Clinical trial results:
A Randomized Phase 3, Multicenter, Open-Label Study Comparing TH-302 in Combination with Doxorubicin vs. Doxorubicin Alone in Subjects with Locally Advanced Unresectable or Metastatic Soft Tissue Sarcoma.

Summary

EudraCT number	2011-003145-17
Trial protocol	ES DE HU PL BE IT AT DK
Global end of trial date	19 October 2015

Results information

Result version number	v1 (current)
This version publication date	08 December 2017
First version publication date	08 December 2017

Trial information

Trial identification

Sponsor protocol code	TH-CR-406/SARC021

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01440088
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Molecular Templates
Sponsor organisation address	9301 Amberglen Blvd, Suite 100, Austin, United States, TX 78729
Public contact	David J. Valacer, MD Chief Medical Officer, Molecular Templates, 201 961-4477, david.valacer@mtem.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	19 October 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2015
Global end of trial reached?	Yes
Global end of trial date	19 October 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

1. To evaluate the efficacy of TH-302 in combination with doxorubicin as determined by overall survival (OS) in subjects with locally advanced unresectable or metastatic soft tissue sarcoma previously untreated with chemotherapy (neoadjuvant and adjuvant chemotherapy permitted) compared with doxorubicin
alone.
2. To assess the safety of TH-302 in combination with doxorubicin in subjects with locally advanced unresectable or metastatic soft tissue sarcoma compared with doxorubicin alone.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and with all appropriate national and local regulations and guidances, including United States (US) Code of Federal Regulations (CFRs) on Good Clinical Practices (GCP) and the International Conference on Harmonisation (ICH) guideline E6: Good Clinical Practices. All subjects eligible for screening signed the consent prior to the performance of any non-routine procedures. Before undertaking any study-related procedure, the investigators or their designees explained the nature and purpose of the study, participation and termination conditions, and risks and benefits to the subject.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 September 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 7
Country: Number of subjects enrolled	Poland: 14
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Denmark: 14
Country: Number of subjects enrolled	France: 38
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 39
Country: Number of subjects enrolled	Italy: 13
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Russian Federation: 16

Country: Number of subjects enrolled	United States: 383
Worldwide total number of subjects	640
EEA total number of subjects	211

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)	431
From 65 to 84 years	209
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study had planned to enroll 620 subjects, however, 640 subjects were enrolled in a 1:1 ratio (317 in TH-302 + doxorubicin arm and 323 in doxorubicin alone arm). Nineteen subjects did not receive treatment and thus, 621 subjects received the study drug (313 to the TH-302 plus doxorubicin arm and 308 to the doxorubicin alone arm).

Pre-assignment

Screening details:

Screening took place within 3 weeks prior to Cycle 1 Day 1.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Doxorubicin

Arm description:

Subjects received doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle; doxorubicin was not administered after 6 cycles of treatment. Doxorubicin administration was to start between 2 to 4 hours after completion of the TH-302 infusion when used in combination with TH-302

Arm type	Active comparator
Investigational medicinal product name	Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion, Injection
Routes of administration	Intravenous bolus use , Intravenous drip use

Dosage and administration details:

Subjects received doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous IV infusion over 6-96 hours on Day 1 of every 21-day cycle; doxorubicin was not administered after 6 cycles of treatment.

Arm title	TH-302 + Doxorubicin

Arm description:

Subjects received TH-302 (300 mg/m2) by IV infusion over 30-60 minutes on Days 1 and 8 of a 21-day cycle and doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle 2 started 2 to 4 hours after completion of TH-302 administration.

Arm type	Experimental
Investigational medicinal product name	TH-302 + Doxorubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Subjects received TH-302 (300 mg/m2) by IV infusion over 30-60 minutes on Days 1 and 8 of a 21-day cycle and doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle 2 started 2 to 4 hours after completion of TH-302 administration.

Number of subjects in period 1	Doxorubicin	TH-302 + Doxorubicin
Started	323	317
Completed	170	160
Not completed	153	157
Ongoing	-	9
Early Termination	153	148

Baseline characteristics

Reporting groups	
Reporting group title	Doxorubicin
Reporting group description:	
Subjects received doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle; doxorubicin was not administered after 6 cycles of treatment. Doxorubicin administration was to start between 2 to 4 hours after completion of the TH-302 infusion when used in combination with TH-302	
Reporting group title	TH-302 + Doxorubicin
Reporting group description:	
Subjects received TH-302 (300 mg/m2) by IV infusion over 30-60 minutes on Days 1 and 8 of a 21-day cycle and doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle 2 started 2 to 4 hours after completion of TH-302 administration.	

Reporting group values	Doxorubicin	TH-302 + Doxorubicin	Total
Number of subjects	323	317	640
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	220	211	431
From 65-84 years	103	106	209
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	56.7	57.4	
standard deviation	± 13.07	± 12.83	-
Gender categorical Units: Subjects			
Female	172	173	345
Male	151	144	295

End points

End points reporting groups

Reporting group title	Doxorubicin

Reporting group description:

Subjects received doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle; doxorubicin was not administered after 6 cycles of treatment. Doxorubicin administration was to start between 2 to 4 hours after completion of the TH-302 infusion when used in combination with TH-302

Reporting group title	TH-302 + Doxorubicin

Reporting group description:

Subjects received TH-302 (300 mg/m2) by IV infusion over 30-60 minutes on Days 1 and 8 of a 21-day cycle and doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle 2 started 2 to 4 hours after completion of TH-302 administration.

Primary: Overal survivial (OS)

End point title	Overal survivial (OS)

End point description:

Overall survival was defined as the duration from date of randomization to date of death by any cause. All randomized subjects (intent-to-treat (ITT) population) were included for the analysis. The analysis was performed when 423 deaths were reported. Overall survival was measured from the date of randomization to death from any cause.

End point type	Primary

End point timeframe:

Every 3 months until up to 3 years from study entry until death/lost to follow-up/study closure. After discontinuation of study treatment without progressive disease: Every 9 weeks for first 18 weeks & then every 9 to 15 weeks thereafter/more frequently.

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	317		
Units: Days				
median (confidence interval 95%)				
OS (Median value)	578 (493 to 681)	561 (475 to 672)		
OS rates at 6 months (Point Estimate)	83 (78 to 87)	85 (81 to 89)		
OS rates at 12 months (Point Estimate)	65 (60 to 70)	65 (59 to 70)		
OS rates at 18 months (Point Estimate)	53 (47 to 58)	50 (45 to 56)		
OS rates at 24 months (Point Estimate)	43 (37 to 48)	40 (35 to 46)		
OS rates at 36 months (Point Estimate)	29 (23 to 35)	19 (12 to 28)		

Statistical analyses

Statistical analysis title	Overall survival

Statistical analysis description:

Kaplan-Meier formula was used to estimate survival. Estimates and confidence intervals were calculated by the product limit method and Greenwood's formula for the variance. A two-sided log-rank test stratified by randomization stratification factors was used to test the significance between the two treatment arms.

Comparison groups	Doxorubicin v TH-302 + Doxorubicin
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.5267
Method	Two-sided log-rank test
Parameter estimate	Hazard ratio (HR)
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.878
upper limit	1.289
Variability estimate	Standard error of the mean
Dispersion value	1.064

Primary: Safety of TH-302 in combination with doxorubicin compared with doxorubicin alone by assessment of the number of adverse events

End point title	Safety of TH-302 in combination with doxorubicin compared with doxorubicin alone by assessment of the number of adverse events[1]

End point description:

To assess the safety of TH-302 in combination of doxorubicin in subjects with locally advanced unresectable or metastatic STS compared with doxorubicin alone

End point type	Primary

End point timeframe:

From the first administration of study drug until 30 days after the last dose of study drug.

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: Primary endpoint was safety, which was presented descriptively and extensively in the posted results.

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	317		
Units: Number				
All AEs	307	312		
AEs Related to TH-302	0	301		
AEs Related to Doxorubicin	292	304		
All Grade ≥ 3 AEs	231	246		
Grade ≥ 3 AEs Related to TH-302	0	208		
Grade ≥ 3 AEs Related to Doxorubicin	200	209		
AEs lead to TH-302 reduciton & interruption	0	197		
AEs lead to doxorubicin reduciton & interruption	102	138		
AEs lead to discontinuation of TH-302	0	41		

AEs lead to discontinuation of doxorubicin	19	26		
All SAEs	99	145		
SAEs Related to TH-302	0	96		
SAEs Related to doxorubicin	58	100		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression-free survival (PFS) was defined as time from randomization to the first occurrence of PD or death from any cause within 63 days of last response assessment or randomization. PFS consisted of all randomized subjects (ITT population) for the analysis. To evaluate the efficacy of TH-302 in combination with doxorubicin as determined by PFS in subjects with locally advanced unresectable or metastatic STS compared with doxorubicin alone.

End point type	Secondary

End point timeframe:

From the date of randomization to the first occurrence of progressive disease (PD) or death from any cause up to 63 days following last response assessment (or from start of treatment for subjects without a response assessment), whichever occurred first

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	317		
Units: Days				
median (confidence interval 95%)				
PFS (Median value)	182 (140 to 190)	191 (183 to 237)		
PFS rates at 6 Months survival (Point	49 (42 to 55)	56 (50 to 61)		
PFS rates at 12 Months survival (Point	16 (10 to 22)	25 (20 to 31)		
PFS rates at 18 Months survival (Point	11 (7 to 17)	15 (11 to 20)		
PFS rates at 24 Months survival (Point	8 (4 to 14)	9 (5 to 14)		
PFS rates at 36 Months survival (Point	8 (4 to 14)	7 (4 to 13)		

Statistical analyses

Statistical analysis title	Progression-free survival (PFS)

Statistical analysis description:

Resection were censored for analysis related to response evaluation criteria in solid tumors (RECIST) response assessment at the time of the last response assessment prior to resection. A two-sided log-rank test stratified by randomization stratification factors was used to test the significance between the two treatment arms.

Comparison groups	Doxorubicin v TH-302 + Doxorubicin

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0986
Method	Two-sided stratified log rank test
Parameter estimate	Hazard ratio
Point estimate	0.849
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.698
upper limit	1.031

Secondary: Tumor response - Best response

End point title	Tumor response - Best response

End point description:

A subject was identified as having a response, if they had a partial response (PR) or complete response (CR) on at least one tumor assessment. A subject was identified as having a best response of at least stable disease (SD), if they had an SD, PR or CR on at least one tumor assessment. The SD response must have occurred at least 5 weeks (> 35 days) after the initial dose.

End point type	Secondary

End point timeframe:

At screening, end of Cycles 2, 4 & 6 (at every 3rd cycle for subjects continuing to Cycle 7 to Cycle 12 & every 3rd to 5th cycle thereafter), termination & every 9 weeks post treatment for 1st 18 weeks; every 9 to 15 weeks thereafter after discontinuation

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	317		
Units: Number				
Complete response	3	5		
Partial response	56	85		
Stable disease	154	142		
Progressive disease	81	64		
Unable to evaluate	1	1		
no resposne assessment on study	28	20		

Statistical analyses

Statistical analysis title	Complete Response
Comparison groups	Doxorubicin v TH-302 + Doxorubicin

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.4541
Method	Cochran-Mantel-Haenszel
Parameter estimate	95% Binomial confidence interval
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	2.4

Statistical analysis title	Partial Response or Better
Comparison groups	Doxorubicin v TH-302 + Doxorubicin
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0026
Method	Cochran-Mantel-Haenszel
Parameter estimate	95% Binomial confidence interval
Point estimate	23.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	20.1
upper limit	26.8

Statistical analysis title	Stable Disease or Better Response
Comparison groups	Doxorubicin v TH-302 + Doxorubicin
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
Method	Cochran-Mantel-Haenszel
Parameter estimate	95% Binomial confidence interval
Point estimate	69.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	65.8
upper limit	73.1

Secondary: Tumor response - Confirmed repsosne	
End point title	Tumor response - Confirmed repsosne

End point description:

A subjects was identified as having a response, if they had a partial response (PR) or complete response (CR) on at least one tumor assessment. A subject was identified as having a best response of at least stable disease (SD), if they had an SD, PR or CR on at least one tumor assessment. The SD response must have occurred at least 5 weeks (> 35 days) after the initial dose

End point type	Secondary

End point timeframe:

At screening, end of Cycles 2, 4 & 6 (at every 3rd cycle for subjects continuing to Cycle 7 to Cycle 12 & every 3rd to 5th cycle thereafter), termination & every 9 weeks post treatment for 1st 18 weeks; every 9 to 15 weeks thereafter after discontinuation

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323	317		
Units: Number				
Complete repsosne	3	3		
Partial resposne	43	67		
Stable disease	167	162		
Progressive disease	81	64		
No repsosne assessment on study	29	21		

Statistical analyses

Statistical analysis title	Confirmed Complete Response
Comparison groups	Doxorubicin v TH-302 + Doxorubicin
Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.9908
Method	Cochran-Mantel-Haenszel
Parameter estimate	95% Binomial confidence interval
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	2

Statistical analysis title	Confirmed Partial Response or Better
Comparison groups	Doxorubicin v TH-302 + Doxorubicin

Number of subjects included in analysis	640
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.0115
Method	Cochran-Mantel-Haenszel
Parameter estimate	95% Binomial confidence interval
Point estimate	18.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	15.2
upper limit	21.3

Secondary: Assessment of time to maximum concentration (Tmax) for TH-302, bromo-isophosphoramide mustard (Br-IPM), doxorubicin and doxorubicinol in plasma

End point title	Assessment of time to maximum concentration (Tmax) for TH-302, bromo-isophosphoramide mustard (Br-IPM), doxorubicin and doxorubicinol in plasma

End point description:

To assess the time to maximum concentration for TH-302, Br-IPM, doxorubicin and doxorubicinol after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[2]	317[3]		
Units: Hour				
geometric mean (standard deviation)				
TH-302 (Participant count = 257)	0 (± 0)	0.86 (± 1.361)		
Br-IPM (Participant count = 199)	0 (± 0)	0.9 (± 1.356)		
Doxorubicin (Participant count = 24)	0.37 (± 1.758)	0 (± 0)		
Doxorubicin (Participant count = 22)	0 (± 0)	0.32 (± 1.649)		
Doxorubicinol (Participant count = 25)	0.92 (± 2.615)	0 (± 0)		
Doxorubicinol (Participant count = 23)	0 (± 0)	0.85 (± 2.303)		

Notes:

[2] - Doxorubicin (Participant count = 24)
Doxorubicinol (Participant count = 25)
[3] - Doxorubicin (Participant count = 22)
Doxorubicinol (Participant count = 23)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Maximum peak observed concentration (Cmax) for TH-302, Br-IPM, doxorubicin and doxorubicinol in plasma

End point title	Assessment of Maximum peak observed concentration (Cmax) for TH-302, Br-IPM, doxorubicin and doxorubicinol in plasma

End point description:

To assess the maximum peak observed concentration (Cmax) for TH-302, Br-IPM, doxorubicin and doxorubicinol after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[4]	317[5]		
Units: µg/mL				
geometric mean (standard deviation)				
TH-302 (Participant count = 257)	0 (± 0)	4.69 (± 1.57)		
Br-IPM (Participant count = 226)	0 (± 0)	0.08 (± 1.601)		
Doxorubicin (Participant count = 26)	2.03 (± 1.871)	0 (± 0)		
Doxorubicin (Participant count = 25)	0 (± 0)	2.08 (± 2.197)		
Doxorubicinol (Participant count = 26)	0.05 (± 1.543)	0 (± 0)		
Doxorubicinol (Participant count = 25)	0 (± 0)	0.04 (± 1.677)		

Notes:

[4] - Doxorubicin (Participant count = 26)
Doxorubicinol (Participant count = 26)
[5] - Doxorubicin (Participant count = 25)
Doxorubicinol (Participant count = 25)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase (Kel (LAMZ)) for TH-302, Br-IPM and doxorubicin in plasma

End point title	Assessment of the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase (Kel (LAMZ)) for TH-302, Br-IPM and doxorubicin in plasma

End point description:

To assess the magnitude of the slope of the linear regression of the log concentration versus time profile during the terminal phase (Kel (LAMZ)) for TH-302, Br-IPM and doxorubicin after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[6]	317[7]		
Units: Hour-1				
geometric mean (standard deviation)				
TH-302 (Participant count = 215)	0 (± 0)	1.24 (± 1.198)		
Br-IPM (Participant count = 1)	0 (± 0)	0.73 (± 0)		
Doxorubicin (Participant count = 10)	0.06 (± 1.224)	0 (± 0)		
Doxorubicin (Participant count = 13)	0 (± 0)	0.06 (± 1.243)		

Notes:

[6] - Doxorubicin (Participant count = 10)

[7] - Doxorubicin (Participant count = 13)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of half-life computed as in(2)/Kel (T1/2) for TH-302, Br-IPM and doxorubicin in plasma

End point title	Assessment of half-life computed as in(2)/Kel (T1/2) for TH-302, Br-IPM and doxorubicin in plasma

End point description:

To assess the half-life computed as in(2)/Kel (T1/2) for TH-302, Br-IPM and doxorubicin after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[8]	317[9]		
Units: Hour				
geometric mean (standard deviation)				
TH-302 (Participant count = 215)	0 (± 0)	0.56 (± 1.198)		
Br-IPM (Participant count = 1)	0 (± 0)	0.95 (± 0)		
Doxorubicin (Participant count = 10)	12.33 (± 1.225)	0 (± 0)		
Doxorubicin (Participant count = 13)	0 (± 0)	12.24 (± 1.243)		

Notes:

[8] - Doxorubicin (Participant count = 10)

[9] - Doxorubicin (Participant count = 13)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of area under the concentration-time curve from hour 0 through the last quantifiable concentration time (AUClast) for TH-302, Br-IPM,

doxorubicin and doxorubicinol in plasma

End point title	Assessment of area under the concentration-time curve from hour 0 through the last quantifiable concentration time (AUClast) for TH-302, Br-IPM, doxorubicin and doxorubicinol in plasma

End point description:

To assess area under the concentration-time curve from hour 0 through the last quantifiable concentration time (AUClast) for TH-302, Br-IPM, doxorubicin and doxorubicinol after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[10]	317[11]		
Units: µg-h/mL				
geometric mean (standard deviation)				
TH-302 (Participant count = 257)	0 (± 0)	4.56 (± 1.522)		
Br-IPM (Participant count = 224)	0 (± 0)	0.06 (± 2.05)		
Doxorubicin (Participant count = 24)	1.64 (± 1.326)	0 (± 0)		
Doxorubicin (Participant count = 22)	0 (± 0)	1.54 (± 1.308)		
Doxorubicinol (Participant count = 25)	0.57 (± 1.514)	0 (± 0)		
Doxorubicinol (Participant count = 23)	0 (± 0)	0.46 (± 1.738)		

Notes:

[10] - Doxorubicin (Participant count = 24)
Doxorubicinol (Participant count = 25)
[11] - Doxorubicin (Participant count = 22)
Doxorubicinol (Participant count = 23)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of area under the concentration-time curve from 0 to infinity, computed using the linear trapezoidal rule as AUClast + CLCLQCT/ Kel (AUC 0-∞) for TH-302, Br-IPM and doxorubicin in plasma

End point title	Assessment of area under the concentration-time curve from 0 to infinity, computed using the linear trapezoidal rule as AUClast + CLCLQCT/ Kel (AUC 0-∞) for TH-302, Br-IPM and doxorubicin in plasma

End point description:

To assess area under the concentration-time curve from 0 to infinity, computed using the linear trapezoidal rule as AUClast + CLCLQCT/ Kel (AUC 0-∞) for TH-302, Br-IPM and doxorubicin after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[12]	317[13]		
Units: µg-h/mL				
geometric mean (standard deviation)				
TH-302 (Participant count = 215)	0 (± 0)	4.87 (± 1.504)		
Br-IPM (Participant count = 1)	0 (± 0)	0.29 (± 0)		
Doxorubicin (Participant count = 10)	2.03 (± 1.261)	0 (± 0)		
Doxorubicin (Participant count = 13)	0 (± 0)	1.75 (± 1.36)		

Notes:

[12] - Doxorubicin (Participant count = 10)

[13] - Doxorubicin (Participant count = 13)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of clearance computed as dose divided by AUC0-∞ (CL) for TH-302 and doxorubicin in plasma

End point title	Assessment of clearance computed as dose divided by AUC0-∞ (CL) for TH-302 and doxorubicin in plasma

End point description:

To assess the time to maximum concentration for TH-302, Br-IPM and doxorubicin after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[14]	317[15]		
Units: L/h/m2				
geometric mean (standard deviation)				
TH-302 (Participant count = 215)	0 (± 0)	61.62 (± 1.504)		
Doxorubicin (Participant count = 10)	36.96 (± 1.261)	0 (± 0)		
Doxorubicin (Participant count = 13)	0 (± 0)	41.96 (± 1.327)		

Notes:

[14] - Doxorubicin (Participant count = 10)

[15] - Doxorubicin (Participant count = 13)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of Apparent steady-state volume of distribution (Vss) for TH-302 and doxorubicin in plasma

End point title	Assessment of Apparent steady-state volume of distribution (Vss) for TH-302 and doxorubicin in plasma

End point description:

To assess the time to maximum concentration for TH-302, Br-IPM and doxorubicin after the IV administration of TH-302 and doxorubicin.

End point type	Secondary

End point timeframe:

TH-302 & Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. Doxorubicin: On Day 1 of Cycle 1; computed as Dose*AUMC/AUC0-∞ 2 - Dose*T/(2*AUC0-∞), where AUMC- area under the first moment of plasma concentration time curve & T- infusion duration

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[16]	317[17]		
Units: L/m2				
geometric mean (standard deviation)				
TH-302 (Participant count = 215)	0 (± 0)	54.9 (± 1.521)		
Doxorubicin (Participant count = 10)	377.36 (± 1.455)	0 (± 0)		
Doxorubicin (Participant count = 13)	0 (± 0)	401.07 (± 1.378)		

Notes:

[16] - Doxorubicin (Participant count = 10)

[17] - Doxorubicin (Participant count = 13)

Statistical analyses

No statistical analyses for this end point

Secondary: Assessment of apparent volume of distribution in the post-distributive phase (Vβ) for TH-302 and doxorubicin in plasma

End point title	Assessment of apparent volume of distribution in the post-distributive phase (Vβ) for TH-302 and doxorubicin in plasma

End point description:

To assess the apparent volume of distribution in the post-distributive phase, computed as the ratio of CL to the terminal elimination rate constant, Kel (TH-302 and doxorubicin only)

End point type	Secondary

End point timeframe:

For TH-302 and Br-IPM: On Day 1 of Cycle 1 for subjects who received TH-302. For doxorubicin: On Day 1 of Cycle 1

End point values	Doxorubicin	TH-302 + Doxorubicin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	323[18]	317[19]		
Units: L/m2				
geometric mean (standard deviation)				
TH-302 (Participant count = 215)	0 (± 0)	49.61 (± 1.508)		
Doxorubicin (Participant count = 10)	657.28 (± 1.287)	0 (± 0)		
Doxorubicin (Participant count = 13)	0 (± 0)	740.58 (± 1.229)		

Notes:

[18] - Doxorubicin (Participant count = 10)

[19] - Doxorubicin (Participant count = 13)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose (Day 1 of Cycle 1) of study drug until 30 days after the last dose of study drug.

Adverse event reporting additional description:

Safety population consisted of all subjects who received any amount of study drug. The safety population was used for all safety analyses (incidence of adverse events (AEs) - serious and non-serious, vital signs, laboratory, physical examination, ECG, LVEF, concomitant medications and medication exposure).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Doxorubicin

Reporting group description:

Subjects received doxorubicin (75 mg/m2) either by bolus injection (no less than 5 minutes) or by continuous intravenous (IV) infusion over 6-96 hours on Day 1 of every 21-day cycle; doxorubicin was not administered after 6 cycles of treatment.

Reporting group title	TH-302 + Doxorubicin

Reporting group description:

Subjects received TH-302 (300 mg/m2) by IV infusion over 30-60 minutes on Days 1 and 8 of a 21-day cycle.
Combination arm overall data were mentioned for the number of subjects affected, AEs (SAE and NSAE) and fatalities of all occurrences. AEs (SAE and NSAE) occurrences and fatalities causally related to treatment data were presented only for TH-302 treatment.

Serious adverse events	Doxorubicin	TH-302 + Doxorubicin	
Total subjects affected by serious adverse events			
subjects affected / exposed	99 / 323 (30.65%)	145 / 317 (45.74%)	
number of deaths (all causes)	3	8	
number of deaths resulting from adverse events	1	5	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant Pleural effusion			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour haemorrhage			

subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour pain			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour rupture			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	5 / 323 (1.55%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	1 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	2 / 323 (0.62%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic venous thrombosis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			

subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasculitis necrotising			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vena cava thrombosis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cytoreductive surgery			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leg amputation			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Partial lung resection			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sarcoma excision			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour excision			
subjects affected / exposed	2 / 323 (0.62%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chills			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Extravasation			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	3 / 323 (0.93%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	1 / 323 (0.31%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	2 / 323 (0.62%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	3 / 323 (0.93%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			

subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 323 (2.17%)	7 / 317 (2.21%)	
occurrences causally related to treatment / all	3 / 9	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic Inflammatory Response Syndrome			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulval disorder			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 323 (0.31%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			

subjects affected / exposed	3 / 323 (0.93%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 323 (0.93%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	3 / 323 (0.93%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	0 / 4	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	9 / 323 (2.79%)	15 / 317 (4.73%)	
occurrences causally related to treatment / all	1 / 9	2 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Completed suicide			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Confusional state			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			

Ejection fraction decreased			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet Count Decreased			
subjects affected / exposed	1 / 323 (0.31%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infusion related reaction			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 323 (0.31%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardiopulmonary failure			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Amputation stump pain			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	4 / 323 (1.24%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Agranulocytosis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			

subjects affected / exposed	10 / 323 (3.10%)	19 / 317 (5.99%)	
occurrences causally related to treatment / all	10 / 12	17 / 20	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	27 / 323 (8.36%)	56 / 317 (17.67%)	
occurrences causally related to treatment / all	30 / 30	68 / 71	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			
subjects affected / exposed	0 / 323 (0.00%)	3 / 317 (0.95%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	7 / 323 (2.17%)	8 / 317 (2.52%)	
occurrences causally related to treatment / all	7 / 7	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	2 / 323 (0.62%)	13 / 317 (4.10%)	
occurrences causally related to treatment / all	2 / 2	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	2 / 323 (0.62%)	13 / 317 (4.10%)	
occurrences causally related to treatment / all	2 / 2	16 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	7 / 323 (2.17%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	1 / 8	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			

subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 323 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 323 (0.31%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal haemorrhage			

subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised intraabdominal fluid collection			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower gastrointestinal haemorrhage			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	5 / 323 (1.55%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctalgia			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Proctitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal fissure			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			

subjects affected / exposed	5 / 323 (1.55%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 323 (0.31%)	9 / 317 (2.84%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 323 (0.00%)	4 / 317 (1.26%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic pain			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			

Decubitus ulcer			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug reaction with eosinophilia and systemic symptoms			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 323 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fistula			

subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flank pain			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neck Pain			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	2 / 323 (0.62%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal abscess			

subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	2 / 323 (0.62%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 323 (0.31%)	6 / 317 (1.89%)	
occurrences causally related to treatment / all	0 / 1	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			

subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incision site infection			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella bacteraemia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Oropharyngeal candidiasis			
subjects affected / exposed	1 / 323 (0.31%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 323 (1.55%)	8 / 317 (2.52%)	
occurrences causally related to treatment / all	0 / 5	6 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia respiratory syncytial viral			

subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 323 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 323 (0.93%)	7 / 317 (2.21%)	
occurrences causally related to treatment / all	2 / 3	3 / 7	
deaths causally related to treatment / all	0 / 0	2 / 3	
Septic shock			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal sepsis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal bacteraemia			

subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 323 (0.31%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	3 / 323 (0.93%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	1 / 3	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 323 (0.00%)	2 / 317 (0.63%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	3 / 323 (0.93%)	5 / 317 (1.58%)	
occurrences causally related to treatment / all	3 / 3	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Failure to thrive			
subjects affected / exposed	0 / 323 (0.00%)	1 / 317 (0.32%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic Acidosis			
subjects affected / exposed	1 / 323 (0.31%)	0 / 317 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

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

Non-serious adverse events	Doxorubicin	TH-302 + Doxorubicin	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	307 / 323 (95.05%)	312 / 317 (98.42%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	10 / 323 (3.10%)	17 / 317 (5.36%)	
occurrences (all)	11	18	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	34 / 323 (10.53%)	40 / 317 (12.62%)	
occurrences (all)	43	61	
Chills			
subjects affected / exposed	10 / 323 (3.10%)	18 / 317 (5.68%)	
occurrences (all)	10	20	
Fatigue			
subjects affected / exposed	162 / 323 (50.15%)	190 / 317 (59.94%)	
occurrences (all)	187	226	
Oedema peripheral			
subjects affected / exposed	36 / 323 (11.15%)	38 / 317 (11.99%)	
occurrences (all)	44	45	
Pyrexia			
subjects affected / exposed	41 / 323 (12.69%)	71 / 317 (22.40%)	
occurrences (all)	51	107	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	43 / 323 (13.31%)	59 / 317 (18.61%)	
occurrences (all)	47	72	
Dyspnoea			
subjects affected / exposed	34 / 323 (10.53%)	66 / 317 (20.82%)	
occurrences (all)	35	83	
Oropharyngeal pain			
subjects affected / exposed	19 / 323 (5.88%)	28 / 317 (8.83%)	
occurrences (all)	19	32	

Pulmonary embolism			
subjects affected / exposed	17 / 323 (5.26%)	21 / 317 (6.62%)	
occurrences (all)	18	21	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	15 / 323 (4.64%)	30 / 317 (9.46%)	
occurrences (all)	15	32	
Depression			
subjects affected / exposed	15 / 323 (4.64%)	30 / 317 (9.46%)	
occurrences (all)	15	31	
Insomnia			
subjects affected / exposed	37 / 323 (11.46%)	23 / 317 (7.26%)	
occurrences (all)	37	24	
Investigations			
Blood alkaline phosphatase increased			
subjects affected / exposed	6 / 323 (1.86%)	18 / 317 (5.68%)	
occurrences (all)	6	20	
Ejection fraction decreased			
subjects affected / exposed	31 / 323 (9.60%)	39 / 317 (12.30%)	
occurrences (all)	31	40	
Lymphocyte count decreased			
subjects affected / exposed	13 / 323 (4.02%)	19 / 317 (5.99%)	
occurrences (all)	22	32	
Neutrophil count decreased			
subjects affected / exposed	44 / 323 (13.62%)	34 / 317 (10.73%)	
occurrences (all)	74	45	
Platelet count decreased			
subjects affected / exposed	20 / 323 (6.19%)	35 / 317 (11.04%)	
occurrences (all)	35	64	
Weight decreased			
subjects affected / exposed	18 / 323 (5.57%)	44 / 317 (13.88%)	
occurrences (all)	18	44	
White blood cell count decreased			
subjects affected / exposed	39 / 323 (12.07%)	45 / 317 (14.20%)	
occurrences (all)	77	77	
Nervous system disorders			

Dizziness			
subjects affected / exposed	20 / 323 (6.19%)	35 / 317 (11.04%)	
occurrences (all)	22	47	
Dysgeusia			
subjects affected / exposed	41 / 323 (12.69%)	70 / 317 (22.08%)	
occurrences (all)	44	75	
Headache			
subjects affected / exposed	36 / 323 (11.15%)	52 / 317 (16.40%)	
occurrences (all)	39	55	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	104 / 323 (32.20%)	189 / 317 (59.62%)	
occurrences (all)	130	287	
Febrile neutropenia			
subjects affected / exposed	34 / 323 (10.53%)	57 / 317 (17.98%)	
occurrences (all)	37	75	
Leukopenia			
subjects affected / exposed	28 / 323 (8.67%)	30 / 317 (9.46%)	
occurrences (all)	56	69	
Neutropenia			
subjects affected / exposed	96 / 323 (29.72%)	60 / 317 (18.93%)	
occurrences (all)	171	118	
Thrombocytopenia			
subjects affected / exposed	19 / 323 (5.88%)	72 / 317 (22.71%)	
occurrences (all)	22	156	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	13 / 323 (4.02%)	16 / 317 (5.05%)	
occurrences (all)	13	16	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	31 / 323 (9.60%)	37 / 317 (11.67%)	
occurrences (all)	32	41	
Abdominal pain upper			
subjects affected / exposed	6 / 323 (1.86%)	16 / 317 (5.05%)	
occurrences (all)	6	16	
Constipation			

subjects affected / exposed	89 / 323 (27.55%)	134 / 317 (42.27%)	
occurrences (all)	99	162	
Diarrhoea			
subjects affected / exposed	68 / 323 (21.05%)	96 / 317 (30.28%)	
occurrences (all)	86	144	
Dry mouth			
subjects affected / exposed	12 / 323 (3.72%)	33 / 317 (10.41%)	
occurrences (all)	13	34	
Dyspepsia			
subjects affected / exposed	39 / 323 (12.07%)	37 / 317 (11.67%)	
occurrences (all)	45	43	
Dysphagia			
subjects affected / exposed	6 / 323 (1.86%)	20 / 317 (6.31%)	
occurrences (all)	6	21	
Gastrooesophageal reflux disease			
subjects affected / exposed	17 / 323 (5.26%)	24 / 317 (7.57%)	
occurrences (all)	17	24	
Haemorrhoids			
subjects affected / exposed	11 / 323 (3.41%)	43 / 317 (13.56%)	
occurrences (all)	11	49	
Nausea			
subjects affected / exposed	180 / 323 (55.73%)	210 / 317 (66.25%)	
occurrences (all)	266	300	
Proctalgia			
subjects affected / exposed	2 / 323 (0.62%)	22 / 317 (6.94%)	
occurrences (all)	2	23	
Stomatitis			
subjects affected / exposed	106 / 323 (32.82%)	162 / 317 (51.10%)	
occurrences (all)	149	232	
Vomiting			
subjects affected / exposed	62 / 323 (19.20%)	101 / 317 (31.86%)	
occurrences (all)	82	136	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	138 / 323 (42.72%)	153 / 317 (48.26%)	
occurrences (all)	138	153	

Dry skin			
subjects affected / exposed	17 / 323 (5.26%)	34 / 317 (10.73%)	
occurrences (all)	18	43	
Erythema			
subjects affected / exposed	6 / 323 (1.86%)	25 / 317 (7.89%)	
occurrences (all)	6	28	
Rash			
subjects affected / exposed	3 / 323 (0.93%)	19 / 317 (5.99%)	
occurrences (all)	3	25	
Rash erythematous			
subjects affected / exposed	4 / 323 (1.24%)	23 / 317 (7.26%)	
occurrences (all)	4	31	
Rash maculo-papular			
subjects affected / exposed	4 / 323 (1.24%)	27 / 317 (8.52%)	
occurrences (all)	4	38	
Skin hyperpigmentation			
subjects affected / exposed	1 / 323 (0.31%)	35 / 317 (11.04%)	
occurrences (all)	1	38	
Palmar-plantar erythrodysaesthesia syndrome			
subjects affected / exposed	2 / 323 (0.62%)	41 / 317 (12.93%)	
occurrences (all)	2	48	
Pruritus			
subjects affected / exposed	1 / 323 (0.31%)	23 / 317 (7.26%)	
occurrences (all)	2	29	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	9 / 323 (2.79%)	16 / 317 (5.05%)	
occurrences (all)	11	18	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	18 / 323 (5.57%)	40 / 317 (12.62%)	
occurrences (all)	21	42	
Back pain			
subjects affected / exposed	26 / 323 (8.05%)	39 / 317 (12.30%)	
occurrences (all)	27	44	
Bone pain			

subjects affected / exposed	12 / 323 (3.72%)	31 / 317 (9.78%)	
occurrences (all)	12	36	
Myalgia			
subjects affected / exposed	12 / 323 (3.72%)	19 / 317 (5.99%)	
occurrences (all)	13	22	
Pain in extremity			
subjects affected / exposed	22 / 323 (6.81%)	32 / 317 (10.09%)	
occurrences (all)	26	41	
Infections and infestations			
Cellulitis			
subjects affected / exposed	4 / 323 (1.24%)	18 / 317 (5.68%)	
occurrences (all)	4	20	
Oral candidiasis			
subjects affected / exposed	5 / 323 (1.55%)	16 / 317 (5.05%)	
occurrences (all)	5	20	
Upper respiratory tract infection			
subjects affected / exposed	8 / 323 (2.48%)	20 / 317 (6.31%)	
occurrences (all)	9	26	
Urinary tract infection			
subjects affected / exposed	26 / 323 (8.05%)	47 / 317 (14.83%)	
occurrences (all)	30	62	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	82 / 323 (25.39%)	113 / 317 (35.65%)	
occurrences (all)	93	128	
Dehydration			
subjects affected / exposed	13 / 323 (4.02%)	28 / 317 (8.83%)	
occurrences (all)	17	37	
Hypoalbuminaemia			
subjects affected / exposed	10 / 323 (3.10%)	18 / 317 (5.68%)	
occurrences (all)	13	22	
Hypokalaemia			
subjects affected / exposed	20 / 323 (6.19%)	35 / 317 (11.04%)	
occurrences (all)	21	44	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 June 2012	Amendment 1: 1. Provide greater clarification of the eligibility criteria including: - The inclusion of subjects with Gilbert's syndrome who had an associated elevated bilirubin - The inclusion of other STSs for which doxorubicin was an appropriate first-time therapy - The inclusion of subjects who were not transfusion dependent if baseline hematological laboratory data met eligibility - The modification of the restriction of prior therapies to only those that were related to the subject's STS - The inclusion of subjects who received low dose non-systemic doxorubicin and - The exclusion of doxorubicin-limiting congestive heart failure 2. Clarified that complete resection of all sites of disease was a reason for treatment discontinuation 3. Provided greater detail on the analyses of PFS 4. Eliminated event-free survival as a secondary objective 5. Re-categorized the secondary efficacy objectives and endpoints into secondary and tertiary objectives and endpoints 6. Expanded the doxorubicin continuous IV infusion to 6.96 hours 7. Clarified the treatment options following tumor resection 8. Correctly specified the statistical test for comparing rates across treatment arms 9. Provided guidance in the event of extravasation 10. Included minor administrative and protocol changes.
20 December 2012	Amendment 2: 1. Added pre-H-302 dose and post-TH-302 dose ECG assessments of the QTc interval 2. Allowed for an increase of the study sample size if over 10 subjects discontinued from study and withdrew consent for future follow-up, including survival 3. Added collection of EQ-5D-5L to collect data on quality of life data and health state utilities 4. Included minor administrative and protocol changes
22 April 2013	Amendment 3: 1. Increased the sample size from 450 subjects to 620 subjects 2. Removed the PFS interim futility analysis 3. Adjusted the timing of the OS interim analysis 4. Clarified one of the exclusion criteria 5. Included minor administrative and protocol changes

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported