



Clinical trial results:

A randomised phase 2 study of paclitaxel with or without GSK1120212 in advanced wt BRAF melanoma

Summary

EudraCT number	2011-002545-35
Trial protocol	GB DE
Global end of trial date	31 December 2016

Results information

Result version number	v1 (current)
This version publication date	11 March 2018
First version publication date	11 March 2018

Trial information

Trial identification

Sponsor protocol code	OCTO_026
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Additional study identifiers

ISRCTN number	ISRCTN43327231
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Joint Research Office, Block 60, Churchill Hospital, Oxford, United Kingdom, OX3 7LE, Oxford, United Kingdom, OX3 7LE
Public contact	Ms Heather House , Clinical Trials & Research Governance Joint Research Office Block 60, Churchill Hospital, 44 186557224, ctrgr@admin.ox.ac.uk
Scientific contact	PACMEL Trial Office Oncology Clinical Trials Office (OCTO) Department of Oncology, University of Oxford Old Road Campus Research Building Oxford OX3 7DQ, UK, 44 1865617003, octo- enquires@oncology.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 December 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 December 2016
Global end of trial reached?	Yes
Global end of trial date	31 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1 - To establish the maximum tolerated dose of GSK1120212 in combination with paclitaxel in the treatment of patients with advanced melanoma.

Phase 2 - To compare the efficacy of GSK1120212 in combination with paclitaxel, compared with paclitaxel alone in the treatment of patients with advanced or metastatic melanoma.

Protection of trial subjects:

This protocol was conducted in compliance with the UK Clinical Trials Regulations³, the principles of Good Clinical Practice (GCP) and the applicable policies of the Sponsoring Organisation. Together, these implement the ethical principles of the Declaration of Helsinki (1996) and the regulatory requirements for clinical trials of an investigational medicinal product under the European Union Clinical Trials Directive. In Germany, country-specific legal requirements were taken into account (the current version of German Drug Law [Arzneimittel Gesetz]).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2011
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	United Kingdom: 86
Country: Number of subjects enrolled	Germany: 25
Worldwide total number of subjects	111
EEA total number of subjects	111

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)	62
From 65 to 84 years	49
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The trial started with two arms (Paclitaxel and paclitaxel+GSK GSK1120212) aiming for three arms. Therefore, between March 2013 and April 2016, 111 eligible participants were recruited to the randomised phase. These were 86 in UK centres and 25 in the German.

Pre-assignment

Screening details:

382 patients assessed for eligibility and consent. out of the total patients screened 271 (185 ineligible and 86 refused to participate) patients excluded from the trial. As a result, 111 eligible patients randomised to the three arms on the ratio of 1:1:1

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Paclitaxel
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Paclitaxel
Investigational medicinal product code	Paclitaxel
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

paclitaxel 80 mg/m² by weekly intravenous infusion 3 weeks out of every 4. Treatment will be given on day 1, 8 and 15 of each cycle for up to 6 cycles

Arm title	GSK1120212 + Paclitaxel
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	GSK1120212
Investigational medicinal product code	trametinib
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Patients will receive the recommended dose of GSK1120212 once a day by mouth – as a result of the dose escalation component of the PACMEL trial the maximum tolerated dose was confirmed to be 2.0mg OD.

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

Dosage and administration details:

Patients will receive paclitaxel 80 mg/m² by weekly intravenous infusion 3 weeks out of every 4. Treatment will be given on day 1, 8 and 15 of each cycle for up to 6 cycles.

Arm title	Pazopanib + Paclitaxel
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Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Pazopanib
Investigational medicinal product code	Pazopanib
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

The recommended dose for the trial is pazopanib 800mg once a day by mouth.

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

Dosage and administration details:

Patients will receive paclitaxel 65 mg/m² by weekly intravenous infusion 3 weeks out of every 4. Treatment will be given on day 1, 8 and 15 of each cycle for up to 6 cycles.

Number of subjects in period 1	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel
Started	38	36	37
Completed	38	36	37

Baseline characteristics

Reporting groups

Reporting group title	Paclitaxel
Reporting group description: -	
Reporting group title	GSK1120212 + Paclitaxel
Reporting group description: -	
Reporting group title	Pazopanib + Paclitaxel
Reporting group description: -	

Reporting group values	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel
Number of subjects	38	36	37
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)	20	24	18
From 65-84 years	18	12	19
85 years and over	0	0	0
Age continuous Units: years			
median	64	60	66
full range (min-max)	35 to 80	27 to 80	41 to 80
Gender categorical Units: Subjects			
Female	11	13	12
Male	27	23	25
NRAS status Units: Subjects			
Yes	15	15	17
No	23	21	20
Prior therapy Units: Subjects			
Yes	13	12	14
No	25	24	23
LDH Units: Subjects			
Elevated	19	18	19
Within normal limits	19	18	18

Reporting group values	Total		
Number of subjects	111		

Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	62		
From 65-84 years	49		
85 years and over	0		
Age continuous Units: years			
median			
full range (min-max)	-		
Gender categorical Units: Subjects			
Female	36		
Male	75		
NRAS status Units: Subjects			
Yes	47		
No	64		
Prior therapy Units: Subjects			
Yes	39		
No	72		
LDH Units: Subjects			
Elevated	56		
Within normal limits	55		

Subject analysis sets

Subject analysis set title	Primary Analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The primary analysis was intention-to-treat and involved all 111 patients who were randomly assigned, irrespective of the treatment they received.

Reporting group values	Primary Analysis		
Number of subjects	111		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	62		
From 65-84 years	49		
85 years and over	0		
Age continuous			
Units: years			
median	63		
full range (min-max)	27 to 84		
Gender categorical			
Units: Subjects			
Female	36		
Male	75		
NRAS status			
Units: Subjects			
Yes	47		
No	64		
Prior therapy			
Units: Subjects			
Yes	39		
No	72		
LDH			
Units: Subjects			
Elevated	56		
Within normal limits	55		

End points

End points reporting groups

Reporting group title	Paclitaxel
Reporting group description: -	
Reporting group title	GSK1120212 + Paclitaxel
Reporting group description: -	
Reporting group title	Pazopanib + Paclitaxel
Reporting group description: -	
Subject analysis set title	Primary Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The primary analysis was intention-to-treat and involved all 111 patients who were randomly assigned, irrespective of the treatment they received.	

Primary: Progression free survival (PFS)

End point title	Progression free survival (PFS)
End point description:	
End point type	Primary
End point timeframe:	
The time from date of randomisation to the first date of progression (using CT scans and RECIST criteria) or date of death from any cause (events).	

End point values	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	37	
Units: Months				
median (confidence interval 90%)	3.43 (2.00 to 3.77)	5.20 (3.73 to 7.00)	5.33 (3.37 to 6.43)	

Statistical analyses

Statistical analysis title	PFS Paclitaxel + GSK1120212 Versus Paclitaxel
Statistical analysis description:	
In the SAP, it was stated that Cox regression model will be used to analyse the PFS, if the proportional hazard assumption was met but if this was not the case an AFT model will be used. Since the proportional hazard assumption did not meet, a log-logistic AFT model adjusted for NRAS mutations, prior treatment and LDH levels was applied.	
Comparison groups	Paclitaxel v GSK1120212 + Paclitaxel

Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
Method	Accelerated failure time (AFT) model
Parameter estimate	Time ratio
Point estimate	1.47
Confidence interval	
level	90 %
sides	2-sided
lower limit	1.08
upper limit	2.01

Statistical analysis title	PFS Paclitaxel + Pazopanib Versus Paclitaxel
Comparison groups	Paclitaxel v Pazopanib + Paclitaxel
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
Method	AFT model
Parameter estimate	Time ratio
Point estimate	1.36
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.96
upper limit	1.93

Secondary: Objective Response Rate (ORR)

End point title	Objective Response Rate (ORR)
End point description:	
End point type	Secondary
End point timeframe:	
This is defined as the best response recorded from date of randomisation to disease progression or date of last follow-up. ORR = (CR + PR)/all patients randomised	

End point values	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	37	
Units: subjects				
Complete response	2	0	0	
Partial response	3	15	8	
Stable disease	13	11	16	
Progressive disease	13	6	9	

Not evaluable	7	4	4	
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Statistical analyses

Statistical analysis title	ORR (GSK + Paclitaxel Vs Paclitaxel)
Statistical analysis description: Objective response rate calculated as the number of patients with CR or PR overall patients randomised. This was analysed using a Chi-Squared test.	
Comparison groups	Paclitaxel v GSK1120212 + Paclitaxel
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.01
Method	Chi-squared

Statistical analysis title	ORR (Pazopanib + Paclitaxel Vs Paclitaxel)
Statistical analysis description: Objective response rate calculated as the number of patients with CR or PR overall patients randomised. This was analysed using a Chi-Squared test.	
Comparison groups	Paclitaxel v Pazopanib + Paclitaxel
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.33
Method	Chi-squared

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
End point type	Secondary
End point timeframe: The time from date of randomisation to date of death for any cause (event). For patients without event, the time is censored at the date of the last follow-up.	

End point values	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	37	
Units: Months				
median (confidence interval 90%)	10.8 (8.77 to 9999)	9.37 (8.3 to 13.47)	10.57 (8.93 to 13.47)	

Statistical analyses

Statistical analysis title	OS Analysis (GSK + Pacli Vs Pacli)
Comparison groups	Paclitaxel v GSK1120212 + Paclitaxel
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.25
Method	Logrank

Statistical analysis title	OS Analysis (Pazo + Pacli Vs Pacli)
Comparison groups	Paclitaxel v Pazopanib + Paclitaxel
Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.22
Method	Logrank

Secondary: PFS at 6 months

End point title	PFS at 6 months
End point description:	
End point type	Secondary
End point timeframe:	
PFS at 6 months is the six month PFS estimate from the primary PFS KM plot with a 90%CI	

End point values	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	36	37	
Units: Percentage				
number (confidence interval 90%)				
6 Months PFS rate	27 (16 to 40)	39 (26 to 52)	41 (28 to 55)	

Statistical analyses

Statistical analysis title	PFS rate at 6 months (GSK+Paclitaxel Vs Paclitaxe)
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Statistical analysis description:

The estimated difference in PFS at 6 months were calculated using the formula for the 90% confidence interval for the difference in survival proportions
 $(P_1 - P_2) \pm 1.645 \times SE(P_1 - P_2)^*$

Where $SE(P_1 - P_2) = \sqrt{SE(P_1)^2 + SE(P_2)^2}$
P= the proportion of survival at 6 months in each arm
SE= Standard error

*Practical statistics for medical research. Douglas G. Altman, Chapman and Hall, London, 1991. Page no. 384

Comparison groups	GSK1120212 + Paclitaxel v Paclitaxel
Number of subjects included in analysis	74
Analysis specification	Pre-specified
Analysis type	other
Method	Kaplan Meier method
Parameter estimate	PFS rate
Point estimate	12
Confidence interval	
level	90 %
sides	2-sided
lower limit	-6
upper limit	30

Statistical analysis title	PFS rate at 6 months (Pazo + Pacli Vs Pacli)
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Statistical analysis description:

PFS at 6 months is the six month PFS estimate from the primary PFS KM plot with a 90%CI. The estimated difference in PFS at 6 months were calculated using the formula for the 90% confidence interval for the difference in survival proportions
 $(P_1 - P_2) \pm 1.645 \times SE(P_1 - P_2)^*$

Where $SE(P_1 - P_2) = \sqrt{SE(P_1)^2 + SE(P_2)^2}$
P= the proportion of survival at 6 months in each arm
SE= Standard error

*Practical statistics for medical research. Douglas G. Altman, Chapman and Hall, London, 1991

Comparison groups	Pazopanib + Paclitaxel v Paclitaxel
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Number of subjects included in analysis	75
Analysis specification	Pre-specified
Analysis type	other
Method	Kaplan Meier method
Parameter estimate	PFS rate
Point estimate	15
Confidence interval	
level	90 %
sides	2-sided
lower limit	-3
upper limit	32

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Event Monitoring starts from the time the patient receives any of the research procedures until they complete the trial (30 days post end of treatment) or beyond this time if the AE is an adverse reaction.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Paclitaxel
Reporting group description: -	
Reporting group title	GSK1120212 + Paclitaxel
Reporting group description: -	
Reporting group title	Pazopanib + Paclitaxel
Reporting group description: -	

Serious adverse events	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 38 (13.16%)	17 / 36 (47.22%)	25 / 37 (67.57%)
number of deaths (all causes)	20	23	23
number of deaths resulting from adverse events			
Vascular disorders			
Phlebitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Infusion site extravasation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Allergic reaction			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic enzymes increased			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver function test increased			

subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infusion related reaction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiomyopathy			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
intracranial haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vasovagal reaction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
other-source unknown			

subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower gastrointestinal haemorrhage			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	1 / 1	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colonic perforation			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Gastric haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oral hemorrhage			

subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
bowel obstruction			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hematuria			
subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Lung infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 38 (2.63%)	1 / 36 (2.78%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 36 (2.78%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			

subjects affected / exposed	0 / 38 (0.00%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	2 / 36 (5.56%)	0 / 37 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Other - source unknown			
subjects affected / exposed	0 / 38 (0.00%)	3 / 36 (8.33%)	2 / 37 (5.41%)
occurrences causally related to treatment / all	0 / 0	0 / 3	2 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 36 (0.00%)	1 / 37 (2.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Paclitaxel	GSK1120212 + Paclitaxel	Pazopanib + Paclitaxel
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 38 (94.74%)	36 / 36 (100.00%)	37 / 37 (100.00%)
Investigations			
Alanine aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 38 (2.63%)	2 / 36 (5.56%)	12 / 37 (32.43%)
occurrences (all)	1	2	21
Aspartate aminotransferase increased			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 38 (2.63%)	3 / 36 (8.33%)	9 / 37 (24.32%)
occurrences (all)	1	3	14
Blood alkaline phosphatase increased			
alternative assessment type: Non-systematic			

subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	3 / 36 (8.33%) 3	8 / 37 (21.62%) 9
Vascular disorders Hypertension alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	3 / 36 (8.33%) 4	6 / 37 (16.22%) 8
Nervous system disorders Dysgeusia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Headache alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3 2 / 38 (5.26%) 2	4 / 36 (11.11%) 4 6 / 36 (16.67%) 7	12 / 37 (32.43%) 12 7 / 37 (18.92%) 7
Blood and lymphatic system disorders Anaemia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Lymphopenia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Neutropenia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	4 / 38 (10.53%) 6 0 / 38 (0.00%) 0 1 / 38 (2.63%) 1	11 / 36 (30.56%) 14 3 / 36 (8.33%) 3 5 / 36 (13.89%) 5	9 / 37 (24.32%) 10 7 / 37 (18.92%) 12 9 / 37 (24.32%) 9
General disorders and administration site conditions Fatigue alternative assessment type: Non-systematic subjects affected / exposed occurrences (all) Pyrexia	17 / 38 (44.74%) 27	23 / 36 (63.89%) 52	18 / 37 (48.65%) 50

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	3 / 38 (7.89%) 3	8 / 36 (22.22%) 8	3 / 37 (8.11%) 3
Gastrointestinal disorders Abdominal pain alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	8 / 38 (21.05%) 9	14 / 36 (38.89%) 15	21 / 37 (56.76%) 24
Constipation alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	12 / 38 (31.58%) 12	16 / 36 (44.44%) 16	2 / 37 (5.41%) 2
Diarrhoea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	20 / 38 (52.63%) 20	35 / 36 (97.22%) 42	29 / 37 (78.38%) 41
Dyspepsia alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	7 / 38 (18.42%) 7	4 / 36 (11.11%) 4	4 / 37 (10.81%) 4
Nausea alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	10 / 38 (26.32%) 11	10 / 36 (27.78%) 12	16 / 37 (43.24%) 17
Vomiting alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	5 / 36 (13.89%) 5	9 / 37 (24.32%) 9
Respiratory, thoracic and mediastinal disorders Cough alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 6	4 / 36 (11.11%) 4	5 / 37 (13.51%) 5
Dyspnoea alternative assessment type: Non-			

systematic			
subjects affected / exposed	8 / 38 (21.05%)	8 / 36 (22.22%)	8 / 37 (21.62%)
occurrences (all)	9	9	10
Epistaxis			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 38 (10.53%)	9 / 36 (25.00%)	6 / 37 (16.22%)
occurrences (all)	4	9	6
Skin and subcutaneous tissue disorders			
Alopecia			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 38 (44.74%)	13 / 36 (36.11%)	13 / 37 (35.14%)
occurrences (all)	21	15	15
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 38 (2.63%)	6 / 36 (16.67%)	6 / 37 (16.22%)
occurrences (all)	2	7	6
Rash			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 38 (15.79%)	34 / 36 (94.44%)	9 / 37 (24.32%)
occurrences (all)	7	103	9
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 38 (18.42%)	2 / 36 (5.56%)	4 / 37 (10.81%)
occurrences (all)	9	2	4
Arthralgia			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 38 (10.53%)	2 / 36 (5.56%)	4 / 37 (10.81%)
occurrences (all)	4	3	4
Infections and infestations			
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 38 (10.53%)	3 / 36 (8.33%)	3 / 37 (8.11%)
occurrences (all)	4	3	3
Urinary tract infection			

alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	2 / 38 (5.26%) 2	5 / 36 (13.89%) 6	5 / 37 (13.51%) 5
Metabolism and nutrition disorders Decreased appetite alternative assessment type: Non-systematic subjects affected / exposed occurrences (all)	6 / 38 (15.79%) 7	13 / 36 (36.11%) 13	11 / 37 (29.73%) 12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 January 2012	N/A
21 June 2013	Protocol changes to reflect the addition of a third treatment (pazopanib in combination with paclitaxel) arm to the PACMEL trial and other additional changes are provided separately with the notification. Pazopanib is an antiangiogenic agent. Evidence suggests that antiangiogenic therapies can enhance the impact of chemotherapy by inducing vascular normalization, alleviating hypoxia and increasing the delivery of cytotoxic chemotherapies to cancer cells. Clinical trials using pazopanib in combination with paclitaxel in the treatment of melanoma have also shown promising results. However, these results could be explained by patient selection. Therefore there is a need to compare the combination against paclitaxel alone. The PACMEL study offers a means to do this very efficiently, as the required control arm is already included in the trial and the entry criteria and safety monitoring of the current study are consistent with what is required for the safety profile of pazopanib.
06 December 2013	<p>Removal of the inclusion criterion "Maximum 2 prior lines of treatment for advanced disease" in the Protocol, to allow patients at any point in the treatment pathway to be considered. Patients are now considering cytotoxic chemotherapy later in the treatment pathway as more agents become available. Prior therapy will not impact upon the primary endpoint and removing this inclusion criterion will make the trial available to more patients.</p> <p>Change to exclusion point 1 (Any systemic anticancer therapy within 28 days prior to starting treatment) to permit eligibility 42 days after prior ipilimumab treatment – in the protocol synopsis this is given as 63 days prior to starting trial treatment, however, no statement has been made previously in the main exclusion criteria with regards ipilimumab. 28 days washout period is too short for ipilimumab, however, 63 is excessive and 42 is sufficient. The Main eligibility criteria have been updated to reflect the Synopsis for consistency.</p> <p>Additional blood sample for genetic testing which could previously be taken at screening is changed to being taken at cycle 1 day 1. Only blood samples donated by randomised patients will be analysed, therefore patients should not be asked to donate blood prior to randomisation as this blood will not be analysed if they are not subsequently randomised.</p> <p>Additions to the list of adverse events which do not require to be reported: medical/surgical procedures, day-to-day fluctuations in preexisting disease or conditions, expected progression or signs of the patients' melanoma. This is done to improve protocol clarity and avoid unnecessary reporting of events which have no impact on patient safety in the trial.</p>
22 September 2014	Addition of details for German sites. None sub-amendment for the UK.
17 June 2015	We were not on target to recruit according to the milestones stated. Recruitment had been lower than expected but has picked up in Q1 2015 due to competing studies/treatments no longer causing an issue, thus we have secured an extension until January 2016. Updates and clarifications to the safety sections of protocol due to amended working practices and amendments to bring the protocol in line with the German version.

01 June 2016	Change to recruitment end date from January 2016 to April 2016 due to slower recruitment rate than expected. Change of wording to MAX of 120 patients as fewer patients now needed according to statistical assessment. Change to definition of the end of the trial due to longer recruitment period. Updates to OCTO contact details throughout the protocol due to changes in staff and new email addresses for the trials unit.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported