Clinical trial results:
A Multicenter, open, randomized, controlled phase IIb trial evaluating efficacy and tolerability of GRASPA (L-asparaginase encapsulated in red blood cells, eryaspase) plus low-dose cytarabine versus low-dose cytarabine alone, in treatment of newly diagnosed acute myeloid leukemia (AML) elderly patients, unfit for intensive chemotherapy. ENFORCE 1 study.

Summary

EudraCT number	2012-002026-78
Trial protocol	IT FI DE ES
Global end of trial date	10 November 2017

Results information

Result version number	v1 (current)
This version publication date	21 March 2020
First version publication date	21 March 2020

Trial information

Trial identification

Sponsor protocol code	GRASPA-AML 2012-01

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01810705
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Erytech Pharma
Sponsor organisation address	60 avenue Rockefeller, Bâtiment Adenine, Lyon, France, 69008
Public contact	Clinical Operations. Jean Baptiste Bertrand, ERYTECH Pharma, 33 4 78 74 44 38, jb.bertrand@erytech.com
Scientific contact	Jason Cain, ERYTECH Pharma, +1 857 285 24 15, ason.cain@erytech.com

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 June 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 November 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate Overall Survival (OS) in AML patients who were 65-85 years old and unfit for intensive chemotherapy, when treated with GRASPA (L-asparaginase encapsulated in erythrocytes) plus low-dose cytarabine compared to low-dose cytarabine alone

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements related to safety of trial subjects were also followed during the conduct of the trial.

An independant DSMB reviewed the interim results from the study as well as safety and futility on a regular basis. The DSMB had the potential to stop the study for overwhelming evidence of benefit or futility.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	24 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 110
Country: Number of subjects enrolled	Norway: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	123
EEA total number of subjects	123

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)	0
From 65 to 84 years	121
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

First patient in: 11MAR2013
Last patient in: 02AUG2016

Territories: Europe (France, Italy, Spain, Finland, Norway, Germany)

Pre-assignment

Screening details:

• Patient >= 65 years old and ≤ 85 years old
• Newly diagnosed Acute Myeloid Leukemia (AML) or post myelodysplastic syndrome diagnosed within 6 months prior to study enrollment
• Unfit for intensive chemotherapy (at risk to suffer treatment related pejorative toxicities /early death)
• ECOG performance status ≤ 2

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	low-dose cytarabine + GRASPA

Arm description:

In the experimental group, the patients will receive one administration of GRASPA (100 IU/kg) at Day 11 in combination with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months.

Arm type	Experimental
Investigational medicinal product name	GRASPA
Investigational medicinal product code	
Other name	Eryaspase
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

In the experimental group, the patients will receive one administration of GRASPA (100 IU/kg) at Day 11 in combination with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months.

Arm title	low-dose cytarabine alone

Arm description:

In the control arm, patients will be treated with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months. Each period of 28 days constitute a cycle of chemotherapy.

Arm type	Standard polychemotherapy with low dose cytarabine

No investigational medicinal product assigned in this arm

Number of subjects in period 1	low-dose cytarabine + GRASPA	low-dose cytarabine alone
Started	83	40
Completed	10	5
Not completed	73	35
Consent withdrawn by subject	1	1
Exclusion criteria (randomized in error)	2	-
Death (all causes)	70	34

Baseline characteristics

Reporting groups	
Reporting group title	low-dose cytarabine + GRASPA

Reporting group description:

In the experimental group, the patients will receive one administration of GRASPA (100 IU/kg) at Day 11 in combination with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months.

Reporting group title	low-dose cytarabine alone

Reporting group description:

In the control arm, patients will be treated with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months. Each period of 28 days constitute a cycle of chemotherapy.

Reporting group values	low-dose cytarabine + GRASPA	low-dose cytarabine alone	Total
Number of subjects	83	40	123
Age categorical Units: Subjects			
65-85 years	83	40	123
Age continuous Units: years			
arithmetic mean	77.2	76.0	
standard deviation	± 4.17	± 4.54	-
Gender categorical Units: Subjects			
Female	37	16	53
Male	46	24	70

End points

End points reporting groups

Reporting group title	low-dose cytarabine + GRASPA

Reporting group description:

In the experimental group, the patients will receive one administration of GRASPA (100 IU/kg) at Day 11 in combination with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months.

Reporting group title	low-dose cytarabine alone

Reporting group description:

In the control arm, patients will be treated with subcutaneous low-dose cytarabine as 40 mg daily (either one single dose of 40 mg or 20 mg twice daily according to local practice) for 10 consecutive days, every 28 days, for duration up to 24 months. Each period of 28 days constitute a cycle of chemotherapy.

Subject analysis set title	Intention-to-Treat efficacy population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The Intent-to-Treat (ITT) efficacy population comprised of all randomised patients in the groups to which they were randomly assigned, regardless of their adherence to the entry criteria, the treatment they actually received, or subsequent withdrawal from treatment or deviation from the protocol.

Subject analysis set title	Per Protocol efficacy population
Subject analysis set type	Per protocol

Subject analysis set description:

The Per-Protocol (PP) efficacy population comprised all patients from the ITT population without major protocol deviations who received trial product and completed at least one course of treatment

Subject analysis set title	Safety population
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety population comprised all patients who received at least one administration of trial products. Data analysis for the Safety population will be according to treatment received. All evaluations of safety will be undertaken based on this population.

Primary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was to be assessed by measuring time elapsed between randomisation and death for any cause. Any patient not known to have died at the time of analysis is censored based on the last recorded date on which the patient was known to be alive

End point type	Primary

End point timeframe:

Whole trial period

End point values	low-dose cytarabine + GRASPA	low-dose cytarabine alone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	40		
Units: months				
median (confidence interval 95%)	4.8 (3.1 to 7.0)	6.4 (3.6 to 10.7)		

Statistical analyses

Statistical analysis title	Analysis of OS

Statistical analysis description:

The p-value for the time to event analysis is associated with the stratified log-rank statistic. The stratification factor is performance status (0-1, 2).
Hazard ratio and 95% confidence interval are estimated from the stratified Cox model. The stratification factor is performance status (0-1, 2).

Comparison groups	low-dose cytarabine + GRASPA v low-dose cytarabine alone
Number of subjects included in analysis	123
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.827 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.69
upper limit	1.59

Notes:

[1] - Not statistically significant. No evidence to support treatment differences for OS

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from signature of the informed consent from first patient and until 4 months after last GRASPA/ low-dose cytarabine administration of last patient.

Adverse event reporting additional description:

Serious adverse events reported in this report (details of serious adverse events table) are treatment emergent serious adverse events with threshold 5.0 %.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	low-dose cytarabine alone
Reporting group description: -	
Reporting group title	low-dose cytarabine + GRASPA

Reporting group description: -

Serious adverse events	low-dose cytarabine alone	low-dose cytarabine + GRASPA	
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 39 (82.05%)	74 / 81 (91.36%)	
number of deaths (all causes)	34	70	
number of deaths resulting from adverse events	16	35	
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	3 / 39 (7.69%)	10 / 81 (12.35%)	
occurrences causally related to treatment / all	1 / 3	1 / 12	
deaths causally related to treatment / all	1 / 3	0 / 7	
Pyrexia			
subjects affected / exposed	2 / 39 (5.13%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	1 / 2	4 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile bone marrow aplasia			
subjects affected / exposed	2 / 39 (5.13%)	8 / 81 (9.88%)	
occurrences causally related to treatment / all	0 / 2	5 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	

Febrile neutropenia			
subjects affected / exposed	3 / 39 (7.69%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	2 / 5	3 / 7	
deaths causally related to treatment / all	0 / 0	0 / 1	
Anaemia			
subjects affected / exposed	1 / 39 (2.56%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	1 / 1	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhagic Events			
subjects affected / exposed	1 / 39 (2.56%)	6 / 81 (7.41%)	
occurrences causally related to treatment / all	0 / 1	2 / 6	
deaths causally related to treatment / all	0 / 1	1 / 2	
Pancytopenia			
subjects affected / exposed	1 / 39 (2.56%)	5 / 81 (6.17%)	
occurrences causally related to treatment / all	0 / 1	6 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 39 (0.00%)	6 / 81 (7.41%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lung disorder			
subjects affected / exposed	3 / 39 (7.69%)	6 / 81 (7.41%)	
occurrences causally related to treatment / all	1 / 3	3 / 6	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	6 / 39 (15.38%)	12 / 81 (14.81%)	
occurrences causally related to treatment / all	1 / 6	5 / 13	
deaths causally related to treatment / all	1 / 3	2 / 6	
Septic shock			

subjects affected / exposed	6 / 39 (15.38%)	7 / 81 (8.64%)	
occurrences causally related to treatment / all	2 / 6	1 / 7	
deaths causally related to treatment / all	2 / 6	1 / 7	
Bronchopulmonary aspergillosis			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences causally related to treatment / all	0 / 2	1 / 5	
deaths causally related to treatment / all	0 / 1	0 / 2	
Lung infection			
subjects affected / exposed	2 / 39 (5.13%)	1 / 81 (1.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	2 / 39 (5.13%)	0 / 81 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	low-dose cytarabine alone	low-dose cytarabine + GRASPA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)	80 / 81 (98.77%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	6 / 39 (15.38%)	10 / 81 (12.35%)	
occurrences (all)	6	12	
Hypertension			
subjects affected / exposed	4 / 39 (10.26%)	10 / 81 (12.35%)	
occurrences (all)	5	12	
Purpura			
subjects affected / exposed	2 / 39 (5.13%)	5 / 81 (6.17%)	
occurrences (all)	2	5	
Haematoma			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Petechiae			

subjects affected / exposed	2 / 39 (5.13%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
General disorders and administration site conditions			
asthenia			
subjects affected / exposed	18 / 39 (46.15%)	28 / 81 (34.57%)	
occurrences (all)	20	34	
Oedema peripheral			
subjects affected / exposed	9 / 39 (23.08%)	13 / 81 (16.05%)	
occurrences (all)	10	17	
Pain			
subjects affected / exposed	2 / 39 (5.13%)	8 / 81 (9.88%)	
occurrences (all)	2	8	
Injection site haematoma			
subjects affected / exposed	2 / 39 (5.13%)	5 / 81 (6.17%)	
occurrences (all)	2	5	
Pyrexia			
subjects affected / exposed	13 / 39 (33.33%)	26 / 81 (32.10%)	
occurrences (all)	27	50	
General physical health deterioration			
subjects affected / exposed	3 / 39 (7.69%)	4 / 81 (4.94%)	
occurrences (all)	3	4	
Immune system disorders			
Alloimmunisation			
subjects affected / exposed	1 / 39 (2.56%)	16 / 81 (19.75%)	
occurrences (all)	1	16	
Allergic transfusion reaction			
subjects affected / exposed	2 / 39 (5.13%)	5 / 81 (6.17%)	
occurrences (all)	2	5	
Hypersensitivity			
subjects affected / exposed	0 / 39 (0.00%)	8 / 81 (9.88%)	
occurrences (all)	0	14	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	8 / 39 (20.51%)	11 / 81 (13.58%)	
occurrences (all)	9	14	
Cough			

subjects affected / exposed	7 / 39 (17.95%)	9 / 81 (11.11%)	
occurrences (all)	7	10	
Acute pulmonary oedema			
subjects affected / exposed	2 / 39 (5.13%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Lung disorder			
subjects affected / exposed	3 / 39 (7.69%)	3 / 81 (3.70%)	
occurrences (all)	3	3	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 39 (10.26%)	11 / 81 (13.58%)	
occurrences (all)	4	12	
Depression			
subjects affected / exposed	3 / 39 (7.69%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Confusional state			
subjects affected / exposed	0 / 39 (0.00%)	4 / 81 (4.94%)	
occurrences (all)	0	5	
Investigations			
Blood albumin decreased			
subjects affected / exposed	6 / 39 (15.38%)	24 / 81 (29.63%)	
occurrences (all)	8	29	
Pancreatic enzymes abnormal			
subjects affected / exposed	5 / 39 (12.82%)	20 / 81 (24.69%)	
occurrences (all)	5	31	
Transaminases increased			
subjects affected / exposed	6 / 39 (15.38%)	15 / 81 (18.52%)	
occurrences (all)	10	40	
Antithrombin III decreased			
subjects affected / exposed	3 / 39 (7.69%)	17 / 81 (20.99%)	
occurrences (all)	3	22	
Gamma-glutamyltransferase increased			

subjects affected / exposed	5 / 39 (12.82%)	15 / 81 (18.52%)	
occurrences (all)	5	18	
Weight decreased			
subjects affected / exposed	7 / 39 (17.95%)	9 / 81 (11.11%)	
occurrences (all)	7	9	
Blood Creatinine increased			
subjects affected / exposed	3 / 39 (7.69%)	12 / 81 (14.81%)	
occurrences (all)	3	15	
Blood chloride increased			
subjects affected / exposed	2 / 39 (5.13%)	11 / 81 (13.58%)	
occurrences (all)	3	15	
Blood urea increased			
subjects affected / exposed	4 / 39 (10.26%)	9 / 81 (11.11%)	
occurrences (all)	6	9	
Blood lactate dehydrogenase increased			
subjects affected / exposed	2 / 39 (5.13%)	7 / 81 (8.64%)	
occurrences (all)	2	8	
Blood alkaline phosphatase increased			
subjects affected / exposed	3 / 39 (7.69%)	5 / 81 (6.17%)	
occurrences (all)	3	5	
Blood chloride decreased			
subjects affected / exposed	3 / 39 (7.69%)	5 / 81 (6.17%)	
occurrences (all)	3	6	
Prothrombin time ratio decreased			
subjects affected / exposed	0 / 39 (0.00%)	8 / 81 (9.88%)	
occurrences (all)	0	10	
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 39 (2.56%)	6 / 81 (7.41%)	
occurrences (all)	1	7	
Injury, poisoning and procedural complications			
fall			
subjects affected / exposed	3 / 39 (7.69%)	10 / 81 (12.35%)	
occurrences (all)	3	12	
Transfusion reaction			

subjects affected / exposed	1 / 39 (2.56%)	7 / 81 (8.64%)	
occurrences (all)	1	8	
Traumatic haematoma			
subjects affected / exposed	3 / 39 (7.69%)	2 / 81 (2.47%)	
occurrences (all)	3	2	
Food poisoning			
subjects affected / exposed	2 / 39 (5.13%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 39 (12.82%)	2 / 81 (2.47%)	
occurrences (all)	5	2	
Cardiac failure			
subjects affected / exposed	1 / 39 (2.56%)	4 / 81 (4.94%)	
occurrences (all)	1	4	
Nervous system disorders			
Headache			
subjects affected / exposed	6 / 39 (15.38%)	12 / 81 (14.81%)	
occurrences (all)	6	13	
Blood and lymphatic system disorders			
thrombocytopenia			
subjects affected / exposed	32 / 39 (82.05%)	59 / 81 (72.84%)	
occurrences (all)	84	149	
Leukopenia			
subjects affected / exposed	19 / 39 (48.72%)	41 / 81 (50.62%)	
occurrences (all)	31	87	
Neutropenia			
subjects affected / exposed	18 / 39 (46.15%)	35 / 81 (43.21%)	
occurrences (all)	34	98	
Lymphopenia			
subjects affected / exposed	6 / 39 (15.38%)	8 / 81 (9.88%)	
occurrences (all)	6	9	
Leukocytosis			
subjects affected / exposed	2 / 39 (5.13%)	8 / 81 (9.88%)	
occurrences (all)	2	8	
Bone marrow failure			

subjects affected / exposed	2 / 39 (5.13%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Leukostasis syndrome			
subjects affected / exposed	1 / 39 (2.56%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Anaemia			
subjects affected / exposed	34 / 39 (87.18%)	62 / 81 (76.54%)	
occurrences (all)	74	170	
Hemorrhagic Events			
subjects affected / exposed	9 / 39 (23.08%)	21 / 81 (25.93%)	
occurrences (all)	11	23	
Febrile neutropenia			
subjects affected / exposed	1 / 39 (2.56%)	7 / 81 (8.64%)	
occurrences (all)	1	8	
Febrile bone marrow aplasia			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Pancytopenia			
subjects affected / exposed	0 / 39 (0.00%)	3 / 81 (3.70%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	15 / 39 (38.46%)	24 / 81 (29.63%)	
occurrences (all)	21	57	
Diarrhoea			
subjects affected / exposed	10 / 39 (25.64%)	24 / 81 (29.63%)	
occurrences (all)	12	32	
Constipation			
subjects affected / exposed	10 / 39 (25.64%)	18 / 81 (22.22%)	
occurrences (all)	11	22	
Vomiting			

subjects affected / exposed	5 / 39 (12.82%)	14 / 81 (17.28%)	
occurrences (all)	14	27	
Stomatitis			
subjects affected / exposed	3 / 39 (7.69%)	7 / 81 (8.64%)	
occurrences (all)	4	7	
Aphthous ulcer			
subjects affected / exposed	1 / 39 (2.56%)	9 / 81 (11.11%)	
occurrences (all)	1	11	
Abdominal pain			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Abdominal pain upper			
subjects affected / exposed	3 / 39 (7.69%)	4 / 81 (4.94%)	
occurrences (all)	4	4	
Haemorrhoids			
subjects affected / exposed	2 / 39 (5.13%)	5 / 81 (6.17%)	
occurrences (all)	2	5	
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 39 (10.26%)	1 / 81 (1.23%)	
occurrences (all)	4	1	
Odynophagia			
subjects affected / exposed	2 / 39 (5.13%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Gingival pain			
subjects affected / exposed	2 / 39 (5.13%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	5 / 39 (12.82%)	15 / 81 (18.52%)	
occurrences (all)	5	25	
Hepatocellular injury			
subjects affected / exposed	1 / 39 (2.56%)	5 / 81 (6.17%)	
occurrences (all)	2	5	
Skin and subcutaneous tissue disorders			
Erythema			

subjects affected / exposed	3 / 39 (7.69%)	8 / 81 (9.88%)	
occurrences (all)	3	10	
Pruritus			
subjects affected / exposed	3 / 39 (7.69%)	4 / 81 (4.94%)	
occurrences (all)	3	4	
Rash			
subjects affected / exposed	1 / 39 (2.56%)	4 / 81 (4.94%)	
occurrences (all)	1	4	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	5 / 39 (12.82%)	12 / 81 (14.81%)	
occurrences (all)	5	13	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 39 (10.26%)	5 / 81 (6.17%)	
occurrences (all)	5	7	
Pain in extremity			
subjects affected / exposed	2 / 39 (5.13%)	8 / 81 (9.88%)	
occurrences (all)	2	10	
Back pain			
subjects affected / exposed	3 / 39 (7.69%)	5 / 81 (6.17%)	
occurrences (all)	3	6	
Musculoskeletal pain			
subjects affected / exposed	1 / 39 (2.56%)	4 / 81 (4.94%)	
occurrences (all)	1	4	
Myalgia			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences (all)	2	5	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	4 / 39 (10.26%)	12 / 81 (14.81%)	
occurrences (all)	6	13	
Bronchitis			
subjects affected / exposed	3 / 39 (7.69%)	6 / 81 (7.41%)	
occurrences (all)	5	6	
Conjunctivitis			

subjects affected / exposed	0 / 39 (0.00%)	7 / 81 (8.64%)	
occurrences (all)	0	7	
Oral candidiasis			
subjects affected / exposed	1 / 39 (2.56%)	6 / 81 (7.41%)	
occurrences (all)	1	6	
Fungal infection			
subjects affected / exposed	2 / 39 (5.13%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	2 / 39 (5.13%)	2 / 81 (2.47%)	
occurrences (all)	2	2	
Gastroenteritis			
subjects affected / exposed	2 / 39 (5.13%)	0 / 81 (0.00%)	
occurrences (all)	2	0	
Sepsis			
subjects affected / exposed	1 / 39 (2.56%)	0 / 81 (0.00%)	
occurrences (all)	1	0	
Bronchopulmonary aspergillosis			
subjects affected / exposed	1 / 39 (2.56%)	2 / 81 (2.47%)	
occurrences (all)	1	2	
Lung infection			
subjects affected / exposed	1 / 39 (2.56%)	1 / 81 (1.23%)	
occurrences (all)	1	1	
Infection			
subjects affected / exposed	0 / 39 (0.00%)	3 / 81 (3.70%)	
occurrences (all)	0	3	
Metabolism and nutrition disorders			
Hypocalcaemia			
subjects affected / exposed	9 / 39 (23.08%)	16 / 81 (19.75%)	
occurrences (all)	13	19	
Decreased appetite			
subjects affected / exposed	6 / 39 (15.38%)	5 / 81 (6.17%)	
occurrences (all)	8	5	
Hyperglycaemia			
subjects affected / exposed	3 / 39 (7.69%)	8 / 81 (9.88%)	
occurrences (all)	4	10	

Hypertriglyceridaemia			
subjects affected / exposed	2 / 39 (5.13%)	8 / 81 (9.88%)	
occurrences (all)	2	9	
Hyperkalaemia			
subjects affected / exposed	3 / 39 (7.69%)	6 / 81 (7.41%)	
occurrences (all)	3	8	
Hypophosphataemia			
subjects affected / exposed	0 / 39 (0.00%)	7 / 81 (8.64%)	
occurrences (all)	0	8	
Hyperuricaemia			
subjects affected / exposed	2 / 39 (5.13%)	4 / 81 (4.94%)	
occurrences (all)	2	4	
Dehydration			
subjects affected / exposed	3 / 39 (7.69%)	2 / 81 (2.47%)	
occurrences (all)	3	2	
Hyperphosphataemia			
subjects affected / exposed	2 / 39 (5.13%)	3 / 81 (3.70%)	
occurrences (all)	2	3	
Vitamin D deficiency			
subjects affected / exposed	2 / 39 (5.13%)	1 / 81 (1.23%)	
occurrences (all)	2	1	
Hypokalaemia			
subjects affected / exposed	8 / 39 (20.51%)	25 / 81 (30.86%)	
occurrences (all)	11	31	
Hyponatraemia			
subjects affected / exposed	5 / 39 (12.82%)	17 / 81 (20.99%)	
occurrences (all)	16	24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 February 2013	Clarification of secondary endpoints. Correction of Pharmacokinetic and pharmacodynamic parameters procedures, and immunogenicity time points.
22 January 2014	Clarification inclusion/exclusion criteria. Clarification of study treatment administration.
21 July 2014	Addition of exclusion criteria to comply with BFArM demand. Clarification of inclusion criteria.
11 December 2015	Based on strong recommendation from several discussions with our coordinator PI as well as statistics experts, primary objective was changed to OS as considered more relevant for the pathology. PFS is now part of secondary objectives. Exploratory objectives were moved as secondary endpoints. Clarification of inclusion/exclusion criteria

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study is not powered explicitly for OS, and statistical significance in favor of GRASPA plus low-dose cytarabine is not anticipated.

Notes: