Clinical trial results:
GAMEC-SHORT (S) & GAMEC-ANTHRACYCLINE (A) RISK-ADAPTED PROTOCOL FOR RELAPSED GERM CELL TUMOURS (GCT)

Summary

EudraCT number	2006-001963-52
Trial protocol	GB
Global end of trial date	14 January 2014

Results information

Result version number	v1 (current)
This version publication date	23 March 2019
First version publication date	23 March 2019

Trial information

Trial identification

Sponsor protocol code	GAMEC II

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Queen Mary University London
Sponsor organisation address	5 Walden Street, London, United Kingdom, E1 2EF
Public contact	CECM Trials Team, CECM Trials Team, Queen Mary University of London, bci-cecmmonitoring@qmul.ac.uk
Scientific contact	CECM Trials Team, CECM Trials Team, Queen Mary University of London, bci-cecmmonitoring@qmul.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	10 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 January 2014
Global end of trial reached?	Yes
Global end of trial date	14 January 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study aimed to address two questions. The first was whether treatment for patients with no identifiable risk factors could be shortened to 6 weeks (GAMEC-S (short)) and whether patients with these risk factors (either raised LDH at relapse or > 35 years old) would benefit from the substitution epirubicin for etoposide (GAMEC-A (anthracycline)).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 July 2006
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 36
Worldwide total number of subjects	36
EEA total number of subjects	36

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)	36
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 21/08/2006 and 06/01/2012, 36 patients with relapsed germ cell tumours were recruited.

Pre-assignment

Screening details:

Patients who relapsed with germ cell tumours after failure of cisplatin based combination chemotherapy were eligible for study entry. Patients had to have evidence of relapse based on the presence of rising tumour markers and/or the development of radiological progression on CT.

Pre-assignment period milestones

Number of subjects started	36
Number of subjects completed	36

Period 1

Period 1 title	GAMEC (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	GAMEC-A

Arm description:

Patients with either a raised LDH and/or were 35 years or older were allocated to therapy with GAMEC-A (actinomycin-D 1mg/m2 day 1, methotrexate 8g/m2 ,cisplatin 50mg/m2, day 2 and 3 and 8, epirubicin 37.5mg/m2 days 1 and 2 followed by pegfilgrastim 6mg on day 3), treatment was given on weeks1, 3 ,6 , 8 and 10 . From week 6 onwards day 8 cisplatin was omitted. The dose of methotrexate was adjusted according to glomerular filtration rate as determined by an EDTA clearance as follows:> 120ml/min-10g/m2, 100-119ml/min 8g/m2, 80-99ml/min 6g/m2, 60-79ml/min 4g/m2, 40-59ml/min 2g/m2, 25-39ml/min.

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

Dosage and administration details:

6 mgs

Investigational medicinal product name	Actinomycin - D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

1 mg/m2

Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection

Routes of administration	Intravenous use

Dosage and administration details:

8 g/m2

Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/m2

Investigational medicinal product name	Cisplatin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

50 mg/m2

Investigational medicinal product name	Epirubicin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

37.5 mg/m2

Arm title	GAMEC-S

Arm description:

Patients with neither risk factor were treated with GAMEC-S. In this protocol epirubicin was replaced by etoposide 90mg/m2 days 1, 2, 3 and 4. Treatment was stopped after 3 cycles (weeks 1, 3, and 6 only). Dose reductions and treatment administration have been described previously.

Arm type	Experimental
Investigational medicinal product name	Etoposide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

90 mg/m2

Number of subjects in period 1	GAMEC-A	GAMEC-S
Started	15	21
Completed	15	21

Baseline characteristics

Reporting groups	
Reporting group title	GAMEC

Reporting group description: -

Reporting group values	GAMEC	Total	
Number of subjects	36	36	
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)		0	
From 65-84 years		0	
85 years and over		0	
Age continuous Units: years			
median	31.5		
full range (min-max)	18 to 56	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	36	36	
IGCCCG at diagnosis Units: Subjects			
Good	16	16	
Intermediate	9	9	
Poor	11	11	
1st Line Chemotherapy Units: Subjects			
BEP/EP	30	30	
EP	1	1	
VIP	2	2	
CBOP/BEP	2	2	
BEP + IPO at relapse	1	1	
IPFSG risk group at relapse Units: Subjects			
Low risk	3	3	
Intermediate risk	24	24	
High Risk	8	8	
n/a (3rd Line)	1	1	
Primary Units: Subjects			

Testes	30	30	
Extra gonadal	5	5	
Mediastinal	1	1	
Histology Units: Subjects			
NSGCT	33	33	
Pure seminoma	3	3	

Subject analysis sets

Subject analysis set title	GAMEC - S
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with neither risk factor were treated with GAMEC-S. In this protocol epirubicin was replaced by etoposide 90mg/m2 days 1, 2, 3 and 4. Treatment was stopped after 3 cycles (weeks 1, 3, and 6 only). Dose reductions and treatment administration have been described previously.

Subject analysis set title	GAMEC-A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with either a raised LDH and/or 35 years or older were allocated to therapy with GAMEC-A (actinomycin-D 1mg/m2 day 1, methotrexate 8g/m2 ,cisplatin 50mg/m2, day 2 and 3 and 8, epirubicin 37.5mg/m2 days 1 and 2 followed by pegfilgrastim 6mg on day 3), treatment was given on weeks1, 3 ,6 , 8 and 10 . From week 6 onwards day 8 cisplatin was omitted. The dose of methotrexate was adjusted according to glomerular filtration rate as determined by an EDTA clearance as follows:> 120ml/min-10g/m2, 100-119ml/min 8g/m2, 80-99ml/min 6g/m2, 60-79ml/min 4g/m2, 40-59ml/min 2g/m2, 25-39ml/min.

Reporting group values	GAMEC - S	GAMEC-A	
Number of subjects	21	15	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	30	38	
full range (min-max)	18 to 36	25 to 56	
Gender categorical Units: Subjects			
Female	0	0	
Male	36	36	
IGCCCG at diagnosis Units: Subjects			
Good	7	9	
Intermediate	6	3	

Poor	8	3	
1st Line Chemotherapy Units: Subjects			
BEP/EP	18	12	
EP	1	0	
VIP	0	2	
CBOP/BEP	2	0	
BEP + IPO at relapse	0	1	
IPFSG risk group at relapse Units: Subjects			
Low risk	2	1	
Intermediate risk	14	10	
High Risk	5	3	
n/a (3rd Line)	0	1	
Primary Units: Subjects			
Testes	18	12	
Extra gonadal	3	2	
Mediastinal	0	1	
Histology Units: Subjects			
NSGCT	20	13	
Pure seminoma	1	2	

End points

End points reporting groups

Reporting group title	GAMEC-A

Reporting group description:

Patients with either a raised LDH and/or were 35 years or older were allocated to therapy with GAMEC-A (actinomycin-D 1mg/m2 day 1, methotrexate 8g/m2 ,cisplatin 50mg/m2, day 2 and 3 and 8, epirubicin 37.5mg/m2 days 1 and 2 followed by pegfilgrastim 6mg on day 3), treatment was given on weeks1, 3 ,6 , 8 and 10 . From week 6 onwards day 8 cisplatin was omitted. The dose of methotrexate was adjusted according to glomerular filtration rate as determined by an EDTA clearance as follows:> 120ml/min-10g/m2, 100-119ml/min 8g/m2, 80-99ml/min 6g/m2, 60-79ml/min 4g/m2, 40-59ml/min 2g/m2, 25-39ml/min.

Reporting group title	GAMEC-S

Reporting group description:

Patients with neither risk factor were treated with GAMEC-S. In this protocol epirubicin was replaced by etoposide 90mg/m2 days 1, 2, 3 and 4. Treatment was stopped after 3 cycles (weeks 1, 3, and 6 only). Dose reductions and treatment administration have been described previously.

Subject analysis set title	GAMEC - S
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with neither risk factor were treated with GAMEC-S. In this protocol epirubicin was replaced by etoposide 90mg/m2 days 1, 2, 3 and 4. Treatment was stopped after 3 cycles (weeks 1, 3, and 6 only). Dose reductions and treatment administration have been described previously.

Subject analysis set title	GAMEC-A
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients with either a raised LDH and/or 35 years or older were allocated to therapy with GAMEC-A (actinomycin-D 1mg/m2 day 1, methotrexate 8g/m2 ,cisplatin 50mg/m2, day 2 and 3 and 8, epirubicin 37.5mg/m2 days 1 and 2 followed by pegfilgrastim 6mg on day 3), treatment was given on weeks1, 3 ,6 , 8 and 10 . From week 6 onwards day 8 cisplatin was omitted. The dose of methotrexate was adjusted according to glomerular filtration rate as determined by an EDTA clearance as follows:> 120ml/min-10g/m2, 100-119ml/min 8g/m2, 80-99ml/min 6g/m2, 60-79ml/min 4g/m2, 40-59ml/min 2g/m2, 25-39ml/min.

Primary: PFS at 2 years

End point title	PFS at 2 years

End point description:

End point type	Primary

End point timeframe:

2 years

End point values	GAMEC - S	GAMEC-A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	15		
Units: Percentage				
number (confidence interval 95%)	57 (33.8 to 74.9)	27 (8.3 to 49.6)		

Statistical analyses

Statistical analysis title	PFS at 2 years

Statistical analysis description:

Progression free survival of GAMEC-A and GAMEC-S patients were compared using Kaplan Meier curves with log-rank tests.

Comparison groups	GAMEC - S v GAMEC-A
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.11 [1]
Method	Logrank

Notes:

[1] - The log rank p-value is a comparison of the K-M curves of the entire study i.e. not at 2 years.

Secondary: Overall survival

End point title	Overall survival

End point description:

End point type	Secondary

End point timeframe:

At 3 years

End point values	GAMEC - S	GAMEC-A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	15		
Units: Percentage				
number (confidence interval 95%)	56 (32 to 74)	23 (5.9 to 47.3)		

Attachments (see zip file)	OS/GAMEC_S_OS Kaplan Meier Curves.docx.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: PFS median

End point title	PFS median

End point description:

End point type	Secondary

End point timeframe:

Until progression or death

End point values	GAMEC - S	GAMEC-A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	15		
Units: years				
median (confidence interval 95%)	4.94 (0.36 to 99999)	0.43 (0.16 to 0.62)		

Attachments (see zip file)	PFS/GAMEC_S_PFS Kaplan Meier Curve.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Response

End point title	Response

End point description:

End point type	Secondary

End point timeframe:

overall

End point values	GAMEC - S	GAMEC-A		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	15		
Units: patients				
CR	8	1		
M-ve PR	8	9		
M+ve PR	1	0		
SD	0	1		
PD	0	3		
Non-evaluable	4	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the start of study treatment to 30 days after the last dose.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI
Dictionary version	3

Reporting groups

Reporting group title	GAMEC-S
Reporting group description: -	
Reporting group title	GAMEC-A
Reporting group description: -	

Serious adverse events	GAMEC-S	GAMEC-A	
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 21 (28.57%)	4 / 15 (26.67%)	
number of deaths (all causes)	9	11	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cerebral metastasis	Additional description: Convulsions and brain stem death		
subjects affected / exposed	1 / 21 (4.76%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
Chest pain	Additional description: Patient was on their way to the hospital for a planned admission, had sudden onset of central burning/pain radiating across chest. ECG showed changes of possible MI. Blood test shows raised Tropinin T- 1.99		
subjects affected / exposed	0 / 21 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fast atrial fibrilation			
subjects affected / exposed	0 / 21 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia	Additional description: Preceded by renal impairment		

subjects affected / exposed	0 / 21 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Death due to prolonged neutropenia	Additional description: Death following prolonged neutropenia leading to infection hypoxia renal failure. ALDs and multiple organ failure.		
subjects affected / exposed	1 / 21 (4.76%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Pneumothorax spontaneous	Additional description: Patient coughed and sustained pneumothorax. Patient is a smoker		
subjects affected / exposed	1 / 21 (4.76%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Required ventilation		
subjects affected / exposed	1 / 21 (4.76%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia sepsis	Additional description: Neutropenia sepsis leading to renal failure. Required ITU intervention and death in ITU		
subjects affected / exposed	0 / 21 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Septic shock	Additional description: Acute repiratory syndrome, refractory to ventilation		
subjects affected / exposed	1 / 21 (4.76%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	GAMEC-S	GAMEC-A	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 21 (95.24%)	15 / 15 (100.00%)	
Investigations			
Weight loss			

subjects affected / exposed	13 / 21 (61.90%)	12 / 15 (80.00%)	
occurrences (all)	25	28	
Neutropenia			
subjects affected / exposed	20 / 21 (95.24%)	15 / 15 (100.00%)	
occurrences (all)	54	40	
Thrombocytopenia			
subjects affected / exposed	20 / 21 (95.24%)	15 / 15 (100.00%)	
occurrences (all)	54	47	
General disorders and administration site conditions			
Skin toxicity			
subjects affected / exposed	4 / 21 (19.05%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Pain			
subjects affected / exposed	10 / 21 (47.62%)	5 / 15 (33.33%)	
occurrences (all)	13	8	
Fatigue			
subjects affected / exposed	19 / 21 (90.48%)	14 / 15 (93.33%)	
occurrences (all)	49	40	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 21 (95.24%)	15 / 15 (100.00%)	
occurrences (all)	44	44	
Gastrointestinal disorders			
Mucositis			
subjects affected / exposed	18 / 21 (85.71%)	15 / 15 (100.00%)	
occurrences (all)	41	36	
Nausea			
subjects affected / exposed	16 / 21 (76.19%)	11 / 15 (73.33%)	
occurrences (all)	34	26	
Vomiting			
subjects affected / exposed	15 / 21 (71.43%)	11 / 15 (73.33%)	
occurrences (all)	28	23	
Constipation			
subjects affected / exposed	6 / 21 (28.57%)	3 / 15 (20.00%)	
occurrences (all)	10	3	
Skin and subcutaneous tissue disorders			

Alopecia subjects affected / exposed occurrences (all)	19 / 21 (90.48%) 43	14 / 15 (93.33%) 42	
Infections and infestations Infection subjects affected / exposed occurrences (all)	18 / 21 (85.71%) 35	15 / 15 (100.00%) 30	
Metabolism and nutrition disorders Anorexia subjects affected / exposed occurrences (all)	17 / 21 (80.95%) 38	13 / 15 (86.67%) 31	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2008	Closed Arm GAMEC-A following a relapse rate of 80% in the first 16 patients, which remained unchanged from previous studies. The regimen offered no advantage in terms of toxicity. Change in Sponsor to Queen Mary University of London
23 December 2008	Supplier change for the IMPs cisplatin and etoposide.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported