Clinical trial results:
AN OPEN LABEL PHASE II STUDY TO EVALUATE THE EFFICACY AND SAFETY OF INDUCTION AND CONSOLIDATION THERAPY WITH NILOTINIB IN COMBINATION WITH CHEMOTHERAPY IN PATIENTS AGED 55 YEARS AND OVER WITH PHILADELPHIA CHROMOSOME POSITIVE (PH+ OR BCR-ABL+) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL).

Summary

EudraCT number	2010-022855-46
Trial protocol	DE IT ES
Global end of trial date	10 March 2020

Results information

Result version number	v1 (current)
This version publication date	02 June 2022
First version publication date	02 June 2022

Trial information

Trial identification

Sponsor protocol code	EWALL-PH-02

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01528085
WHO universal trial number (UTN)	-
Other trial identifiers	Novartis internal Code: CAMN107ADE03T

Notes:

Sponsors

Sponsor organisation name	Goethe University
Sponsor organisation address	Theodor-Stern-Kai 7, Frankfurt, Germany, 60590
Public contact	Universitätsklinikum Studienzentrale, Med. Klinik II, Goethe University, +49 (0)6963016366, gmall@em.uni-frankfurt.de
Scientific contact	Universitätsklinikum Studienzentrale, Med. Klinik II, Goethe University, +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	10 March 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a nilotinib-based induction and consolidation therapy.

Protection of trial subjects:

A Data Safty Monitoring Board (DSMB) has been instituted for this study in order to ensure its ongoing safety. Safety review meeting will be held as required by the sponsor.
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 (not part of the protocol): Dexamethasone; Intrathecal (i.th.) injection no.1(MTX); Optional: Cyclophosphamide
INDUCTION (day 1) : Vincristine; Dexamethasone; Intrathecal injection (triple); G-CSF
CONS I (week 8), CONS III (week 16) and CONS V (week 24): Methotrexate with folinic acid rescue; Asparaginase; G-CSF; Intrathecal injection (triple)
CONS II (week 12), CONS IV (week 20), CONS VI (week 28): Cytarabine; G-CSF
MAINTENANCE (month 8 to month 24): 6-MP; methotrexate; Dexamethasone; vincristine; Intrathecal injection (i.th.)

Nilotinib 400mg BID d1 throughout induction, consolidation and maintenance until month 24

Evidence for comparator:

N.A.

Actual start date of recruitment	17 November 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 46
Country: Number of subjects enrolled	Germany: 33
Worldwide total number of subjects	79
EEA total number of subjects	79

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)	29
From 65 to 84 years	49
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

09-Feb-2012 FPI (First Patient In); 08-Jun-2015 LPI (Last Patient In), Trial has been activated in Germany, France and Spain. No Patient in Spain had been recruited.

Pre-assignment

Screening details:

Screening applies to confirmed new diagnosis of Philadelphia chromosome or BCR-ABL positive acute lymphoblastic leukaemia (ALL) in Patients 55 years or older.BCR-ABL Assessment is standard of care for ALL. 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) Nilotinib+ Chemotherapy

Arms

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

Arm description:

Nilotinib + Backbone Chemotherapy as described above

Arm type	open-label single-arm study
Investigational medicinal product name	Nilotinib
Investigational medicinal product code	
Other name	Tasigna
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

400mg BID, in case of toxicitiy dose reduction possible

Number of subjects in period 1	Nilotinib + Chemotherapy (open-label single-arm study)
Started	79
Completed	74
Not completed	5
not evaluabl. and Premat. discontinuation	5

Baseline characteristics

Reporting groups	
Reporting group title	overall trial (overall period)
Reporting group description:	
All PAtients enrolled, 74 of them evaluable	

Reporting group values	overall trial (overall period)	Total	
Number of subjects	79	79	
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 66 55 to 85	 -	
Gender categorical Units: Subjects			
Female	44	44	
Male	35	35	

Subject analysis sets	
Subject analysis set title	Evaluable Patients
Subject analysis set type	Full analysis
Subject analysis set description:	
All Evaluable Patients	

Reporting group values	Evaluable Patients		
Number of subjects	74		
Age categorical Units: Subjects			
Age continuous Units: years median full range (min-max)	 66 55 to 85		
Gender categorical Units: Subjects			
Female	40		
Male	34		

End points

End points reporting groups

Reporting group title	Nilotinib + Chemotherapy (open-label single-arm study)
Reporting group description:	
Nilotinib + Backbone Chemotherapy as described above	
Subject analysis set title	Evaluable Patients
Subject analysis set type	Full analysis
Subject analysis set description:	
All Evaluable Patients	

Primary: Event Free Survival

End point title	Event Free Survival[1]
End point description:	
To evaluate the efficacy of a nilotinib-based induction and consolidation therapy.	
End point type	Primary
End point timeframe:	
12 Months	

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: Only descriptive statistics

End point values	Evaluable Patients			
Subject group type	Subject analysis set			
Number of subjects analysed	74			
Units: Percent	76			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs collected under Nilotinib treatment up to max 2 years.

Adverse event reporting additional description:

Only Non-Serious-Adverse-Events with max. CTCAE Grade 3 or 4 are collected.
Observed SAEs are listed with all reported events (One case can include more than one event.)

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Evaluable Patients

Reporting group description:

All Patients until EOT (Nilo Treatment max 2 years+ safety Intervall, No post SCT Events included)

Serious adverse events	Evaluable Patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	51 / 74 (68.92%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
central nervous system leukaemia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal adenocarcinoma			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Prostate cancer recurrent			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Squamous cell carcinoma			

subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Tyroid cancer metastatic				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular disorders				
Hypotension				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Stent placement				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Asthenia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Drug effect prolonged				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General physical health deterioration				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Injection site thrombosis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Malaise				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Mucosal inflammation				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyrexia				
subjects affected / exposed	5 / 74 (6.76%)			
occurrences causally related to treatment / all	0 / 6			
deaths causally related to treatment / all	0 / 0			
Reproductive system and breast disorders				
Prostatitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory distress syndrome	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.			
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Dyspnoea	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.			
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	1 / 1			
Epistaxis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung disorder				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleural effusion			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary embolism			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.		
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Respiratory failure			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Bipolar I disorder			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
C-reactive protein increased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Chemotherapeutic drug level increased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Liver function test increased			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Brain Oedema	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.		

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Cerebral haemorrhage	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.		
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Headache			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Intracranial haematoma			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic cerebral infarction	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.		
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Paresis cranial nerve			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		

Bone Marrow failure			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Cytopenia			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile bone marrow aplasia			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	10 / 74 (13.51%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	4 / 74 (5.41%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	6 / 74 (8.11%)		
occurrences causally related to treatment / all	3 / 6		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Eyelid ptosis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			

Abdominal Pain				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Colitis ischaemic				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Constipation				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Duodenal obstruction				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ileus paralytic				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Intestinal obstruction				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				

subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Stomatitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatocellular injury			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematuria			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Renal failure			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Bone Pain			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fasciitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain in extremity			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess limb			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial infection			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bacterial sepsis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Cellulitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cystitis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	3 / 74 (4.05%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Enterobacter sepsis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Escherichia bacteraemia			
subjects affected / exposed	2 / 74 (2.70%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Escherichia sepsis			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastroenteritis norovirus			
subjects affected / exposed	1 / 74 (1.35%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Lung infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Mucormycosis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumocystis jirovecii infection	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.			
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pneumocystis jirovecii pneumonia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	3 / 74 (4.05%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Pneumonia fungal				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Prostate infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pseudomonas infection	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.			

subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Pyelonephritis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	2 / 74 (2.70%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Septic shock				
subjects affected / exposed	4 / 74 (5.41%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection	Additional description: Observed SAEs are listed with all reported events and one case can include more than one event. Therfore single cases of fatality may be documented in more than one event.			
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	1 / 1			
Tonsillitis				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Hyperglycaemia				
subjects affected / exposed	1 / 74 (1.35%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	Evaluable Patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 74 (95.95%)		
Vascular disorders			
Thrombosis/embolism (vascular access-related)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Hemoglobin	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	24		
Leukocytes (total WBC)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	13 / 74 (17.57%)		
occurrences (all)	20		
Neutrophils/granulocytes (ANC/AGC)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	23 / 74 (31.08%)		
occurrences (all)	60		
Platelets	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	38 / 74 (51.35%)		
occurrences (all)	71		
Blood/Bone Marrow - Other (Specify, __)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	14		
General disorders and administration site conditions			
Weight loss	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Pain	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	6		
Gastrointestinal disorders			
Anorexia	Additional description: Occurrence of CTCAE Grad 3 and 4		

subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Diarrhea	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Mucositis/stomatitis (clinical exam)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Nausea	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	6		
Hepatobiliary disorders			
Hepatobiliary/Pancreas - Other (Specify, __)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis/pulmonary infiltrates	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Renal and urinary disorders			
Cystitis	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Renal failure	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	9 / 74 (12.16%)		
occurrences (all)	10		
Renal/Genitourinary - Other (Specify, __)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Infections and infestations			
Febrile neutropenia (fever of unknown origin without clinically or microb. infection)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	19 / 74 (25.68%)		
occurrences (all)	32		
Infection (documented clinically or microbiologically) with Grade 3 or 4	Additional description: Occurrence of CTCAE Grad 3 and 4		

neutrophils (ANC <1.0 x 10e			
subjects affected / exposed	20 / 74 (27.03%)		
occurrences (all)	24		
Infection - Other (Specify, __)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	4 / 74 (5.41%)		
occurrences (all)	4		
Infection with normal ANC or Grade 1 or 2 neutrophils	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	10 / 74 (13.51%)		
occurrences (all)	14		
Infection with unknown ANC	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	4		
Metabolism and nutrition disorders			
ALT, SGPT (serum glutamic pyruvic transaminase)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	11 / 74 (14.86%)		
occurrences (all)	13		
AST, SGOT(serum glutamic oxaloacetic transaminase)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Bilirubin (hyperbilirubinemia)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	9 / 74 (12.16%)		
occurrences (all)	13		
GGT (gamma-Glutamyl transpeptidase)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	14 / 74 (18.92%)		
occurrences (all)	19		
Glucose, serum-high (hyperglycemia)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	3 / 74 (4.05%)		
occurrences (all)	3		
Metabolic/Laboratory - Other (Specify, __)	Additional description: Occurrence of CTCAE Grad 3 and 4		
subjects affected / exposed	5 / 74 (6.76%)		
occurrences (all)	5		
Uric acid, serum-high (hyperuricemia)	Additional description: Occurrence of CTCAE Grad 3 and 4		

subjects affected / exposed occurrences (all)	3 / 74 (4.05%) 5		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 January 2014	Protocol V3 (prolongation of recruitment phase)
15 September 2014	Protocol V4 (Number of patients/Sample Size increased: 75 evaluable Patients)
19 March 2015	Protocol V5 (Change in the Position of the "Clinical Trial Leader" / "Leiter der Klinischen Prüfung" according to German AMG)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported