Clinical trial results:
A MULTICENTER, DOUBLE-BLIND, RANDOMIZED, PARALLEL-GROUP, PHASE III STUDY OF THE EFFICACY AND SAFETY OF HERCULES PLUS TAXANE VERSUS HERCEPTIN® PLUS TAXANE AS FIRST LINE THERAPY IN PATIENTS WITH HER2-POSITIVE METASTATIC BREAST CANCER

Summary

EudraCT number	2011-001965-42
Trial protocol	DE HU BG CZ SK LV ES GR AT
Global end of trial date	03 August 2018

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	MYL-Her-3001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02472964
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Mylan GmbH
Sponsor organisation address	Thurgauerstrasse 40, Zurich, Switzerland, 8050
Public contact	Senior Clinical Project Manager, Gail Tribble, Mylan Inc. 1000 Mylan Boulevard Canonsburg, PA, 15317 USA, 1 7244856124 , gail.tribble@mylan.com
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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	03 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Part 1: To compare the independently assessed best overall response rate (ORR) (according to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 criteria) at Week 24 with MYL-1402O plus taxane versus Herceptin® plus taxane in patients who have not received previous first line treatment for HER2+ MBC.
Part 2: To continue to evaluate the safety and tolerability profile of MYL-1402O and Herceptin® given as a single agent. And to compare the immunogenicity of MYL-1402O and Herceptin® by examining clinical immunogenic response.
To compare the clinical activity at Week 48 between treatment arms by measuring PFS, OS and duration of response (DR), and OS at 36 months or after 240 deaths, whichever occurs first, as observed from the time of randomization of the last patient.

Protection of trial subjects:

Monitoring of adverse events and serious adverse events. Regularly scheduled IDMC review.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 July 2012
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	Bulgaria: 2
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Slovakia: 3
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Hungary: 14
Country: Number of subjects enrolled	Latvia: 6
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 151
Country: Number of subjects enrolled	Philippines: 51
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	South Africa: 15
Country: Number of subjects enrolled	Thailand: 47
Country: Number of subjects enrolled	Ukraine: 55

Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Georgia: 62
Country: Number of subjects enrolled	India: 55
Worldwide total number of subjects	500
EEA total number of subjects	54

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)	415
From 65 to 84 years	85
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

500 subjects enrolled at 95 sites across Eastern Europe, Russia, Asia Pacific, Africa aand South America. The intent-to-treat1 (ITT1) population of 458 was used to determine Primary Outcome of Overall Response Rate.

Pre-assignment

Screening details:

The primary efficacy analysis was derived from ITT1 population 230 (MYL-1401O) + 228 (Herceptin) = 458. Safety analysis was derived from the Safety Population 247(MYL-1401O) + 246 (Herceptin) = 493. Total Randomized population 249 (MYL-1401O) + 251 (Herceptin) = 500.

Period 1

Period 1 title	Part I (up to week 24)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Herceptin® + Taxane

Arm description:

Part 1: Herceptin® (trastuzumab) intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	Herceptin®
Other name	
Pharmaceutical forms	Powder for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab 8mg/kg IV over 90 minutes x 1 then Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

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

Dosage and administration details:

Paclitaxel 80mg/m2 IV over 60 minutes weekly.

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

Dosage and administration details:

Docetaxel 75mg/m2 IV over 60 minutes on day 1 of a 3 week cycle

Arm title	MYL-1401O + Taxane

Arm description:

Part 1: MYL-1401O Intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2

intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint.

Arm type	Experimental
Investigational medicinal product name	MYL-1401O
Investigational medicinal product code	trastuzumab
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

MYL-1401O 8mg/kg Iv over 90 minutes x 1 then MYL-1401O Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

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

Dosage and administration details:

Paclitaxel 80mg/m2 IV over 60 minutes weekly.

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

Dosage and administration details:

Docetaxel 75mg/m2 IV over 60 minutes on day 1 of a 3 week cycle

Number of subjects in period 1	Herceptin® + Taxane	MYL-1401O + Taxane
Started	251	249
Protocol Amendment 2	228	230
Completed	171	185
Not completed	80	64
Adverse event, serious fatal	3	6
Physician decision	5	1
Consent withdrawn by subject	9	2
Disease progression	58	49
unknown	2	1
Adverse event, non-fatal	2	4
Death before treatment start	1	-
Lost to follow-up	-	1

Period 2

Period 2 title	Part 2 (Week 24-week 48)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Herceptin®

Arm description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Herceptin® (trastuzumab) alone once every 3 weeks until DP or subject withdrawal .

Arm type	Active comparator
Investigational medicinal product name	Herceptin®
Investigational medicinal product code	trastuzumab
Other name	
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

Arm title	Myl-1401O

Arm description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Myl 1401O alone once every 3 weeks until DP or subject withdrawal.

Arm type	Experimental
Investigational medicinal product name	MYL-1401O
Investigational medicinal product code	trastuzumab
Other name	Hercules
Pharmaceutical forms	Powder for concentrate for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

MYL-1401O Trastuzumab 6 mg/kg IV over 30 minutes every 3 weeks

Number of subjects in period 2[1]	Herceptin®	Myl-1401O
Started	163	179
Completed	98	116
Not completed	65	63
Adverse event, serious fatal	-	1
Physician decision	1	1
Consent withdrawn by subject	3	1
Disease progression	52	56
Adverse event, non-fatal	4	2
Other	3	-
Lost to follow-up	2	1

Protocol deviation	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: A total of 14 patients who completed Part 1 of the study did not enter Part 2 (MYL-1401O 6 patients, Herceptin 8 patients).
Reasons for not entering Part 2 monotherapy were disease progression (MYL-1401O 4 patients/Herceptin 4 patients), withdrawal of consent (2/1), death (0/1), AE not due to disease progression (0/1), no reason (0/1).

Baseline characteristics

Reporting groups	
Reporting group title	Herceptin® + Taxane
Reporting group description:	
Part 1: Herceptin® (trastuzumab) intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint.	
Reporting group title	MYL-1401O + Taxane
Reporting group description:	
Part 1: MYL-1401O Intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint.	

Reporting group values	Herceptin® + Taxane	MYL-1401O + Taxane	Total
Number of subjects	251	249	500
Age categorical			
The primary efficacy endpoint analysis was conducted in the intention to treat (IIT1)population (only those patients randomized after the second amendment of the protocol)			
Units: Subjects			
18-49 years	93	80	173
>/= 50 years	158	169	327
Gender categorical			
Units: Subjects			
Female	251	249	500
Male	0	0	0

End points

End points reporting groups

Reporting group title	Herceptin® + Taxane
Reporting group description:	
Part 1: Herceptin® (trastuzumab) intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint.	
Reporting group title	MYL-1401O + Taxane
Reporting group description:	
Part 1: MYL-1401O Intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint.	
Reporting group title	Herceptin®
Reporting group description:	
Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Herceptin® (trastuzumab) alone once every 3 weeks until DP or subject withdrawal .	
Reporting group title	Myl-1401O
Reporting group description:	
Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Myl 1401O alone once every 3 weeks until DP or subject withdrawal.	

Primary: Compare Best Overall Response Rate (ORR) (According to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 Criteria) at Week 24 of MYL-1401O Plus Taxane Versus Herceptin® Plus Taxane in the ITT1 Population

End point title	Compare Best Overall Response Rate (ORR) (According to Response Evaluation Criteria in Solid Tumor [RECIST] 1.1 Criteria) at Week 24 of MYL-1401O Plus Taxane Versus Herceptin® Plus Taxane in the ITT1 Population
End point description:	
Tumor measurements were performed by centralized blinded reviewers using RECIST 1.1 criteria. Per RECIST 1.1: Complete Response (CR): Disappearance of all target lesions. Any pathological lymph node must have reduction in short axis to <10 mm.Partial Response (PR): >/= 30% decrease sum of the diameters of target lesions from baseline sum diameters. Progressive Disease (PD): </= 20% increase in the sum of the diameters of target lesions, from the smallest sum on study with at least a 5 mm absolute increase in the sum of all lesions. The appearance of one or more new lesions* denotes disease progression. Stable Disease (SD): Neither sufficient decrease or increase. Evaluation of Non-Target Lesions Complete Response (CR): Disappearance of all non-target lesions. Non-complete Response/Non-Progressive Disease: Persistence of one or more non-target lesions. Progressive Disease (PD): Substantial, unequivocal progression of existing non-target lesions.	
End point type	Primary
End point timeframe:	
from time of First treatment to week 24	

End point values	Herceptin® + Taxane	MYL-1401O + Taxane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228[1]	230[2]		
Units: participants				
Complete Response	0	3		
Partial Response	146	157		

Stable Disease	49	48		
Progressive Disease	20	9		
Not Evaluable	13	13		

Notes:

[1] - ITT1

[2] - ITT1

Statistical analyses

Statistical analysis title	Difference of Best ORR* at week 24

Statistical analysis description:

*ORR = Overall Response Rate
The following hypotheses were set up with the EMA's equivalence margin of (-15%, 15%):
H0: (RT - RC ≤ -15%) or (RT - RC ≥ 15%)
H1: -15% < (RT - RC) < 15%,
where, RT and RC were the best ORR of test (MYL-1401O) and control (Herceptin®), respectively.
A two-sided 95% CI for the difference of the best ORRs at Week 24 was calculated. Equivalence was declared if the CI was completely within the equivalence range of (-15%, 15%)

Comparison groups	Herceptin® + Taxane v MYL-1401O + Taxane
Number of subjects included in analysis	458
Analysis specification	Pre-specified
Analysis type	equivalence
Parameter estimate	Risk difference (RD)
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.08
upper limit	14.04

Secondary: PFS (Progression-Free-Survival) at week 48

End point title	PFS (Progression-Free-Survival) at week 48

End point description:

To compare the clinical activity at Week 48 between treatment arms by measuring PFS, as observed from the time of randomization.

End point type	Secondary

End point timeframe:

week 48

End point values	Herceptin® + Taxane	MYL-1401O + Taxane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	230		
Units: Months				
median (confidence interval 95%)	11.1 (8.60 to 11.20)	11.1 (8.81 to 11.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: DR (duration of response) at week 48

End point title	DR (duration of response) at week 48

End point description:

To compare the clinical activity at Week 48 between treatment arms by measuring duration of response (DR), as observed from the time of randomization.

End point type	Secondary

End point timeframe:

48 weeks

End point values	Herceptin® + Taxane	MYL-1401O + Taxane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228[3]	230[4]		
Units: months				
median (confidence interval 95%)	9.7 (7.68 to 9.87)	9.7 (7.38 to 9.89)		

Notes:

[3] - number of patients with data available: 182

[4] - number of patients with data available: 191

Statistical analyses

No statistical analyses for this end point

Secondary: OS (Overall Survival) at month 36

End point title	OS (Overall Survival) at month 36

End point description:

To compare the clinical activity between treatment arms by measuring OS at 36 months as observed from the time of randomization of the last patient.

End point type	Secondary

End point timeframe:

36 months

End point values	Herceptin® + Taxane	MYL-1401O + Taxane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	230		
Units: months				
median (confidence interval 95%)	30.2 (25.00 to 39.86)	35.0 (26.75 to 39.88)		

Statistical analyses

No statistical analyses for this end point

Secondary: TTP (Time to Tumor Progression) at week 48

End point title	TTP (Time to Tumor Progression) at week 48

End point description:

To compare the clinical activity at Week 48 between treatment arms by measuring TTP, as observed from the time of randomization.

End point type	Secondary

End point timeframe:

week 48

End point values	Herceptin® + Taxane	MYL-1401O + Taxane		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	230		
Units: months				
median (confidence interval 95%)	11.1 (8.88 to 11.20)	11.1 (8.83 to 11.20)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Active AE reporting period is from first dose until 28 days (+/- 7 days) after last administered dose of IMP per patient. SAEs should be reported any time after the active reporting period when SAE is considered related to study drug.

Adverse event reporting additional description:

Investigator is responsible for detection and documentation of events meeting the criteria of an AE/SAE. At each visit, the patient will be allowed time to report any issues since the last evaluation.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	Herceptin® + Taxane (up to wk 24)

Reporting group description:

Part 1: Herceptin® (trastuzumab) intravenously+ paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigators choice) for 8 cycles then evaluate for primary endpoint. Timeframe: up to week 24

Reporting group title	MYL-1401O + Taxane (up to wk 24)

Reporting group description:

Part 1: MYL-1401O intravenously + paclitaxel 80 mg/m2 weekly intravenously or docetaxel 75 mg/m2 intravenously once every three weeks (investigator's choice) for 8 cycles then evaluate for primary endpoint. Timeframe: up to week 24

Reporting group title	Herceptin® (wk 25 up to 36 months)

Reporting group description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Herceptin® (trastuzumab) alone once every 3 weeks until DP or subject withdrawal. Timeframe: week 25 up to 36 months

Reporting group title	MYL-1401O (wk 25 up to 36 months)

Reporting group description:

Part 2: If SD or PR, CR at cycle 9 (week 24) proceed to Myl 1401O alone once every 3 weeks until DP or subject withdrawal. Timeframe: week 25 up to 36 months

Serious adverse events	Herceptin® + Taxane (up to wk 24)	MYL-1401O + Taxane (up to wk 24)	Herceptin® (wk 25 up to 36 months)
Total subjects affected by serious adverse events			
subjects affected / exposed	90 / 246 (36.59%)	95 / 247 (38.46%)	10 / 164 (6.10%)
number of deaths (all causes)	4	4	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Hepatocellular carcinoma			

subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Thrombophlebitis superficial			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Hyperthermia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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

Malaise			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Multi-organ disorder	Additional description: Multi-organ failure		
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pyrexia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	0 / 164 (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
Drug hypersensitivity			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Hypersensitivity			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pneumonitis			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 1	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Pulmonary embolism			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Pulmonary haemorrhage			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Respiratory failure			
subjects affected / exposed	1 / 246 (0.41%)	2 / 247 (0.81%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	1 / 1	1 / 2	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood uric acid increased			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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

White blood cell count decreased			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Infusion related reaction			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Cardiac failure			
subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Carditis			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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	10 / 246 (4.07%)	11 / 247 (4.45%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 11	0 / 13	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	12 / 246 (4.88%)	5 / 247 (2.02%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 13	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	62 / 246 (25.20%)	68 / 247 (27.53%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 78	0 / 92	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Anaemia			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lymphopenia			

subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Anal fissure			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Diarrhoea			
subjects affected / exposed	4 / 246 (1.63%)	3 / 247 (1.21%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal ulcer perforation			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Gastritis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Gastrointestinal toxicity			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Nausea			
subjects affected / exposed	0 / 246 (0.00%)	2 / 247 (0.81%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal perforation			

subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Vomiting			
subjects affected / exposed	2 / 246 (0.81%)	1 / 247 (0.40%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	1 / 2	1 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhoids			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Cholelithiasis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Hepatic failure			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bile duct stone			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 246 (0.41%)	1 / 247 (0.40%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue			

disorders			
Pathological fracture			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 246 (0.41%)	3 / 247 (1.21%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Mastitis			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Paronychia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Pneumonia			
subjects affected / exposed	5 / 246 (2.03%)	4 / 247 (1.62%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Rectal abscess			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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

Renal abscess			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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	3 / 246 (1.22%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Tubo-ovarian abscess			
subjects affected / exposed	0 / 246 (0.00%)	0 / 247 (0.00%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Urinary tract infection			
subjects affected / exposed	1 / 246 (0.41%)	2 / 247 (0.81%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 1	1 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	0 / 164 (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
Wound infection			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (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
Metabolism and nutrition disorders			

Hypernatraemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	2 / 246 (0.81%)	2 / 247 (0.81%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	0 / 246 (0.00%)	1 / 247 (0.40%)	1 / 164 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	2 / 246 (0.81%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour lysis syndrome			
subjects affected / exposed	1 / 246 (0.41%)	0 / 247 (0.00%)	0 / 164 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

Serious adverse events	MYL-1401O (wk 25 up to 36 months)		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 179 (5.59%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphangiosis carcinomatosa			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatocellular carcinoma			

subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Accelerated hypertension			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Deep vein thrombosis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Peripheral ischaemia			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Thrombophlebitis superficial			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Fatigue			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyperthermia			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Malaise				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Multi-organ disorder	Additional description: Multi-organ failure			
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Immune system disorders				
Anaphylactic reaction				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Drug hypersensitivity				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hypersensitivity				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Dyspnoea				
subjects affected / exposed	2 / 179 (1.12%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 1			
Pleural effusion				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pneumonitis				
subjects affected / exposed	1 / 179 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumothorax spontaneous				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary embolism				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pulmonary haemorrhage				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory failure				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Anxiety				
subjects affected / exposed	1 / 179 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood uric acid increased				
subjects affected / exposed	1 / 179 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ejection fraction decreased				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

White blood cell count decreased				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Femur fracture				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infusion related reaction				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute myocardial infarction				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Carditis				
subjects affected / exposed	1 / 179 (0.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cerebral infarction				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Headache				

subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
Febrile neutropenia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Leukopenia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Neutropenia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancytopenia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Thrombocytopenia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Anaemia				
subjects affected / exposed	0 / 179 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Lymphopenia				

subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Anal fissure			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Duodenal ulcer perforation			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal toxicity			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Rectal perforation			

subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Haemorrhoids			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis chronic			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatic failure			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bile duct stone			
subjects affected / exposed	1 / 179 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue			

disorders			
Pathological fracture			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Mastitis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paronychia			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	2 / 179 (1.12%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Rectal abscess			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Renal abscess			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tubo-ovarian abscess			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			

Hypernatraemia			
subjects affected / exposed	1 / 179 (0.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperuricaemia			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Tumour lysis syndrome			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Herceptin® + Taxane (up to wk 24)	MYL-1401O + Taxane (up to wk 24)	Herceptin® (wk 25 up to 36 months)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	231 / 246 (93.90%)	235 / 247 (95.14%)	119 / 164 (72.56%)
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	21 / 246 (8.54%)	18 / 247 (7.29%)	7 / 164 (4.27%)
occurrences (all)	36	26	12
Aspartate aminotransferase increased			
subjects affected / exposed	22 / 246 (8.94%)	13 / 247 (5.26%)	7 / 164 (4.27%)
occurrences (all)	38	20	10
Ejection fraction decreased			

subjects affected / exposed	3 / 246 (1.22%)	5 / 247 (2.02%)	6 / 164 (3.66%)
occurrences (all)	3	6	8
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	10 / 246 (4.07%)	17 / 247 (6.88%)	1 / 164 (0.61%)
occurrences (all)	18	30	1
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 246 (3.25%)	7 / 247 (2.83%)	9 / 164 (5.49%)
occurrences (all)	10	7	25
Nervous system disorders			
Headache			
subjects affected / exposed	14 / 246 (5.69%)	15 / 247 (6.07%)	23 / 164 (14.02%)
occurrences (all)	18	15	31
Neuropathy peripheral			
subjects affected / exposed	28 / 246 (11.38%)	28 / 247 (11.34%)	9 / 164 (5.49%)
occurrences (all)	43	36	10
Peripheral sensory neuropathy			
subjects affected / exposed	34 / 246 (13.82%)	29 / 247 (11.74%)	2 / 164 (1.22%)
occurrences (all)	39	38	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	40 / 246 (16.26%)	40 / 247 (16.19%)	17 / 164 (10.37%)
occurrences (all)	66	76	39
Leukopenia			
subjects affected / exposed	40 / 246 (16.26%)	40 / 247 (16.19%)	4 / 164 (2.44%)
occurrences (all)	57	62	5
Neutropenia			
subjects affected / exposed	79 / 246 (32.11%)	90 / 247 (36.44%)	6 / 164 (3.66%)
occurrences (all)	114	133	9
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	32 / 246 (13.01%)	28 / 247 (11.34%)	7 / 164 (4.27%)
occurrences (all)	58	61	7
Oedema peripheral			

subjects affected / exposed	28 / 246 (11.38%)	35 / 247 (14.17%)	4 / 164 (2.44%)
occurrences (all)	38	53	4
Pyrexia			
subjects affected / exposed	28 / 246 (11.38%)	21 / 247 (8.50%)	4 / 164 (2.44%)
occurrences (all)	33	27	4
Asthenia			
subjects affected / exposed	40 / 246 (16.26%)	54 / 247 (21.86%)	7 / 164 (4.27%)
occurrences (all)	78	123	8
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	49 / 246 (19.92%)	49 / 247 (19.84%)	2 / 164 (1.22%)
occurrences (all)	69	80	4
Nausea			
subjects affected / exposed	34 / 246 (13.82%)	48 / 247 (19.43%)	6 / 164 (3.66%)
occurrences (all)	60	79	6
Vomiting			
subjects affected / exposed	17 / 246 (6.91%)	25 / 247 (10.12%)	6 / 164 (3.66%)
occurrences (all)	22	41	6
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	16 / 246 (6.50%)	14 / 247 (5.67%)	3 / 164 (1.83%)
occurrences (all)	17	16	5
Dyspnoea			
subjects affected / exposed	17 / 246 (6.91%)	13 / 247 (5.26%)	2 / 164 (1.22%)
occurrences (all)	22	15	2
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	135 / 246 (54.88%)	142 / 247 (57.49%)	5 / 164 (3.05%)
occurrences (all)	162	175	5
Nail disorder			
subjects affected / exposed	20 / 246 (8.13%)	17 / 247 (6.88%)	0 / 164 (0.00%)
occurrences (all)	21	18	0
Rash			
subjects affected / exposed	23 / 246 (9.35%)	21 / 247 (8.50%)	4 / 164 (2.44%)
occurrences (all)	41	26	5
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	11 / 246 (4.47%)	30 / 247 (12.15%)	3 / 164 (1.83%)
occurrences (all)	17	46	3
Bone pain			
subjects affected / exposed	13 / 246 (5.28%)	17 / 247 (6.88%)	3 / 164 (1.83%)
occurrences (all)	23	21	3
Myalgia			
subjects affected / exposed	23 / 246 (9.35%)	23 / 247 (9.31%)	4 / 164 (2.44%)
occurrences (all)	39	45	4
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	4 / 246 (1.63%)	14 / 247 (5.67%)	4 / 164 (2.44%)
occurrences (all)	6	14	4
Urinary tract infection			
subjects affected / exposed	16 / 246 (6.50%)	20 / 247 (8.10%)	5 / 164 (3.05%)
occurrences (all)	26	30	7
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	19 / 246 (7.72%)	13 / 247 (5.26%)	7 / 164 (4.27%)
occurrences (all)	29	15	39
Decreased appetite			
subjects affected / exposed	24 / 246 (9.76%)	21 / 247 (8.50%)	5 / 164 (3.05%)
occurrences (all)	44	56	7

Non-serious adverse events	MYL-1401O (wk 25 up to 36 months)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	121 / 179 (67.60%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	11 / 179 (6.15%)		
occurrences (all)	17		
Aspartate aminotransferase increased			
subjects affected / exposed	9 / 179 (5.03%)		
occurrences (all)	13		
Ejection fraction decreased			

subjects affected / exposed	10 / 179 (5.59%)		
occurrences (all)	13		
Injury, poisoning and procedural complications			
Infusion related reaction			
subjects affected / exposed	0 / 179 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Hypertension			
subjects affected / exposed	12 / 179 (6.70%)		
occurrences (all)	17		
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 179 (10.61%)		
occurrences (all)	25		
Neuropathy peripheral			
subjects affected / exposed	5 / 179 (2.79%)		
occurrences (all)	5		
Peripheral sensory neuropathy			
subjects affected / exposed	5 / 179 (2.79%)		
occurrences (all)	6		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 179 (3.35%)		
occurrences (all)	9		
Leukopenia			
subjects affected / exposed	2 / 179 (1.12%)		
occurrences (all)	3		
Neutropenia			
subjects affected / exposed	2 / 179 (1.12%)		
occurrences (all)	4		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	9 / 179 (5.03%)		
occurrences (all)	11		
Oedema peripheral			

subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) Asthenia subjects affected / exposed occurrences (all)	2 / 179 (1.12%) 2 6 / 179 (3.35%) 6 7 / 179 (3.91%) 7		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 8 / 179 (4.47%) 13 8 / 179 (4.47%) 10 10 / 179 (5.59%) 11		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all)	 9 / 179 (5.03%) 12 6 / 179 (3.35%) 8		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) Nail disorder subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all)	 7 / 179 (3.91%) 7 1 / 179 (0.56%) 1 6 / 179 (3.35%) 6		
Musculoskeletal and connective tissue disorders			

Arthralgia subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all)	9 / 179 (5.03%) 12 4 / 179 (2.23%) 4 7 / 179 (3.91%) 10		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all)	10 / 179 (5.59%) 12 6 / 179 (3.35%) 14		
Metabolism and nutrition disorders Hyperglycaemia subjects affected / exposed occurrences (all) Decreased appetite subjects affected / exposed occurrences (all)	5 / 179 (2.79%) 9 4 / 179 (2.23%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 September 2013	Amendment 2 addressed the following: - Incorporate the current standards of care practices for treatment of metastatic breast cancer (MBC); - Address delays related to the centrally performed IHC testing for patient randomization by switching the laboratory vendor to Phenopath Laboratories to avoid continued protocol violations; - Remove the requirement of the central safety laboratory and move solely to local laboratory testing for safety labs for treatment decisions; - Adjust and control for the global variances in MBC patients through appropriate stratification at randomization; - Provide an adaptable study design allowing an interim sample size estimation to ensure a sufficiently statistically powered clinical trial; and - Address the need for subject treatment until disease progression (i.e., Identified as a continuation study outlined in Amendment 1).
10 April 2015	Amendment 6: The goal of this protocol amendment was to 1) reflect updates in the current SmPC of Herceptin® 2) modify some operational procedures that allow appropriate management of the trial and 3) update the Data Analysis and Statistical Methods section to reflect updates made to the SAP. Additionally, content of the document "Errata" dated 21 November 2013, has been incorporated in this amended global protocol.
03 March 2017	Amendment 7: The goal of this protocol amendment was to 1) include the analysis for best ORR difference and to describe the associated statistical assumptions as indicated in the statistical analysis plan; and 2) modify select operational procedures that allow appropriate management of the trial. Additionally, content of the document "Errata," dated 21 November 2013, has been incorporated in this amended global protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
23 July 2013	Following careful evaluation and review of the current study protocol and the need to address scientific advice from both, the U.S. Food & Drug Administration and the European Medicines Agency, Mylan has decided to put a temporary hold on site initiations and patient screening (patients currently in screening with a signed consent form will be allowed to proceed to randomization, if eligible) into the Her-3001 clinical trial effective immediately until the amendment to the protocol is approved and the study has been re-initiated.	13 September 2013

Notes:

Limitations and caveats

None reported