Clinical trial results:
A Phase IIb/III randomised, double-blind, placebo-controlled study comparing first-line therapy with or without TG4010 immunotherapy product in patients with stage IV non-small cell lung cancer (NSCLC).

Summary

EudraCT number	2011-001468-23
Trial protocol	BE HU GB DE ES PL IT
Global end of trial date	06 July 2015

Results information

Result version number	v1 (current)
This version publication date	20 July 2017
First version publication date	20 July 2017

Trial information

Trial identification

Sponsor protocol code	TG4010.14

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Transgene S.A.
Sponsor organisation address	400, Boulevard Gonthier d'Andernach,Parc d’Innovation - CS80166, Illkirch Graffenstaden Cedex, France, 67405
Public contact	Transgene Medical Affairs, Transgene S.A., clinical.trials@transgene.fr
Scientific contact	Transgene Medical Affairs, Transgene S.A., clinical.trials@transgene.fr

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	06 July 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2014
Global end of trial reached?	Yes
Global end of trial date	06 July 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Phase IIb part: to prospectively validate the level of Triple Positive Activated Lymphocytes (TrPAL), as a predictive biomarker of TG4010's activity by comparing Progression-Free Survival (PFS) between the TG4010 arm (TG4010 + first-line therapy) and the placebo arm (placebo + first-line therapy) in the 2 subgroups of subjects according to their level of TrPAL before randomisation (normal and high level of TrPAL).

Phase III part: To demonstrate that TG4010 improves overall survival (OS) as compared to placebo in stage IV NSCLC patients with non-squamous tumour histology receiving first-line chemotherapy.

Protection of trial subjects:

This study was conducted in accordance with the updated Declaration of Helsinki adopted by the World Medical Association, in compliance with the approved protocol and its amendments, the International Council for Harmonisation good clinical practice, and national regulatory requirements in the participating countries.

Background therapy:

Chemotherapy was given as 21-day cycles starting from Day 1 of Cycle 1 for a minimum of 4 cycles and up to 6 cycles. The platinum doublet chemotherapy regimen administered was determined by histology and at Investigator discretion as follows:

- Non-squamous cell: Paclitaxel (200 milligrams/square metre [mg/m²]) and carboplatin (target area under the curve [AUC] 6.0) on Day 1 of each cycle with the next course of chemotherapy on Day 22; OR pemetrexed (500 mg/m²) and cisplatin (75 mg/m²) on Day 1 of each cycle with the next course of chemotherapy on Day 22
- Squamous cell: Paclitaxel (200 mg/m²) and carboplatin (AUC 6.0) on Day 1 of each cycle with the next course of chemotherapy on Day 22; OR gemcitabine (1250 mg/m²) on Day 1 and Day 8 of each cycle and cisplatin (75 mg/m²) on Day 1 of each cycle with the next course of chemotherapy on Day 22.

Bevacizumab was allowed for patients with non-squamous carcinoma (if initiated at the same time as chemotherapy) and was administered at a dose of 7.5 or 15 mg/kilogram (kg) according to country-specific approved labelling or prescribing information. Bevacizumab treatment was given on Day 1 of each cycle (starting from Day 1 of Cycle 1) until disease progression or premature discontinuation due to any reason.

Pemetrexed (for non-squamous carcinoma) or erlotinib (whatever the histology) were to be given as maintenance therapy in eligible patients who have not progressed after 4 to 6 cycles of chemotherapy (according to labeling in each country) unless they received bevacizumab as part of first-line therapy. Pemetrexed (at the dose of 500 mg/m² every 3 weeks, given on the same day as TG4010/placebo) or erlotinib (at the dose of 150 mg daily) were administered in combination with TG4010/placebo until disease progression or premature discontinuation due to any reason.

Evidence for comparator: -

Actual start date of recruitment	10 April 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Israel: 3
Country: Number of subjects enrolled	United States: 9
Country: Number of subjects enrolled	Poland: 22
Country: Number of subjects enrolled	Spain: 20
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	France: 90
Country: Number of subjects enrolled	Hungary: 41
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	222
EEA total number of subjects	210

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)	143
From 65 to 84 years	79
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study consisted of a Phase IIb and a Phase III part. 222 subjects were randomised into the Phase IIb part in a 1:1 ratio of TG4010 to placebo. The cut-off date for primary analysis of PFS was 15 December 2014 and OS cut off date was 6 July 2015. The study was prematurely terminated after completion of Phase IIb and Phase III did not proceed.

Pre-assignment

Screening details:

The level of TrPAL (percentage of triple positive CD16+ CD56+ CD69+ cells among the total lymphocyte population) was evaluated before randomisation. For the phase IIb part, subjects were categorised in 1 of the 2 groups (normal and high TrPAL) by using a cut-off value determined in adult healthy donors as being the upper limit of normal (ULN).

Period 1

Period 1 title	Phase IIb Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Blinding implementation details:

The monitors, data managers, investigators and subjects remained blinded to drug identity until the date of the last final analysis of the Phase IIb. The statistician was unblinded for all subjects at the time of final analysis in subjects with normal TrPAL. The sponsor was unblinded for the treatment code firstly for subjects with normal TrPAL at the time of the final analysis in this subgroup and secondly for subjects with high TrPAL at the time of the final analysis in this subgroup.

Arms

Are arms mutually exclusive?	Yes
Arm title	TG4010

Arm description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by subcutaneous (SC) injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Arm type	Experimental
Investigational medicinal product name	TG4010
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TG4010 is a suspension of recombinant modified Vaccinia virus strain Ankara (MVA) carrying coding sequences for human Mucin 1 (MUC1) antigen and human interleukin-2 in the diluent named TG0008.

TG4010 was administered at a dose of 1 x 10^8 plaque-forming unit (pfu) (corresponding to 0.5 millilitre [mL] of TG4010) once every week for 6 weeks, starting on Day 1 of Cycle 1, and then every 3 weeks thereafter until disease progression or premature discontinuation due to any reason. Each SC injection was performed in a single site. Four injection sites were used successively (left and right arm, left and right thigh) according to a rotation schedule.

Arm title	Placebo

Arm description:

Subjects received placebo plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	TG0008
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

The placebo used in this study was the diluent of TG4010 (TG0008) and was administered as a single SC injection in a volume of 0.5 mL. Placebo was administered once every week for 6 weeks, starting on Day 1 of Cycle 1, and then every 3 weeks thereafter until disease progression or premature discontinuation due to any reason. Four injection sites were used successively (left and right arm, left and right thigh) according to a rotation schedule.

Number of subjects in period 1	TG4010	Placebo
Started	111	111
Completed	105	98
Not completed	6	13
Consent withdrawn by subject	4	7
Investigator's Decision	2	2
Administrative problems	-	1
Lost to follow-up	-	3

Baseline characteristics

Reporting groups

Reporting group title	TG4010

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by subcutaneous (SC) injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Reporting group values	TG4010	Placebo	Total
Number of subjects	111	111	222
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)	66	77	143
From 65-84 years	45	34	79
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.8	59.5	
standard deviation	± 8.5	± 8.8	-
Gender categorical Units: Subjects			
Female	39	41	80
Male	72	70	142
Histology Units: Subjects			
Adenocarcinoma	95	90	185
Squamous cell carcinoma	13	13	26

Large cell carcinoma	2	3	5
Undifferentiated carcinoma	0	3	3
Other	1	2	3
Performance status (PS)			
Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.			
Units: Subjects			
PS=0	33	35	68
PS=1	77	76	153
Missing	1	0	1
Smoking Status Units: Subjects			
Never smoked	7	12	19
Current or ex-smoker	104	99	203
TrPAL Level based on ULN cut-off value Units: Subjects			
≤ ULN (normal)	85	85	170
>ULN (high)	26	26	52
TrPAL level based on Third quartile (Q3) cut-off value Units: Subjects			
≤ Q3 (non-elevated)	71	76	147
> Q3 (elevated)	40	35	75

End points

End points reporting groups

Reporting group title	TG4010

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by subcutaneous (SC) injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Subject analysis set title	TG4010: Normal TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the TG4010 arm, 85 were categorised with a level of TrPAL less than or equal to the ULN (normal TrPAL).

Subject analysis set title	Placebo: Normal TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the placebo arm, 85 were categorised with a level of TrPAL less than or equal to the ULN (normal TrPAL).

Subject analysis set title	TG4010: High TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the TG4010 arm, 26 were categorised with a level of TrPAL greater than the ULN (high TrPAL).

Subject analysis set title	Placebo: High TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Analyses were performed independently in each group of subjects according to their level of TrPAL before randomisation, based on a predetermined ULN cut-off. Of 111 subjects randomised to the placebo arm, 26 were categorised with a level of TrPAL greater than the ULN (high TrPAL).

Subject analysis set title	TG4010: Non-elevated TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

By using a quartile approach for categorisation, subjects with less than or equal to Q3 cut-off value for TrPAL at baseline were categorised into the non-elevated TrPAL subgroup. Of 111 subjects randomised to the TG4010 arm, 71 were categorised with non-elevated TrPAL levels.

Subject analysis set title	Placebo: Non-elevated TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

By using a quartile approach for categorisation, subjects with less than or equal to Q3 cut-off value for TrPAL at baseline were categorised into the non-elevated TrPAL subgroup. Of 111 subjects randomised to the placebo arm, 76 were categorised with non-elevated TrPAL levels.

Subject analysis set title	TG4010: Elevated TrPAL Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

By using a quartile approach for categorisation, subjects with greater than the Q3 cut-off value for TrPAL at baseline were categorised into the elevated TrPal subgroup. Of 111 subjects randomised to the TG4010 arm, 40 were categorised with elevated TrPAL levels.

Subject analysis set title	Placebo: Elevated TrPal Subgroup
Subject analysis set type	Sub-group analysis

Subject analysis set description:

By using a quartile approach for categorisation, subjects with greater than the Q3 cut-off value for TrPAL at baseline were categorised into the non-elevated TrPal subgroup. Of 111 subjects randomised to the placebo arm, 35 were categorised with elevated TrPAL levels.

Primary: Comparison of PFS Events in Subjects Treated with TG4010 or Placebo.

End point title	Comparison of PFS Events in Subjects Treated with TG4010 or Placebo.

End point description:

The primary analysis of PFS was performed in the 2 groups of subjects defined by their level of TrPAL at baseline (≤ ULN [normal] or > ULN [high]). This analysis was repeated in the 2 groups of subjects defined by the quartile approach, non-elevated (corresponding to ≤ Q3) and elevated (corresponding to >Q3) TrPAL levels. PFS events were recorded from the date of randomisation to the date of first documented tumour progression or death due to any cause, whichever occurred first. PFS was censored if no progression or death was observed at the cut-off date for analysis, or at the date when a further antineoplastic therapy was started. Determination of progression was based on local evaluations of baseline and post-baseline scans and by evaluation of target and non-target disease according to the Response Evaluation Criteria In Solid Tumours (RECIST) Version 1.1.

End point type	Primary

End point timeframe:

Tumour progression was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

End point values	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup	TG4010: High TrPAL Subgroup	Placebo: High TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	85	85	26	26
Units: Events	76	75	21	22

End point values	TG4010: Non-elevated TrPAL Subgroup	Placebo: Non-elevated TrPAL Subgroup	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	71	76	40	35
Units: Events	62	67	35	30

Statistical analyses

Statistical analysis title	Bayesian analysis: Normal TrPAL subgroup

Statistical analysis description:

A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 89 PFS events had been observed in the normal TrPAL subgroup, the null hypothesis H0: HR ≥ 1 was tested against the alternative hypothesis HA: HR < 1, where HR is the PFS hazard ratio for first-line therapy plus TG4010 (TG4010 arm) relative to first-line therapy plus placebo (placebo arm).

Comparison groups	TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.016 [2]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.03

Notes:

[1] - The null hypothesis H0: HR ≥ 1 was tested against the alternative hypothesis HA: HR < 1, where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[2] - Efficacy criteria: 1- P (HR < 1 / observed data) <=0.05

Statistical analysis title	Bayesian analysis: High TrPAL subgroup

Statistical analysis description:

A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 38 PFS events had been observed in the high TrPAL subgroup, the null hypothesis H0: HR ≤ 1 was tested against the alternative hypothesis HA: HR > 1, where HR was the PFS hazard ratio for first-line therapy plus TG4010 relative to first-line therapy plus placebo.

Comparison groups	TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.687 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.4

Notes:

[3] - The null hypothesis H0: HR ≤ 1 was tested against the alternative hypothesis HA: HR ≥ 1, where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[4] - Efficacy criteria: 1-P (HR >1 / observed data) <= 0.20

Statistical analysis title	Bayesian analysis: Non-elevated TrPAL subgroup

Statistical analysis description:

A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 89 PFS events had been observed in the non elevated TrPAL subgroup, the null hypothesis H0: HR ≥ 1 was tested against the alternative hypothesis HA: HR < 1, where HR is the PFS hazard ratio for first-line therapy plus TG4010 (TG4010 arm) relative to first-line therapy plus placebo (placebo arm).

Comparison groups	TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.005 [6]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.96

Notes:

[5] - The null hypothesis H0: HR ≥ 1 was tested against the alternative hypothesis HA: HR < 1, where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[6] - Efficacy criteria: 1- P (HR < 1 / observed data) <=0.05

Statistical analysis title	Bayesian analysis: Elevated TrPAL subgroup

Statistical analysis description:

A Bayesian analysis was performed to prospectively validate the level of TrPAL as a predictive biomarker of TG4010's activity. After 38 PFS events had been observed in the high TrPAL subgroup, the null hypothesis H0: HR ≤ 1 was tested against the alternative hypothesis HA: HR > 1, where HR was the PFS hazard ratio for first-line therapy plus TG4010 relative to first-line therapy plus placebo.

Comparison groups	Placebo: Elevated TrPal Subgroup v TG4010: Elevated TrPAL Subgroup
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.553 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	1.47

Notes:

[7] - The null hypothesis H0: HR ≤ 1 was tested against the alternative hypothesis HA: HR ≥ 1, where HR is the PFS hazard ratio for first-line therapy+TG4010 (TG4010 arm) relative to first-line therapy+placebo (placebo arm). The hypothesis was tested by using the posterior distribution of an estimator of the log HR.

[8] - Efficacy criteria: 1-P (HR >1 / observed data) <= 0.20

Statistical analysis title	Frequentist analysis: Normal TrPAL subgroup

Statistical analysis description:

As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test.

Comparison groups	TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.032
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.02

Notes:

[9] - Hazard ratio and corresponding 95% confidence intervals (CIs) were derived using the Cox proportional hazards model.

Statistical analysis title	Frequentist analysis: High TrPAL subgroup

Statistical analysis description:

As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test.

Comparison groups	TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.195
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.4

Notes:

[10] - Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Statistical analysis title	Frequentist analysis: Non-elevated TrPAL subgroup

Statistical analysis description:

As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test.

Comparison groups	TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-

	elevated TrPAL Subgroup
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.94

Notes:

[11] - Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Statistical analysis title	Frequentist analysis: Elevated TrPAL subgroup

Statistical analysis description:

As a supportive analysis, a frequentist analysis was also performed to compare PFS between the 2 study arms in each TrPAL subgroup by using a one-sided non-stratified log rank test.

Comparison groups	TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.343
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	1.48

Notes:

[12] - Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Secondary: Comparison of OS Events in Subjects Treated with TG4010 or Placebo.

End point title	Comparison of OS Events in Subjects Treated with TG4010 or Placebo.

End point description:

OS was defined as the time from the date of randomisation to the date of death due to any cause. Analysis of OS was conducted when at least 70% of subjects had died. The number of deaths at the cut-off date for OS was recorded for the whole population and in each TrPAL subgroup. If a subject was not known to have died, survival was censored at the date of last contact.

End point type	Secondary

End point timeframe:

Subjects were followed for survival every 3 months up to a maximum of 169 weeks (until cut-off date for OS analysis).

End point values	TG4010	Placebo	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	111	111	85	85
Units: Events (Deaths)	78	87	58	69

End point values	TG4010: High TrPAL Subgroup	Placebo: High TrPAL Subgroup	TG4010: Non-elevated TrPAL Subgroup	Placebo: Non-elevated TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	71	76
Units: Events (Deaths)	20	18	47	62

End point values	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Events (Deaths)	31	25		

Statistical analyses

Statistical analysis title	Comparison of OS in Whole Population

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010 v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.055
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.06

Statistical analysis title	Comparison of OS in Normal TrPAL Subgroup

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.052
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.75
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.06

Statistical analysis title	Comparison of OS in High TrPAL Subgroup

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.362
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.47
upper limit	1.7

Statistical analysis title	Comparison of OS in Non-elevated TrPAL Subgroup

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.018
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	0.98

Statistical analysis title	Comparison of OS in Elevated TrPAL Subgroup

Statistical analysis description:

The distribution of OS was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.444
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.76

Secondary: Median OS in Subjects Treated with TG4010 or Placebo.

End point title	Median OS in Subjects Treated with TG4010 or Placebo.

End point description:

OS was defined as the time from the date of randomisation to the date of death due to any cause. Analysis of OS was conducted when at least 70 % of subjects had died for the whole population and in each TrPAL group. If a subject is not known to have died, survival was censored at the date of last contact.

End point type	Secondary

End point timeframe:

Subjects were followed for survival every 3 months up to a maximum of 169 weeks (until cut-off date for OS analysis).

End point values	TG4010	Placebo	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	111	111	85	85
Units: Months				
median (confidence interval 95%)	12.7 (9.8 to 16.4)	10.5 (9.5 to 14.3)	12.6 (9.7 to 15.6)	10.5 (8.9 to 14.3)

End point values	TG4010: High TrPAL Subgroup	Placebo: High TrPAL Subgroup	TG4010: Non-elevated TrPAL Subgroup	Placebo: Non-elevated TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	71	76
Units: Months				
median (confidence interval 95%)	14.2 (7.1 to 22.4)	10.9 (7.7 to 21.7)	13 (9.7 to 18.4)	10.4 (8.2 to 14.1)

End point values	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Months				
median (confidence interval 95%)	12.4 (7.3 to 17)	13.7 (8.8 to 21)		

Statistical analyses

No statistical analyses for this end point

Secondary: Comparison of Overall Response Rate (ORR) in Subjects Treated with TG4010 or Placebo.

End point title	Comparison of Overall Response Rate (ORR) in Subjects Treated with TG4010 or Placebo.

End point description:

ORR was defined as the percentage of subjects whose best overall response to tumour evaluation was either complete response (CR) or partial response (PR) confirmed at least 4 weeks after initial documentation. Objective response rate was the percentage of subjects whose best overall response is either CR or PR according to RECIST version 1.1. Results are presented by treatment arm and by TrPAL subgroup for objective response rate and also percentage of subjects with best overall response (CR, PR, stable disease and progressive disease).

End point type	Secondary

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

End point values	TG4010	Placebo	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	111	111	85	85
Units: Percentage of Subjects				
number (not applicable)				
Objective Response Rate	39.6	28.8	38.8	30.6
CR	0.9	0	0	0
PR	38.7	28.8	38.8	30.6
Stable Disease	44.1	48.6	44.7	48.2
Progressive Disease	11.7	13.5	12.9	12.9
Unknown	4.5	9	3.5	8.2

End point values	TG4010: High TrPAL Subgroup	Placebo: High TrPAL Subgroup	TG4010: Non-elevated TrPAL Subgroup	Placebo: Non-elevated TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	71	76
Units: Percentage of Subjects				
number (not applicable)				
Objective Response Rate	42.3	23.1	39.4	31.6
CR	3.8	0	0	0
PR	38.5	23.1	39.4	31.6
Stable Disease	42.3	50	45.1	46.1
Progressive Disease	7.7	15.4	11.3	14.5
Unknown	7.7	11.5	4.2	7.9

End point values	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Percentage of Subjects				
number (not applicable)				
Objective Response Rate	40	22.9		
CR	2.5	0		
PR	37.5	22.9		
Stable Disease	42.5	54.3		
Progressive Disease	12.5	11.4		
Unknown	5	11.4		

Statistical analyses

Statistical analysis title	Comparison of ORR in Whole Population

Statistical analysis description:

The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance.

Comparison groups	TG4010 v Placebo
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.03
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Comparison of ORR in Normal TrPAl Subgroup

Statistical analysis description:

The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance.

Comparison groups	TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup
Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.088
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Comparison of ORR in High TrPAL Subgroup

Statistical analysis description:

The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance.

Comparison groups	TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.092
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Comparison of ORR in Non-elevated TrPAL Subgroup

Statistical analysis description:

The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance.

Comparison groups	TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup

Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.079
Method	Cochran-Mantel-Haenszel

Statistical analysis title	Comparison of ORR in Elevated TrPAL Subgroup

Statistical analysis description:

The Cochran-Mantel-Haenszel chi-square test stratified by tumour histology, bevacizumab administration, chemotherapy regimen, and performance status was used to compare the 2 treatment arms with respect to the ORR at one-sided 2.5% level of significance.

Comparison groups	TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.06
Method	Cochran-Mantel-Haenszel

Secondary: Comparison of Percentage of Subjects with a 9 Month Time to Overall Response (TOR) in Subjects Treated with TG4010 or Placebo.

End point title	Comparison of Percentage of Subjects with a 9 Month Time to Overall Response (TOR) in Subjects Treated with TG4010 or Placebo.

End point description:

TOR events were recorded from the time between date of randomisation to the date of first documented response (CR or PR). TOR was censored if no progression or death was observed at the cut-off date for analysis, or at the date when a further antineoplastic therapy was started. A Kaplan-Meier curve was constructed for each treatment arm and subgroup. The percentage of subjects with a time to overall response of 9 months are reported.

End point type	Secondary

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

End point values	TG4010	Placebo	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	111	111	85	85
Units: Percentage of Subjects				
number (confidence interval 95%)	42 (27 to 56)	59 (47 to 70)	45 (28 to 60)	59 (46 to 70)

End point values	TG4010: High	Placebo: High	TG4010: Non-	Placebo: Non-

	TrPAL Subgroup	TrPAL Subgroup	elevated TrPAL Subgroup	elevated TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	26	26	71	76
Units: Percentage of Subjects				
number (confidence interval 95%)	33 (8 to 62)	61 (32 to 81)	49 (34 to 62)	57 (43 to 69)

End point values	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	40	35		
Units: Percentage of Subjects				
number (confidence interval 95%)	29 (7 to 57)	65 (41 to 81)		

Statistical analyses

Statistical analysis title	Comparison of TOR in Whole Population

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	Placebo v TG4010
Number of subjects included in analysis	222
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.108
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.84
upper limit	2.1

Statistical analysis title	Comparison of TOR in Normal TrPAL Subgroup

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: Normal TrPAL Subgroup v Placebo: Normal TrPAL Subgroup

Number of subjects included in analysis	170
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.218
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.05

Statistical analysis title	Comparison of TOR in High TrPAL Subgroup

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: High TrPAL Subgroup v Placebo: High TrPAL Subgroup
Number of subjects included in analysis	52
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.152
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	4.51

Statistical analysis title	Comparison of TOR in Non-elevated TrPAL Subgroup

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: Non-elevated TrPAL Subgroup v Placebo: Non-elevated TrPAL Subgroup
Number of subjects included in analysis	147
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.315
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.97

Statistical analysis title	Comparison of TOR in Elevated TrPAL Subgroup

Statistical analysis description:

The distribution of TOR was compared between the treatment arms using a one-sided non-stratified log-rank test. Hazard ratio and corresponding 95% CIs were derived using the Cox proportional hazards model.

Comparison groups	TG4010: Elevated TrPAL Subgroup v Placebo: Elevated TrPal Subgroup
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.082
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.77
upper limit	4.22

Secondary: Duration of Overall Response (DOR) in Subjects Treated with TG4010 or Placebo.

End point title	Duration of Overall Response (DOR) in Subjects Treated with TG4010 or Placebo.

End point description:

DOR in weeks applied only to patients whose best overall tumour response was CR or PR. The start date was the date of first documented response (CR or PR) and the end date was the date of event defined as first documented disease progression or death due to underlying cancer. DoR was censored if progression or death due to underlying cancer was not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date was the date of the last evaluable tumour assessment.

For the purpose of reporting data, where the result was recorded as 'not reached' (i.e. infinity) an arbitrary value of 999999 has been assigned.

End point type	Secondary

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9 months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

End point values	TG4010	Placebo	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	44[13]	32[14]	33[15]	26[16]
Units: weeks				
median (confidence interval 95%)	30.1 (21.9 to 43.1)	18.7 (14.9 to 36.4)	31 (19.9 to 54.1)	20.4 (14.3 to 36.4)

Notes:

[13] - Only subjects whose best overall response was classed as CR or PR were analysed.

[14] - Only subjects whose best overall response was classed as CR or PR were analysed.

[15] - Only subjects whose best overall response was classed as CR or PR were analysed.

[16] - Only subjects whose best overall response was classed as CR or PR were analysed.

End point values	TG4010: High TrPAL Subgroup	Placebo: High TrPAL Subgroup	TG4010: Non-elevated TrPAL Subgroup	Placebo: Non-elevated TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11[17]	6[18]	28[19]	24[20]
Units: weeks				
median (confidence interval 95%)	27.4 (12.3 to 55.4)	17.2 (11.1 to 999999)	41.4 (19.9 to 54.7)	18.7 (13.4 to 30.3)

Notes:

[17] - Only subjects whose best overall response was classed as CR or PR were analysed.

[18] - Only subjects whose best overall response was classed as CR or PR were analysed (999999=infinity).

[19] - Only subjects whose best overall response was classed as CR or PR were analysed.

[20] - Only subjects whose best overall response was classed as CR or PR were analysed.

End point values	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[21]	8[22]		
Units: weeks				
median (confidence interval 95%)	27.4 (15.6 to 40.9)	32.2 (11.1 to 999999)		

Notes:

[21] - Only subjects whose best overall response was classed as CR or PR were analysed.

[22] - Only subjects whose best overall response was classed as CR or PR were analysed (999999=infinity).

Statistical analyses

No statistical analyses for this end point

Secondary: Number of DOR Events in Subjects Treated with TG4010 or Placebo.

End point title	Number of DOR Events in Subjects Treated with TG4010 or Placebo.

End point description:

DOR applied only to patients whose best overall tumour response was CR or PR and number of DOR events were recorded for ach treatment arm and subgroup. DOR was censored if progression or death due to underlying cancer was not observed at the cut-off date for the analysis or start of further antineoplastic therapy. The censoring date was the date of the last evaluable tumour assessment.

End point type	Secondary

End point timeframe:

Tumour response was evaluated every 6 weeks until documented progression or for a period of 9

months. Beyond 9 months, evaluations were performed every 12 weeks until documented disease progression. Up to a maximum of 140 weeks (until cut-off date).

End point values	TG4010	Placebo	TG4010: Normal TrPAL Subgroup	Placebo: Normal TrPAL Subgroup
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	44[23]	32[24]	33[25]	26[26]
Units: DOR Events	35	28	27	23

Notes:

[23] - Only subjects whose best overall response was classed as CR or PR were analysed.

[24] - Only subjects whose best overall response was classed as CR or PR were analysed.

[25] - Only subjects whose best overall response was classed as CR or PR were analysed.

[26] - Only subjects whose best overall response was classed as CR or PR were analysed.

End point values	TG4010: High TrPAL Subgroup	Placebo: High TrPAL Subgroup	TG4010: Non-elevated TrPAL Subgroup	Placebo: Non-elevated TrPAL Subgroup
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	11[27]	6[28]	28[29]	24[30]
Units: DOR Events	8	5	22	22

Notes:

[27] - Only subjects whose best overall response was classed as CR or PR were analysed.

[28] - Only subjects whose best overall response was classed as CR or PR were analysed.

[29] - Only subjects whose best overall response was classed as CR or PR were analysed.

[30] - Only subjects whose best overall response was classed as CR or PR were analysed.

End point values	TG4010: Elevated TrPAL Subgroup	Placebo: Elevated TrPal Subgroup		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16[31]	8[32]		
Units: DOR Events	13	6		

Notes:

[31] - Only subjects whose best overall response was classed as CR or PR were analysed.

[32] - Only subjects whose best overall response was classed as CR or PR were analysed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first day of study treatment until 28 days after the last dose of study treatment (up to a maximum of 107 weeks + 28 days).

Adverse event reporting additional description:

Adverse events were summarised by treatment arm (TG4010 or placebo) in subjects that had received at least one injection ofTG4010 or placebo (110 patients in TG4010 arm and 107 patients in the placebo arm). Causality was assessed in relation to TG4010 or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	TG4010

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by TG4010 plus maintenance therapy if appropriate.

TG4010 was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with TG4010 and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Reporting group title	Placebo

Reporting group description:

Subjects received TG4010 plus chemotherapy as first-line treatment followed by placebo plus maintenance therapy if appropriate.

Placebo was administered on Day 1 of Cycle 1 of chemotherapy and then weekly for 6 weeks by SC injections, then once every 3 weeks until disease progression or premature discontinuation. Chemotherapy was given as 21-day cycles for a minimum of 4 cycles and up to 6 cycles. If prescribed, bevacizumab was continued in combination with placebo and administered every 3 weeks until disease progression, premature discontinuation, or toxicity.

Serious adverse events	TG4010	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 110 (46.36%)	58 / 107 (54.21%)	
number of deaths (all causes)	18	14	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	1 / 110 (0.91%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			

subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to bone			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metastatic pain			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tumour associated fever			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Peripheral ischaemia			
subjects affected / exposed	2 / 110 (1.82%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Superior vena cava syndrome			
subjects affected / exposed	0 / 110 (0.00%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 110 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arterial occlusive disease			

subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iliac artery occlusion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	10 / 110 (9.09%)	8 / 107 (7.48%)	
occurrences causally related to treatment / all	0 / 10	0 / 8	
deaths causally related to treatment / all	0 / 8	0 / 5	
Pyrexia			
subjects affected / exposed	1 / 110 (0.91%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 1	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	2 / 110 (1.82%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	1 / 110 (0.91%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 2	
Malaise			

subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
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			
Pulmonary embolism			
subjects affected / exposed	4 / 110 (3.64%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	3 / 110 (2.73%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 110 (0.91%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	2 / 110 (1.82%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
Acute pulmonary oedema			
subjects affected / exposed	1 / 110 (0.91%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 110 (0.91%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory distress			
subjects affected / exposed	2 / 110 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Acquired tracheo-oesophageal fistula			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumothorax			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 110 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac tamponade			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery insufficiency			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pericardial effusion			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Cerebral ischaemia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Brain oedema			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Convulsion			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised non-convulsive epilepsy			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (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	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 110 (1.82%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	1 / 110 (0.91%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Febrile bone marrow aplasia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	3 / 110 (2.73%)	6 / 107 (5.61%)	
occurrences causally related to treatment / all	0 / 3	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Diplopia			
subjects affected / exposed	1 / 110 (0.91%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 110 (0.91%)	5 / 107 (4.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	2 / 110 (1.82%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 110 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			

subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer perforation			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 110 (0.00%)	3 / 107 (2.80%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Adrenal insufficiency			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 110 (0.00%)	2 / 107 (1.87%)	
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 / 110 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 110 (1.82%)	4 / 107 (3.74%)	
occurrences causally related to treatment / all	0 / 2	2 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory tract infection			
subjects affected / exposed	3 / 110 (2.73%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Erysipelas			
subjects affected / exposed	2 / 110 (1.82%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 110 (0.91%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lobar pneumonia			

subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung infection			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pyelonephritis			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 110 (2.73%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			

subjects affected / exposed	0 / 110 (0.00%)	2 / 107 (1.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Food intolerance			
subjects affected / exposed	0 / 110 (0.00%)	1 / 107 (0.93%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 110 (0.91%)	0 / 107 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TG4010	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	109 / 110 (99.09%)	102 / 107 (95.33%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	10 / 110 (9.09%)	6 / 107 (5.61%)	
occurrences (all)	10	6	
Vascular disorders			
Hypertension			
subjects affected / exposed	9 / 110 (8.18%)	13 / 107 (12.15%)	
occurrences (all)	10	16	
Hypotension			
subjects affected / exposed	9 / 110 (8.18%)	3 / 107 (2.80%)	
occurrences (all)	9	4	
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	60 / 110 (54.55%)	59 / 107 (55.14%)	
occurrences (all)	91	81	
Injection site erythema			
subjects affected / exposed	17 / 110 (15.45%)	1 / 107 (0.93%)	
occurrences (all)	28	1	
Injection site induration			
subjects affected / exposed	9 / 110 (8.18%)	0 / 107 (0.00%)	
occurrences (all)	12	0	
Injection site pain			
subjects affected / exposed	13 / 110 (11.82%)	1 / 107 (0.93%)	
occurrences (all)	23	1	
Oedema peripheral			
subjects affected / exposed	22 / 110 (20.00%)	19 / 107 (17.76%)	
occurrences (all)	26	21	
Pyrexia			
subjects affected / exposed	15 / 110 (13.64%)	11 / 107 (10.28%)	
occurrences (all)	20	12	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	19 / 110 (17.27%)	22 / 107 (20.56%)	
occurrences (all)	20	25	
Dyspnoea			
subjects affected / exposed	28 / 110 (25.45%)	14 / 107 (13.08%)	
occurrences (all)	29	15	
Epistaxis			
subjects affected / exposed	12 / 110 (10.91%)	11 / 107 (10.28%)	
occurrences (all)	13	14	
Haemoptysis			
subjects affected / exposed	2 / 110 (1.82%)	8 / 107 (7.48%)	
occurrences (all)	2	9	
Productive Cough			
subjects affected / exposed	8 / 110 (7.27%)	6 / 107 (5.61%)	
occurrences (all)	9	7	
Rhinorrhoea			

subjects affected / exposed	8 / 110 (7.27%)	1 / 107 (0.93%)	
occurrences (all)	9	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	12 / 110 (10.91%)	4 / 107 (3.74%)	
occurrences (all)	12	4	
Insomnia			
subjects affected / exposed	8 / 110 (7.27%)	5 / 107 (4.67%)	
occurrences (all)	8	5	
Investigations			
Blood creatinine increased			
subjects affected / exposed	9 / 110 (8.18%)	5 / 107 (4.67%)	
occurrences (all)	10	6	
Weight decreased			
subjects affected / exposed	21 / 110 (19.09%)	19 / 107 (17.76%)	
occurrences (all)	22	21	
Weight increased			
subjects affected / exposed	5 / 110 (4.55%)	7 / 107 (6.54%)	
occurrences (all)	5	7	
Nervous system disorders			
Dizziness			
subjects affected / exposed	9 / 110 (8.18%)	3 / 107 (2.80%)	
occurrences (all)	11	5	
Dysgeusia			
subjects affected / exposed	13 / 110 (11.82%)	9 / 107 (8.41%)	
occurrences (all)	15	9	
Headache			
subjects affected / exposed	14 / 110 (12.73%)	11 / 107 (10.28%)	
occurrences (all)	15	12	
Neuropathy Peripheral			
subjects affected / exposed	4 / 110 (3.64%)	8 / 107 (7.48%)	
occurrences (all)	6	10	
Paraesthesia			
subjects affected / exposed	11 / 110 (10.00%)	13 / 107 (12.15%)	
occurrences (all)	11	18	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	50 / 110 (45.45%)	38 / 107 (35.51%)	
occurrences (all)	66	50	
Leukopenia			
subjects affected / exposed	10 / 110 (9.09%)	11 / 107 (10.28%)	
occurrences (all)	11	16	
Lymphopenia			
subjects affected / exposed	4 / 110 (3.64%)	7 / 107 (6.54%)	
occurrences (all)	5	9	
Neutropenia			
subjects affected / exposed	49 / 110 (44.55%)	38 / 107 (35.51%)	
occurrences (all)	119	85	
Thrombocytopenia			
subjects affected / exposed	27 / 110 (24.55%)	20 / 107 (18.69%)	
occurrences (all)	42	32	
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	11 / 110 (10.00%)	7 / 107 (6.54%)	
occurrences (all)	11	9	
Eye disorders			
Lacrimation Increased			
subjects affected / exposed	7 / 110 (6.36%)	5 / 107 (4.67%)	
occurrences (all)	8	5	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	15 / 110 (13.64%)	9 / 107 (8.41%)	
occurrences (all)	16	13	
Abdominal Pain upper			
subjects affected / exposed	10 / 110 (9.09%)	8 / 107 (7.48%)	
occurrences (all)	10	9	
Constipation			
subjects affected / exposed	22 / 110 (20.00%)	29 / 107 (27.10%)	
occurrences (all)	26	35	
Diarrhoea			
subjects affected / exposed	27 / 110 (24.55%)	21 / 107 (19.63%)	
occurrences (all)	35	31	
Nausea			

subjects affected / exposed	54 / 110 (49.09%)	44 / 107 (41.12%)	
occurrences (all)	89	76	
Stomatitis			
subjects affected / exposed	9 / 110 (8.18%)	14 / 107 (13.08%)	
occurrences (all)	12	15	
Vomiting			
subjects affected / exposed	32 / 110 (29.09%)	35 / 107 (32.71%)	
occurrences (all)	47	68	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	13 / 110 (11.82%)	8 / 107 (7.48%)	
occurrences (all)	13	8	
Erythema			
subjects affected / exposed	6 / 110 (5.45%)	6 / 107 (5.61%)	
occurrences (all)	8	6	
Rash			
subjects affected / exposed	6 / 110 (5.45%)	5 / 107 (4.67%)	
occurrences (all)	9	6	
Renal and urinary disorders			
Renal Failure			
subjects affected / exposed	3 / 110 (2.73%)	8 / 107 (7.48%)	
occurrences (all)	4	8	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 110 (8.18%)	8 / 107 (7.48%)	
occurrences (all)	11	12	
Back pain			
subjects affected / exposed	14 / 110 (12.73%)	12 / 107 (11.21%)	
occurrences (all)	15	13	
Musculoskeletal pain			
subjects affected / exposed	10 / 110 (9.09%)	4 / 107 (3.74%)	
occurrences (all)	10	5	
Myalgia			
subjects affected / exposed	7 / 110 (6.36%)	3 / 107 (2.80%)	
occurrences (all)	7	4	
Pain in Extremity			

subjects affected / exposed	16 / 110 (14.55%)	6 / 107 (5.61%)	
occurrences (all)	18	10	
Infections and infestations			
Bronchitis			
subjects affected / exposed	10 / 110 (9.09%)	11 / 107 (10.28%)	
occurrences (all)	11	12	
Respiratory tract infection			
subjects affected / exposed	6 / 110 (5.45%)	4 / 107 (3.74%)	
occurrences (all)	7	5	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	24 / 110 (21.82%)	27 / 107 (25.23%)	
occurrences (all)	30	32	
Hypokalaemia			
subjects affected / exposed	7 / 110 (6.36%)	13 / 107 (12.15%)	
occurrences (all)	8	16	
Hyponatraemia			
subjects affected / exposed	7 / 110 (6.36%)	6 / 107 (5.61%)	
occurrences (all)	7	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 April 2012	Major changes included the following: • Inclusion criteria were modified for some laboratory parameters and additional laboratory parameters were added for routine monitoring (e.g. bilirubin) • TOR was added as a secondary objective • PS was added as a stratification factor for statistical analyses (as it is a stratification factor in the randomisation process) • Changes were made to the sensitivity analyses and secondary objectives for the Phase III part of the study
02 July 2013	Major changes included the following: • An exploratory objective evaluating the response rate (i.e. proportion of patients with CR or PR) at tumour evaluation #2 was added • The statistical methods were modified to allow for a preliminary analysis of the subgroup of patients with a high level of TrPAL, at the same time as the primary analysis was performed in the subgroup of patients with normal TrPAL
06 November 2013	Major changes included the following: • Due to the increased time lag in the occurrence of the required number of PFS events in the subgroups of normal and high TrPAL patients necessary for the final analysis, implicating that final analysis in each subgroup could not be performed at the same time, time points for unblinding were revised and delayed for the high TrPAL subgroup until the final analysis results were available in this subgroup to avoid the introduction of possible biases.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
06 July 2015	A decision was taken by the sponsor for business reasons to not proceed with Phase III part after the completion of Phase IIb.	-

Notes:

Limitations and caveats

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

Due to the early termination of this study, this results posting is a complete record of the Phase IIb part of the study only. Phase III did not proceed and is therefore not included in any part.

Notes: