
Bulky disease refers to the size of the tumor.			
Units: Subjects			
Yes = tumor diameter >= 7.0 cm No = tumor diameter < 7.0 cm			
International Prognostic Index (IPSS) Score			
The IPI assesses risk of central nervous system disease according to the following scale: - 0-1: Low risk - 2: Low-Intermediate risk - 3: High-Intermediate risk - 4-5: High risk			
Units: Subjects			
0-1: Low risk 2: Low-Intermediate risk 3: High-Intermediate risk 4-5: High risk Missing			

Reporting group values	Low Group for PDL1 % of total cells	High Group for PDL1 % of tumor cells	Low Group for PDL1 % of tumor cells
Number of subjects	5	11	9
Age Categorical			
Units: participants			
<65 years			
>=65 years			
Age Continuous			
Units: years			
arithmetic mean	20	64	56
standard deviation	±	±	±
Sex: Female, Male			
Units: participants			
Female			
Male			
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race/Ethnicity, Customized			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Black or African American			
Native Hawaiian or Other Pacific Islander			
White			
Not Colected or Reported			
Other			
Eastern Cooperative Oncology Group			
ECOG performance status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. - 0 = Fully Active (most favorable status); - 1 = Restricted activity but ambulatory; - 2 = Ambulatory but unable to carry out work activities; - 3 = Limited Self-Care; - 4 = Completely Disabled, No self-care (least favorable status)			
Units: Subjects			
0 = Fully Active			
1 = Restricted activity but ambulatory			
2 = Ambulatory but unable to work			
3 = Limited Self-Care			
4 = Completely Disabled, No self-care			
Ann Arbor Stage at Diagnosis			
The criteria for Clinical Stage (Ann Arbor staging) are as below: - I: involvement of a single nodal region. - II: involvement of 2 or more lymph node regions on the same side of the diaphragm. - III: involvement of lymph node regions on both sides of the diaphragm. - IV: disseminated involvement of 1 or more extra-lymphatic sites with or without associated lymph node involvement.			
Units: Subjects			
Stage I			
Stage II			
Stage III			
Stage IV			
Presence of Bulky Disease (Baseline)			

Bulky disease refers to the size of the tumor.			
Units: Subjects			
Yes = tumor diameter >= 7.0 cm No = tumor diameter < 7.0 cm			
International Prognostic Index (IPSS) Score			
The IPI assesses risk of central nervous system disease according to the following scale: - 0-1: Low risk - 2: Low-Intermediate risk - 3: High-Intermediate risk - 4-5: High risk			
Units: Subjects			
0-1: Low risk 2: Low-Intermediate risk 3: High-Intermediate risk 4-5: High risk Missing			

Reporting group values	High Group for RNA IFN Gamma Score	Low Group for RNA IFN Gamma Score	
Number of subjects	7	20	
Age Categorical Units: participants			
<65 years >=65 years			
Age Continuous Units: years			
arithmetic mean	43	60	
standard deviation	±	±	
Sex: Female, Male Units: participants			
Female Male			
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino Not Hispanic or Latino Unknown or Not Reported			
Race/Ethnicity, Customized Units: Subjects			
American Indian or Alaska Native Asian Black or African American Native Hawaiian or Other Pacific Islander White Not Colected or Reported Other			
Eastern Cooperative Oncology Group			
ECOG performance status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. - 0 = Fully Active (most favorable status); - 1 = Restricted activity but ambulatory; - 2 = Ambulatory but unable to carry out work activities; - 3 = Limited Self-Care; - 4 = Completely Disabled, No self-care (least favorable status)			
Units: Subjects			
0 = Fully Active			

1 = Restricted activity but ambulatory 2 = Ambulatory but unable to work 3 = Limited Self-Care 4 = Completely Disabled, No self-care			
Ann Arbor Stage at Diagnosis			
The criteria for Clinical Stage (Ann Arbor staging) are as below: - I: involvement of a single nodal region. - II: involvement of 2 or more lymph node regions on the same side of the diaphragm. - III: involvement of lymph node regions on both sides of the diaphragm. - IV: disseminated involvement of 1 or more extra-lymphatic sites with or without associated lymph node involvement.			
Units: Subjects			
Stage I Stage II Stage III Stage IV			
Presence of Bulky Disease (Baseline)			
Bulky disease refers to the size of the tumor.			
Units: Subjects			
Yes = tumor diameter >= 7.0 cm No = tumor diameter < 7.0 cm			
International Prognostic Index (IPSS) Score			
The IPI assesses risk of central nervous system disease according to the following scale: - 0-1: Low risk - 2: Low-Intermediate risk - 3: High-Intermediate risk - 4-5: High risk			
Units: Subjects			
0-1: Low risk 2: Low-Intermediate risk 3: High-Intermediate risk 4-5: High risk Missing			

End points reporting groups

Reporting group title	DUR + R-CHOP

Reporting group description:

Participants receive Induction Therapy (21-day cycles): Durvalumab 1125 mg intravenously (IV) on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5). Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

Reporting group title	DUR + R2-CHOP

Reporting group description:

Participants receive Induction Therapy (21-day cycles): Cycle 1 - induction therapy of durvalumab in combination with R-CHOP (as described in DUR + R-CHOP arm). Starting at cycle 2 - Durvalumab 1125 mg IV on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R2-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5; daily oral lenalidomide 15 mg from Day 1 to 14) from the cycle following COO determination until end of induction therapy (Cycle 6 or Cycle 8) or starting Cycle 1 if ABC subtype is identified prior to C1D1. Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

Subject analysis set title	High Group for CD8 Density
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their CD8 density evaluation was above threshold,defined as the median of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for CD8 Density
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their CD8 density evaluation was below threshold,defined as the median of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Subject analysis set title	High Group for PDL1 % of total cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PDL1 % of total cell evaluation was above threshold,defined as the median of 13.8% found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for PDL1 % of total cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PDL1 % of total cell evaluation was below threshold,defined as the median of 13.8% found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Subject analysis set title	High Group for PDL1 % of tumor cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PD-1 % of tumor cell evaluation was above threshold,defined as the median of 6.2% found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for PDL1 % of tumor cells
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had IHC analysis performed on a biopsy sample collected before treatment on this protocol. The result of their PDL1 % of tumor cell evaluation was below threshold,defined as the median of 6.2% found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Subject analysis set title	High Group for RNA IFN Gamma Score
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had RNA IFN Gamma Score calculated based on a biopsy sample collected before treatment on this protocol. The result of their RNA IFN Gamma Score was above threshold,defined as the median of 3.28 found in commercial DLBCL samples using matched analytical methods. Participants with values above threshold were predicted to be responders.

Subject analysis set title	Low Group for RNA IFN Gamma Score
Subject analysis set type	Full analysis

Subject analysis set description:

Participants had RNA IFN Gamma Score calculated based on a biopsy sample collected before treatment on this protocol. The result of their RNA IFN Gamma Score was below threshold,defined as the median of 3.28 found in commercial DLBCL samples using matched analytical methods. Participants with values below threshold were predicted to be non-responders.

Primary: Percentage of Participants Who Achieved a Complete Response (CR) at the End of Induction Therapy

End point title	Percentage of Participants Who Achieved a Complete Response (CR) at the End of Induction Therapy[1]

End point description:

The primary efficacy analysis evaluated the complete response rate (CRR) at the end of the induction therapy in the efficacy evaluable population in a comparative manner against historical control. The response to treatment was assessed according to the 2014 International Working Group (IWG) Response Criteria for Non-Hodgkin's Lymphoma (NHL) (Cheson, 2014). CR was defined as a complete metabolic response and radiographic evidence showing target nodes/nodal masses regressed to ≤ 1.5 cm in longest diameter, no new lesions, regression of lymph nodes to normal size, absence of splenomegaly, and absence of bone marrow involvement. Clopper-Pearson two-sided 95% confidence interval is reported. Null hypothesis for the primary endpoint was rejected if the lower limit of the confidence interval for the complete response rate at the completion of the induction therapy in the efficacy evaluable population is above 55%.

End point type	Primary

End point timeframe:

From first dose of study drug to end of Induction therapy (Day 1 up to Week 26 – maximum duration of Induction Period).

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only summary statistics were planned for this endpoint.

End point values	DUR + R-CHOP	DUR + R2-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: percentage of participants				
number (confidence interval 95%)	54.1 (36.9 to 70.5)	66.7 (9.4 to 99.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for Immunohistochemistry (IHC) CD8 T-Cell Density

End point title	Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for Immunohistochemistry (IHC) CD8 T-Cell Density

End point description:

Data in the analysis include all participants who received durvalumab, irrespective of the study arm in which they enrolled, because the selected biomarkers have been associated with response in other anti-PD1 or anti-PDL1 studies, such as durvalumab. IHC analysis was performed on the baseline tumor biopsy to quantify CD8 T-cell density. Participants with 'high' values, i.e. above the threshold defined as the median value of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods, were predicted to be responders to treatment with durvalumab. The definition of a complete response was that used in the primary outcome.

End point type	Secondary

End point timeframe:

Biomarker biopsies: Days -28 to Day -1. Clinical response: From first dose of study drug to end of Induction therapy (Day 1 up to Week 26 – maximum duration of Induction Period).

End point values	High Group for CD8 Density	Low Group for CD8 Density		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	11		
Units: percentage of participants	67	64		

Statistical analyses

Statistical analysis title	CD8 T-cell density
Comparison groups	High Group for CD8 Density v Low Group for CD8 Density
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.99 [2]
Method	Fisher exact

Notes:

[2] - Significance defined as 0.05.

Statistical analysis title	CD8 T-cell density

Statistical analysis description:

The Area Under the Receiver Operator Characteristic Curve (AUC-ROC) is the estimated parameter. Responders were compared to non-responders by ranking them according to their CD8 density.

Comparison groups	High Group for CD8 Density v Low Group for CD8 Density
Number of subjects included in analysis	26
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.872 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Significance defined as 0.05.

Secondary: Percentage of Participants Who Responded During Induction and Continued into Consolidation Therapy (Database cutoff date: 02-Aug-2018)

End point title	Percentage of Participants Who Responded During Induction and Continued into Consolidation Therapy (Database cutoff date: 02-Aug-2018)

End point description:

The percentage of participants who achieved a partial response (PR) or complete response (CR) at the end of Induction and continued into consolidation period in the efficacy evaluable population in a comparative manner against historical control. The response to treatment was assessed according to the 2014 International Working Group (IWG) Response Criteria for Non-Hodgkin's Lymphoma (NHL) (Cheson, 2014). CR was defined in outcome #1. PR was defined as a partial metabolic response and radiographic evidence showing ≥ 50% decrease in sum of perpendicular diameters (SPD) of up to 6 target measurable nodes and extranodal sites, no new lesions, spleen must have regressed > 50% in length beyond normal, and residual bone marrow involvement improved from baseline. Clopper-Pearson two-sided 95% confidence interval is reported. Null hypothesis was rejected if the lower limit of the confidence interval for the rate of subjects who continue consolidation therapy out of all subjects.

End point type	Secondary

End point timeframe:

From first dose of study drug to completion of at least one cycle in the Consolidation Period (Day 1 up to Week 52)

End point values	DUR + R-CHOP	DUR + R2-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	3		
Units: percentage of participants				
number (confidence interval 95%)	67.6 (50.2 to 82.0)	66.7 (9.4 to 99.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for Immunohistochemistry (IHC) Programmed Death Ligand – 1 (PDL1) Total Percentage

End point title	Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for Immunohistochemistry (IHC) Programmed Death Ligand – 1 (PDL1) Total Percentage

End point description:

Data in the analysis include all participants who received durvalumab, irrespective of the study arm in which they enrolled, because the selected biomarkers have been associated with response in other anti-PD1 or anti-PDL1 studies, such as durvalumab. IHC analysis was performed on the baseline tumor biopsy to quantify CD8 T-cell density. Participants with 'high' values, i.e. above the threshold defined as the median value of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods, were predicted to be responders to treatment with durvalumab. The definition of a complete response was that used in the primary outcome.

End point type	Secondary

End point timeframe:

Biomarker biopsies: Days -28 to Day -1. Clinical response: From first dose of study drug to end of Induction therapy (Day 1 up to Week 26 – maximum duration of Induction Period).

End point values	High Group for PDL1 % of total cells	Low Group for PDL1 % of total cells		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	20	5		
Units: percentage of participants	75	20		

Statistical analyses

Statistical analysis title	PDL1 (Total Percentage)

Statistical analysis description:

The Area Under the Receiver Operator Characteristic Curve (AUC-ROC) is the estimated parameter. Responders were compared to non-responders by ranking them according to their PDL1 % of total cells.

Comparison groups	High Group for PDL1 % of total cells v Low Group for PDL1 % of total cells
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.523 [4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[4] - Significance defined as 0.05.

Statistical analysis title	PDL1 (Total Percentage)
Comparison groups	High Group for PDL1 % of total cells v Low Group for PDL1 % of total cells
Number of subjects included in analysis	25
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0403 [5]
Method	Fisher exact

Notes:

[5] - Significance defined as 0.05.

Secondary: Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for Immunohistochemistry (IHC) Programmed Death Ligand – 1 (PDL1) Percentage of Tumor Cells

End point title	Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for Immunohistochemistry (IHC) Programmed Death Ligand – 1 (PDL1) Percentage of Tumor Cells

End point description:

Data in the analysis include all participants who received durvalumab, irrespective of the study arm in which they enrolled, because the selected biomarkers have been associated with response in other anti-PD1 or anti-PDL1 studies, such as durvalumab. IHC analysis was performed on the baseline tumor biopsy to quantify CD8 T-cell density. Participants with 'high' values, i.e. above the threshold defined as the median value of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods, were predicted to be responders to treatment with durvalumab. The definition of a complete response was that used in the primary outcome.

End point type	Secondary

End point timeframe:

Biomarker biopsies: Days -28 to Day -1. Clinical response: From first dose of study drug to end of Induction therapy (Day 1 up to Week 26 – maximum duration of Induction Period).

End point values	High Group for PDL1 % of tumor cells	Low Group for PDL1 % of tumor cells		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	9		
Units: percentage of participants	64	56		

Statistical analyses

Statistical analysis title	PDL1 (Percentage of tumor cells)

Statistical analysis description:

The Area Under the Receiver Operator Characteristic Curve (AUC-ROC) is the estimated parameter. Responders were compared to non-responders by ranking them according to their PDL1 % of tumor cells.

Comparison groups	High Group for PDL1 % of tumor cells v Low Group for PDL1 % of tumor cells
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.557 [6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[6] - Significance defined as 0.05.

Statistical analysis title	PDL1 (Percentage of tumor cells)
Comparison groups	High Group for PDL1 % of tumor cells v Low Group for PDL1 % of tumor cells
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	
P-value	> 0.99 [7]
Method	Fisher exact

Notes:

[7] - Significance defined as 0.05.

Secondary: Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for the Interferon Gamma Score (IFNG-Score) from Ribonucleic Acid (RNA)-Sequencing Data

End point title	Percentage of Participants Who Achieved a Clinical Response in the Biomarker Subpopulation for the Interferon Gamma Score (IFNG-Score) from Ribonucleic Acid (RNA)-Sequencing Data

End point description:

Data in the analysis include all participants who received durvalumab, irrespective of the study arm in which they enrolled, because the selected biomarkers have been associated with response in other anti-

PD1 or anti-PDL1 studies, such as durvalumab. IHC analysis was performed on the baseline tumor biopsy to quantify CD8 T-cell density. Participants with 'high' values, i.e. above the threshold defined as the median value of 774 cells/mm^2 found in commercial DLBCL samples using matched analytical methods, were predicted to be responders to treatment with durvalumab. The definition of a complete response was that used in the primary outcome.

End point type	Secondary

End point timeframe:

Biomarker biopsies: Days -28 to Day -1. Clinical response: From first dose of study drug to end of Induction therapy (Day 1 up to Week 26 – maximum duration of Induction Period).

End point values	High Group for RNA IFN Gamma Score	Low Group for RNA IFN Gamma Score		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	20		
Units: percentage of participants	43	60		

Statistical analyses

Statistical analysis title	RNA Sequencing

Statistical analysis description:

The Area Under the Receiver Operator Characteristic Curve (AUC-ROC) is the estimated parameter. Responders were compared to non-responders by ranking them according to their IFNG-Score.

Comparison groups	High Group for RNA IFN Gamma Score v Low Group for RNA IFN Gamma Score
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.399 [8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[8] - Significance defined as 0.05.

Statistical analysis title	RNA Sequencing
Comparison groups	High Group for RNA IFN Gamma Score v Low Group for RNA IFN Gamma Score
Number of subjects included in analysis	27
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.662 [9]
Method	Fisher exact

Notes:

[9] - Significance defined as 0.05.

Secondary: Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Participants with Treatment Emergent Adverse Events (TEAE)

End point description:

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen during a

study. A serious AE is any AE occurring at any dose that: • Results in death; • Is life-threatening; • Requires or prolongs existing inpatient hospitalization; • Results in persistent or significant disability/incapacity; • Is a congenital anomaly/birth defect; • Constitutes an important medical event. The Investigator assessed the relationship of each AE to study drug and graded the severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03): - Grade 1 = Mild (no limitation in activity or intervention); - Grade 2 = Moderate (some limitation in activity; no/minimal medical intervention required); - Grade 3 = Severe (marked limitation in activity; medical intervention required, hospitalization possible); - Grade 4 = Life-threatening; - Grade 5 = Death. Relation to IP is determined by the investigator. 99999= N/A

End point type	Secondary

End point timeframe:

From the date of the first dose of study drug to within 90 days after the last dose of durvalumab or 28 days after the last dose of any investigational product (IP) whichever is greater. (Up to approximately 72 weeks)

End point values	DUR + R-CHOP	DUR + R2-CHOP		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	3		
Units: participants				
>= 1 Treatment-emergent adverse event (TEAE)	43	3		
>=1 TEAE related to durvalumab	33	3		
>=1 TEAE related to R-CHOP	40	3		
>=1 TEAE related to lenalidomide	99999	3		
>=1 TEAE related to durvalumab or any other IP	41	3		
>=1 TEAE severity grade 3-4	37	3		
>=1 TEAE severity grade 3-4 related to durvalumab	18	1		
>=1 TEAE severity grade 3-4 related to R-CHOP	27	3		
>=1 TEAE severity grade 3-4 related to lenalidomid	99999	2		
>=1 TEAE severity grade 3-4 related to any IP	31	3		
>=1 TEAE severity grade 5	3	0		
>=1 TEAE severity grade 5 related to any IP	0	0		
>=1 serious TEAE	23	1		
>=1 serious TEAE related to durvalumab	10	1		
>=1 serious TEAE related to R-CHOP	10	1		
>=1 serious TEAE related to lenalidomide	99999	1		
>=1 serious TEAE related to any IP	14	1		
>=1 leading to discontinuation of durvalumab	13	0		
>=1 leading to discontinuation of R-CHOP	4	0		
>=1 leading to discontinuation of lenalidomide	99999	0		
>=1 leading to discontinuation of any IP	13	0		
>=1 leading to interruption of durvalumab	15	2		
>=1 leading to interruption of R-CHOP	12	1		

>=1 leading to interruption of lenalidomide	99999	2		
>=1 leading to interruption of any IP	18	3		
>=1 leading to infusion interruption of durvalumab	2	0		
>=1 leading to dose reduction of vincristine	4	1		
>=1 leading to dose reduction of lenalidomide	99999	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed from first dose to 90 days after the last dose of durvalumab or 28 days after other IP and up to 5 years after C1D1 of the last lenalidomide dose. All-Cause Mortality was assessed in participants from first dose to study completion.

Adverse event reporting additional description:

Participants treated with lenalidomide during any stage of the study will be continued to be followed for Second Primary Malignancies (SPM) for up to 5 years after enrollment (C1D1) of the last Participant to receive lenalidomide as part of their study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	DUR + R-CHOP

Reporting group description:

Participants receive Induction Therapy (21-day cycles): Durvalumab 1125 mg intravenously (IV) on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5). Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

Reporting group title	DUR + R2-CHOP

Reporting group description:

Participants receive Induction Therapy (21-day cycles): Cycle 1 - induction therapy of durvalumab in combination with R-CHOP (as described in DUR + R-CHOP arm). Starting at cycle 2 - Durvalumab 1125 mg IV on Day 1 of each 21-day cycle in combination with 6 to 8 cycles R2-CHOP (IV rituximab, doxorubicin, vincristine and cyclophosphamide on Day 1; daily oral/IV prednisone/prednisolone from Day 1 to 5; daily oral lenalidomide 15 mg from Day 1 to 14) from the cycle following COO determination until end of induction therapy (Cycle 6 or Cycle 8) or starting Cycle 1 if ABC subtype is identified prior to C1D1. Participants then receive Consolidation Therapy (28-day cycles): Durvalumab 1500 mg IV on Day 1 of each 28-day cycle for up to a total of 12 months from C1D1 of induction therapy.

Serious adverse events	DUR + R-CHOP	DUR + R2-CHOP	
Total subjects affected by serious adverse events			
subjects affected / exposed	23 / 43 (53.49%)	1 / 3 (33.33%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Diffuse large B-cell lymphoma recurrent			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clear cell renal cell carcinoma			

subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	2 / 43 (4.65%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial ischaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 43 (4.65%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	6 / 43 (13.95%)	1 / 3 (33.33%)	
occurrences causally related to treatment / all	5 / 6	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 43 (4.65%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Seborrhoeic dermatitis			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Musculoskeletal and connective tissue disorders			
Spinal pain			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	2 / 43 (4.65%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	2 / 43 (4.65%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral diarrhoea			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis bacterial			

subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Perirectal abscess			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 43 (4.65%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 43 (2.33%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	DUR + R-CHOP	DUR + R2-CHOP	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 43 (100.00%)	3 / 3 (100.00%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Histiocytic necrotising lymphadenitis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Hot flush			

subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Chills			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Fatigue			
subjects affected / exposed	26 / 43 (60.47%)	2 / 3 (66.67%)	
occurrences (all)	29	3	
Mucosal inflammation			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Oedema peripheral			
subjects affected / exposed	6 / 43 (13.95%)	1 / 3 (33.33%)	
occurrences (all)	6	1	
Pyrexia			
subjects affected / exposed	9 / 43 (20.93%)	0 / 3 (0.00%)	
occurrences (all)	9	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 43 (20.93%)	0 / 3 (0.00%)	
occurrences (all)	13	0	
Dyspnoea			
subjects affected / exposed	10 / 43 (23.26%)	0 / 3 (0.00%)	
occurrences (all)	10	0	
Oropharyngeal pain			
subjects affected / exposed	6 / 43 (13.95%)	0 / 3 (0.00%)	
occurrences (all)	6	0	
Pulmonary embolism			
subjects affected / exposed	1 / 43 (2.33%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Psychiatric disorders			
Depression			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Insomnia			

subjects affected / exposed	11 / 43 (25.58%)	0 / 3 (0.00%)	
occurrences (all)	18	0	
Investigations			
Blood pressure increased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Platelet count decreased			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	2	
Weight decreased			
subjects affected / exposed	7 / 43 (16.28%)	0 / 3 (0.00%)	
occurrences (all)	7	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Infusion related reaction			
subjects affected / exposed	5 / 43 (11.63%)	1 / 3 (33.33%)	
occurrences (all)	6	1	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Dizziness			
subjects affected / exposed	9 / 43 (20.93%)	1 / 3 (33.33%)	
occurrences (all)	10	1	
Dysgeusia			
subjects affected / exposed	6 / 43 (13.95%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Headache			
subjects affected / exposed	11 / 43 (25.58%)	0 / 3 (0.00%)	
occurrences (all)	11	0	
Peripheral sensory neuropathy			
subjects affected / exposed	23 / 43 (53.49%)	2 / 3 (66.67%)	
occurrences (all)	24	2	
Restless legs syndrome			

subjects affected / exposed	2 / 43 (4.65%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Sensory disturbance			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Taste disorder			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 43 (16.28%)	1 / 3 (33.33%)	
occurrences (all)	8	3	
Neutropenia			
subjects affected / exposed	21 / 43 (48.84%)	3 / 3 (100.00%)	
occurrences (all)	39	5	
Thrombocytopenia			
subjects affected / exposed	4 / 43 (9.30%)	1 / 3 (33.33%)	
occurrences (all)	4	2	
Leukopenia			
subjects affected / exposed	7 / 43 (16.28%)	1 / 3 (33.33%)	
occurrences (all)	10	1	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Eye disorders			
Vision blurred			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	5 / 43 (11.63%)	0 / 3 (0.00%)	
occurrences (all)	7	0	
Constipation			

subjects affected / exposed	9 / 43 (20.93%)	2 / 3 (66.67%)	
occurrences (all)	9	2	
Diarrhoea			
subjects affected / exposed	13 / 43 (30.23%)	1 / 3 (33.33%)	
occurrences (all)	18	1	
Dry mouth			
subjects affected / exposed	8 / 43 (18.60%)	0 / 3 (0.00%)	
occurrences (all)	9	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 43 (2.33%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	18 / 43 (41.86%)	2 / 3 (66.67%)	
occurrences (all)	24	2	
Stomatitis			
subjects affected / exposed	8 / 43 (18.60%)	2 / 3 (66.67%)	
occurrences (all)	12	2	
Vomiting			
subjects affected / exposed	10 / 43 (23.26%)	0 / 3 (0.00%)	
occurrences (all)	17	0	
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Erythema			
subjects affected / exposed	1 / 43 (2.33%)	1 / 3 (33.33%)	
occurrences (all)	1	2	
Generalised erythema			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	5 / 43 (11.63%)	0 / 3 (0.00%)	
occurrences (all)	6	0	
Rash			
subjects affected / exposed	8 / 43 (18.60%)	1 / 3 (33.33%)	
occurrences (all)	11	1	

Alopecia			
subjects affected / exposed	10 / 43 (23.26%)	0 / 3 (0.00%)	
occurrences (all)	10	0	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 43 (4.65%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Back pain			
subjects affected / exposed	7 / 43 (16.28%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Muscle spasms			
subjects affected / exposed	4 / 43 (9.30%)	1 / 3 (33.33%)	
occurrences (all)	4	1	
Myalgia			
subjects affected / exposed	7 / 43 (16.28%)	0 / 3 (0.00%)	
occurrences (all)	8	0	
Pain in extremity			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Spinal pain			
subjects affected / exposed	1 / 43 (2.33%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	5 / 43 (11.63%)	0 / 3 (0.00%)	
occurrences (all)	5	0	
Influenza			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Lung infection			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	7	0	

Nasopharyngitis			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Oral herpes			
subjects affected / exposed	2 / 43 (4.65%)	1 / 3 (33.33%)	
occurrences (all)	2	1	
Pneumonia			
subjects affected / exposed	0 / 43 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	
Urinary tract infection			
subjects affected / exposed	4 / 43 (9.30%)	0 / 3 (0.00%)	
occurrences (all)	4	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	12 / 43 (27.91%)	0 / 3 (0.00%)	
occurrences (all)	13	0	
Hypokalaemia			
subjects affected / exposed	8 / 43 (18.60%)	1 / 3 (33.33%)	
occurrences (all)	8	1	
Hypomagnesaemia			
subjects affected / exposed	3 / 43 (6.98%)	0 / 3 (0.00%)	
occurrences (all)	3	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 October 2019	Discontinuation of Follow-up Period, assessments and data collection. Second Primary Malignancies (SPMs) data collection.

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.

After the US FDA Partial Clinical Hold, enrollment of new subjects into Arm B was discontinued.

Notes: