



## Clinical trial results:

### **RANDOMIZED, DOUBLE-BLIND, PHASE 3 STUDY OF TAS-102 PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO PLUS BSC IN PATIENTS WITH METASTATIC COLORECTAL CANCER REFRACTORY TO STANDARD CHEMOTHERAPIES**

#### **Summary**

EudraCT number	2012-000109-66
Trial protocol	GB DE SE AT ES IE CZ BE IT
Global end of trial date	23 May 2016

#### **Results information**

Result version number	v1 (current)
This version publication date	01 June 2017
First version publication date	01 June 2017

#### **Trial information**

##### **Trial identification**

Sponsor protocol code	TPU-TAS-102-301
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##### **Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01607957
WHO universal trial number (UTN)	-

Notes:

##### **Sponsors**

Sponsor organisation name	Taiho Oncology, Inc.
Sponsor organisation address	101 Carnegie Center, Suite 101, Princeton, United States, NJ 08540
Public contact	Robert Winkler, MD, Taiho Oncology, Inc., 001 609/455.3893, <a href="mailto:rwinkler@taihooncology.com">rwinkler@taihooncology.com</a>
Scientific contact	Robert Winkler, MD, Taiho Oncology, Inc., 001 609/455.3893, <a href="mailto:rwinkler@taihooncology.com">rwinkler@taihooncology.com</a>

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:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	31 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 January 2014
Global end of trial reached?	Yes
Global end of trial date	23 May 2016
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

Objectives: To compare the following endpoints for the TAS-102 (experimental) arm with the placebo (control) arm in patients with refractory metastatic colorectal cancer:

Primary

Overall survival (OS)

Key Secondary

Progression-free survival (PFS)

Safety and tolerability

Other Secondary

Time to treatment failure (TTF)

Overall response rate (ORR)

Disease control rate (DCR)

Duration of response (DR)

Subgroup analysis by KRAS status on OS and PFS

Exploratory (Pharmacokinetic assessments performed at selected sites)

To explore the effect of intrinsic and extrinsic factors on the pharmacokinetics (PK) of TAS-102

To explore the relationship between plasma concentrations of TAS-102 components (FTD and TPI) and safety and efficacy parameters

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practices (GCP), ICH Guidelines, the ethical principles that have their origin in the Declaration of Helsinki, and all applicable regulatory requirements. The Investigator (according to applicable regulatory requirements) or a person designated by the Investigator and under the Investigator's responsibility fully informed patients of all pertinent aspects of the clinical trial. All participants were informed to the fullest extent possible about the study in a language and in terms they are able to understand.

Prior to participation in the trial, the written ICF was signed and personally dated by the patient or by the patient's legal representative and by the person who conducted the ICF discussion. A copy of the signed and dated ICF was provided to the patient. The ICF used had had prior approval by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

An independent data monitoring committee (DMC) monitored the safe conduct of the study.

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Background therapy: -

Evidence for comparator:

A placebo-controlled design was selected for this study since, at the time the study was initiated, there were no standard therapies for patients with metastatic colorectal cancer who had been previously treated with fluoropyrimidines, oxaliplatin, irinotecan, monoclonal anti-VEGF and anti-EGFR antibodies for KRAS wild-type patients, and had become refractory or intolerant to those chemotherapies.

Regorafenib became authorised for the treatment of patients with metastatic colorectal cancer in all participating RECURSE countries (Australia, EU, Japan and the US) only after most of the study enrollment was complete (>80%). Patients in both the TAS-102 and placebo treatment groups received best supportive care in addition to study medication.

Actual start date of recruitment	17 June 2012
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	Austria: 20
Country: Number of subjects enrolled	Spain: 112
Country: Number of subjects enrolled	Belgium: 64
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	France: 50
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Ireland: 8
Country: Number of subjects enrolled	Italy: 108
Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	United States: 99
Country: Number of subjects enrolled	Japan: 266
Worldwide total number of subjects	800
EEA total number of subjects	403

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)	448
From 65 to 84 years	352
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

800 patients were randomized at a total of 101 study centers in 13 countries United States (21), Japan (20), Spain (11), Italy (9), Germany (8), Belgium (6), France (6), Australia (5), United Kingdom (5), Austria (4), Ireland (3), Sweden (2), Czech Republic (1). The first patient was randomized on 17 June 2012 and the last on 08 October 2013.

### Pre-assignment

Screening details:

A total of 1002 patients provided signed informed consent for participation in the study. Of these, 800 were randomized and 202 (20%) did not meet eligibility criteria and were not randomised (ie, screen failures).

### Period 1

Period 1 title	Baseline Period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Experimental Arm

Arm description:

TAS-102 plus Best supportive care (BSC)

Arm type	Experimental
Investigational medicinal product name	TAS-102
Investigational medicinal product code	TAS-102
Other name	Lonsurf
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-102 was supplied as an immediate-release film coated tablet in 2 strengths (expressed as FTD (trifluridine) content):

- 15-mg white, round tablet containing 15 mg FTD and 7.065 mg TPI (tipiracil hydrochloride) as active ingredients.
- 20-mg pale-red, round tablet containing 20 mg FTD and 9.420 mg TPI as active ingredients.

TAS-102 dosing was based on body surface area (BSA). The starting dose was 35 mg/m<sup>2</sup>/dose administered twice daily (BID) after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle), repeated every 4 weeks.

<b>Arm title</b>	Control Arm
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Arm description:

Placebo plus best supportive care (BSC)

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	NA
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Manufactured to look identical to the TAS-102 15-mg (white, round) and 20-mg (pale-red, round) tablets.

Number of subjects in period 1	Experimental Arm	Control Arm
Started	534	266
Completed	534	266

## Period 2

Period 2 title	On-treatment period
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Blinding implementation details:

TAS-102 tablets (15-mg / 20-mg) and the corresponding placebo tablets were identical in appearance and were packaged in identical containers. Unblinding of the study treatment by the Investigator was not to occur unless needed to manage a patient's medical condition. In this emergency, the Investigator could unblind the patient by calling the IWRS to obtain the patient's treatments. If unblinding occurred, the Investigator was not to disclose the unblinding information.

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Experimental arm

Arm description:

TAS-102 plus Best supportive care (BSC)

Arm type	Experimental
Investigational medicinal product name	TAS-102
Investigational medicinal product code	TAS-102
Other name	Lonsurf
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

TAS-102 was supplied as an immediate-release film coated tablet in 2 strengths (expressed as FTD content):

- 15-mg white, round tablet containing 15 mg FTD and 7.065 mg TPI as active ingredients.
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TAS-102 dosing was based on body surface area (BSA). The starting dose was 35 mg/m<sup>2</sup>/dose administered twice daily (BID) after morning and evening meals for 5 days a week with 2 days rest for 2 weeks, followed by a 14-day rest (1 treatment cycle), repeated every 4 weeks.

<b>Arm title</b>	Control arm
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Arm description:

Placebo plus best supportive care (BSC)

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Manufactured to look identical to the TAS-102 15-mg (white, round) and 20-mg (pale-red, round) tablets.

<b>Number of subjects in period 2<sup>[1]</sup></b>	Experimental arm	Control arm
Started	533	265
Completed	496	263
Not completed	37	2
Continued study treatment	37	2

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: Number of subjects starting the on-treatment period does not include 1 patient in each arm (TAS-102 and placebo) that was not treated.

## Baseline characteristics

### Reporting groups

Reporting group title	Experimental Arm
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Reporting group description:

TAS-102 plus Best supportive care (BSC)

Reporting group title	Control Arm
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Reporting group description:

Placebo plus best supportive care (BSC)

Reporting group values	Experimental Arm	Control Arm	Total
Number of subjects	534	266	800
Age categorical Units: Subjects			

Age continuous Units: years median full range (min-max)	63 27 to 82	63 27 to 82	-
Gender categorical Units: Subjects			
Female	208	101	309
Male	326	165	491

## End points

### End points reporting groups

Reporting group title	Experimental Arm
Reporting group description: TAS-102 plus Best supportive care (BSC)	
Reporting group title	Control Arm
Reporting group description: Placebo plus best supportive care (BSC)	
Reporting group title	Experimental arm
Reporting group description: TAS-102 plus Best supportive care (BSC)	
Reporting group title	Control arm
Reporting group description: Placebo plus best supportive care (BSC)	

### Primary: Overall Survival

End point title	Overall Survival
End point description: Tumour assessments were performed throughout the study based on Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1, 2009. Computed tomography (CT) scans were performed at the end of every 8 weeks until disease progression. If a patient discontinued study medication for reasons other than radiologic disease progression (eg, with intolerable side effects), the patient was followed for tumour response until radiologic disease progression or initiation of new anticancer therapy (whichever occurred first). All patients were followed for survival at scheduled 8-week time intervals until death. Patients were followed until 12 months after the first dose of study medication for the last patient randomised, even if consent for study participation had been withdrawn.	
End point type	Primary
End point timeframe: Overall survival data: 24 January 2014 (observation of the 571st death in the study) The time from the date of randomization to the death date.	

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	265		
Units: months				
median (confidence interval 95%)	7.1 (6.5 to 7.8)	5.3 (4.6 to 6)		

### Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	Experimental arm v Control arm



Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[1]</sup>
Method	Stratified log-rank test p-value

Notes:

[1] - (1-sided and 2-sided)

## Secondary: Progression-Free Survival

End point title	Progression-Free Survival
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End point description:

End point type	Secondary
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End point timeframe:

All clinical data except overall survival: 31 January 2014

The time (in months) from the date of randomization until the date of the investigator-assessed radiological disease progression or death due to any cause.

End point values	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	265		
Units: Months				
median (confidence interval 95%)	2 (1.9 to 2.1)	1.7 (1.7 to 1.8)		

## Statistical analyses

<b>Statistical analysis title</b>	Progression-Free Survival
Comparison groups	Experimental arm v Control arm
Number of subjects included in analysis	798
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 <sup>[2]</sup>
Method	Stratified log-rank test p-value

Notes:

[2] - (1-sided and 2-sided)

## Secondary: Safety and Tolerability

End point title	Safety and Tolerability
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End point description:

End point type	Secondary
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End point timeframe:

All clinical data except overall survival: 31 January 2014

The time from when patient signs ICF through the period of patient follow-up (30 days after the last dose of study medication or until the start of new antitumor therapy, whichever is earlier)

<b>End point values</b>	Experimental arm	Control arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	533	265		
Units: Percentage				
number (not applicable)				
Any adverse event (AE)	98.3	93.2		
Any treatment-related AE	85.7	54.7		
Any ≥Grade 3 AE	69.4	51.7		
Any treatment-related ≥Grade 3 AE	49	9.8		
Any serious AE (SAE)	29.6	33.6		
Any AE resulting in discontinuation	10.3	13.6		
Any AE with outcome of death	3.2	11.3		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs will be reported from the time a patient signs informed consent through the period of patient follow-up (30 days after the last dose of study medication or until the start of new antitumor therapy, whichever is earlier).

Adverse event reporting additional description:

Document all AEs in the source documents. Documentation should include onset and resolution/stabilization dates, severity/grade, relationship to study medication, and outcome of the event. All AEs should be entered in the CRF within 10 business days or as soon as possible from the time the Investigator first becomes aware of them.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	16

### Reporting groups

Reporting group title	Experimental Arm
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Reporting group description:

TAS-102 plus Best supportive care (BSC)

Reporting group title	Control Arm
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Reporting group description:

Placebo plus best supportive care (BSC)

Serious adverse events	Experimental Arm	Control Arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	158 / 533 (29.64%)	89 / 265 (33.58%)	
number of deaths (all causes)	368	212	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (inc cysts and polps)			
subjects affected / exposed	6 / 533 (1.13%)	7 / 265 (2.64%)	
occurrences causally related to treatment / all	0 / 6	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	1 / 533 (0.19%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

General disorders and administration site conditions			
subjects affected / exposed	27 / 533 (5.07%)	16 / 265 (6.04%)	
occurrences causally related to treatment / all	3 / 27	0 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	15 / 533 (2.81%)	12 / 265 (4.53%)	
occurrences causally related to treatment / all	1 / 15	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Investigations			
subjects affected / exposed	5 / 533 (0.94%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	3 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	10 / 533 (1.88%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 10	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorders			
subjects affected / exposed	4 / 533 (0.75%)	3 / 265 (1.13%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorders			
subjects affected / exposed	9 / 533 (1.69%)	10 / 265 (3.77%)	
occurrences causally related to treatment / all	0 / 9	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			

subjects affected / exposed	28 / 533 (5.25%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	26 / 28	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Eye disorders			
subjects affected / exposed	1 / 533 (0.19%)	0 / 265 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	40 / 533 (7.50%)	26 / 265 (9.81%)	
occurrences causally related to treatment / all	12 / 40	0 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatobiliary disorders			
subjects affected / exposed	19 / 533 (3.56%)	13 / 265 (4.91%)	
occurrences causally related to treatment / all	1 / 19	0 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	13 / 533 (2.44%)	2 / 265 (0.75%)	
occurrences causally related to treatment / all	0 / 13	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			
subjects affected / exposed	6 / 533 (1.13%)	6 / 265 (2.26%)	
occurrences causally related to treatment / all	0 / 6	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and Infestations			
subjects affected / exposed	24 / 533 (4.50%)	12 / 265 (4.53%)	
occurrences causally related to treatment / all	9 / 24	1 / 12	
deaths causally related to treatment / all	1 / 1	0 / 0	
Metabolism and nutrition disorders			

Metabolism and nutrition disorders			
subjects affected / exposed	8 / 533 (1.50%)	7 / 265 (2.64%)	
occurrences causally related to treatment / all	3 / 8	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Experimental Arm	Control Arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	524 / 533 (98.31%)	247 / 265 (93.21%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (inc cysts and polps)			
subjects affected / exposed	46 / 533 (8.63%)	35 / 265 (13.21%)	
occurrences (all)	46	35	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	51 / 533 (9.57%)	25 / 265 (9.43%)	
occurrences (all)	51	25	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	1 / 533 (0.19%)	0 / 265 (0.00%)	
occurrences (all)	7	0	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	373 / 533 (69.98%)	141 / 265 (53.21%)	
occurrences (all)	373	141	
Immune system disorders			
Immune system disorders			
subjects affected / exposed	2 / 533 (0.38%)	1 / 265 (0.38%)	
occurrences (all)	2	1	
Reproductive system and breast disorders			
Reproductive system and breast disorders			
subjects affected / exposed	12 / 533 (2.25%)	4 / 265 (1.51%)	
occurrences (all)	12	4	
Respiratory, thoracic and mediastinal			

disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	142 / 533 (26.64%) 142	80 / 265 (30.19%) 80	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	50 / 533 (9.38%) 50	42 / 265 (15.85%) 42	
Investigations Investigations subjects affected / exposed occurrences (all)	291 / 533 (54.60%) 291	92 / 265 (34.72%) 92	
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	26 / 533 (4.88%) 26	7 / 265 (2.64%) 7	
Congenital, familial and genetic disorders Congenital, familial and genetic disorders subjects affected / exposed occurrences (all)	0 / 533 (0.00%) 0	1 / 265 (0.38%) 1	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	21 / 533 (3.94%) 21	12 / 265 (4.53%) 12	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	113 / 533 (21.20%) 113	52 / 265 (19.62%) 52	
Blood and lymphatic system disorders Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	304 / 533 (57.04%) 304	29 / 265 (10.94%) 29	
Ear and labyrinth disorders Ear and labyrinth disorders subjects affected / exposed occurrences (all)	11 / 533 (2.06%) 11	1 / 265 (0.38%) 1	

Eye disorders Eye disorders subjects affected / exposed occurrences (all)	18 / 533 (3.38%) 18	5 / 265 (1.89%) 5	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	413 / 533 (77.49%) 413	161 / 265 (60.75%) 161	
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	55 / 533 (10.32%) 55	28 / 265 (10.57%) 28	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	127 / 533 (23.83%) 127	48 / 265 (18.11%) 48	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	70 / 533 (13.13%) 70	30 / 265 (11.32%) 30	
Endocrine disorders Endocrine disorders subjects affected / exposed occurrences (all)	0 / 533 (0.00%) 0	1 / 265 (0.38%) 1	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	117 / 533 (21.95%) 117	55 / 265 (20.75%) 55	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	144 / 533 (27.02%) 144	42 / 265 (15.85%) 42	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	248 / 533 (46.53%) 248	104 / 265 (39.25%) 104	





## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 March 2012	<ul style="list-style-type: none"><li>• v1.0 - ROW, v2.0 Japan</li><li>• Names of Sponsor's Medical Monitors updated/added.</li><li>• Clarification of the following: stratification variables; duration of survival follow-up; duration of baseline period; definition of end of treatment; definition of non-target lesions; definition of best overall response; definition of population evaluable for tumour response; and size of population for PK analysis.</li><li>• Modification of Inclusion Criterion #8 to specify that verification of adequate organ function should be based on laboratory data obtained within 7 days prior to Day 1 of Cycle 1; and specified an exception to requirement of total serum bilirubin of <math>\leq 1.5</math> mg/dL (ie, except for Grade 1 hyperbilirubinaemia due solely to a medical diagnosis of Gilbert's syndrome).</li><li>• Addition of Exclusion Criterion #1j for patients with autoimmune disorders and/or requiring immunosuppressive therapy</li><li>• Specified requirement for fractionation (direct/indirect) in case of elevation of total bilirubin.</li></ul>
22 April 2012	<ul style="list-style-type: none"><li>• v2.0 ROW, v3.0 Japan</li><li>• Addition of mobile phone number of Medical Monitor for Japan.</li><li>• Removal of carbon dioxide from required serum chemistry tests.</li></ul>
13 November 2012	<ul style="list-style-type: none"><li>• v3.0 ROW, v4.0 Japan, v4.0 Sweden, v5.0 Germany</li><li>• Addition of generic name and updated chemical name for TPI</li><li>• Clarification of timing of end of treatment assessments of ECG, urinalysis, and tumour measurements.</li><li>• Modification of Exclusion Criterion #4 regarding unresolved toxicities associated with prior therapies.</li><li>• Addition of a caution statement when using human thymidine analogues concomitantly with TAS-102.</li><li>• Clarification of procedures to be followed in case of need to break the study blind.</li></ul>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

NA

Notes: