



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 \geq 65 years old and \leq 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 \leq 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 Intention-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 occurrences (all) | 2 / 39 (5.13%) 2 | 3 / 81 (3.70%) 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 occurrences (all) | 7 / 39 (17.95%) 7 | 9 / 81 (11.11%) 10 | |
| Acute pulmonary oedema subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | 0 / 81 (0.00%) 0 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | 0 / 81 (0.00%) 0 | |
| Lung disorder subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | 3 / 81 (3.70%) 3 | |
| Psychiatric disorders | | | |
| Anxiety subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 4 | 11 / 81 (13.58%) 12 | |
| Depression subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | 5 / 81 (6.17%) 5 | |
| Confusional state subjects affected / exposed occurrences (all) | 0 / 39 (0.00%) 0 | 4 / 81 (4.94%) 5 | |
| Investigations | | | |
| Blood albumin decreased subjects affected / exposed occurrences (all) | 6 / 39 (15.38%) 8 | 24 / 81 (29.63%) 29 | |
| Pancreatic enzymes abnormal subjects affected / exposed occurrences (all) | 5 / 39 (12.82%) 5 | 20 / 81 (24.69%) 31 | |
| Transaminases increased subjects affected / exposed occurrences (all) | 6 / 39 (15.38%) 10 | 15 / 81 (18.52%) 40 | |
| Antithrombin III decreased subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | 17 / 81 (20.99%) 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 occurrences (all) | 3 / 39 (7.69%) 3 | 8 / 81 (9.88%) 10 | |
| Pruritus subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | 4 / 81 (4.94%) 4 | |
| Rash subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | 4 / 81 (4.94%) 4 | |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) | 5 / 39 (12.82%) 5 | 12 / 81 (14.81%) 13 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 5 | 5 / 81 (6.17%) 7 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | 8 / 81 (9.88%) 10 | |
| Back pain subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | 5 / 81 (6.17%) 6 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 1 / 39 (2.56%) 1 | 4 / 81 (4.94%) 4 | |
| Myalgia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | 4 / 81 (4.94%) 5 | |
| Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 39 (10.26%) 6 | 12 / 81 (14.81%) 13 | |
| Bronchitis subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 5 | 6 / 81 (7.41%) 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: