



Clinical trial results:

SGI-110 to potentiate platinum response: A phase Ib/randomised IIa open label clinical trial combining SGI-110 with cisplatin and gemcitabine chemotherapy

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2015-004062-29 |
| Trial protocol | GB |
| Global end of trial date | 01 June 2020 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 21 March 2022 |
| First version publication date | 21 March 2022 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | RHMCAN1142 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|----------------|
| ISRCTN number | ISRCTN16332228 |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University Hospital Southampton NHS Foundation |
| Sponsor organisation address | Tremona Road, Southampton, United Kingdom, |
| Public contact | Denise Dunkley, Southampton Clinical Trials Unit, 44 2381205154, ctu@soton.ac.uk |
| Scientific contact | Denise Dunkley, Southampton Clinical Trials Unit, 44 2381205154, ctu@soton.ac.uk |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 01 July 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 July 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 01 June 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To find a safe and effective dose of the trial drug when given in combination with gemcitabine and cisplatin chemotherapy.

Protection of trial subjects:

Independent Ethics Committee (REC): The protocol, amendments and informed consent forms (ICFs) for this study were reviewed and approved by the REC prior to implementation. No subject was treated until the REC had provided written approval of the study and the ICF to the investigator and the sponsor. Protocol amendments and all revisions to the ICF after initial REC approval were submitted for REC review and approval before implementation in accordance with regulatory requirements.

Ethical Conduct of the Study: The study was conducted in accordance with the principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP) guidelines, applicable local regulatory requirements, and the principles enunciated in the Declaration of Helsinki.

Subject Information and Consent: The ICF(s) used for each study centre complied with ICH, the principles enunciated in the Declaration of Helsinki, local regulatory requirements, and ICH GCP guidelines and was approved by the sponsor and the REC. The investigator, or a person delegated by the investigator, explained the medical aspects of the study, including the nature and purpose of the study and the treatment, the procedures involved, and the potential benefits and risks. Other tasks in the informed consent process may have been delegated by the investigator. After having been informed that participation was voluntary and that subjects may withdraw from the study at any time, without prejudice, each subject signed the REC-approved ICF prior to undergoing any study specific procedures and enrolment in the study.

Concomitant medications and therapies deemed necessary for supportive care and safety of the subject were allowed, including antiemetics and intravenous hydration, per local institutional policy.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 01 March 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 19 |
| Worldwide total number of subjects | 19 |
| EEA total number of subjects | 0 |

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) | 10 |
| From 65 to 84 years | 9 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 8 principal investigators at 8 study centres in the UK enrolled 40 eligible patients in this study between May 2016 and September 2019. Phase I = 17 evaluable patients and 3 non-evaluable patients due to rapid disease progression leading to death (were replaced). Phase II = 20 patients with muscle invasive bladder cancer.

Pre-assignment

Screening details:

Screening criteria: age ≥ 16 y, ECOG 0-1, glomerular filtration rate ≥ 60 ml/min, adequate haematological/biochemical parameters, life expectancy > 3 m, written informed consent. Also in Phase I: incurable metastatic solid cancers; and in Phase II: bladder cancer with pure/predominant transitional cell Carcinoma, T2-4a N0 M0, planned GC for 3-4 cycles.

Period 1

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

Arms

| | |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 2 - 20 mg + G-CSF |

Arm description: -

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | Guadecitabine |
| Investigational medicinal product code | SGI-110 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Injection , Intraabdominal use , Subcutaneous use |

Dosage and administration details:

SGI-110 administration has been established as 20 mg/m², daily, on days 1-5, by sub-cutaneous injection to all patients and preferably in the abdominal area.

- Care must be taken to avoid intradermal injection as this may result in injection site pain.
- SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may occasionally be experienced.
- If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pretreatment with topical or systemic analgesics can be considered.

| | |
|--|---------------------------------------|
| Investigational medicinal product name | Granulocyte Colony Stimulating Factor |
| Investigational medicinal product code | GCSF |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use, Injection |

Dosage and administration details:

300µg GCSF, daily, on days 15-21, by subcutaneous injection

| | |
|--|---------------------------|
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use, Infusion |

Dosage and administration details:

Gemcitabine 1000 mg/m² on days 8 and 15 of each cycle by IV infusion over 30-60 minutes (and prior to cisplatin on day 8)

| | |
|--|--|
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion , Intravenous use |
| Dosage and administration details: | |
| Cisplatin 70 mg/m2 on day 8 of each cycle by IV infusion over 2-4 hours | |
| Arm title | Cohort 3 - 30 mg + G-CSF |
| Arm description: - | |
| Arm type | Experimental |
| Investigational medicinal product name | Guadecitabine |
| Investigational medicinal product code | SGI-110 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intraabdominal use , Subcutaneous use, Injection |
| Dosage and administration details: | |
| SGI-110 administration has been established as 30 mg/m2, daily, on days 1-5, by sub-cutaneous injection to all patients and preferably in the abdominal area. | |
| <ul style="list-style-type: none"> • Care must be taken to avoid intradermal injection as this may result in injection site pain. • SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may occasionally be experienced. • If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pretreatment with topical or systemic analgesics can be considered. | |
| Investigational medicinal product name | Granulocyte Colony Stimulating Factor |
| Investigational medicinal product code | GCSF |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use, Injection |
| Dosage and administration details: | |
| 300µg GCSF, daily, on days 15-21, by subcutaneous injection | |
| Investigational medicinal product name | Cisplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Infusion , Intravenous use |
| Dosage and administration details: | |
| Cisplatin 70 mg/m2 on day 8 of each cycle by IV infusion over 2-4 hours | |
| Investigational medicinal product name | Gemcitabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use, Infusion |
| Dosage and administration details: | |
| Gemcitabine 1000 mg/m2 on days 8 and 15 of each cycle by IV infusion over 30-60 minutes (and prior to cisplatin on day 8) | |
| Arm title | Cohort 1 20mg |
| Arm description: - | |
| Arm type | Experimental |

| | |
|--|---|
| Investigational medicinal product name | Guadecitabine |
| Investigational medicinal product code | SGI-110 |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Injection , Intraabdominal use , Subcutaneous use |

Dosage and administration details:

SGI-110 administration has been established as 20 mg/m², daily, on days 1-5, by sub-cutaneous injection to all patients and preferably in the abdominal area.

- Care must be taken to avoid intradermal injection as this may result in injection site pain.
- SGI-110 should be injected slowly (up to one minute) as some injection site discomfort or pain may occasionally be experienced.
- If injection site pain is reported upon injection, apply ice packs to the injection site both before and after injection. If injection site events are reported at subsequent injections despite slow injection and the use of ice packs, pretreatment with topical or systemic analgesics can be considered.

| Number of subjects in period 1 | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg |
|---------------------------------------|-----------------------------|-----------------------------|---------------|
| Started | 9 | 6 | 4 |
| Completed | 8 | 5 | 4 |
| Not completed | 1 | 1 | 0 |
| Death prior to cycle 2 | 1 | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--------------------------------|--------------------------|
| Reporting group title | Cohort 2 - 20 mg + G-CSF |
| Reporting group description: - | |
| Reporting group title | Cohort 3 - 30 mg + G-CSF |
| Reporting group description: - | |
| Reporting group title | Cohort 1 20mg |
| Reporting group description: - | |

| Reporting group values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg |
|--|--------------------------|--------------------------|---------------|
| Number of subjects | 9 | 6 | 4 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 5 | 2 | 2 |
| From 65-84 years | 3 | 3 | 2 |
| Not recorded | 1 | 1 | 0 |
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| median | 56 | 68 | 63 |
| inter-quartile range (Q1-Q3) | 52.5 to 65 | 47 to 70 | 57.5 to 70 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 3 | 1 | 2 |
| Male | 5 | 4 | 2 |
| Not recorded | 1 | 1 | 0 |
| ECOG Performance Status | | | |
| Eastern Cooperative Oncology Group (ECOG) performance status | | | |
| Units: Subjects | | | |
| 0 - Fully Active | 5 | 2 | 2 |
| 1 - Restricted in Physically Strenuous Activity | 3 | 3 | 2 |
| Not recorded | 1 | 1 | 0 |

| Reporting group values | Total | | |
|------------------------------|-------|--|--|
| Number of subjects | 19 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 9 | | |
| From 65-84 years | 8 | | |
| Not recorded | 2 | | |
| Age continuous | | | |
| Age continuous description | | | |
| Units: years | | | |
| median | | | |
| inter-quartile range (Q1-Q3) | - | | |

| | | | |
|--|----|--|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 6 | | |
| Male | 11 | | |
| Not recorded | 2 | | |
| ECOG Performance Status | | | |
| Eastern Cooperative Oncology Group (ECOG) performance status | | | |
| Units: Subjects | | | |
| 0 - Fully Active | 9 | | |
| 1 - Restricted in Physically Strenuous Activity | 8 | | |
| Not recorded | 2 | | |

End points

End points reporting groups

| | |
|--------------------------------|--------------------------|
| Reporting group title | Cohort 2 - 20 mg + G-CSF |
| Reporting group description: - | |
| Reporting group title | Cohort 3 - 30 mg + G-CSF |
| Reporting group description: - | |
| Reporting group title | Cohort 1 20mg |
| Reporting group description: - | |

Primary: Dose Limiting Toxicity

| | |
|-----------------|---------------------------------------|
| End point title | Dose Limiting Toxicity ^[1] |
|-----------------|---------------------------------------|

End point description:

Any of the following events occurring between the first dose administration of SGI-110 and day 1 of the second cycle of treatment will constitute a DLT if, in the opinion of the investigator, the event is defined as definitely or probably related to the combination of SGI-110, cisplatin and gemcitabine:

- Greater than 14 days of delay in commencing a second cycle of treatment due to drug toxicity
- Grade 4 neutropenia ≥ 7 days duration
- Grade 3 – 4 neutropenia associated with a temperature $\geq 38.5^{\circ}\text{C}$
- Grade 3 – 4 neutropenia associated with bacteriologically proven sepsis
- Any grade 4 thrombocytopenia ≥ 7 days duration
- Grade 3 thrombocytopenia associated with non-traumatic bleeding
- Any other clinically significant grade 3 or above toxicity except nausea or vomiting

A DLT excludes isolated laboratory changes of any grade (except as specified above) without clinical sequelae or clinical significance.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Phase I - Trial Period

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: Phase 1 trial, no statistical analyses

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|--|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Subjects | | | | |
| ≥ 14 days of delay commencing 2nd cycle | 0 | 1 | 0 | |
| Grade 4 Neutropenia ≥ 7 days | 0 | 1 | 1 | |
| Grade 3 or Grade 4 Febrile Neutropenia ($\geq 38.5^{\circ}\text{C}$) | 2 | 1 | 1 | |
| Grade 3 or Grade 4 Neutropenic Sepsis | 0 | 0 | 0 | |
| Grade 4 Thrombocytopenia ≥ 7 days | 0 | 2 | 0 | |
| G3 Thrombocytopenia with non-traumatic bleeding | 0 | 0 | 0 | |
| Other Clinically Significant G3 or above toxicity | 0 | 2 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of complete cycles of Guadecitabine

| | |
|-----------------|--|
| End point title | Number of complete cycles of Guadecitabine |
|-----------------|--|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment Period

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|-----------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Subjects | | | | |
| 1 cycle | 1 | 2 | 0 | |
| 2 cycles | 1 | 2 | 0 | |
| 3 cycles | 2 | 0 | 1 | |
| 4 cycles | 1 | 0 | 0 | |
| 5 cycles | 2 | 0 | 2 | |
| 6 cycles | 1 | 1 | 1 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Gemcitabine - Number of cycles received

| | |
|-----------------|---|
| End point title | Gemcitabine - Number of cycles received |
|-----------------|---|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Treatment Period

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|-------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Cycles | | | | |
| median (full range (min-max)) | 3.5 (1.0 to 6.0) | 2.0 (1.0 to 6.0) | 5 (3 to 6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Cisplatin - Number of Cycles Received

End point title Cisplatin - Number of Cycles Received

End point description:

End point type Secondary

End point timeframe:

Treatment Period

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|-------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Cycles | | | | |
| median (full range (min-max)) | 3.5 (1.0 to 6.0) | 2.0 (1.0 to 6.0) | 5 (3 to 6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: G-CSF Administration as Per Protocol

End point title G-CSF Administration as Per Protocol^[2]

End point description:

End point type Secondary

End point timeframe:

Treatment Period

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Phase 1 trial, no statistical analyses

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | | |
|-----------------------------|--------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 5 | | |
| Units: Subjects | | | | |
| Yes | 7 | 4 | | |
| No | 1 | 1 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of deaths on trial

| | |
|------------------------|---------------------------|
| End point title | Number of deaths on trial |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Trial Period | |

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|-----------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Subjects | 0 | 0 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in Line 1 Percentage Methylation from Cycle 1 Day 1

| | |
|--|---|
| End point title | Mean Change in Line 1 Percentage Methylation from Cycle 1 Day 1 |
| End point description: AT EACH TIME-POINT (plot is attached; no mean over all time periods is available). | |
| End point type | Secondary |
| End point timeframe: | |
| Trial Period | |

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|----------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Percentage | | | | |
| arithmetic mean (standard error) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |

| | |
|-----------------------------------|------------------|
| Attachments (see zip file) | Line-1 plot1.pdf |
|-----------------------------------|------------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Hgb-F Fold Change from Cycle 1 Day 1

| | |
|------------------------|--|
| End point title | Hgb-F Fold Change from Cycle 1 Day 1 |
| End point description: | AT EACH TIME-POINT (plot is attached; no mean over all time periods is available). |
| End point type | Secondary |
| End point timeframe: | |
| Trial Period | |

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|-----------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Percentage | | | | |
| number (not applicable) | 0 | 0 | 0 | |

| | |
|-----------------------------------|---------------------|
| Attachments (see zip file) | Hbf panel plot1.pdf |
|-----------------------------------|---------------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in LTR12C

| | |
|------------------------|--|
| End point title | Mean Change in LTR12C |
| End point description: | AT EACH TIME-POINT (plot is attached; no mean over all time periods is available). |
| End point type | Secondary |
| End point timeframe: | |
| Trial Period | |

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|----------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Percentage | | | | |
| arithmetic mean (standard error) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |

| | |
|-----------------------------------|------------------|
| Attachments (see zip file) | LTR12C plot1.pdf |
|-----------------------------------|------------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in SAT2 percentage methylation

| | |
|------------------------|--|
| End point title | Mean Change in SAT2 percentage methylation |
| End point description: | AT EACH TIME-POINT (plot is attached; no mean over all time periods is available). |
| End point type | Secondary |
| End point timeframe: | |
| Trial Period | |

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|----------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Percentage | | | | |
| arithmetic mean (standard error) | 0 (± 0) | 0 (± 0) | 0 (± 0) | |

| | |
|-----------------------------------|----------------|
| Attachments (see zip file) | SAT2 plot1.pdf |
|-----------------------------------|----------------|

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in D4Z4 percentage methylation

| | |
|------------------------|--|
| End point title | Mean Change in D4Z4 percentage methylation |
| End point description: | AT EACH TIME-POINT (plot is attached; no mean over all time periods is available). |
| End point type | Secondary |

End point timeframe:

Trial Period

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|----------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Percentage | | | | |
| arithmetic mean (standard error) | 0 (\pm 0) | 0 (\pm 0) | 0 (\pm 0) | |

Attachments (see zip file)

D4Z4 plot1.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in NBL2 percentage methylation

| | |
|-----------------|--|
| End point title | Mean Change in NBL2 percentage methylation |
|-----------------|--|

End point description:

AT EACH TIME-POINT (plot is attached; no mean over all time periods is available).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Trial Period

| End point values | Cohort 2 - 20 mg + G-CSF | Cohort 3 - 30 mg + G-CSF | Cohort 1 20mg | |
|----------------------------------|--------------------------|--------------------------|-----------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 8 | 5 | 4 | |
| Units: Percentage | | | | |
| arithmetic mean (standard error) | 0 (\pm 0) | 0 (\pm 0) | 0 (\pm 0) | |

Attachments (see zip file)

NBL2 plot1.pdf

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The reporting requirement applies for all adverse events occurring up to 4 weeks after the last administration of study drugs. SAEs, SARs and SUSARs should be reported within 24 hours of the site becoming aware of the event.

Adverse event reporting additional description:

AE additional description

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|------------------------|
| Reporting group title | Phase I - 20mg + G-CSF |
|-----------------------|------------------------|

Reporting group description: -

| | |
|-----------------------|----------------|
| Reporting group title | Phase I - 20mg |
|-----------------------|----------------|

Reporting group description: -

| | |
|-----------------------|------------------------|
| Reporting group title | Phase I - 30mg + G-CSF |
|-----------------------|------------------------|

Reporting group description: -

| Serious adverse events | Phase I - 20mg + G-CSF | Phase I - 20mg | Phase I - 30mg + G-CSF |
|---|--|----------------|------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 8 (62.50%) | 3 / 4 (75.00%) | 4 / 5 (80.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Peripheral ischaemia | Additional description: Peripheral ischaemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Seizure | Additional description: Seizure | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Thrombocytopenia | Additional description: Thrombocytopenia | | |

| | | | |
|--|--|----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | Additional description: Neutropenia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | Additional description: Febrile neutropenia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Pyrexia | Additional description: Pyrexia | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Vomiting | Additional description: Vomiting | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | Additional description: Diarrhoea | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Ureteric obstruction | Additional description: Ureteric obstruction | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---------------|----------------|
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | Additional description: Pain in extremity | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Urinary tract infection | Additional description: Urinary tract infection | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth infection | Additional description: Tooth infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | Additional description: Infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | Additional description: Pneumonia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Phase I - 20mg + G-CSF | Phase I - 20mg | Phase I - 30mg + G-CSF |
|---|--------------------------------------|-----------------|------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 4 / 4 (100.00%) | 5 / 5 (100.00%) |
| Vascular disorders | Additional description: Flushing | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Hypertension | Additional description: Hypertension | | |

| | | | |
|--|---|----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Embolism | Additional description: Embolism | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Phlebitis | Additional description: Phlebitis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Face oedema | Additional description: Face oedema | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Injection site pain | Additional description: Injection site pain | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 2 / 4 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 21 | 17 | 3 |
| Malaise | Additional description: Malaise | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injection site discomfort | Additional description: Injection site discomfort | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Mucosal inflammation | Additional description: Mucosal inflammation | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 | 1 |
| Injection site bruising | Additional description: Injection site bruising | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pyrexia | Additional description: Pyrexia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Injection site erythema | Additional description: Injection site erythema | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Chills | Additional description: Chills | | |

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|---|--|----------------|-----------------|
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Fatigue | Additional description: Fatigue | | |
| subjects affected / exposed | 8 / 8 (100.00%) | 3 / 4 (75.00%) | 5 / 5 (100.00%) |
| occurrences (all) | 15 | 9 | 8 |
| Oedema peripheral | Additional description: Oedema peripheral | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Injection site reaction | Additional description: Injection site reaction | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 15 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | Additional description: Cough | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Dyspnoea | Additional description: Dyspnoea | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 4 | 1 | 1 |
| Epistaxis | Additional description: Epistaxis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspnoea exertional | Additional description: Dyspnoea exertional | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Psychiatric disorders | | | |
| Insomnia | Additional description: Insomnia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Investigations | | | |
| White blood cell count decreased | Additional description: White blood cell count decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 1 | 1 | 20 |
| Gamma-glutamyltransferase increased | Additional description: Gamma-glutamyltransferase increased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Aspartate aminotransferase | Additional description: Aspartate aminotransferase increased | | |

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| increased | | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood alkaline phosphatase increased | Additional description: Blood alkaline phosphatase increased | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Blood urea increased | Additional description: Blood urea increased | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Monocyte count decreased | Additional description: Monocyte count decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Blood creatinine increased | Additional description: Blood creatinine increased | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 2 |
| Platelet count increased | Additional description: Platelet count increased | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Alanine aminotransferase increased | Additional description: Alanine aminotransferase increased | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 4 | 1 | 0 |
| Red blood cell count decreased | Additional description: Red blood cell count decreased | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | Additional description: Contusion | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stoma site haemorrhage | Additional description: Stoma site haemorrhage | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Arthropod bite | Additional description: Arthropod bite | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |

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|---|---|-----------------|----------------|
| Palpitations subjects affected / exposed occurrences (all) | Additional description: Palpitations | | |
| | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| | 1 | 0 | 0 |
| Nervous system disorders Paraesthesia subjects affected / exposed occurrences (all) Peripheral motor neuropathy subjects affected / exposed occurrences (all) Peripheral sensory neuropathy subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dysgeusia subjects affected / exposed occurrences (all) Extrapyramidal disorder subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Lethargy subjects affected / exposed occurrences (all) | Additional description: Paraesthesia | | |
| | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| | 1 | 0 | 0 |
| | Additional description: Peripheral motor neuropathy | | |
| | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| | 0 | 1 | 0 |
| | Additional description: Peripheral sensory neuropathy | | |
| | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| | 1 | 1 | 1 |
| | Additional description: Headache | | |
| | 2 / 8 (25.00%) | 2 / 4 (50.00%) | 1 / 5 (20.00%) |
| | 2 | 2 | 1 |
| | Additional description: Dysgeusia | | |
| | 0 / 8 (0.00%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| | 0 | 4 | 0 |
| | Additional description: Extrapyramidal disorder | | |
| | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| | 0 | 1 | 0 |
| | Additional description: Dizziness | | |
| | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| | 2 | 0 | 1 |
| | Additional description: Lethargy | | |
| | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| | 1 | 0 | 1 |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) Neutropenia | Additional description: Anaemia | | |
| | 6 / 8 (75.00%) | 2 / 4 (50.00%) | 2 / 5 (40.00%) |
| | 9 | 8 | 19 |
| | Additional description: Thrombocytopenia | | |
| | 7 / 8 (87.50%) | 4 / 4 (100.00%) | 4 / 5 (80.00%) |
| | 25 | 16 | 31 |
| | Additional description: Neutropenia | | |

| | | | |
|-----------------------------|---|-----------------|-----------------|
| subjects affected / exposed | 5 / 8 (62.50%) | 4 / 4 (100.00%) | 5 / 5 (100.00%) |
| occurrences (all) | 15 | 5 | 12 |
| Lymphopenia | Additional description: Lymphopenia | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 4 | 0 | 0 |
| Pancytopenia | Additional description: Pancytopenia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ear and labyrinth disorders | | | |
| Deafness | Additional description: Deafness | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tinnitus | Additional description: Tinnitus | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 2 / 4 (50.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 3 | 7 |
| Vestibular disorder | Additional description: Vestibular disorder | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypoacusis | Additional description: Hypoacusis | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Gastrointestinal disorders | | | |
| Vomiting | Additional description: Vomiting | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 6 | 1 | 1 |
| Abdominal pain | Additional description: Abdominal pain | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dyspepsia | Additional description: Dyspepsia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Toothache | Additional description: Toothache | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diarrhoea | Additional description: Diarrhoea | | |

| | | | |
|--|--|-----------------|----------------|
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 3 | 2 |
| Abdominal distension | Additional description: Abdominal distension | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Melaena | Additional description: Melaena | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nausea | Additional description: Nausea | | |
| subjects affected / exposed | 6 / 8 (75.00%) | 4 / 4 (100.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 12 | 13 | 4 |
| Stomatitis | Additional description: Stomatitis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Constipation | Additional description: Constipation | | |
| subjects affected / exposed | 4 / 8 (50.00%) | 4 / 4 (100.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 4 | 5 | 3 |
| Mouth ulceration | Additional description: Mouth ulceration | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral pain | Additional description: Oral pain | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Skin induration | Additional description: Skin induration | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Dermatitis acneiform | Additional description: Dermatitis acneiform | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Rash maculo-papular | Additional description: Rash maculo-papular | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Acne | Additional description: Acne | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|-----------------------------|--|---------------------|---------------------|
| Purpura | Additional description: Purpura | | |
| | 0 / 8 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 |
| Pruritis | Additional description: Pruritis | | |
| | 1 / 8 (12.50%) 1 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Alopecia | Additional description: Alopecia | | |
| | 3 / 8 (37.50%) 3 | 3 / 4 (75.00%) 4 | 1 / 5 (20.00%) 1 |
| Erythema | Additional description: Erythema | | |
| | 1 / 8 (12.50%) 1 | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 |
| Urticaria | Additional description: Urticaria | | |
| | 1 / 8 (12.50%) 5 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Rash | Additional description: Rash | | |
| | 0 / 8 (0.00%) 0 | 1 / 4 (25.00%) 1 | 1 / 5 (20.00%) 3 |
| Rash macular | Additional description: Rash macular | | |
| | 1 / 8 (12.50%) 1 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Renal and urinary disorders | | | |
| Urinary tract pain | Additional description: Urinary tract pain | | |
| | 1 / 8 (12.50%) 1 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Acute kidney injury | Additional description: Acute kidney injury | | |
| | 0 / 8 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Nocturia | Additional description: Nocturia | | |
| | 0 / 8 (0.00%) 0 | 0 / 4 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Urine odour abnormal | Additional description: Urine odour abnormal | | |
| | 0 / 8 (0.00%) 0 | 1 / 4 (25.00%) 1 | 0 / 5 (0.00%) 0 |
| Haematuria | Additional description: Haematuria | | |
| | | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 0 | 1 |
| Pollakiuria | Additional description: Pollakiuria | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Groin pain | Additional description: Groin pain | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pain in extremity | Additional description: Pain in extremity | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 3 |
| Myalgia | Additional description: Myalgia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Muscle spasms | Additional description: Muscle spasms | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Back pain | Additional description: Back pain | | |
| subjects affected / exposed | 3 / 8 (37.50%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 0 | 1 |
| Arthralgia | Additional description: Arthralgia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 2 | 1 |
| Infections and infestations | | | |
| Rhinitis | Additional description: Rhinitis | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 1 | 0 | 1 |
| Pneumonia | Additional description: Pneumonia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary tract infection | Additional description: Urinary tract infection | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 2 / 4 (50.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 5 | 0 |
| Nasopharyngitis | Additional description: Nasopharyngitis | | |

| | | | |
|---|---|----------------|----------------|
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lower respiratory tract infection | Additional description: Lower respiratory tract infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Furuncle | Additional description: Furuncle | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Viral upper respiratory tract infection | Additional description: Viral upper respiratory tract infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lip infection | Additional description: Lip infection | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Corona Virus Infection | Additional description: Corona Virus Infection | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Influenza | Additional description: Influenza | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | Additional description: Decreased appetite | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 1 / 4 (25.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 3 | 1 |
| Hypomagnesaemia | Additional description: Hypomagnesaemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 0 / 4 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 0 | 6 |
| Hyponatraemia | Additional description: Hyponatraemia | | |
| subjects affected / exposed | 0 / 8 (0.00%) | 1 / 4 (25.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypocalcaemia | Additional description: Hypocalcaemia | | |
| subjects affected / exposed | 2 / 8 (25.00%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 3 | 0 | 1 |
| Hypokalaemia | Additional description: Hypokalaemia | | |
| subjects affected / exposed | 1 / 8 (12.50%) | 0 / 4 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 2 | 0 | 1 |

| | | | |
|--|--------------------------------------|--------------------|--------------------|
| Dehydration subjects affected / exposed occurrences (all) | Additional description: Dehydration | | |
| | 1 / 8 (12.50%) 1 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Hypocalcemia subjects affected / exposed occurrences (all) | Additional description: Hypocalcemia | | |
| | 1 / 8 (12.50%) 1 | 0 / 4 (0.00%) 0 | 0 / 5 (0.00%) 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 08 February 2016 | MHRA requested changes to the protocol, PIS/ICF updates and addition of a 4th site (Rob Jones). |
| 08 December 2016 | Updated IB v07 18 Aug 2016, updated protocol RIS, PIS/ICF side effects and exposure numbers updated in line with new IB. |
| 25 May 2018 | <p>-Provide clarification to ensure that, as was the original intention, all patients in the control arm (GC alone) should not have a delay in treatment (Gemcitabine and Cisplatin) administration following randomisation, is clear.</p> <p>-Alter the neutrophil and platelet count criteria for proceeding to subsequent cycles to ensure patients are not unduly delayed. It has been noted in the dose escalation phase that patients were experiencing dose delays enforced by the protocol that would not have usually clinically been implemented and that those patients with reduced neutrophil and platelets counts were returning to within limits within 2 weeks. The TMG have agreed that unnecessary dose delays should be avoided in the neoadjuvant setting that the dose expansion phase will be conducted in.</p> <p>-Request additional sites to be added for dose expansion phase.</p> <p>- Include updates to IMPD previously sent only to the MHRA</p> |
| 07 February 2019 | Updated IB v08 18 Aug 2016, updated protocol RIS, PIS/ICF side effects and exposure numbers updated in line with new IB. |
| 02 July 2019 | <p>Amendment changes:</p> <ul style="list-style-type: none">• Pre-treatment assessments permitted within 3 days prior to Day 1, 8 and 15.• Gemcitabine SmPC updated.• Cisplatin SmPC updated.• RSI table in protocol updated.• PIS – new common side effect of Cisplatin added.• ICF – updated to reflect change in version of PIS.• Changes to predicted timelines – recruitment completion, patient follow-up and final report. <p>Dr Crabb (SPIRE Chief Investigator) has stated 'The changes within this amendment take into account the greater level of safety data now available for this combination of drugs and brings the protocol into line with standard levels of monitoring and toxicity assessment for this form of treatment.'</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33472913>