



Clinical trial results:

Lenalidomide in conjunction with methotrexate, leucovorin, cytarabine and rituximab for the treatment of relapsed or refractory CD20-positive aggressive lymphomas: an open-label, multicenter phase I/II trial

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2012-001891-13 |
| Trial protocol | DE |
| Global end of trial date | 20 February 2020 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 06 June 2022 |
| First version publication date | 06 June 2022 |

Trial information

Trial identification

| | |
|-----------------------|--------|
| Sponsor protocol code | LeMLAR |
|-----------------------|--------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01788189 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | University Hospital Essen |
| Sponsor organisation address | Hufelandstrasse 55, Essen, Germany, 45147 |
| Public contact | Prof. Dr. Ulrich Dührsen, University Hospital Essen, 0049 2102847374, ulrich.duehrsen@uk-essen.de |
| Scientific contact | Prof. Dr. Ulrich Dührsen, University Hospital Essen, 0049 2102847374, ulrich.duehrsen@uk-essen.de |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 20 February 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 February 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 February 2020 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Phase 1:

Evaluation of the feasibility, safety and dose-limiting toxicity of the LeMLAR regimen

Phase 2:

Evaluation of the efficacy of the LeMLAR regimen at the maximum tolerated dose

Protection of trial subjects:

Documentation of adverse events according to CTCAE version 3.0

Background therapy: -

Evidence for comparator:

Phase 2:

The objective response rate of patients with relapsed or refractory diffuse large B-cell lymphoma to lenalidomide alone had been reported to be 20% (J Clin Oncol 26: 4952-4957, 2008). The phase II part of the LeMLAR trial tested the hypothesis that the objective response rate will be increased to $\geq 40\%$ by combining lenalidomide with MLAR at the maximum tolerated dose ($p < 0.05$, power=0.4).

| | |
|---|------------------|
| Actual start date of recruitment | 18 December 2012 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 34 |
| Worldwide total number of subjects | 34 |
| EEA total number of subjects | 34 |

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) | 16 |
| From 65 to 84 years | 18 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Patients ≥ 18 years with relapsed or refractory CD20-positive aggressive B cell lymphoma (excluding mantle cell lymphoma and central nervous system involvement) lacking other treatment options were eligible. Exclusion criteria included inadequate organ function and uncontrolled infection.

First patient in: 25/01/2013

Last patient in: 23/05/2018

Pre-assignment

Screening details:

Details specified in the inclusion and exclusion criteria (publication of the LeMLAR trial, Blood Cancer J 11: 95, 2021).

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Phase 1 and 2 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

No blinding.

Arms

| | |
|------------------------------|-------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | 1. Dose level 3-1 |

Arm description:

Lenalidomide 25 mg, methotrexate and cytarabine dose level 1

| | |
|--|-------------------|
| Arm type | Phase 1 Level 3-1 |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

25 mg, day 1-21 of each 28-day cycle, maximum 6 cycles

| | |
|--|-----------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

30 mg/m², day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles

| | |
|--|------------|
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles

| | |
|--|------------|
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |

| | |
|--|-------------------|
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 75 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² , day 1 of each 28-day cycle, maximum 6 cycles | |
| Arm title | 2. Dose level 3-2 |
| Arm description: | |
| Lenalidomide 25 mg, methotrexate and cytarabine dose level 2 | |
| Arm type | Phase 1 Level 3-2 |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 25 mg, day 1-21 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 60 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 150 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² , day 1 of each 28-day cycle, maximum 6 cycles | |
| Arm title | 3. Dose level 2-2 |

| | |
|--|-------------------|
| Arm description: | |
| Lenalidomide 20 mg, methotrexate and cytarabine dose level 2 | |
| Arm type | Phase 1 Level 2-2 |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 20 mg, day 1-21 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 60 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 150 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² , day 1 of each 28-day cycle, maximum 6 cycles | |
| Arm title | 4. Dose level 2-3 |
| Arm description: | |
| Lenalidomide 20 mg, methotrexate and cytarabine dose level 3 | |
| Arm type | Phase 1 Level 2-3 |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 20 mg, day 1-21 of each 28-day cycle, maximum 6 cycles | |

| | |
|---|----------------------------|
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 90 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 225 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Rituximab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 375 mg/m ² , day 1 of each 28-day cycle, maximum 6 cycles | |
| Arm title | Phase 2 at MTD level (2-2) |
| Arm description: | |
| Treatment at MTD level and comparison with published results for lenalidomide monotherapy | |
| Arm type | Experimental |
| Investigational medicinal product name | Lenalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 20 mg, day 1-21 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Methotrexate |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |
| Dosage and administration details: | |
| 60 mg/m ² , day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles | |
| Investigational medicinal product name | Leucovorin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

45 mg four times per day, day 2, 9 and 16 of each 28-day cycle, maximum 6 cycles

| | |
|--|-----------------|
| Investigational medicinal product name | Cytarabine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

150 mg/m², day 1, 8 and 15 of each 28-day cycle, maximum 6 cycles

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

Dosage and administration details:

375 mg/m², day 1 of each 28-day cycle, maximum 6 cycles

| Number of subjects in period 1 | 1. Dose level 3-1 | 2. Dose level 3-2 | 3. Dose level 2-2 |
|---------------------------------------|-------------------|-------------------|-------------------|
| Started | 4 | 4 | 8 |
| Completed | 4 | 4 | 8 |

| Number of subjects in period 1 | 4. Dose level 2-3 | Phase 2 at MTD level (2-2) |
|---------------------------------------|-------------------|----------------------------|
| Started | 6 | 12 |
| Completed | 6 | 12 |

Baseline characteristics

Reporting groups

| | |
|---|----------------------------|
| Reporting group title | 1. Dose level 3-1 |
| Reporting group description: | |
| Lenalidomide 25 mg, methotrexate and cytarabine dose level 1 | |
| Reporting group title | 2. Dose level 3-2 |
| Reporting group description: | |
| Lenalidomide 25 mg, methotrexate and cytarabine dose level 2 | |
| Reporting group title | 3. Dose level 2-2 |
| Reporting group description: | |
| Lenalidomide 20 mg, methotrexate and cytarabine dose level 2 | |
| Reporting group title | 4. Dose level 2-3 |
| Reporting group description: | |
| Lenalidomide 20 mg, methotrexate and cytarabine dose level 3 | |
| Reporting group title | Phase 2 at MTD level (2-2) |
| Reporting group description: | |
| Treatment at MTD level and comparison with published results for lenalidomide monotherapy | |

| Reporting group values | 1. Dose level 3-1 | 2. Dose level 3-2 | 3. Dose level 2-2 |
|--|-------------------|-------------------|-------------------|
| Number of subjects | 4 | 4 | 8 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 2 | 4 |
| From 65-84 years | 4 | 2 | 4 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 72 | 68 | 68 |
| full range (min-max) | 70 to 74 | 56 to 80 | 56 to 80 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 1 | 2 |
| Male | 0 | 3 | 6 |

| Reporting group values | 4. Dose level 2-3 | Phase 2 at MTD level (2-2) | Total |
|------------------------|-------------------|----------------------------|-------|
| Number of subjects | 6 | 12 | 34 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |

| | | | |
|---|----------|----------|----|
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 3 | 7 | 16 |
| From 65-84 years | 3 | 5 | 18 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| median | 64 | 61 | |
| full range (min-max) | 49 to 72 | 40 to 82 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 1 | 7 | 15 |
| Male | 5 | 5 | 19 |

End points

End points reporting groups

| | |
|---|----------------------------|
| Reporting group title | 1. Dose level 3-1 |
| Reporting group description: | |
| Lenalidomide 25 mg, methotrexate and cytarabine dose level 1 | |
| Reporting group title | 2. Dose level 3-2 |
| Reporting group description: | |
| Lenalidomide 25 mg, methotrexate and cytarabine dose level 2 | |
| Reporting group title | 3. Dose level 2-2 |
| Reporting group description: | |
| Lenalidomide 20 mg, methotrexate and cytarabine dose level 2 | |
| Reporting group title | 4. Dose level 2-3 |
| Reporting group description: | |
| Lenalidomide 20 mg, methotrexate and cytarabine dose level 3 | |
| Reporting group title | Phase 2 at MTD level (2-2) |
| Reporting group description: | |
| Treatment at MTD level and comparison with published results for lenalidomide monotherapy | |

Primary: Dose-limiting toxicity

| | |
|--|--|
| End point title | Dose-limiting toxicity ^{[1][2]} |
| End point description: | |
| Treatment tolerance was assumed if none of three or only one of six patients experienced dose limiting toxicity (DLT). | |
| Definition of DLT: Neutrophils <0.5 /nl, platelets <25 /nl, creatinine clearance <60 ml/min, bilirubine ≥3 mg/dl, serum AST or ALT ≥6× ULN, or mucositis grade ≥3 on day 8 (plus a maximum of 3 extra days), day 15 (plus ≤6 days), or day 29 (plus ≤7 days). Failure to reach these thresholds at the indicated time-points prevented timely administration of methotrexate and cytarabine. Adverse events requiring dose reduction in cycle 1 or 2, receipt of <21 lenalidomide doses per cycle, cycle length >35 days, and any adverse event preventing continuation according to the protocol were also rated as DLT. Patients without DLT terminating treatment in cycle 1 or 2 prematurely due to disease progression were replaced by new patients. They were rated as not evaluable. | |
| The maximum tolerated dose (MTD) was the dose level immediately below the level where DLT occurred. | |
| End point type | Primary |
| End point timeframe: | |
| Phase 1, first two treatment cycles (56-70 days from first treatment day) | |

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: The first four arms represent groups of patients treated at escalating dose levels and are not meant to be compared by standard statistical methods. Dose escalation followed the 3+3 design whereby dose-limiting toxicity (DLT) was defined as an occurrence of toxicity in ≥1 of 3 or ≥2 of 6 patients treated at a given dose level. The maximum tolerated dose (2-2) was the level immediately below the level at which DLT occurred (2-3).

[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: The first four arms represent groups of patients treated at escalating dose levels and are not meant to be compared by standard statistical methods. Dose escalation followed the 3+3 design whereby dose-limiting toxicity (DLT) was defined as an occurrence of toxicity in ≥1 of 3 or ≥2 of 6 patients treated at a given dose level. The maximum tolerated dose (2-2) was the level immediately below the level at which DLT occurred (2-3).

| End point values | 1. Dose level 3-1 | 2. Dose level 3-2 | 3. Dose level 2-2 | 4. Dose level 2-3 |
|-----------------------------|----------------------|----------------------|----------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 4 | 8 | 6 |
| Units: Patients | | | | |
| No DLT | 3 | 1 | 5 | 4 |
| DLT | 0 | 2 | 1 | 2 |
| Not evaluable | 1 | 1 | 2 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Objective response rate

| | |
|-----------------|---|
| End point title | Objective response rate ^[3] ^[4] |
|-----------------|---|

End point description:

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

End point timeframe:

End of treatment (4 weeks after the last LeMLAR cycle)

Notes:

[3] - 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: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from phase 1 and 12 patients additionally recruited in phase 2. These groups were not meant to be compared with each other, but to be combined to describe the objective response rate (ORR). The hypothesis of the phase 2 part was that the published ORR of lenalidomide monotherapy (20%) would be increased to $\geq 40\%$ by combining lenalidomide with MLAR. This was confirmed (ORR=55%).

[4] - 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: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from phase 1 and 12 patients additionally recruited in phase 2. These groups were not meant to be compared with each other, but to be combined to describe the objective response rate (ORR). The hypothesis of the phase 2 part was that the published ORR of lenalidomide monotherapy (20%) would be increased to $\geq 40\%$ by combining lenalidomide with MLAR. This was confirmed (ORR=55%).

| End point values | 3. Dose level 2-2 | Phase 2 at MTD level (2-2) | | |
|-----------------------------|----------------------|-------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 12 | | |
| Units: Patients | | | | |
| Objective response | 3 | 8 | | |
| No objective response | 3 | 4 | | |
| Not evaluable | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Complete remission rate

| | |
|-----------------|--|
| End point title | Complete remission rate ^[5] |
|-----------------|--|

End point description:

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

End point timeframe:

End of treatment (4 weeks after the last LeMLAR cycle)

Notes:

[5] - 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: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from the phase 1 part and 12 patients additionally recruited in the phase 2 part. These groups were not meant to be compared with each other, but to be combined to describe the complete remission rate.

| End point values | 3. Dose level 2-2 | Phase 2 at MTD level (2-2) | | |
|-----------------------------|-------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 | 12 | | |
| Units: Patients | | | | |
| Complete remission | 1 | 4 | | |
| Partial remission | 2 | 4 | | |
| Stable disease | 2 | 1 | | |
| Progressive disease | 1 | 3 | | |
| Not evaluable | 2 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response

| | |
|-----------------|-------------------------------------|
| End point title | Duration of response ^[6] |
|-----------------|-------------------------------------|

End point description:

This analysis includes patients from Phase 1, Arm 3 (dose level 2-2) and Phase 2 at MTD level (2-2) combined

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

End point timeframe:

From achievement of an objective response to progression or last follow-up

Notes:

[6] - 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: The study aimed at including 20 patients treated at the maximum tolerated dose (MTD = level 2-2). These were 8 patients from phase 1 and 12 patients additionally recruited in phase 2. These groups were not meant to be compared with each other, but to be combined to describe the duration of response. This was compared to other therapies in similar patient groups (see LeMLAR publication, Blood Cancer J 11:95, 2021)

| | | | | |
|-------------------------------|-------------------|----------------------------|--|--|
| End point values | 3. Dose level 2-2 | Phase 2 at MTD level (2-2) | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 3 | 12 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 19 (1 to 32) | 19 (1 to 32) | | |

| | |
|-----------------------------------|--|
| Attachments (see zip file) | Duration of response to LeMLAR/Figure 2 - LeMLAR.jpg |
|-----------------------------------|--|

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the consent form for trial participation to 4 weeks after the last treatment cycle

Only for overall deaths: From signing the consent form to death or last follow-up (median follow-up: 31 months)

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|-------|
| Dictionary name | CTCAE |
| Dictionary version | 3.0 |

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Phase 1 |
|-----------------------|---------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Phase 2 |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Phase 1 | Phase 2 | |
|--|------------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 22 (63.64%) | 6 / 12 (50.00%) | |
| number of deaths (all causes) | 22 | 7 | |
| number of deaths resulting from adverse events | 1 | 0 | |
| Vascular disorders | | | |
| Thromboembolism | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anemia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Fever | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|----------------|-----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Worsening of general condition | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 12 (16.67%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter-related infection | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhea | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucositis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinuria | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal | | | |

| | | | |
|---|----------------|-----------------|--|
| disorders | | | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 2 / 12 (16.67%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 12 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypercalcemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 12 (8.33%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Phase 1 | Phase 2 | |
|---|------------------|-----------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 22 (77.27%) | 6 / 12 (50.00%) | |
| Blood and lymphatic system disorders | | | |
| Anemia, grade 3 or 4 | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 3 / 12 (25.00%) | |
| occurrences (all) | 4 | 3 | |
| Leukopenia, grade 3 or 4 | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 1 | |
| Neutropenia, grade 3 or 4 | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 2 / 12 (16.67%) | |
| occurrences (all) | 2 | 2 | |
| Thrombocytopenia, grade 3 or 4 | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 3 / 12 (25.00%) | |
| occurrences (all) | 4 | 3 | |
| Gastrointestinal disorders | | | |
| Diarrhea, grade 3 or 4 | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 12 (8.33%) | |
| occurrences (all) | 2 | 1 | |
| Infections and infestations | | | |
| Infection, grade 3 to 4 | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 12 (0.00%) | |
| occurrences (all) | 3 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|--|
| 31 October 2014 | Deescalation of lenalidomide dose from 25 mg to 20 mg and from 20 mg to 15 mg, if chemotherapy dose level 1 cannot be escalated at a lenalidomide dose of 25 mg or 20 mg, respectively |

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/34001867>