Clinical trial results:
A Randomized, Open-Label, Multicenter, Phase II Trial Evaluating the Safety and Activity of DNIB0600A Compared to Pegylated Liposomal Doxorubicin Administered Intravenously to Patients With Platinum-Resistant Ovarian Cancer

Summary

EudraCT number	2012-005776-34
Trial protocol	GB FR PL ES BE
Global end of trial date	17 August 2016

Results information

Result version number	v1 (current)
This version publication date	31 August 2017
First version publication date	31 August 2017

Trial information

Trial identification

Sponsor protocol code	GO28609

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01991210
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com
Scientific contact	Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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	17 August 2016
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 August 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of lifastuzumab vedotin (DNIB0600A) compared with pegylated liposomal doxorubicin (PLD) in participants with platinum-resistant ovarian cancer (PROC) as assessed by progression-free survival (PFS) in participants with sodium-dependent phosphate co-transporter (NaPi2b)-high tumors as well as in the overall participant population

Protection of trial subjects:

The study was conducted in full conformance with the International Conference on Harmonization (ICH) E6 guidelines for Good Clinical Practice (GCP) and the principles of the "Declaration of Helsinki", or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). The studies conducted in the United States under a U.S. Investigational New Drug (IND) application complied with FDA regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU)/European Economic Area complied with the EU Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	France: 12
Country: Number of subjects enrolled	United Kingdom: 17
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	95
EEA total number of subjects	45

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)	55
From 65 to 84 years	39
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 95 participants were randomized in the study. Two participants, 1 in each arm, were randomized but did not receive any study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Lifastuzumab Vedotin

Arm description:

Lifastuzumab vedotin was administered at a dose of 2.4 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each cycle (1 cycle = 21 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Arm type	Experimental
Investigational medicinal product name	Lifastuzumab Vedotin
Investigational medicinal product code	
Other name	DNIB0600A
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Lifastuzumab vedotin was administered at a dose of 2.4 mg/kg via IV infusion on Day 1 of each cycle (1 cycle = 21 days).

Arm title	Pegylated Liposomal Doxorubicin (PLD)

Arm description:

PLD was administered at a dose of 40 milligrams per meter-squared (mg/m^2) via IV infusion on Day 1 of each cycle (1 cycle = 28 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin Hydrochloride
Investigational medicinal product code	
Other name	PLD, Caelyx, Doxil, and Lipodox
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

PLD was administered at a dose of 40 mg/m^2 via IV infusion on Day 1 of each cycle (1 cycle = 28 days).

Number of subjects in period 1	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)
Started	47	48
Completed	0	0
Not completed	47	48
Consent withdrawn by subject	1	3
Death	17	18
Unspecified	1	1
Study Terminated by Sponsor	28	26

Baseline characteristics

Reporting groups	
Reporting group title	Lifastuzumab Vedotin

Reporting group description:

Lifastuzumab vedotin was administered at a dose of 2.4 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each cycle (1 cycle = 21 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Reporting group title	Pegylated Liposomal Doxorubicin (PLD)

Reporting group description:

PLD was administered at a dose of 40 milligrams per meter-squared (mg/m^2) via IV infusion on Day 1 of each cycle (1 cycle = 28 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Reporting group values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)	Total
Number of subjects	47	48	95
Age Categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	62.7	62.9	
standard deviation	± 9.2	± 7.4	-
Gender Categorical Units: Subjects			
Female	47	48	95
Male	0	0	0

End points

End points reporting groups

Reporting group title	Lifastuzumab Vedotin

Reporting group description:

Lifastuzumab vedotin was administered at a dose of 2.4 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each cycle (1 cycle = 21 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Reporting group title	Pegylated Liposomal Doxorubicin (PLD)

Reporting group description:

PLD was administered at a dose of 40 milligrams per meter-squared (mg/m^2) via IV infusion on Day 1 of each cycle (1 cycle = 28 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Primary: Percentage of Participants With Disease Progression as Assessed by Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) or Death

End point title	Percentage of Participants With Disease Progression as Assessed by Investigator According to Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1) or Death[1]

End point description:

Progressive disease (PD) was defined as greater than or equal to (>/=) 20 percent (%) relative increase and >/=5 millimeter (mm) of absolute increase in the sum of diameters (SD) of target lesions (TLs), taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Unequivocal progression of existing non-TLs or appearance of 1 or more new lesions. Percentage of participants with PD event or death as assessed by investigator is reported. Analysis was performed on Intent-to-treat (ITT) population, which included all participants who were randomized to any of the study treatments.

End point type	Primary

End point timeframe:

From baseline up to disease progression or death within 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: percentage of participants				
number (not applicable)	89.4	81.3		

Statistical analyses

No statistical analyses for this end point

Primary: PFS as Assessed by Investigator According to RECIST v1.1

End point title	PFS as Assessed by Investigator According to RECIST v1.1

End point description:

PFS was defined as the time from first intake of any study medication until the first radiographically documented progression of disease or death from any cause, whichever occurred first. Participants with no PFS events were censored at the time of the last evaluable tumor assessment. Participants with no baseline or no tumor assessment after the baseline visit were censored at the time of randomization plus 1 day. PD: >/=20% relative increase and >/=5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Unequivocal progression of existing non-TLs or appearance of 1 or more new lesions. PFS was estimated using Kaplan-Meier estimates. 95% confidence interval (CI) for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

From baseline up to disease progression or death within 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: months				
median (confidence interval 95%)	5.36 (3.91 to 5.55)	3.14 (1.87 to 5.85)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Unstratified Analysis	
Comparison groups	Pegylated Liposomal Doxorubicin (PLD) v Lifastuzumab Vedotin
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[2]
P-value	= 0.718
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.44

Notes:

[2] - Hazard ratio was estimated by Cox regression.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: The stratification variables were platinum-free interval (less than [<] 3 months, >/=3 months), number of prior platinum-containing regimens (<2, >/=2) and number of prior therapies received in platinum-resistance setting (0, >/=1).

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	= 0.52
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.36

Notes:

[3] - Hazard ratio was estimated by Cox regression.

Primary: Percentage of Participants With Disease Progression as Assessed by Investigator According to RECIST v1.1 or Death in Participants With NaPi2b-High Tumors

End point title	Percentage of Participants With Disease Progression as Assessed by Investigator According to RECIST v1.1 or Death in Participants With NaPi2b-High Tumors[4]

End point description:

PD: >/=20% relative increase and >/=5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Unequivocal progression of existing non-TLs or appearance of 1 or more new lesions. Percentage of participants with PD event or death as assessed by investigator is reported. Analysis was performed on NaPi2b-high population, which included all randomized participants with high NaPi2b expression in tumor tissues classified as immunohistochemistry (IHC) 2+/3+.

End point type	Primary

End point timeframe:

From baseline up to disease progression or death within 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

Notes:

[4] - 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: Results were reported descriptively and were not planned to be analyzed for statistically significant differences between groups.

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: percentage of participants				
number (not applicable)	90.5	81.4		

Statistical analyses

No statistical analyses for this end point

Primary: PFS as Assessed by Investigator According to RECIST v1.1 in Participants with NaPi2b-High Tumors

End point title	PFS as Assessed by Investigator According to RECIST v1.1 in Participants with NaPi2b-High Tumors

End point description:

PFS was defined as the time from first intake of any study medication until the first radiographically documented progression of disease or death from any cause, whichever occurred first. Participants with no PFS events were censored at the time of the last evaluable tumor assessment. Participants with no baseline or no tumor assessment after the baseline visit were censored at the time of randomization plus 1 day. PD: >/=20% relative increase and >/=5 mm of absolute increase in the SD of TLs, taking as reference the smallest SD recorded since treatment started, or appearance of 1 or more new lesions. Unequivocal progression of existing non-TLs or appearance of 1 or more new lesions. PFS was estimated using Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on NaPi2b-high population.

End point type	Primary

End point timeframe:

From baseline up to disease progression or death within 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: months				
median (confidence interval 95%)	5.36 (3.91 to 6.97)	3.42 (1.87 to 5.85)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Unstratified Analysis

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)

Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[5]
P-value	= 0.7582
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.48

Notes:

[5] - Hazard ratio was estimated by Cox regression.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: The stratification variables were platinum-free interval (<3 months, >/=3 months), number of prior platinum-containing regimens (<2, >/=2) and number of prior therapies received in platinum-resistance setting (0, >/=1).

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.4536
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	1.35

Notes:

[6] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants With Objective Response According to RECIST v1.1

End point title	Percentage of Participants With Objective Response According to RECIST v1.1

End point description:

Objective response was defined as percentage of participants with a confirmed complete response (CR) or partial response (PR) as assessed by the investigator according to RECIST v1.1. CR was defined as the disappearance of all TLs and short axis (SA) reduction to <10 mm for nodal TLs/ non-TLs. PR was defined as >/=30% decrease in SD of TLs, taking as reference the baseline SD. Confirmation of response at a consecutive tumor assessment at least 4 weeks apart was required. The 95% CI was computed using Blyth-Still-Casella approach. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From baseline up to 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: percentage of participants				
number (confidence interval 95%)	36.2 (22.67 to 51.48)	16.7 (7.65 to 29.48)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0309
Method	Chi-squared
Parameter estimate	Difference in Response Rates
Point estimate	19.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.19
upper limit	36.82

Secondary: Percentage of Participants With Objective Response According to RECIST v1.1 in Participants with NaPi2b-High Tumors

End point title	Percentage of Participants With Objective Response According to RECIST v1.1 in Participants with NaPi2b-High Tumors

End point description:

Objective response was defined as percentage of participants with a confirmed CR or PR as assessed by the investigator according to RECIST v1.1. CR was defined as the disappearance of all TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR was defined as >/=30% decrease in SD of TLs, taking as reference the baseline SD. Confirmation of response at a consecutive tumor assessment at least 4 weeks apart was required. The 95% CI was computed using Blyth-Still-Casella approach. Analysis was performed on NaPi2b-high population.

End point type	Secondary

End point timeframe:

From baseline up to 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: percentage of participants				
number (confidence interval 95%)	38.1 (24.74 to 54.36)	16.3 (7.31 to 29.47)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0236
Method	Chi-squared
Parameter estimate	Difference in Response Rates
Point estimate	21.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.45
upper limit	40.19

Secondary: Duration of Objective Response (DOR)

End point title	Duration of Objective Response (DOR)

End point description:

DOR was defined as the time from first documented objective response to first documented PD or death from any cause, whichever occurred earlier. Objective response was defined as percentage of participants with a confirmed CR or PR as assessed by the investigator according to RECIST v1.1. CR: disappearance of all TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR: >/=30% decrease in SD of TLs, taking as reference the baseline SD. PD: >/=20% increase in the SD, taking as reference the smallest SD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, CR: disappearance of all non-TLs; PR: persistence of 1 or more non-TLs; and PD: appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. DOR was planned to be estimated using Kaplan-Meier estimates in ITT population. The data "99999" in results indicate that the Median was not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From occurrence of a documented objective response until relapse or death from any cause (overall up to approximately 2.5 years)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: DOR in Participants with NaPi2b-High Tumors

End point title	DOR in Participants with NaPi2b-High Tumors

End point description:

DOR was defined as the time from first documented objective response to first documented PD or death from any cause, whichever occurred earlier. Objective response was defined as percentage of participants with a confirmed CR or PR as assessed by the investigator according to RECIST v1.1. CR: disappearance of all TLs and SA reduction to <10 mm for nodal TLs/ non-TLs. PR: >/=30% decrease in SD of TLs, taking as reference the baseline SD. PD: >/=20% increase in the SD, taking as reference the smallest SD recorded since treatment started or the appearance of 1 or more new lesions. For non-TLs, CR: disappearance of all non-TLs; PR: persistence of 1 or more non-TLs; and PD: appearance of 1 or more new lesions and/or unequivocal progression of existing non-TLs. DOR was planned to be estimated using Kaplan-Meier estimates in NaPi2b-high population. The data "99999" in results indicate that the Median was not reached due to insufficient number of participants with event.

End point type	Secondary

End point timeframe:

From occurrence of a documented objective response until relapse or death from any cause (overall up to approximately 2.5 years)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants Who Died due to any Cause

End point title	Percentage of Participants Who Died due to any Cause

End point description:

Percentage of Participants who died due to any cause is reported. All deaths were included, whether they occurred during the study or following treatment discontinuation. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

From baseline up to death from any cause (overall up to approximately 2.5 years)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: percentage of participants				
number (not applicable)	36.2	37.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from first intake of any study medication to the date of death, regardless of the cause of death. Participants who were known to be alive at the time of the analysis were censored at the date of the last follow-up assessment. OS was estimated using Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on ITT population. The data '99999' in the results signifies that Median and Upper Limit could not be calculated due to insufficient number of participants who had an event.

End point type	Secondary

End point timeframe:

From baseline up to death from any cause (overall up to approximately 2.5 years)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: months				
median (confidence interval 95%)	99999 (11.992 to 99999)	18.858 (12.55 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Unstratified Analysis

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[7]
P-value	= 0.9166
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1.88

Notes:

[7] - Hazard ratio was estimated by Cox regression.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: The stratification variables were platinum-free interval (<3 months, >/=3 months), number of prior platinum-containing regimens (<2, >/=2) and number of prior therapies received in platinum-resistance setting (0, >/=1).

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[8]
P-value	= 0.6291
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.71

Notes:

[8] - Hazard ratio was estimated by Cox regression.

Secondary: Percentage of Participants Who Died due to any Cause in Participants with NaPi2b-High Tumors

End point title	Percentage of Participants Who Died due to any Cause in Participants with NaPi2b-High Tumors

End point description:

Percentage of Participants who died due to any cause is reported. All deaths were included, whether they occurred during the study or following treatment discontinuation. Analysis was performed on NaPi2b-high population.

End point type	Secondary

End point timeframe:

From baseline up to death from any cause (overall up to approximately 2.5 years)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: percentage of participants				
number (not applicable)	33.3	39.5		

Statistical analyses

No statistical analyses for this end point

Secondary: OS in Participants with NaPi2b-High Tumors

End point title	OS in Participants with NaPi2b-High Tumors

End point description:

OS was defined as the time from first intake of any study medication to the date of death, regardless of the cause of death. Participants who were known to be alive at the time of the analysis were censored at the date of the last follow-up assessment. OS was estimated using Kaplan-Meier estimates. 95% CI for median was computed using the method of Brookmeyer and Crowley. Analysis was performed on NaPi2b-high population. The data '99999' in the results signifies that Median and Upper Limit could not be calculated due to insufficient number of participants who had an event.

End point type	Secondary

End point timeframe:

From baseline up to death from any cause (overall up to approximately 2.5 years)

End point values	Lifastuzumab Vedotin	Pegylated Liposomal Doxorubicin (PLD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	43		
Units: months				
median (confidence interval 95%)	99999 (11.992 to 99999)	18.858 (12.386 to 99999)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Unstratified Analysis

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[9]
P-value	= 0.6743
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.75

Notes:

[9] - Hazard ratio was estimated by Cox regression.

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Stratified Analysis: The stratification variables were platinum-free interval (<3 months, >/=3 months), number of prior platinum-containing regimens (<2, >/=2) and number of prior therapies received in platinum-resistance setting (0, >/=1).

Comparison groups	Lifastuzumab Vedotin v Pegylated Liposomal Doxorubicin (PLD)
Number of subjects included in analysis	85
Analysis specification	Pre-specified
Analysis type	superiority[10]
P-value	= 0.2509
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.38

Notes:

[10] - Hazard ratio was estimated by Cox regression.

Secondary: Area Under the Serum Concentration-time Curve From Time Zero to Extrapolated Infinite Time (AUC0-inf) of Lifastuzumab Vedotin Total Antibody

End point title	Area Under the Serum Concentration-time Curve From Time Zero to Extrapolated Infinite Time (AUC0-inf) of Lifastuzumab Vedotin Total Antibody[11]

End point description:

AUC0-inf indicates the serum concentration of the total antibody (conjugated and unconjugated antibody) over time. Analysis was performed on pharmacokinetic (PK)-evaluable population, which included all participants who received any amount of study drug and who had any available PK data. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post-infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: day*microgram/milliliter (day*mcg/mL)				
arithmetic mean (standard deviation)	234.85 (± 50.75)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-inf of Lifastuzumab Vedotin Antibody-Conjugated Monomethyl Auristatin E (acMMAE)

End point title	AUC0-inf of Lifastuzumab Vedotin Antibody-Conjugated Monomethyl Auristatin E (acMMAE)[12]

End point description:

AUC0-inf indicated the plasma concentration of the acMMAE over time. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post-infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[12] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: day*nanogram (ng)/mL				
arithmetic mean (standard deviation)	2549.53 (± 566.86)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Serum Concentration (Cmax) of Lifastuzumab Vedotin Total

Antibody

End point title	Maximum Serum Concentration (Cmax) of Lifastuzumab Vedotin Total Antibody[13]

End point description:

Cmax is the maximum total antibody serum concentration observed during dosing period. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: mcg/mL				
arithmetic mean (standard deviation)	41.97 (± 14.81)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Lifastuzumab Vedotin acMMAE

End point title	Cmax of Lifastuzumab Vedotin acMMAE[14]

End point description:

Cmax is the maximum acMMAE plasma concentration observed during dosing period. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng/mL				
arithmetic mean (standard deviation)	748.89 (± 274.22)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Unconjugated Monomethyl Auristatin E (MMAE)

End point title	Cmax of Unconjugated Monomethyl Auristatin E (MMAE)[15]

End point description:

Cmax is the maximum unconjugated MMAE plasma concentration observed during dosing period. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ng/mL				
arithmetic mean (standard deviation)	2.78 (± 2.47)			

Statistical analyses

No statistical analyses for this end point

Secondary: Clearance (CL) of Lifastuzumab Vedotin Total Antibody

End point title	Clearance (CL) of Lifastuzumab Vedotin Total Antibody[16]

End point description:

CL is a quantitative measure of the rate at which total antibody is removed from the body. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: mL/day/kilogram (kg)				
arithmetic mean (standard deviation)	10.75 (± 2.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: CL of Lifastuzumab Vedotin acMMAE

End point title	CL of Lifastuzumab Vedotin acMMAE[17]

End point description:

CL is a quantitative measure of the rate at which acMMAE is removed from the body. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: mL/day/kg				
arithmetic mean (standard deviation)	16.95 (± 3.57)			

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life (t1/2) of Lifastuzumab Vedotin Total Antibody

End point title	Elimination Half-life (t1/2) of Lifastuzumab Vedotin Total Antibody[18]

End point description:

Elimination half-life is the time measured for the total antibody serum concentration to decrease by one half. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: days				
median (full range (min-max))	6.28 (3.2 to 10.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2 of Lifastuzumab Vedotin acMMAE

End point title	t1/2 of Lifastuzumab Vedotin acMMAE[19]

End point description:

Elimination half-life is the time measured for the acMMAE plasma concentration to decrease by one half. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of Cycle 1 (1 cycle=21 days); Day 8 of Cycle 1; Day 15 of Cycle 1

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: days				
median (full range (min-max))	4.78 (3.1 to 9.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Volume of Distribution at Steady State (Vss) of Lifastuzumab Vedotin Total Antibody

End point title	Volume of Distribution at Steady State (Vss) of Lifastuzumab Vedotin Total Antibody[20]

End point description:

Volume of distribution is defined as the theoretical volume in which the total antibody would need to be uniformly distributed to produce the desired serum concentration. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of each Cycle (1 cycle=21 days) (overall up to approximately 2 years); Day 8 of Cycle 1; Day 15 of Cycles 1-4

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	22			
Units: mL/kg				
arithmetic mean (standard deviation)	77.27 (± 21.55)			

Statistical analyses

No statistical analyses for this end point

Secondary: Vss of Lifastuzumab Vedotin acMMAE

End point title	Vss of Lifastuzumab Vedotin acMMAE[21]

End point description:

Volume of distribution is defined as the theoretical volume in which the acMMAE would need to be uniformly distributed to produce the desired plasma concentration. Steady state volume of distribution (Vss) is the apparent volume of distribution at steady-state. Analysis was performed on PK-evaluable population. Here 'Number of Subject Analysed' indicates number of participants evaluable for this outcome measure.

End point type	Secondary

End point timeframe:

Pre-infusion (Hour 0), 30 minutes post infusion (infusion length=90 minutes) on Day 1 of each Cycle (1 cycle=21 days) (overall up to approximately 2 years); Day 8 of Cycle 1; Day 15 of Cycles 1-4

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: PK analyses were carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: mL/kg				
arithmetic mean (standard deviation)	72.21 (± 19.34)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Anti-therapeutic Antibodies (ATAs) Against Lifastuzumab Vedotin

End point title	Percentage of Participants With Anti-therapeutic Antibodies (ATAs) Against Lifastuzumab Vedotin[22]

End point description:

Percentage of participants with positive ATA results was reported. Analysis was performed on immunogenicity-evaluable population, which included all participants who received any amount of study drug and who had any available ATA data. Here 'n' indicates number of participants evaluable at indicated time points.

End point type	Secondary

End point timeframe:

Baseline (Pre-infusion [Hour 0] on Day 1 of Cycle 1); Post-baseline (Pre-infusion [Hour 0] on Day 1 of Cycles 2-4, at approximately 15-30 days after last infusion administration [maximum up to approximately 2 years]) (1 cycle=21 days)

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: ATA analysis was carried out only in the Lifastuzumab Vedotin arm (PLD arm was excluded).

End point values	Lifastuzumab Vedotin			
Subject group type	Reporting group			
Number of subjects analysed	46			
Units: percentage of participants				
number (not applicable)				
Baseline (n=46)	6.5			
Post-baseline (n=44)	34.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 30 days of last study drug administration (overall up to approximately 2 years and 1 month)

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Lifastuzumab Vedotin (DNIB0600A)

Reporting group description:

DNIB0600A was administered at a dose of 2.4 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each cycle (1 cycle = 21 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Reporting group title	Pegylated Liposomal Doxorubicin (PLD)

Reporting group description:

PLD was administered at a dose of 40 milligrams per meter-squared (mg/m^2) via IV infusion on Day 1 of each cycle (1 cycle = 28 days) until significant toxicity, disease progression, or withdrawal from the study, which corresponded to study treatment discontinuation date (overall up to approximately 2 years). After study treatment discontinuation, participants were followed on the study until withdrawal of consent, death, or lost to follow-up or study closure by the Sponsor.

Serious adverse events	Lifastuzumab Vedotin (DNIB0600A)	Pegylated Liposomal Doxorubicin (PLD)	
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 47 (31.91%)	16 / 48 (33.33%)	
number of deaths (all causes)	17	18	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma gastric			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Spinal fracture			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebrovascular accident			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (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			
Anaemia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (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			
Asthenia			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	2 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 47 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyrexia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	4 / 47 (8.51%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal tenderness			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal wall haematoma			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 47 (2.13%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 47 (2.13%)	3 / 48 (6.25%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			

subjects affected / exposed	0 / 47 (0.00%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal abscess			
subjects affected / exposed	1 / 47 (2.13%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical pneumonia			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 47 (0.00%)	1 / 48 (2.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 47 (2.13%)	2 / 48 (4.17%)	
occurrences causally related to treatment / all	1 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 47 (4.26%)	0 / 48 (0.00%)	
occurrences causally related to treatment / all	2 / 3	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	Lifastuzumab Vedotin (DNIB0600A)	Pegylated Liposomal Doxorubicin (PLD)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	46 / 47 (97.87%)	45 / 48 (93.75%)	
Vascular disorders			
Hypertension			

subjects affected / exposed	6 / 47 (12.77%)	6 / 48 (12.50%)	
occurrences (all)	7	10	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 47 (17.02%)	7 / 48 (14.58%)	
occurrences (all)	26	7	
Chest discomfort			
subjects affected / exposed	0 / 47 (0.00%)	7 / 48 (14.58%)	
occurrences (all)	0	7	
Chills			
subjects affected / exposed	1 / 47 (2.13%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Fatigue			
subjects affected / exposed	21 / 47 (44.68%)	27 / 48 (56.25%)	
occurrences (all)	33	43	
Mucosal inflammation			
subjects affected / exposed	2 / 47 (4.26%)	6 / 48 (12.50%)	
occurrences (all)	2	8	
Oedema peripheral			
subjects affected / exposed	3 / 47 (6.38%)	5 / 48 (10.42%)	
occurrences (all)	3	10	
Pyrexia			
subjects affected / exposed	8 / 47 (17.02%)	6 / 48 (12.50%)	
occurrences (all)	10	8	
Reproductive system and breast disorders			
Pelvic pain			
subjects affected / exposed	4 / 47 (8.51%)	0 / 48 (0.00%)	
occurrences (all)	4	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 47 (4.26%)	8 / 48 (16.67%)	
occurrences (all)	2	11	
Dyspnoea			
subjects affected / exposed	6 / 47 (12.77%)	9 / 48 (18.75%)	
occurrences (all)	9	10	

Oropharyngeal pain			
subjects affected / exposed	2 / 47 (4.26%)	4 / 48 (8.33%)	
occurrences (all)	2	5	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 47 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Insomnia			
subjects affected / exposed	4 / 47 (8.51%)	5 / 48 (10.42%)	
occurrences (all)	4	5	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	7 / 47 (14.89%)	3 / 48 (6.25%)	
occurrences (all)	11	5	
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 47 (10.64%)	2 / 48 (4.17%)	
occurrences (all)	15	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 47 (2.13%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Neutrophil count decreased			
subjects affected / exposed	1 / 47 (2.13%)	3 / 48 (6.25%)	
occurrences (all)	2	6	
Weight decreased			
subjects affected / exposed	2 / 47 (4.26%)	5 / 48 (10.42%)	
occurrences (all)	3	5	
White blood cell count decreased			
subjects affected / exposed	0 / 47 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	9	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 47 (4.26%)	5 / 48 (10.42%)	
occurrences (all)	2	5	
Dysgeusia			
subjects affected / exposed	3 / 47 (6.38%)	5 / 48 (10.42%)	
occurrences (all)	3	6	

Headache			
subjects affected / exposed	9 / 47 (19.15%)	7 / 48 (14.58%)	
occurrences (all)	9	9	
Neuropathy peripheral			
subjects affected / exposed	3 / 47 (6.38%)	0 / 48 (0.00%)	
occurrences (all)	3	0	
Peripheral sensory neuropathy			
subjects affected / exposed	8 / 47 (17.02%)	3 / 48 (6.25%)	
occurrences (all)	17	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	10 / 47 (21.28%)	8 / 48 (16.67%)	
occurrences (all)	14	9	
Leukopenia			
subjects affected / exposed	1 / 47 (2.13%)	3 / 48 (6.25%)	
occurrences (all)	1	4	
Neutropenia			
subjects affected / exposed	14 / 47 (29.79%)	8 / 48 (16.67%)	
occurrences (all)	27	28	
Eye disorders			
Vision blurred			
subjects affected / exposed	1 / 47 (2.13%)	3 / 48 (6.25%)	
occurrences (all)	1	3	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	4 / 47 (8.51%)	1 / 48 (2.08%)	
occurrences (all)	5	1	
Abdominal distension			
subjects affected / exposed	3 / 47 (6.38%)	3 / 48 (6.25%)	
occurrences (all)	3	4	
Abdominal pain			
subjects affected / exposed	19 / 47 (40.43%)	11 / 48 (22.92%)	
occurrences (all)	35	16	
Abdominal pain upper			
subjects affected / exposed	4 / 47 (8.51%)	4 / 48 (8.33%)	
occurrences (all)	5	4	
Ascites			

subjects affected / exposed	2 / 47 (4.26%)	3 / 48 (6.25%)	
occurrences (all)	2	5	
Constipation			
subjects affected / exposed	12 / 47 (25.53%)	18 / 48 (37.50%)	
occurrences (all)	17	23	
Diarrhoea			
subjects affected / exposed	18 / 47 (38.30%)	9 / 48 (18.75%)	
occurrences (all)	26	10	
Dyspepsia			
subjects affected / exposed	1 / 47 (2.13%)	5 / 48 (10.42%)	
occurrences (all)	1	10	
Flatulence			
subjects affected / exposed	0 / 47 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 47 (8.51%)	0 / 48 (0.00%)	
occurrences (all)	4	0	
Nausea			
subjects affected / exposed	21 / 47 (44.68%)	22 / 48 (45.83%)	
occurrences (all)	38	27	
Stomatitis			
subjects affected / exposed	3 / 47 (6.38%)	15 / 48 (31.25%)	
occurrences (all)	4	25	
Vomiting			
subjects affected / exposed	13 / 47 (27.66%)	12 / 48 (25.00%)	
occurrences (all)	21	16	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	3 / 47 (6.38%)	0 / 48 (0.00%)	
occurrences (all)	11	0	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	6 / 47 (12.77%)	4 / 48 (8.33%)	
occurrences (all)	7	4	
Erythema			

subjects affected / exposed	2 / 47 (4.26%)	3 / 48 (6.25%)	
occurrences (all)	2	3	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	0 / 47 (0.00%)	12 / 48 (25.00%)	
occurrences (all)	0	17	
Pruritus			
subjects affected / exposed	0 / 47 (0.00%)	4 / 48 (8.33%)	
occurrences (all)	0	5	
Rash			
subjects affected / exposed	2 / 47 (4.26%)	4 / 48 (8.33%)	
occurrences (all)	2	7	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 47 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 47 (8.51%)	4 / 48 (8.33%)	
occurrences (all)	4	4	
Back pain			
subjects affected / exposed	5 / 47 (10.64%)	7 / 48 (14.58%)	
occurrences (all)	5	9	
Groin pain			
subjects affected / exposed	0 / 47 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	4	
Muscle spasms			
subjects affected / exposed	4 / 47 (8.51%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 47 (0.00%)	3 / 48 (6.25%)	
occurrences (all)	0	5	
Myalgia			
subjects affected / exposed	5 / 47 (10.64%)	2 / 48 (4.17%)	
occurrences (all)	6	2	
Pain in extremity			

subjects affected / exposed	4 / 47 (8.51%)	1 / 48 (2.08%)	
occurrences (all)	4	4	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 47 (6.38%)	1 / 48 (2.08%)	
occurrences (all)	3	2	
Sinusitis			
subjects affected / exposed	3 / 47 (6.38%)	1 / 48 (2.08%)	
occurrences (all)	3	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 47 (4.26%)	5 / 48 (10.42%)	
occurrences (all)	2	5	
Urinary tract infection			
subjects affected / exposed	8 / 47 (17.02%)	9 / 48 (18.75%)	
occurrences (all)	8	10	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	19 / 47 (40.43%)	16 / 48 (33.33%)	
occurrences (all)	23	18	
Dehydration			
subjects affected / exposed	3 / 47 (6.38%)	2 / 48 (4.17%)	
occurrences (all)	4	2	
Hyperglycaemia			
subjects affected / exposed	4 / 47 (8.51%)	2 / 48 (4.17%)	
occurrences (all)	5	5	
Hypokalaemia			
subjects affected / exposed	4 / 47 (8.51%)	3 / 48 (6.25%)	
occurrences (all)	6	5	
Hypomagnesaemia			
subjects affected / exposed	5 / 47 (10.64%)	8 / 48 (16.67%)	
occurrences (all)	7	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 February 2014	Protocol was amended to include the following changes: Clinical data on lifastuzumab vedotin was updated as of 18 September 2013; An inclusion criterion was added specifying that participants must have at least one lesion that is measurable per RECIST v1.1 criteria; The inclusion criteria was modified to allow enrollment of participants who had received no more than one prior cytotoxic chemotherapy regimen for the treatment of PROC and no more than two total regimens; Due to the global shortage of PLD ongoing at the time of amendment, it was clarified that the Sponsor will supply PLD to U.S. sites in cases where they were unable to obtain or were relying on their own local supply; For participants who had a change in bodyweight of +/- 10%, allowance was made for dose adjustment of PLD after discussion with the medical monitor; Allowance was made for dose modifications for PLD to be made in accordance with local institutional standards; Information on cardiotoxicity and PLD dose modification was added; The study treatment designation for PLD was changed from the "standard of care non-investigational drug" to an "investigational study drug" because it was administered at a lower dose than what was indicated on the approved drug label; The timing of pregnancy testing for women of childbearing potential was modified; Additional electrocardiogram (ECG) monitoring was added in the PLD arm due to cardiac toxicity being a known risk for the drug; A clarification was added that the timing of the first electronic patient-reported outcome (ePRO) collection was on Cycle 1, Day 1 but prior to the participant being informed of their study drug assignment; The schedule of assessments in the protocol was corrected.
17 March 2014	Language regarding study drug discontinuation in participants who developed increases in QT intervals was modified.

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.

Sponsor discontinued the survival follow-up in January 2016 and terminated the study in July 2016, because the primary objective of PFS did not meet pre-specified criteria.

Notes: