



## Clinical trial results:

**Phase I dose escalation study with expansion cohort of the addition of nab-paclitaxel to capecitabine and oxaliplatin (CapOx) as first line treatment of metastatic esophagogastric adenocarcinoma (ACTION study).**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2014-001333-88 |
| Trial protocol           | NL             |
| Global end of trial date | 03 August 2018 |

### Results information

|                                   |                                             |
|-----------------------------------|---------------------------------------------|
| Result version number             | v1 (current)                                |
| This version publication date     | 12 January 2020                             |
| First version publication date    | 12 January 2020                             |
| Summary attachment (see zip file) | ACTION article Cancers (ACTION Cancers.pdf) |

### Trial information

#### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | ACTION |
|-----------------------|--------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02273713 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                                        |
|------------------------------|----------------------------------------------------------------------------------------|
| Sponsor organisation name    | Amsterdam UMC, location AMC                                                            |
| Sponsor organisation address | Meibergdreef 9, Amsterdam, Netherlands, 1105 AZ                                        |
| Public contact               | Lyda ter Hofstede, Amsterdam UMC, location AMC, 0031 205668229, trialmedonc@amc.uva.nl |
| Scientific contact           | Lyda ter Hofstede, Amsterdam UMC, location AMC, 0031 205668229, trialmedonc@amc.uva.nl |

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:

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**Results analysis stage**

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|                                                      |             |
|------------------------------------------------------|-------------|
| Analysis stage                                       | Final       |
| Date of interim/final analysis                       | 02 May 2018 |
| Is this the analysis of the primary completion data? | No          |

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|                                  |                |
|----------------------------------|----------------|
| Global end of trial reached?     | Yes            |
| Global end of trial date         | 03 August 2018 |
| Was the trial ended prematurely? | No             |

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Notes:

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**General information about the trial**

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Main objective of the trial:

Phase 1: To assess the safety and tolerability of Nab-paclitaxel added to oxaliplatin and capecitabine at their currently optimal doses.

Phase 2: To determine the anti-tumor activity of Nab-paclitaxel when co-administered with oxaliplatin and capecitabine in patients with irresectable or metastasized oesophagogastric cancer in terms of progression free survival.

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Protection of trial subjects:

All patients received best supportive care besides the trial regimen.

Safety was discussed in a weekly meeting. SAE's were discussed and when necessary safety was corresponded with the IRB.

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Background therapy: -

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Evidence for comparator: -

|                                                           |                 |
|-----------------------------------------------------------|-----------------|
| Actual start date of recruitment                          | 01 October 2014 |
| Long term follow-up planned                               | No              |
| Independent data monitoring committee (IDMC) involvement? | No              |

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Notes:

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**Population of trial subjects**

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**Subjects enrolled per country**

|                                      |                 |
|--------------------------------------|-----------------|
| Country: Number of subjects enrolled | Netherlands: 26 |
| Worldwide total number of subjects   | 26              |
| EEA total number of subjects         | 26              |

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Notes:

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**Subjects enrolled per age group**

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|                                           |   |
|-------------------------------------------|---|
| 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 |

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|                      |    |
|----------------------|----|
| Adults (18-64 years) | 17 |
| From 65 to 84 years  | 9  |
| 85 years and over    | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Between December 2014 and November 2016, 36 patients were assessed and 26 eligible patients were enrolled, all in Dutch hospitals.

### Pre-assignment

Screening details:

36 patients assessed for eligibility

10 excluded before treatment

Not meeting inclusion criteria (n=7)

No measurable lesion (n=2)

Temporary inclusion stop (n=1)

### Period 1

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

### Arms

|           |                     |
|-----------|---------------------|
| Arm title | Investigational arm |
|-----------|---------------------|

Arm description:

This was a single-arm study where all subjects received the experimental regime of capecitabine, oxaliplatin and nab-paclitaxel up to the maximum of 6 cycles

|                                        |                                       |
|----------------------------------------|---------------------------------------|
| Arm type                               | Experimental                          |
| Investigational medicinal product name | nab-paclitaxel                        |
| Investigational medicinal product code |                                       |
| Other name                             |                                       |
| Pharmaceutical forms                   | Concentrate for solution for infusion |
| Routes of administration               | Intravenous use                       |

Dosage and administration details:

Dosage

on days 1 and 8 of a 21 day cycle

dose level 1: 60 mg/kg/m<sup>2</sup>

dose level 2: 80 mg/kg/m<sup>2</sup>

dose level 3: 100 mg/kg/m<sup>2</sup>

dose level 4: 120 mg/kg/m<sup>2</sup>

- Supply: Nab-paclitaxel is supplied by Celgene as a sterile, lyophilized powder for reconstitution.
- Solution preparation: Nab-paclitaxel (Abraxane ®) is a solvent-free, protein-bound particle form of paclitaxel for intravenous infusion with a mean particle size of approximately 130 nanometers. A 50-mL vial contains 100 mg of paclitaxel and human albumin as a stabilizer. Each vial of the lyophilized product is reconstituted

| Number of subjects in period 1 | Investigational arm |
|--------------------------------|---------------------|
| Started                        | 26                  |
| Completed                      | 20                  |
| Not completed                  | 6                   |
| Adverse event, serious fatal   | 2                   |
| Adverse event, non-fatal       | 2                   |

|                     |   |
|---------------------|---|
| Progressive Disease | 2 |
|---------------------|---|

## Baseline characteristics

### Reporting groups

|                                |               |
|--------------------------------|---------------|
| Reporting group title          | Overall trial |
| Reporting group description: - |               |

| Reporting group values | Overall trial | Total |  |
|------------------------|---------------|-------|--|
| Number of subjects     | 26            | 26    |  |
| Age categorical        |               |       |  |
| Units: Subjects        |               |       |  |
| Adults (18-64 years)   | 17            | 17    |  |
| From 65-84 years       | 9             | 9     |  |
| Age continuous         |               |       |  |
| Units: years           |               |       |  |
| median                 | 63            |       |  |
| full range (min-max)   | 45 to 75      | -     |  |
| Gender categorical     |               |       |  |
| Units: Subjects        |               |       |  |
| Female                 | 3             | 3     |  |
| Male                   | 23            | 23    |  |

### Subject analysis sets

|                                                      |               |
|------------------------------------------------------|---------------|
| Subject analysis set title                           | Overall trial |
| Subject analysis set type                            | Full analysis |
| Subject analysis set description:                    |               |
| All patients treated with the investigational regime |               |

| Reporting group values | Overall trial |  |  |
|------------------------|---------------|--|--|
| Number of subjects     | 26            |  |  |
| Age categorical        |               |  |  |
| Units: Subjects        |               |  |  |
| Adults (18-64 years)   | 17            |  |  |
| From 65-84 years       | 9             |  |  |
| Age continuous         |               |  |  |
| Units: years           |               |  |  |
| median                 | 63            |  |  |
| full range (min-max)   | 45 to 75      |  |  |
| Gender categorical     |               |  |  |
| Units: Subjects        |               |  |  |
| Female                 | 3             |  |  |
| Male                   | 23            |  |  |

## End points

### End points reporting groups

|                                                                                                                                                                                               |                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| Reporting group title                                                                                                                                                                         | Investigational arm |
| Reporting group description:<br>This was a single-arm study where all subjects received the experimental regime of capecitabine, oxaliplatin and nab-paclitaxel up to the maximum of 6 cycles |                     |
| Subject analysis set title                                                                                                                                                                    | Overall trial       |
| Subject analysis set type                                                                                                                                                                     | Full analysis       |
| Subject analysis set description:<br>All patients treated with the investigational regime                                                                                                     |                     |

### Primary: RP2D

|                                                                                                                                                                                                                                                                                                            |                     |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|
| End point title                                                                                                                                                                                                                                                                                            | RP2D <sup>[1]</sup> |
| End point description:                                                                                                                                                                                                                                                                                     |                     |
| End point type                                                                                                                                                                                                                                                                                             | Primary             |
| End point timeframe:<br>entire trial, 3+3 dose escalation scheme with safety expansion cohort                                                                                                                                                                                                              |                     |
| Notes:<br>[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.<br>Justification: no statistical analyses were needed for a standard 3+3 dose escalation design with safety expansion cohort |                     |

|                             |                     |  |  |  |
|-----------------------------|---------------------|--|--|--|
| <b>End point values</b>     | Investigational arm |  |  |  |
| Subject group type          | Reporting group     |  |  |  |
| Number of subjects analysed | 26                  |  |  |  |
| Units: mg/kg/m2             | 60                  |  |  |  |

|                                   |                                                          |
|-----------------------------------|----------------------------------------------------------|
| <b>Attachments (see zip file)</b> | DLT and RP2D/Figure 2. Dose escalation and dose limiting |
|-----------------------------------|----------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: AE, SAE according to NCTCAE

|                                                                                                                                         |                             |
|-----------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                         | AE, SAE according to NCTCAE |
| End point description:                                                                                                                  |                             |
| End point type                                                                                                                          | Secondary                   |
| End point timeframe:<br>AEs and SAEs were recorded during the entire trial and at least up to 30 days after cessation of nab-paclitaxel |                             |

|                               |                     |  |  |  |
|-------------------------------|---------------------|--|--|--|
| <b>End point values</b>       | Investigational arm |  |  |  |
| Subject group type            | Reporting group     |  |  |  |
| Number of subjects analysed   | 26                  |  |  |  |
| Units: AEs in % and SAEs in N |                     |  |  |  |
| AEs                           | 100                 |  |  |  |
| SAEs                          | 18                  |  |  |  |

|                                   |                                                             |
|-----------------------------------|-------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Treatment related adverse events/Table 2. Treatment Related |
|-----------------------------------|-------------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Response rate according to RECIST 1.1

|                 |                                       |
|-----------------|---------------------------------------|
| End point title | Response rate according to RECIST 1.1 |
|-----------------|---------------------------------------|

End point description:

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

End point timeframe:

Best response according to RECIST 1.1 over the trial period was registered

|                             |                     |  |  |  |
|-----------------------------|---------------------|--|--|--|
| <b>End point values</b>     | Investigational arm |  |  |  |
| Subject group type          | Reporting group     |  |  |  |
| Number of subjects analysed | 26                  |  |  |  |
| Units: PD, SD, PR, CR       |                     |  |  |  |
| Complete Response           | 1                   |  |  |  |
| Partial Response            | 13                  |  |  |  |
| Stable Disease              | 9                   |  |  |  |
| Progressive Disease         | 2                   |  |  |  |
| Non-evaluable               | 1                   |  |  |  |

|                                   |                                                              |
|-----------------------------------|--------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Radiological Response/Figure 3. Swimmer plot of radiological |
|-----------------------------------|--------------------------------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression Free Survival and Overall Survival

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Progression Free Survival and Overall Survival |
|-----------------|------------------------------------------------|

End point description:

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

End point timeframe:

From study start till data cut-off at may 2nd 2018

| End point values                 | Investigational arm |  |  |  |
|----------------------------------|---------------------|--|--|--|
| Subject group type               | Reporting group     |  |  |  |
| Number of subjects analysed      | 26                  |  |  |  |
| Units: months                    |                     |  |  |  |
| median (confidence interval 95%) |                     |  |  |  |
| PFS                              | 8.0 (5.6 to 10.4)   |  |  |  |
| OS                               | 12.8 (7.0 to 18.6)  |  |  |  |

|                            |                                     |
|----------------------------|-------------------------------------|
| Attachments (see zip file) | PFS and OS/Figure 4. PFS and OS.pdf |
|----------------------------|-------------------------------------|

### Statistical analyses

No statistical analyses for this end point

### Secondary: Self reported neurotoxicity according to the EORTC QLQ CIPN20

|                 |                                                               |
|-----------------|---------------------------------------------------------------|
| End point title | Self reported neurotoxicity according to the EORTC QLQ CIPN20 |
|-----------------|---------------------------------------------------------------|

End point description:

Twenty-four patients completed the baseline questionnaires before start of treatment. Compliance of follow-up questionnaires was high and all patients but one were on active CapOx-nab-paclitaxel treatment up until cycle 7. Thereafter, all patients were on capecitabine monotherapy. Four patients that were eligible for reintroduction completed questionnaires before reintroduction and after the first cycle of reintroduction. Mean global health, functioning scores, as well as symptom scores of the QLQ-C30 questionnaire remained relatively stable during treatment as well as after cessation of triple therapy. The other functioning and symptom scores also remained relatively stable. Self-reported sensory neuropathy, however, showed an increase from a mean score of 1.39 at baseline to 28.8 after 9 cycles, subsequently decreasing to 17.0 after 15 cycles. The motor- and autonomic neuropathy scores demonstrated a similar pattern albeit with a smaller amplitude.

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

End point timeframe:

Baseline questionnaires completed before start of investigational treatment, before start of the second and fourth cycle and subsequently with a 3-cycle interval.

| End point values                     | Investigational arm |  |  |  |
|--------------------------------------|---------------------|--|--|--|
| Subject group type                   | Reporting group     |  |  |  |
| Number of subjects analysed          | 24 <sup>[2]</sup>   |  |  |  |
| Units: CIPN20 score                  |                     |  |  |  |
| arithmetic mean (standard deviation) | 28.8 (± 17.7)       |  |  |  |

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Notes:

[2] - 2 patients did not fill in the baseline questionnaire

|                                   |                                                                                                                                                                                                                                                    |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Attachments (see zip file)</b> | Figure 5. Health related quality of life and neurotoxicity.pdf<br>Supplementary figure 1. Health related quality of life and<br>Table 4. Baseline Health Related Quality of Life and<br>Supplementary table 2. Responses Health Related Quality of |
|-----------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From start of study until at least 30 days after last infusion of nab-paclitaxel

Adverse event reporting additional description:

Subjects with adverse event: Treatment related adverse events are all events that can (possibly) be attributed to one or more drugs of the investigational regime (capecitabine, oxaliplatin, nab-paclitaxel).

Occurrences adverse event: all occurrences regardless of attribution

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

### Dictionary used

|                 |       |
|-----------------|-------|
| Dictionary name | CTCAE |
|-----------------|-------|

|                    |      |
|--------------------|------|
| Dictionary version | 4.03 |
|--------------------|------|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | 60 mg/kg/m2 |
|-----------------------|-------------|

Reporting group description:

Ultimately this dose level was decided as RP2D

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | 80 mg/kg/m2 and 100 mg/kg/m2 |
|-----------------------|------------------------------|

Reporting group description:

patients treated at dose levels 2 and 3

| Serious adverse events                            | 60 mg/kg/m2                                                    | 80 mg/kg/m2 and 100 mg/kg/m2 |  |
|---------------------------------------------------|----------------------------------------------------------------|------------------------------|--|
| Total subjects affected by serious adverse events |                                                                |                              |  |
| subjects affected / exposed                       | 4 / 11 (36.36%)                                                | 14 / 15 (93.33%)             |  |
| number of deaths (all causes)                     | 11                                                             | 14                           |  |
| number of deaths resulting from adverse events    | 0                                                              | 2                            |  |
| Vascular disorders                                |                                                                |                              |  |
| Cerebrovascular accident                          |                                                                |                              |  |
| subjects affected / exposed                       | 0 / 11 (0.00%)                                                 | 1 / 15 (6.67%)               |  |
| occurrences causally related to treatment / all   | 0 / 0                                                          | 0 / 1                        |  |
| deaths causally related to treatment / all        | 0 / 0                                                          | 0 / 0                        |  |
| Shock haemorrhagic                                |                                                                |                              |  |
| subjects affected / exposed                       | 0 / 11 (0.00%)                                                 | 1 / 15 (6.67%)               |  |
| occurrences causally related to treatment / all   | 0 / 0                                                          | 0 / 1                        |  |
| deaths causally related to treatment / all        | 0 / 0                                                          | 0 / 0                        |  |
| Cardiac disorders                                 |                                                                |                              |  |
| Non-cardiac chest pain                            | Additional description: eventual conclusion, esophageal spasms |                              |  |
| subjects affected / exposed                       | 0 / 11 (0.00%)                                                 | 1 / 15 (6.67%)               |  |
| occurrences causally related to treatment / all   | 0 / 0                                                          | 1 / 1                        |  |
| deaths causally related to treatment / all        | 0 / 0                                                          | 0 / 0                        |  |

|                                                      |                                                                     |                 |  |
|------------------------------------------------------|---------------------------------------------------------------------|-----------------|--|
| Nervous system disorders                             |                                                                     |                 |  |
| Seizure                                              |                                                                     |                 |  |
| subjects affected / exposed                          | 1 / 11 (9.09%)                                                      | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1                                                               | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0                                                               | 0 / 0           |  |
| General disorders and administration site conditions |                                                                     |                 |  |
| Pain                                                 | Additional description: pain of bone metastases/progressive disease |                 |  |
| subjects affected / exposed                          | 1 / 11 (9.09%)                                                      | 0 / 15 (0.00%)  |  |
| occurrences causally related to treatment / all      | 0 / 1                                                               | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0                                                               | 0 / 0           |  |
| Multi-organ disorder                                 | Additional description: Multi-organ failure                         |                 |  |
| subjects affected / exposed                          | 0 / 11 (0.00%)                                                      | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all      | 0 / 0                                                               | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0                                                               | 0 / 0           |  |
| Gastrointestinal disorders                           |                                                                     |                 |  |
| Oesophageal stenosis                                 |                                                                     |                 |  |
| subjects affected / exposed                          | 0 / 11 (0.00%)                                                      | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all      | 0 / 0                                                               | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0                                                               | 0 / 0           |  |
| Diarrhoea                                            |                                                                     |                 |  |
| subjects affected / exposed                          | 0 / 11 (0.00%)                                                      | 2 / 15 (13.33%) |  |
| occurrences causally related to treatment / all      | 0 / 0                                                               | 2 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0                                                               | 0 / 0           |  |
| Nausea                                               |                                                                     |                 |  |
| subjects affected / exposed                          | 0 / 11 (0.00%)                                                      | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all      | 0 / 0                                                               | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0                                                               | 0 / 0           |  |
| Vomiting                                             |                                                                     |                 |  |
| subjects affected / exposed                          | 1 / 11 (9.09%)                                                      | 0 / 15 (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      |                                                                     |                 |  |
| Chylothorax                                          |                                                                     |                 |  |

|                                                 |                |                 |  |
|-------------------------------------------------|----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 1           |  |
| Renal and urinary disorders                     |                |                 |  |
| Renal failure                                   |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Infections and infestations                     |                |                 |  |
| Sepsis                                          |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 1 / 1           |  |
| Skin infection                                  |                |                 |  |
| Additional description: cellulitis of the ear   |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Lung infection                                  |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Infection                                       |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 1 / 15 (6.67%)  |  |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |
| Metabolism and nutrition disorders              |                |                 |  |
| Dehydration                                     |                |                 |  |
| subjects affected / exposed                     | 0 / 11 (0.00%) | 2 / 15 (13.33%) |  |
| occurrences causally related to treatment / all | 0 / 0          | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                           | 60 mg/kg/m2                                     | 80 mg/kg/m2 and<br>100 mg/kg/m2 |  |
|-------------------------------------------------------------|-------------------------------------------------|---------------------------------|--|
| Total subjects affected by non-serious adverse events       |                                                 |                                 |  |
| subjects affected / exposed                                 | 11 / 11 (100.00%)                               | 15 / 15 (100.00%)               |  |
| <b>Vascular disorders</b>                                   |                                                 |                                 |  |
| Hypertension                                                |                                                 |                                 |  |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                  | 1 / 15 (6.67%)                  |  |
| occurrences (all)                                           | 0                                               | 1                               |  |
| Thrombo-embolic event                                       |                                                 |                                 |  |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                  | 1 / 15 (6.67%)                  |  |
| occurrences (all)                                           | 0                                               | 1                               |  |
| <b>Nervous system disorders</b>                             |                                                 |                                 |  |
| Peripheral sensory neuropathy                               |                                                 |                                 |  |
| subjects affected / exposed                                 | 9 / 11 (81.82%)                                 | 15 / 15 (100.00%)               |  |
| occurrences (all)                                           | 14                                              | 20                              |  |
| Dysgeusia                                                   |                                                 |                                 |  |
| subjects affected / exposed                                 | 6 / 11 (54.55%)                                 | 9 / 15 (60.00%)                 |  |
| occurrences (all)                                           | 6                                               | 10                              |  |
| Anorexia                                                    |                                                 |                                 |  |
| subjects affected / exposed                                 | 7 / 11 (63.64%)                                 | 7 / 15 (46.67%)                 |  |
| occurrences (all)                                           | 8                                               | 11                              |  |
| Dizziness                                                   |                                                 |                                 |  |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                                  | 1 / 15 (6.67%)                  |  |
| occurrences (all)                                           | 1                                               | 1                               |  |
| <b>Blood and lymphatic system disorders</b>                 |                                                 |                                 |  |
| Thrombocytopenia                                            |                                                 |                                 |  |
| subjects affected / exposed                                 | 1 / 11 (9.09%)                                  | 2 / 15 (13.33%)                 |  |
| occurrences (all)                                           | 1                                               | 3                               |  |
| White blood cell count decreased                            | Additional description: only grade 3/4/5        |                                 |  |
| subjects affected / exposed                                 | 0 / 11 (0.00%)                                  | 1 / 15 (6.67%)                  |  |
| occurrences (all)                                           | 0                                               | 1                               |  |
| Neutropenia                                                 | Additional description: non febrile neutropenia |                                 |  |
| subjects affected / exposed                                 | 2 / 11 (18.18%)                                 | 4 / 15 (26.67%)                 |  |
| occurrences (all)                                           | 2                                               | 7                               |  |
| <b>General disorders and administration site conditions</b> |                                                 |                                 |  |
| Fatigue                                                     |                                                 |                                 |  |

|                             |                 |                  |  |
|-----------------------------|-----------------|------------------|--|
| subjects affected / exposed | 8 / 11 (72.73%) | 12 / 15 (80.00%) |  |
| occurrences (all)           | 9               | 15               |  |
| Pain                        |                 |                  |  |
| subjects affected / exposed | 2 / 11 (18.18%) | 4 / 15 (26.67%)  |  |
| occurrences (all)           | 4               | 5                |  |
| Fever                       |                 |                  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 3 / 15 (20.00%)  |  |
| occurrences (all)           | 0               | 3                |  |
| Flu like symptoms           |                 |                  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 2 / 15 (13.33%)  |  |
| occurrences (all)           | 0               | 2                |  |
| Malaise                     |                 |                  |  |
| subjects affected / exposed | 2 / 11 (18.18%) | 2 / 15 (13.33%)  |  |
| occurrences (all)           | 2               | 2                |  |
| Non-cardiac chest pain      |                 |                  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 1 / 15 (6.67%)   |  |
| occurrences (all)           | 0               | 3                |  |
| Gastrointestinal disorders  |                 |                  |  |
| Nausea                      |                 |                  |  |
| subjects affected / exposed | 7 / 11 (63.64%) | 11 / 15 (73.33%) |  |
| occurrences (all)           | 11              | 21               |  |
| Diarrhoea                   |                 |                  |  |
| subjects affected / exposed | 9 / 11 (81.82%) | 12 / 15 (80.00%) |  |
| occurrences (all)           | 11              | 23               |  |
| Vomiting                    |                 |                  |  |
| subjects affected / exposed | 4 / 11 (36.36%) | 10 / 15 (66.67%) |  |
| occurrences (all)           | 7               | 10               |  |
| Mucositis oral              |                 |                  |  |
| subjects affected / exposed | 1 / 11 (9.09%)  | 5 / 15 (33.33%)  |  |
| occurrences (all)           | 1               | 6                |  |
| Constipation                |                 |                  |  |
| subjects affected / exposed | 3 / 11 (27.27%) | 2 / 15 (13.33%)  |  |
| occurrences (all)           | 5               | 4                |  |
| Dysphagia                   |                 |                  |  |
| subjects affected / exposed | 0 / 11 (0.00%)  | 2 / 15 (13.33%)  |  |
| occurrences (all)           | 0               | 5                |  |

|                                                                                                                                                                                                                                                                                              |                                                                            |                                                                              |  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|------------------------------------------------------------------------------|--|
| Abdominal pain<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                           | 1 / 11 (9.09%)<br>1                                                        | 1 / 15 (6.67%)<br>1                                                          |  |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                 | 0 / 11 (0.00%)<br>0                                                        | 2 / 15 (13.33%)<br>2                                                         |  |
| Skin and subcutaneous tissue disorders<br>Alopecia<br>subjects affected / exposed<br>occurrences (all)<br><br>Palmar-plantar erythrodysaesthesia syndrome<br>subjects affected / exposed<br>occurrences (all)<br><br>Rash maculo-papular<br>subjects affected / exposed<br>occurrences (all) | 3 / 11 (27.27%)<br>3<br><br>1 / 11 (9.09%)<br>1<br><br>0 / 11 (0.00%)<br>0 | 8 / 15 (53.33%)<br>8<br><br>2 / 15 (13.33%)<br>2<br><br>2 / 15 (13.33%)<br>2 |  |
| Metabolism and nutrition disorders<br>Dehydration<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                        | 0 / 11 (0.00%)<br>0                                                        | 4 / 15 (26.67%)<br>4                                                         |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                     |
|------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 17 June 2015     | due to an SAE outside of the DLT period, a further 3 patients were treated at dose level 2                                                                                                                                                                                    |
| 22 February 2016 | INR and CK were added to laboratory tests. + changes because of a change in the dutch law                                                                                                                                                                                     |
| 20 June 2016     | because of a high percentage of diarrhea/vomiting/dehydration necessitating hospitalization at dose level 2, the remainder of the safety expansion cohort were treated at dose level 1. + HER2 positive patients not eligible for trastuzumab treatment could now be included |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date         | Interruption                           | Restart date |
|--------------|----------------------------------------|--------------|
| 01 June 2016 | a SUSAR turned out to be a regular SAE | 08 June 2016 |

Notes:

### Limitations and caveats

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

a clearer, more comprehensible and completer overview of the results is provided in the article

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/31207904>