



Clinical trial results:

Phase 2 study of MCLA-128-based combinations in metastatic breast cancer (MBC): MCLA-128/trastuzumab/chemotherapy in HER2-positive MBC and MCLA-128/endocrine therapy in estrogen receptor positive and low HER2 expression MBC

Summary

EudraCT number	2017-002821-39
Trial protocol	BE PT ES GB NL
Global end of trial date	26 July 2023

Results information

Result version number	v1 (current)
This version publication date	22 August 2025
First version publication date	22 August 2025

Trial information

Trial identification

Sponsor protocol code	MCLA-128-CL02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03321981
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merus N.V.
Sponsor organisation address	Uppsalalaan 17, Utrecht, Netherlands,
Public contact	MCLA-128-CL02 project manager, Oncology Therapeutic Development, 33 147150101, otd@oncotd.com
Scientific contact	MCLA-128-CL02 project manager, Oncology Therapeutic Development, 33 147150101, otd@oncotd.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	26 October 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 October 2022
Global end of trial reached?	Yes
Global end of trial date	26 July 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Cohort 1 (HER2-positive/amplified MBC): MCLA-128 + trastuzumab ± vinorelbine:

Evaluate efficacy of MCLA-128 combined with trastuzumab ± vinorelbine in terms of clinical benefit rate (CBR) at 24 weeks based on RECIST 1.1 (per investigator review) in HER2-positive/amplified MBC patients who have progressed on prior HER2-directed therapy that included trastuzumab with pertuzumab, and an HER2 antibody drug conjugate (ADC)

Cohort 2 (estrogen receptor [ER]-positive/low HER2 expression MBC): MCLA-128 + endocrine therapy:

Evaluate efficacy of MCLA-128 combined with endocrine therapy in terms of CBR at 24 weeks based on RECIST 1.1 (per investigator review) in ER-positive and low HER2 expression MBC patients who have previously progressed on the same endocrine therapy

Protection of trial subjects:

Premedication with paracetamol/acetaminophen, antihistamines, and corticosteroids was mandatory immediately before every zenocutuzumab administration, per local standard practices:

- Paracetamol/ acetaminophen 1000 mg per os (PO) or IV.
- Dexchlorpheniramine 5 mg IV (or equivalent PO or IV).
- Dexamethasone 10 mg IV (or equivalent PO or IV).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 November 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	Netherlands: 4
Country: Number of subjects enrolled	Portugal: 13
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	France: 47
Country: Number of subjects enrolled	United States: 16
Worldwide total number of subjects	104
EEA total number of subjects	85

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)	77
From 65 to 84 years	27
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was enrolled on 18 Jan 2018. The last patient last visit/death in the study was 26 July 2023.

Pre-assignment

Screening details:

For this study 105 were enrolled, but only 104 patients were treated. The non-treated patient was excluded prior to initiation of study treatment due to failure to meet inclusion criteria 2.2d (No progression under Cyclin-Dependent Kinase (CDK) inhibitor).

Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 Doublet

Arm description:

zenocutuzumab + trastuzumab

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Arm type	Experimental
Investigational medicinal product name	Zenocutuzumab
Investigational medicinal product code	
Other name	MCLA-128
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Flat dose of 750 mg administered intravenously (IV) over 2 h, on Day 1 once every 3 weeks. Dose reductions were not permitted.

Arm title	Cohort 1 Triplet
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Arm description:

zenocutuzumab + trastuzumab + vinorelbine

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Vinorelbine: antineoplastic drug of vinca alkaloid family

Arm type	Experimental
Investigational medicinal product name	Zenocutuzumab
Investigational medicinal product code	
Other name	MCLA-128
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Flat dose of 750 mg administered intravenously (IV) over 2 h, on Day 1 once every 3 weeks. Dose reductions were not permitted.

Arm title	Cohort 2
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Arm description:

zenocutuzumab + endocrine therapy

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Endocrine therapy: same endocrine therapy is administered as the last line of endocrine therapy

Arm type	Experimental
Investigational medicinal product name	Zenocutuzumab
Investigational medicinal product code	
Other name	MCLA-128
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Flat dose of 750 mg administered intravenously (IV) over 2 h, on Day 1 once every 3 weeks. Dose reductions were not permitted.

Number of subjects in period 1	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2
Started	15	39	50
Completed	15	39	50

Period 2

Period 2 title	Overall Trial
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 Doublet

Arm description:

zenocutuzumab + trastuzumab

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Arm type	Experimental
Investigational medicinal product name	Zenocutuzumab
Investigational medicinal product code	
Other name	MCLA-128
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Flat dose of 750 mg administered intravenously (IV) over 2 h, on Day 1 once every 3 weeks. Dose reductions were not permitted.

Arm title	Cohort 1 Triplet
------------------	------------------

Arm description:

zenocutuzumab + trastuzumab + vinorelbine

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Vinorelbine: antineoplastic drug of vinca alkaloid family

Arm type	Experimental
Investigational medicinal product name	Zenocutuzumab
Investigational medicinal product code	
Other name	MCLA-128
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Flat dose of 750 mg administered intravenously (IV) over 2 h, on Day 1 once every 3 weeks. Dose reductions were not permitted.

Arm title	Cohort 2
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Arm description:

zenocutuzumab + endocrine therapy

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Endocrine therapy: same endocrine therapy is administered as the last line of endocrine therapy

Arm type	Experimental
Investigational medicinal product name	Zenocutuzumab
Investigational medicinal product code	
Other name	MCLA-128
Pharmaceutical forms	Solution for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Flat dose of 750 mg administered intravenously (IV) over 2 h, on Day 1 once every 3 weeks. Dose reductions were not permitted.

Number of subjects in period 2	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2
Started	15	39	50
Completed	0	0	0
Not completed	15	39	50
Physician decision	-	1	-
Symptomatic deterioration	-	1	1
Adverse event, non-fatal	-	-	2
Death	-	1	-
Scans showed PD 01JUL2019 (but the PT has received	-	1	-
Progressive Disease	15	30	47
Subject withdrawal of all treatment and follow-up	-	2	-
Subject withdrawal of investigational product	-	1	-
Lack of compliance	-	1	-

Subject withdrawal with disagreement for contact	-	1	-
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Baseline characteristics

Reporting groups

Reporting group title	Cohort 1 Doublet
Reporting group description: zenocutuzumab + trastuzumab	
Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3	
Trastuzumab: humanised IgG1 monoclonal antibody	
Reporting group title	Cohort 1 Triplet
Reporting group description: zenocutuzumab + trastuzumab + vinorelbine	
Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3	
Trastuzumab: humanised IgG1 monoclonal antibody	
Vinorelbine: antineoplastic drug of vinca alkaloid family	
Reporting group title	Cohort 2
Reporting group description: zenocutuzumab + endocrine therapy	
Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3	
Endocrine therapy: same endocrine therapy is administered as the last line of endocrine therapy	

Reporting group values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2
Number of subjects	15	39	50
Age categorical			
Units: Subjects			
Adults (18-64 years)	11	27	39
From 65-84 years	4	12	11
Gender categorical			
Units: Subjects			
Female	15	39	50
Male	0	0	0
Ethnicity			
Units: Subjects			
Hispanic or Latino	0	3	4
Not Hispanic or Latino	12	31	44
Unknown or Not Reported	3	5	2
Race			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	3	0
White	9	22	46
More than one race	0	0	0
Unknown or Not Reported	5	14	4

Reporting group values	Total		
Number of subjects	104		
Age categorical			
Units: Subjects			
Adults (18-64 years)	77		
From 65-84 years	27		
Gender categorical			
Units: Subjects			
Female	104		
Male	0		
Ethnicity			
Units: Subjects			
Hispanic or Latino	7		
Not Hispanic or Latino	87		
Unknown or Not Reported	10		
Race			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	0		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	4		
White	77		
More than one race	0		
Unknown or Not Reported	23		

End points

End points reporting groups

Reporting group title	Cohort 1 Doublet
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Reporting group description:

zenocutuzumab + trastuzumab

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Reporting group title	Cohort 1 Triplet
-----------------------	------------------

Reporting group description:

zenocutuzumab + trastuzumab + vinorelbine

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Vinorelbine: antineoplastic drug of vinca alkaloid family

Reporting group title	Cohort 2
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Reporting group description:

zenocutuzumab + endocrine therapy

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Endocrine therapy: same endocrine therapy is administered as the last line of endocrine therapy

Reporting group title	Cohort 1 Doublet
-----------------------	------------------

Reporting group description:

zenocutuzumab + trastuzumab

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Reporting group title	Cohort 1 Triplet
-----------------------	------------------

Reporting group description:

zenocutuzumab + trastuzumab + vinorelbine

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Vinorelbine: antineoplastic drug of vinca alkaloid family

Reporting group title	Cohort 2
-----------------------	----------

Reporting group description:

zenocutuzumab + endocrine therapy

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Endocrine therapy: same endocrine therapy is administered as the last line of endocrine therapy

Primary: Clinical Benefit Rate at 24 weeks per Investigator assessment

End point title	Clinical Benefit Rate at 24 weeks per Investigator assessment ^[1]
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End point description:

Clinical benefit rate (CBR) at 24 weeks per investigator assessment. CBR is the proportion of patients with confirmed Complete Response (CR) or Partial Response (PR), or Stable Disease (SD) lasting 24 weeks.

End point type	Primary
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End point timeframe:

24 weeks

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: There was no statistical comparison between the cohorts. The analysis was performed independently for each cohort; only descriptive statistics were calculated.

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	31	43	
Units: Count of participants				
Count of Participants	3	18	9	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival per Investigator Assessment

End point title	Progression Free Survival per Investigator Assessment
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End point description:

For assessment per Response Evaluation Criteria In Solid Tumors Guidelines (RECIST) v1.1, PFS is the time from the date of treatment start to the date of event defined as the first documented progression or death due to any cause.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	31	43	
Units: Months				
median (confidence interval 90%)				
Median (90% Confidence Interval)	1.41 (1.38 to 1.45)	5.52 (4.11 to 7.16)	2.61 (1.45 to 2.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) Per Central Review

End point title	Progression Free Survival (PFS) Per Central Review
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End point description:

For assessment per RECIST v1.1, PFS is the time from the date of treatment start to the date of event defined as the first documented progression or death due to any cause.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	31	43	
Units: Months				
median (confidence interval 90%)				
Median (90% Confidence Interval)	1.41 (1.38 to 1.45)	5.59 (4.11 to 7.39)	1.45 (1.45 to 2.73)	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate per Investigator Assessment

End point title	Overall Response Rate per Investigator Assessment
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End point description:

The proportion of patients with overall response of Complete Response or Partial Response based upon RECIST 1.1 (confirmed response).

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	31	43	
Units: Count of Participants	0	10	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate per Central Review

End point title	Overall Response Rate per Central Review
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End point description:

The proportion of patients with overall response of Complete Response or Partial Response based upon RECIST 1.1 (confirmed response).

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	31	43	
Units: Count of Participants	0	6	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

End point title	Overall Survival
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End point description:

The time from treatment start until death due to any cause.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14 ^[2]	31 ^[3]	43 ^[4]	
Units: Months				
median (confidence interval 90%)				
Median (90% CI)	14.09 (9.63 to 999999)	27.33 (19.94 to 999999)	26.41 (17.51 to 999999)	

Notes:

[2] - The upper limit of the confidence interval could not be estimated.

[3] - The upper limit of the confidence interval could not be estimated.

[4] - The upper limit of the confidence interval could not be estimated.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response per Investigator Assessment

End point title	Duration of Response per Investigator Assessment
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End point description:

DoR applies only to patients with a Best Overall Response (BOR) of confirmed CR or PR (RECIST v1.1). For RECIST v1.1, DoR is defined as the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to any cause.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Triplet	Cohort 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10 ^[5]	1 ^[6]		
Units: Months				
median (confidence interval 90%)				
Median (90% CI)	4.21 (2.79 to 999999)	4.50 (0 to 999999)		

Notes:

[5] - The upper limit of the Confidence interval could not be estimated.

[6] - As there was only one subject analyzed, the confidence interval cannot be estimated.

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response Per Central Review

End point title	Duration of Response Per Central Review
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End point description:

DoR applies only to patients with a BOR of confirmed CR or PR (RECIST v1.1). For RECIST v1.1, DOR is defined as the time from the date of the first documented response (CR or PR) to the date of first documented progression, or death due to any cause.

End point type	Secondary
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End point timeframe:

Baseline, every 6 weeks until end of treatment, every 3 months thereafter up to 1 year after treatment (if not progressed at end of treatment)

End point values	Cohort 1 Triplet			
Subject group type	Reporting group			
Number of subjects analysed	6 ^[7]			
Units: Months				
median (confidence interval 90%)				
Median (90% CI)	6.36 (4.17 to 999999)			

Notes:

[7] - The upper limit of the confidence interval could not be estimated.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with AEs Leading to Discontinuation of Study Drug

End point title	Number of Patients with AEs Leading to Discontinuation of Study Drug
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End point description:

Evaluation of number of participants with Adverse Events leading to leading to discontinuation of study drug

End point type	Secondary
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End point timeframe:

During study treatment and up to 30 days after last administration of study drug (median duration of zenocutuzumab exposure was 6.0 weeks for Cohort 1 doublet, 19.3 weeks for Cohort 1 triplet and 11.8 weeks for Cohort 2).

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	39	50	
Units: Count of Participants				
Count of Participants	0	1	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with AEs of Special Interest (AESI)

End point title	Number of Patients with AEs of Special Interest (AESI)
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End point description:

AESIs for MCLA-128 combinations include:

Infusion-related reactions (for any antibodies, known AESI for MCLA-128) Cardiotoxicity (anti-Human Epidermal Growth Factor Receptor (HER)2 therapy) Diarrhea (anti-HER2 therapy) Myelosuppression (vinorelbine)

End point type	Secondary
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End point timeframe:

During study treatment and up to 30 days after last administration of study drug (median duration of zenocutuzumab exposure was 6.0 weeks for Cohort 1 doublet, 19.3 weeks for Cohort 1 triplet and 11.8 weeks for Cohort 2).

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	39	50	
Units: Count of Participants				
Cardiotoxicity (anti-HER2 therapy)	1	3	0	
Diarrhea (anti-HER2 therapy)	7	28	17	
Infusion-Related Reaction	1	7	12	

Myelosuppression (vinorelbine)	0	18	0	
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Statistical analyses

No statistical analyses for this end point

Secondary: Anti-Drug Antibodies Serum Titers

End point title	Anti-Drug Antibodies Serum Titers
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End point description:

Number of patients with anti-drug antibodies at baseline and on treatment

End point type	Secondary
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End point timeframe:

Pre-dose for each of cycles 1, 3 and 5, and every 4 cycles thereafter, and at the End of Treatment visit.

End point values	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	15	39	50	
Units: Count of Participants				
Baseline Anti-Drug Antibody-Negative	12	29	46	
Baseline, ADA-Positive	3	9	3	
On-treatment, evaluable	8	32	38	
On-treatment, ADA-Negative	8	32	35	
On-treatment, ADA-Positive	0	0	3	
Treatment-induced ADA	0	0	3	
Treatment-boosted ADA	0	0	0	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Safety was assessed from signature of informed consent until 30 days after the last study drug administration in terms of AEs, SAEs, laboratory abnormalities, electrocardiogram (ECG) and LVEF measurements, and vital signs.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Cohort 1 Doublet
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Reporting group description:

zenocutuzumab + trastuzumab

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Reporting group title	Cohort 1 Triplet
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Reporting group description:

zenocutuzumab + trastuzumab + vinorelbine

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Trastuzumab: humanised IgG1 monoclonal antibody

Vinorelbine: antineoplastic drug of vinca alkaloid family

Reporting group title	Cohort 2
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Reporting group description:

zenocutuzumab + endocrine therapy

Zenocutuzumab: full length IgG1 bispecific antibody targeting HER2 and HER3

Endocrine therapy: same endocrine therapy is administered as the last line of endocrine therapy

Serious adverse events	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)	8 / 39 (20.51%)	9 / 50 (18.00%)
number of deaths (all causes)	0	1	1
number of deaths resulting from adverse events			
Investigations			
Blood calcium increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Cancer pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Seizure			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Febrile Neutropenia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Dysphagia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnea			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			

subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Erysipelas			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Cohort 1 Doublet	Cohort 1 Triplet	Cohort 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 15 (100.00%)	39 / 39 (100.00%)	48 / 50 (96.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	3
Hot flush			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	3 / 50 (6.00%)
occurrences (all)	0	3	3
Hypertension			

subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	6
Hypotension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Orthostatic hypotension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Subclavian vein thrombosis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 15 (26.67%)	18 / 39 (46.15%)	5 / 50 (10.00%)
occurrences (all)	7	28	6
Axillary pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Chest pain			
subjects affected / exposed	1 / 15 (6.67%)	4 / 39 (10.26%)	0 / 50 (0.00%)
occurrences (all)	1	4	0
Chills			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	2 / 50 (4.00%)
occurrences (all)	0	2	2
Fatigue			
subjects affected / exposed	5 / 15 (33.33%)	13 / 39 (33.33%)	11 / 50 (22.00%)
occurrences (all)	5	18	14
Feeling hot			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Gait disturbance			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hyperthermia			

subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Inflammation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Influenza like illness			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Infusion site erythema			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Localised oedema			
subjects affected / exposed	1 / 15 (6.67%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Mucosal inflammation			
subjects affected / exposed	3 / 15 (20.00%)	3 / 39 (7.69%)	2 / 50 (4.00%)
occurrences (all)	4	3	2
Non-cardiac chest pain			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Oedema peripheral			
subjects affected / exposed	1 / 15 (6.67%)	3 / 39 (7.69%)	1 / 50 (2.00%)
occurrences (all)	1	3	1
Pain			
subjects affected / exposed	1 / 15 (6.67%)	2 / 39 (5.13%)	3 / 50 (6.00%)
occurrences (all)	1	2	3
Peripheral swelling			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	0 / 15 (0.00%)	5 / 39 (12.82%)	6 / 50 (12.00%)
occurrences (all)	0	9	8
Sense of oppression			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Temperature regulation disorder			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Reproductive system and breast disorders Breast inflammation subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Breast pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	2 / 50 (4.00%) 2
Cystocele subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Vaginal haemorrhage subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Vulvovaginal discomfort subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 39 (0.00%) 0	0 / 50 (0.00%) 0
Vulvovaginal dryness subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 39 (0.00%) 0	0 / 50 (0.00%) 0
Vulvovaginal inflammation subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1	0 / 39 (0.00%) 0	0 / 50 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	7 / 39 (17.95%) 8	4 / 50 (8.00%) 4
Dyspnoea subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 2	6 / 39 (15.38%) 6	5 / 50 (10.00%) 5
Epistaxis			

subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	2 / 50 (4.00%)
occurrences (all)	0	2	2
Haemoptysis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Nasal congestion			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Oropharyngeal pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Productive cough			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Pulmonary pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Rhinitis allergic			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Upper-airway cough syndrome			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Confusional state			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Depression			
subjects affected / exposed	1 / 15 (6.67%)	3 / 39 (7.69%)	0 / 50 (0.00%)
occurrences (all)	1	4	0

Emotional disorder subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Insomnia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 39 (5.13%) 3	3 / 50 (6.00%) 3
Irritability subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Stress subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 2	0 / 50 (0.00%) 0
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 39 (5.13%) 3	0 / 50 (0.00%) 0
Blood calcium decreased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 4	0 / 50 (0.00%) 0
Blood calcium increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Blood cholesterol increased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Blood magnesium decreased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Blood phosphorus decreased subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Blood potassium decreased			

subjects affected / exposed	1 / 15 (6.67%)	4 / 39 (10.26%)	1 / 50 (2.00%)
occurrences (all)	1	9	1
Blood sodium decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	5	0
Body temperature increased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Ejection fraction decreased			
subjects affected / exposed	1 / 15 (6.67%)	3 / 39 (7.69%)	0 / 50 (0.00%)
occurrences (all)	1	3	0
Electrocardiogram QRS complex abnormal			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Neutrophil count decreased			
subjects affected / exposed	0 / 15 (0.00%)	7 / 39 (17.95%)	0 / 50 (0.00%)
occurrences (all)	0	16	0
Platelet count decreased			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	6	0
Weight decreased			
subjects affected / exposed	1 / 15 (6.67%)	7 / 39 (17.95%)	1 / 50 (2.00%)
occurrences (all)	1	10	1
Weight increased			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
White blood cells urine positive			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Foot fracture			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Humerus fracture			

subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Infusion related reaction			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Procedural dizziness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Aphasia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Burning sensation			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Cognitive disorder			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Dysaesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Dysgeusia			
subjects affected / exposed	0 / 15 (0.00%)	4 / 39 (10.26%)	0 / 50 (0.00%)
occurrences (all)	0	4	0
Headache			

subjects affected / exposed	0 / 15 (0.00%)	7 / 39 (17.95%)	3 / 50 (6.00%)
occurrences (all)	0	7	7
Hypoaesthesia			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Metabolic encephalopathy			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nervous system disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Neuropathy peripheral			
subjects affected / exposed	2 / 15 (13.33%)	6 / 39 (15.38%)	2 / 50 (4.00%)
occurrences (all)	2	8	2
Paraesthesia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	1 / 50 (2.00%)
occurrences (all)	0	4	1
Peripheral motor neuropathy			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Restless legs syndrome			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Somnolence			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Tremor			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Vocal cord paralysis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	11 / 39 (28.21%) 27	1 / 50 (2.00%) 2
Leukopenia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 2	0 / 50 (0.00%) 0
Neutropenia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 2	0 / 50 (0.00%) 0
Thrombocytopenia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 39 (5.13%) 4	0 / 50 (0.00%) 0
Ear and labyrinth disorders			
Tinnitus subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 39 (5.13%) 2	1 / 50 (2.00%) 1
Vertigo subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 3	5 / 50 (10.00%) 8
Eye disorders			
Blepharitis subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Chalazion subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Dry eye subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 39 (5.13%) 2	1 / 50 (2.00%) 1
Eye allergy			

subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Eyelid sensory disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Glaucoma			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Photophobia			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Ulcerative keratitis			
subjects affected / exposed	1 / 15 (6.67%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Vision blurred			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Visual acuity reduced			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Visual impairment			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	1 / 15 (6.67%)	9 / 39 (23.08%)	6 / 50 (12.00%)
occurrences (all)	1	11	8
Abdominal pain upper			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	7 / 50 (14.00%)
occurrences (all)	0	1	7
Aphthous ulcer			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Colitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	2 / 15 (13.33%)	12 / 39 (30.77%)	6 / 50 (12.00%)
occurrences (all)	2	15	6
Diarrhoea			
subjects affected / exposed	7 / 15 (46.67%)	28 / 39 (71.79%)	17 / 50 (34.00%)
occurrences (all)	12	46	29
Dry mouth			
subjects affected / exposed	2 / 15 (13.33%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Dyspepsia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Dysphagia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	3	0
Gastritis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain			
subjects affected / exposed	1 / 15 (6.67%)	2 / 39 (5.13%)	1 / 50 (2.00%)
occurrences (all)	1	2	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Haemorrhoids			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypoaesthesia oral			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Malabsorption			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	2	0

Mouth ulceration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nasal discharge discolouration			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	3 / 15 (20.00%)	18 / 39 (46.15%)	14 / 50 (28.00%)
occurrences (all)	4	23	17
Oesophageal pain			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Oesophagitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Oral dysaesthesia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Rectal haemorrhage			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Stomatitis			
subjects affected / exposed	0 / 15 (0.00%)	4 / 39 (10.26%)	3 / 50 (6.00%)
occurrences (all)	0	4	3
Tootache			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Ulcerative gastritis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	4 / 15 (26.67%)	6 / 39 (15.38%)	4 / 50 (8.00%)
occurrences (all)	4	7	5
Skin and subcutaneous tissue disorders			
Alopecia			

subjects affected / exposed	1 / 15 (6.67%)	5 / 39 (12.82%)	2 / 50 (4.00%)
occurrences (all)	1	5	2
Dry skin			
subjects affected / exposed	2 / 15 (13.33%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Erythema			
subjects affected / exposed	1 / 15 (6.67%)	1 / 39 (2.56%)	2 / 50 (4.00%)
occurrences (all)	1	1	2
Hyperhidrosis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nail discolouration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Nail disorder			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Onychoclasia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Onycholysis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Pruritus			
subjects affected / exposed	1 / 15 (6.67%)	3 / 39 (7.69%)	1 / 50 (2.00%)
occurrences (all)	1	3	1
Rash			
subjects affected / exposed	2 / 15 (13.33%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	2	1	1
Rash erythematous			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Rash maculopapular			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin fissures			

subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	2 / 50 (4.00%) 2
Skin ulcer subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Telangiectasia subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Renal and urinary disorders			
Dysuria subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	0 / 39 (0.00%) 0	0 / 50 (0.00%) 0
Haematuria subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 2
Stress urinary incontinence subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	1 / 39 (2.56%) 1	0 / 50 (0.00%) 0
Urinary incontinence subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	2 / 39 (5.13%) 2	0 / 50 (0.00%) 0
Urinary tract pain subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Endocrine disorders			
Hyperthyroidism subjects affected / exposed occurrences (all)	0 / 15 (0.00%) 0	0 / 39 (0.00%) 0	1 / 50 (2.00%) 1
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2	2 / 39 (5.13%) 3	5 / 50 (10.00%) 8
Back pain subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 4	3 / 39 (7.69%) 3	4 / 50 (8.00%) 6
Bone pain			

subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	2
Enthesopathy			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Flank pain			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	3
Mobility decreased			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)	6 / 39 (15.38%)	4 / 50 (8.00%)
occurrences (all)	1	6	4
Muscular weakness			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 15 (0.00%)	5 / 39 (12.82%)	3 / 50 (6.00%)
occurrences (all)	0	8	5
Neck pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Osteopenia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	2 / 50 (4.00%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	2 / 50 (4.00%)
occurrences (all)	0	2	3
Pain in jaw			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Spinal pain			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			

Abscess limb			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	4
Cellulitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Corona virus infection			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Erysipelas			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Folliculitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Laryngitis			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Lung infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Mastitis fungal			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

Nail infection			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	2 / 50 (4.00%)
occurrences (all)	0	2	3
Oral candidiasis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Oral fungal infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Paronychia			
subjects affected / exposed	0 / 15 (0.00%)	2 / 39 (5.13%)	1 / 50 (2.00%)
occurrences (all)	0	4	1
Pharyngitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Rash pustular			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	1 / 15 (6.67%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	2
Sinusitis			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Skin infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	2 / 50 (4.00%)
occurrences (all)	0	1	2
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)	6 / 39 (15.38%)	2 / 50 (4.00%)
occurrences (all)	3	9	2

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 15 (20.00%)	6 / 39 (15.38%)	4 / 50 (8.00%)
occurrences (all)	3	11	4
Dehydration			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hypoglycaemia			
subjects affected / exposed	0 / 15 (0.00%)	0 / 39 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Iron deficiency			
subjects affected / exposed	0 / 15 (0.00%)	1 / 39 (2.56%)	0 / 50 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 April 2018	Protocol MCLA-128-CL01, Version 2.0. Specification of the modality of treatment assignment in Cohort 1 once the doublet and triplet cohorts are both open. Clarification of inclusion criteria. Clarification of cardiac follow-up assessments. Correction of incoherence in table of assessments. Addition of compliance definition for endocrine therapy. Clarification of NCI-CTCAE v4.03 hyperlink and SAE/SUSAR reporting procedures. Correction of Appendix 3 LVEF algorithm. Minor modifications for text corrections/clarifications/coherence.
06 September 2018	MCLA-128-CL02 Protocol Version 3.0 Modification of the number of previous lines of therapy. The number of lines of systemic treatment permitted prior to study entry was increased in Cohort 1 and Cohort 2. Cohort 1: Patients with up to 5 lines of anti-HER2 therapies previously given in the metastatic setting will be permitted. The original protocol states that up to 4 lines are allowed but doesn't specify the setting of the disease. Cohort 2: Patients with up to 3 lines of endocrine and 2 lines of chemotherapy previously given in the metastatic setting will be permitted. The original protocol states that up to 2 lines of hormone therapy and 1 line of chemotherapy in the metastatic setting are allowed. Modification of the criterion for measurable/non-measurable disease in Cohort 2 to include bone- only disease with lytic or mixed lesions. Modification of the permitted time frame for tissue collection of biomarkers. The amendment allows for the testing of archival tumor tissue collected within 24 months prior to screening. Clarification of the wording of the primary objective. Minor modifications for text corrections/clarifications/coherence. Change of contact details for the Sponsor Medical Expert.
30 April 2021	MCLA-128-CL02 Protocol Version 4.0 Modification of duration of LVEF Follow-up. Sponsor proposed stopping the follow-up period for each patient 1 year after their last MCLA-128 dose instead of 2 years after the last dose. Clarification of duration of provision of MCLA-128 following disease progression. Removal of ADA and PK sample collection. Collection of blood samples for pharmacokinetics and immunogenicity analyses are no longer necessary as sufficient samples have been collected to date to characterize these parameters for MCLA- 128 treatment, thereby avoiding unnecessary sample collection for patients. Addition of 1 mL vials of vinorelbine. For patients in Cohort 1, vinorelbine may be provided in 1-mL vials in addition to the 5-mL vials. Update of IMP details.

11 April 2022	MCLA-128-CL02 Version 5.0 Study Duration: The initial anticipated "Completion of the data analysis" date of October 2019 has been exceeded due to a handful of patients who still benefit from the study drug. Protocol Version 5 .0 provides a new expected date. Update to reduce the study procedures. The Sponsor proposed for the remaining patients who have been on treatment for at least 24 months in this study, to reduce the study procedures in order to decrease their burden, but to offer the opportunity to continually derive benefit from the Study drug. LVEF and ECG: Updated from every 4 cycles (3 months) to every 6 months due to the current Safety Profile and the focus on the appropriate level of safety surveillance. Tumor assessments: Updated from every 6 weeks to every 12 weeks to reduce the patient's burden, but still allows the possibility to have a Tumor Assessment done in between in case of symptomatic deterioration signs or signs of disease progression. Efficacy assessments central review: Enough independent central analysis of patient imaging has been completed and additional assessment of imaging for those patients currently on treatment for at least 24 months is no longer required. Therefore, central review of imaging by an independent radiologist (s) for all patients on- study is no longer applicable as of Protocol Version 5.0. The Sponsor relies on the local Investigator assessment and continued focus will be on the appropriate level of safety surveillance. Biomarkers: Enough biomarker data has been accumulated from all patients treated on the trial. Therefore the additional data from the few patients who have been on treatment for 24 months is not needed as per Protocol Version 5 .0.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported