Clinical trial results:
OPEN LABEL PHASE II STUDY TO EVALUATE THE SAFETY OF STANDARD INDUCTION AND CONSOLIDATION THERAPY IN COMBINATION WITH DASATINIB IN NEWLY DIAGNOSED ADULT PATIENTS WITH PHILADELPHIA CHROMOSOME POSITIVE ACUTE LYMPHOBLASTIC LEUKEMIA (PH+ALL)

Summary

EudraCT number	2010-022854-18
Trial protocol	DE
Global end of trial date	30 September 2015

Results information

Result version number	v1 (current)
This version publication date	09 April 2020
First version publication date	09 April 2020

Trial information

Trial identification

Sponsor protocol code	GMALL-PH-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01724879
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Goethe Universität Frankfurt
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt, Germany, 60590
Public contact	Studienzentrale, Med. Klinik II, Goethe Universität Frankfurt, +49 (0)6963016366, gmall@em.uni-frankfurt.de
Scientific contact	Studienzentrale, Med. Klinik II, Goethe Universität Frankfurt, +49 (0)6963016366, gmall@em.uni-frankfurt.de

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	18 April 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 April 2013
Global end of trial reached?	Yes
Global end of trial date	30 September 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the feasibility of a combination of Dasatinib and standard chemotherapy in adult ALL

Protection of trial subjects:

A Data Safety Monitoring Board (DSMB) has been instituted for this study in order to ensure its ongoing safety. The committee includes 3 members. Safety review meeting will be held as required by the sponsor. Enrollment to the study will continue throughout the scheduled meetings of the DSMB. Decisions on trial termination, amendment or cessation of patient recruitment based on safety findings will be based on recommendations of the DSMB.

Background therapy:

PREPHASE (recommended standard of care): Dexamethasone; Cyclophosphamide; Intrathecal (IT) MTX
INDUCTION PHASE I (starting at day 6): Dexamethasone; Vincristine; PEG-asparaginase; G-CSF
INDUCTIONPHASE II (starting at day 26): Methotrexat i.th.; Cyclophosphamide; Cytarabine; 6-Mercaptopurine; G-CSF; Cranial irradiation parallel to Induction II in CR patients
CONSOLIDATION I (starting at "day 71" for patients in CR after induction therapy): Dexamethasone (orally); Vindesine; HD-Methotrexate; VP16; HD-Cytarabine; G-CSF;
intrathecal MTX/AraC/DEX

Evidence for comparator:

N.A.

Actual start date of recruitment	08 August 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 19
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	19
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

17-Nov-2011 FPI (First Patient In)
11-Apr-2013 19th Patient out
03-May-2013 Recruitment interrupted after interim safety analysis for DSUR and consultation of DSMB (decision not to amend the study, but to stop the trial finaly was done later in 2015)

Pre-assignment

Screening details:

Screening applies to confirmed new diagnosis of Philadelphia chromosome or BCR-ABL positive acute lymphoblastic leukaemia (ALL).
BCR-ABL Assessment is standard of care for ALL.
Patients aged 18-55 years.
First-line-Therapy (Not previously treated except for prephase therapy)

Period 1

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

Blinding implementation details:

N.A.
(open-label single-arm phase II study)
Dasatinib+ Chemotherapy

Arms

Arm title	Dasatinib+ Chemotherapy (open-label single-arm study)

Arm description:

Dasatinib + Backbone Chemotherapy as described above

Arm type	open-label single-arm study
Investigational medicinal product name	Dasatinib
Investigational medicinal product code	ATC: LO1XE06
Other name	Sprycel
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

140mg /day, in case of toxicitiy dose reduction to 70mg/day possible

Number of subjects in period 1	Dasatinib+ Chemotherapy (open-label single-arm study)
Started	19
Induction I	19
Induction II	19
Interval 1	14
Consolidation I	13
Interval 2	12

Completed	12
Not completed	7
Adverse event, serious fatal	4
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description:

Planned subject number was a maximum of 20 patients evaluable for feasibility. Before halt of recruitment in April 2013, 19 patients had been enrolled and could be analyzed. The analysis was performed based on the data available from the closed database (29-Oct-2013). All enrolled Patients (N=19) belong to the intention-to-treat analysis set, which is therofre identical to the full analysis set. All Patients enter feasibility analysis. For the purpose of this report no further analysis set has been defined.

Reporting group values	overall trial	Total	
Number of subjects	19	19	
Age categorical			
ALL Patients 18-55 Years old			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
18-55 Years	19	19	
Age continuous			
Age Median: 45 yrs Range: 31-53 yrs 18-25 yrs: N=0; 0% 25-45 yrs: N=11; 58% 46-55 yrs: N=8; 42%			
Units: years			
median	45		
full range (min-max)	31 to 53	-	
Gender categorical			
Gender Male: N=12; 63%			
Units: Subjects			
Female	7	7	
Male	12	12	

End points

End points reporting groups

Reporting group title	Dasatinib+ Chemotherapy (open-label single-arm study)
Reporting group description:	
Dasatinib + Backbone Chemotherapy as described above	

Primary: survival and treatment related discontinuation

End point title	survival and treatment related discontinuation[1]

End point description:

20 eligible subjects with newly diagnosed Philadelphia positive ALL will be included in the study for assessment of feasibility. Patients who are enrolled but do not receive the first dose of Dasatinib will be replaced. A death rate of greater than 20% during induction therapy and a discontinuation rate of greater than 35% by or before end of study treatment due to death or treatment-related toxicity will be considered to constitute non-feasibility. If these thresholds, based on projected recruitment of 20 patients, are already exceeded before 20 patients are enrolled, the study will be stopped.
Results:
19 patients were evaluable. Four patients died during induction therapy (21%) and one patient discontinued induction II therapy due to adverse events (PR on day 26, CR achieved after end of study on day 46). 2 additional patients discontinued therapy after induction in CR due to adverse events (due to probably chemotherapy related events). Overall Discontinuation Rate = 37%

End point type	Primary

End point timeframe:

after consolidation (after approx. 3 Month of treatment)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Analysis is done by descriptive statistics:
It is expected that the mortality rate (excluding mortality due to persisting or progressive leukema) will not exceed 20% during study treatment, and that the rate of treatment-related discontinuation due to death or treatment-related toxicity will not exceed 35%. Rates exceeding these thresholds will be considered to constitute non-feasibility. Analysis will be made by descriptive statistics.

End point values	Dasatinib+ Chemotherapy (open-label single-arm study)			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients (percentages)				
treatment related discontinuation	3			
Death	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Molecular CR rate

End point title	Molecular CR rate

End point description:

MRD analysis, i.e. the determination of the molecular remission status based on the quantitative measurement of the BCR-ABL transcript was scheduled at screening/time point of diagnosis and at different time-points during treatment.
Patients with non quantifiable MRD status or insufficient sensitivity (less than 10-4) remained unevaluable. On Day 46 (after induction therapy) 11 patients with cytologic CR were evaluable for MRD analysis. 6 of these patients had achieved a molecular CR (55%). At end of study 8 patients were evaluable for MRD testing and 6 had a molecular CR (75%).

End point type	Secondary

End point timeframe:

After consolidation (after approx 3 Month of treatment)

End point values	Dasatinib+ Chemotherapy (open-label single-arm study)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: Patients with molecular CR after Cons.	6			

Statistical analyses

No statistical analyses for this end point

Secondary: Hematologic CR rate at end of induction II

End point title	Hematologic CR rate at end of induction II

End point description:

In 14 of 19 enrolled patients (74%) a CR was achieved on day 46 during study.

End point type	Secondary

End point timeframe:

After induction II

End point values	Dasatinib+ Chemotherapy (open-label single-arm study)			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Number of Patients with CR after Ind II	14			

Statistical analyses

No statistical analyses for this end point

Secondary: BCR-ABL mutations occuring during treatment

End point title	BCR-ABL mutations occuring during treatment

End point description:

no mutations have been observed

End point type	Secondary

End point timeframe:

Sequencing of MRD-Testings until EOS

End point values	Dasatinib+ Chemotherapy (open-label single-arm study)			
Subject group type	Reporting group			
Number of subjects analysed	19			
Units: Patients with Mutations in BCR-ABL	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Grade III and IV toxicity by CTC

End point title	Grade III and IV toxicity by CTC

End point description:

Induction I (14/19 Patients)
Hemoglobin (6), Leukocytes (7), Neutrophils (4), Platelets (10), Fibrinogen (2), Diarrhea (2), Pleural effusion - grade 2 (2)
Induction II (17/19 Patients)
Hemoglobin (8), Leukocytes (6), Neutrophils (5), Platelets (10), Fibrinogen (2), Coagluation Other - ATIII deficiency (3), Anorexia / Nausea (3) Febrile Neutropenia (2), Infection -documented clinically - with grade 3 or 4 ANC/unknown ANC (2/1), ALT (3), Bilirubin (4), GGT (3), Pain - Headache (2), Pleural effusion - grade 2 (2)
Intervall 1 (10/14 Patients)
Hemoglobin (7), Leukocytes (3), Neutrophils (4), Platelets (7), Nausea (2), ALT (2), Bilirubin (2), GGT (3), Pain – Head/headache (2).
Consolidation I (11/13 Patients)
Hemoglobin (6), Leukocytes (2), Neutrophils (4), Platelets (5) Mucositis/stomatitis (4), Renal failure (2).
Intervall 2 (8/12 Patients)
Hemoglobin (5), Leukocytes (3), Neutrophils (4), Platelets (6), Mucositis/stomatitis (5), Vomiting (2), ALT (2), AST (2).

End point type	Secondary

End point timeframe:

separate anlysis for therapyphases:
Induction I (19 Patients); Induction II (19 Patients); Intervall 1 (14 Patients); Consolidation I (13 Patients); Intervall 2 (12 Patients)

End point values	Dasatinib+ Chemotherapy (open-label single-arm study)			
Subject group type	Reporting group			
Number of subjects analysed	19[2]			
Units: Patients				
Induction I (N=19)	14			
Induction II (N=19)	17			
Interval 1 (N=14)	10			
Consolidation I (N=13)	11			
Interval 2 (N=12)	8			

Notes:

[2] - Patients with AEs

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Overall timeframe divided into therapy phases as reporting groups:
Induction I, Induction II, Interval 1, Consolidation I, Interval 2

Adverse event reporting additional description:

only events with CTCAE grade 3 or 4 and pleural effusions of any grade
12 SAE reported under Therapy
(1 SAE reported post study after EOS: "Metabolic Laboratory, Liver Associated", has been included as non-serious-AE in this report)

Assessment type	Non-systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	1 - Induction I

Reporting group description:

Patients in Induciton I (N=19)

Reporting group title	2 - Induction II

Reporting group description: -

Reporting group title	3 - Interval 1

Reporting group description: -

Reporting group title	4 - Consolidation I

Reporting group description: -

Reporting group title	5 - Inverval 2

Reporting group description: -

Serious adverse events	1 - Induction I	2 - Induction II	3 - Interval 1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	7 / 19 (36.84%)	0 / 14 (0.00%)
number of deaths (all causes)	0	4	0
number of deaths resulting from adverse events	0	4	0
Nervous system disorders			
Seizure (1 SAE, non fatal, not attributed to study drug)	Additional description: In one patient a seizure occurred and subsequently a temporary behavioral change was reported as SAE. The case was classified as neurological event. Magnetic resonance imaging was performed and revealed lesions		
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (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
General disorders and administration site conditions			
CNS hemorrhage (2 SAE, 1 fatal outcome, 2 with possible attribution to study drug)	Additional description: One fatal subdural bleeding occurred in association with thrombocytopenia grade 3 in induction phase II. A second subdural and cerebral bleeding was observed after consolidation I and is resolved in the meantime.		

subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Lung hemorrhage (1 SAE, 1 fatal outcome, 1 with potential attribution to study drug)	Additional description: One fatal lung bleeding occurred in association with thrombocytopenia grade 4 during induction phase II.		
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Gastrointestinal disorders			
Sepsis (2 SAE, 2 fatal outcome, 2 not attributed to study drug)	Additional description: Two cases of fatal sepsis have been reported as SAE. Sepsis in neutropenia is a well known risk in the therapy of ALL with chemotherapy alone independent of the additional use of tyrosine kinase inhibitors such as Dasatinib.		
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Vomiting/Nausea (1 SAE, non fatal, 1 with potential attribution to study drug)	Additional description: Nausea and vomiting are documented side effects of chemotherapy for ALL. In one patient recurrent vomiting was observed and reported as SAE. The patient has been admitted to hospital. The vomitus contained haematin. A gastroscopy revealed no abnormal		
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatotoxicity (5 SAEs, non fatal, 4 with potential attribution to study drug)	Additional description: Elevated liver enzymes and hyperbilirubinemia are documented side effect of chemotherapy for ALL. 5 SAEs have been reported, 1 SAE was reported post study and is not listed below		
subjects affected / exposed	0 / 19 (0.00%)	3 / 19 (15.79%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal toxicity (1 SAE, non fatal, 1 potential attribution to study drug)	Additional description: Elevated creatinine levels after consolidation I have been reported in one patient. Consolidation I includes a 24h-infusion with high-dose methotrexate. The patient displayed prolonged methotrexate clearance.		
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	4 - Consolidation I	5 - Inverval 2	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 13 (23.08%)	2 / 12 (16.67%)	
number of deaths (all causes)	0	0	

number of deaths resulting from adverse events	0	0	
Nervous system disorders			
Seizure (1 SAE, non fatal, not attributed to study drug)	Additional description: In one patient a seizure occurred and subsequently a temporary behavioral change was reported as SAE. The case was classified as neurological event. Magnetic resonance imaging was performed and revealed lesions		
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
CNS hemorrhage (2 SAE, 1 fatal outcome, 2 with possible attribution to study drug)	Additional description: One fatal subdural bleeding occurred in association with thrombocytopenia grade 3 in induction phase II. A second subdural and cerebral bleeding was observed after consolidation I and is resolved in the meantime.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung hemorrhage (1 SAE, 1 fatal outcome, 1 with potential attribution to study drug)	Additional description: One fatal lung bleeding occurred in association with thrombocytopenia grade 4 during induction phase II.		
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Sepsis (2 SAE, 2 fatal outcome, 2 not attributed to study drug)	Additional description: Two cases of fatal sepsis have been reported as SAE. Sepsis in neutropenia is a well known risk in the therapy of ALL with chemotherapy alone independent of the additional use of tyrosine kinase inhibitors such as Dasatinib.		
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting/Nausea (1 SAE, non fatal, 1 with potential attribution to study drug)	Additional description: Nausea and vomiting are documented side effects of chemotherapy for ALL. In one patient recurrent vomiting was observed and reported as SAE. The patient has been admitted to hospital. The vomitus contained haematin. A gastroscopy revealed no abnormal		
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatotoxicity (5 SAEs, non fatal, 4 with potential attribution to study drug)	Additional description: Elevated liver enzymes and hyperbilirubinemia are documented side effect of chemotherapy for ALL. 5 SAEs have been reported, 1 SAE was reported post study and is not listed below		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Renal and urinary disorders			
Renal toxicity (1 SAE, non fatal, 1 potential attribution to study drug)	Additional description: Elevated creatinine levels after consolidation I have been reported in one patient. Consolidation I includes a 24h-infusion with high-dose methotrexate. The patient displayed prolonged methotrexate clearance.		
subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	1 - Induction I	2 - Induction II	3 - Interval 1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 19 (73.68%)	17 / 19 (89.47%)	10 / 14 (71.43%)
Vascular disorders			
Thrombosis/thrombus/embolism			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Fibrinogen			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	0 / 14 (0.00%)
occurrences (all)	2	2	0
Coagulation Other - AT-III deficiency			
subjects affected / exposed	0 / 19 (0.00%)	2 / 19 (10.53%)	0 / 14 (0.00%)
occurrences (all)	0	2	0
Constitutional Symptomes - Fatigue			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Hemorrhage GU- Vagina			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Hemorrhage - Rectum			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Pain Headache			
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Immune system disorders			

Allergy			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
pleural effusion (grade 2)			
subjects affected / exposed	2 / 19 (10.53%)	2 / 19 (10.53%)	1 / 14 (7.14%)
occurrences (all)	2	2	1
Pain upper respiratory			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pulmonary edema (grade 2)			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Hypertension			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Pericardial Effusion Grade 1			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Neuropahty: sensory			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0
Mood alteration - Depression			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			
Hemoglobin	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	6 / 19 (31.58%)	8 / 19 (42.11%)	7 / 14 (50.00%)
occurrences (all)	6	8	7
Leucocytes	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	7 / 19 (36.84%)	6 / 19 (31.58%)	3 / 14 (21.43%)
occurrences (all)	7	6	3

Neutrophils	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	4 / 19 (21.05%)	5 / 19 (26.32%)	4 / 14 (28.57%)
occurrences (all)	4	5	4
Platelets	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	10 / 19 (52.63%)	10 / 19 (52.63%)	7 / 14 (50.00%)
occurrences (all)	10	10	7
Eye disorders			
Eylid dysfunction			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	1 / 19 (5.26%)	3 / 19 (15.79%)	1 / 14 (7.14%)
occurrences (all)	1	3	1
Nausea			
subjects affected / exposed	1 / 19 (5.26%)	3 / 19 (15.79%)	2 / 14 (14.29%)
occurrences (all)	1	3	2
Mucositis/Stomatitis			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Diarrhea			
subjects affected / exposed	2 / 19 (10.53%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	2	0	0
Dysphagia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	0 / 14 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Metabolic/Laboratory - GGT			
subjects affected / exposed	1 / 19 (5.26%)	3 / 19 (15.79%)	3 / 14 (21.43%)
occurrences (all)	1	3	3
Skin and subcutaneous tissue disorders			

Rash Dermatitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Renal failure	Additional description: Only cases without SAE-report summarized		
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Febrile neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	2 / 19 (10.53%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
infection with grade 3-4 ANC	Additional description: (middle ear)		
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Infection with unknown ANC	Additional description: cases of infections without SAE cirteria		
subjects affected / exposed	0 / 19 (0.00%)	1 / 19 (5.26%)	2 / 14 (14.29%)
occurrences (all)	0	1	2
Metabolism and nutrition disorders			
Metabolic/Laboratory - ALT	Additional description: Standard Laboratory Assessment, only cases without SAE-report summarized		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 19 (5.26%)	1 / 19 (5.26%)	0 / 14 (0.00%)
occurrences (all)	1	1	0
Metabolic/Laboratory - AST	Additional description: Standard Laboratory Assessment, only cases without SAE-report summarized		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	0	0	0
Metabolic/Laboratory - Bilirubin	Additional description: Standard Laboratory Assessment, only cases without SAE-report summarized		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 19 (0.00%)	3 / 19 (15.79%)	1 / 14 (7.14%)
occurrences (all)	0	3	1
Metabolic/Lab - Other (FSP D-Dimer)			
subjects affected / exposed	1 / 19 (5.26%)	0 / 19 (0.00%)	0 / 14 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	4 - Consolidation I	5 - Inverval 2	

Total subjects affected by non-serious adverse events subjects affected / exposed	11 / 13 (84.62%)	8 / 12 (66.67%)	
Vascular disorders Thrombosis/thrombus/embolism subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1	0 / 12 (0.00%) 0	
General disorders and administration site conditions Fibrinogen subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Coagulation Other - AT-III deficiency subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Constitutional Symptomes - Fatigue subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Hemorrhage GU- Vagina subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Hemorrhage - Rectum subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	1 / 12 (8.33%) 1	
Pain Headache subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Immune system disorders Allergy subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Respiratory, thoracic and mediastinal disorders pleural effusion (grade 2) subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	
Pain upper respiratory subjects affected / exposed occurrences (all)	0 / 13 (0.00%) 0	0 / 12 (0.00%) 0	

Pulmonary edema (grade 2)			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Cardiac disorders			
Hypertension			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Pericardial Effusion Grade 1			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Neuropahty: sensory			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Mood alteration - Depression			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Hemoglobin	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	6 / 13 (46.15%)	5 / 12 (41.67%)	
occurrences (all)	6	5	
Leucocytes	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	2 / 13 (15.38%)	3 / 12 (25.00%)	
occurrences (all)	2	3	
Neutrophils	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	4 / 13 (30.77%)	4 / 12 (33.33%)	
occurrences (all)	4	4	
Platelets	Additional description: Standard Laboratory Assessment		
alternative assessment type: Systematic			
subjects affected / exposed	5 / 13 (38.46%)	6 / 12 (50.00%)	
occurrences (all)	5	6	
Eye disorders			

Eylid dysfunction			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Anorexia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Nausea			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Mucositis/Stomatitis			
subjects affected / exposed	4 / 13 (30.77%)	5 / 12 (41.67%)	
occurrences (all)	4	5	
Diarrhea			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Dysphagia			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolic/Laboratory - GGT			
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Skin and subcutaneous tissue disorders			
Rash Dermatitis			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Renal and urinary disorders			
Renal failure	Additional description: Only cases without SAE-report summarized		
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Infections and infestations			
Febrile neutropenia			
alternative assessment type: Systematic			

subjects affected / exposed	1 / 13 (7.69%)	0 / 12 (0.00%)	
occurrences (all)	1	0	
infection with grade 3-4 ANC	Additional description: (middle ear)		
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Infection with unknown ANC	Additional description: cases of infections without SAE cirteria		
subjects affected / exposed	1 / 13 (7.69%)	1 / 12 (8.33%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Metabolic/Laboratory - ALT	Additional description: Standard Laboratory Assessment, only cases without SAE-report summarized		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolic/Laboratory - AST	Additional description: Standard Laboratory Assessment, only cases without SAE-report summarized		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 13 (0.00%)	1 / 12 (8.33%)	
occurrences (all)	0	1	
Metabolic/Laboratory - Bilirubin	Additional description: Standard Laboratory Assessment, only cases without SAE-report summarized		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	
Metabolic/Lab - Other (FSP D-Dimer)			
subjects affected / exposed	0 / 13 (0.00%)	0 / 12 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
30 April 2013	30.04.2013 - Temporary halt of the study. Due to interim safety results, recruitment put on hold until planned protocol amendment 30.9.2015 - "Study End" (i.e. final decision not to reopen/restart the trial with amended chemotherapy backbone and study-protocol)	-

Notes:

Limitations and caveats

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

None, due to interim results recruitment was prematurely stoped

Notes: