



## Clinical trial results:

**ICE II: An investigational randomized phase II-(III) study on epirubicin plus cyclophosphamide (or CMF) vs nab-paclitaxel plus capecitabine as adjuvant chemotherapy for elderly non frail patients with an increased risk for relapse of a primary carcinoma of the breast**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2008-003995-23  |
| Trial protocol           | DE              |
| Global end of trial date | 24 January 2014 |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 24 November 2021  |
| First version publication date    | 24 November 2021  |
| Summary attachment (see zip file) | ICE II CSR Synopsis (CSR ICE 2 Synopse Version 2 10.01.2020 signed.pdf) |

### Trial information

#### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | GBG52 |
|-----------------------|-------|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01204437 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | GBG Forschungs GmbH  |
| Sponsor organisation address | Martin Behaim Str. 12, Neu-Isenburg, Germany, 63263                            |
| Public contact               | Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.de |
| Scientific contact           | Medicine and Research, GBG Forschungs GmbH, +49 610274800, publications@gbg.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                       | 11 September 2014 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 30 November 2013  |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 24 January 2014   |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To determine the compliance and safety of epirubicin plus cyclophosphamide or CMF (EC/CMF) and nab-paclitaxel in combination with capecitabine (nPX)

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving.

Background therapy: -

Evidence for comparator: -

|   |                     |
|---|---------------------|
| Actual start date of recruitment                          | 31 March 2009       |
| Long term follow-up planned                               | Yes                 |
| Long term follow-up rationale                             | Scientific research |
| Long term follow-up duration                              | 10 Years            |
| Independent data monitoring committee (IDMC) involvement? | Yes                 |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |              |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 391 |
| Worldwide total number of subjects   | 391          |
| EEA total number of subjects         | 391          |

Notes:

### Subjects enrolled per age group

|   |   |
|---|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |

|                      |     |
|----------------------|-----|
| Adults (18-64 years) | 0   |
| From 65 to 84 years  | 391 |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Approximately 4 years (Q-II 2009 –Q-II 2013) in 63 sites in Germany. 400 patients were randomized and 391 started Treatment: 198 in EC/CMF arm (EC: 182; CMF: 16) and 193 in nPX arm).

### Pre-assignment

Screening details:

Female or male  $\geq 65$  yrs, Charlson comorbidity index  $\leq 2$ , ECOG  $\leq 2$ , life expect.  $\geq 5$  yrs, completely resected uni-/bilateral, nonmetastatic primary invasive BC. Patients with pT1/2 pN0/1 and either HER2-positive, HR-negative, grade 3, high uPA or PAI-1 BC or any pT3/4 pN2/3 BC irrespectively of additional risk factors and time since axillary surgery of  $\leq 3$  months

### Pre-assignment period milestones

|                              |     |
|------------------------------|-----|
| Number of subjects started   | 391 |
| Number of subjects completed | 391 |

### Period 1

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

### Arms

|                              |        |
|------------------------------|--------|
| Are arms mutually exclusive? | Yes    |
| Arm title                    | EC/CMF |

Arm description:

Standard treatment with either 4 cycles EC (epirubicin 90mg/m<sup>2</sup> and cyclophosphamide 600mg/m<sup>2</sup> IV on day 1 every 3 weeks) (N=182 patients) or 6 cycles CMF (cyclophosphamide 500 mg/m<sup>2</sup>, methotrexate 40mg/m<sup>2</sup>, 5-fluorouracil 600 mg/m<sup>2</sup> IV on days 1+8 every 4 weeks) (N=16 patients) based on investigators decision

|  |                                  |
|--|----------------------------------|
| Arm type                               | Active comparator                |
| Investigational medicinal product name | Epirubicin plus cyclophosphamide |
| Investigational medicinal product code |                                  |
| Other name                             |                                  |
| Pharmaceutical forms                   | Solution for infusion            |
| Routes of administration               | Intravenous use                  |

Dosage and administration details:

Dose: Epirubicin 90 mg/m<sup>2</sup>, Cyclophosphamide 600 mg/m<sup>2</sup>

Route: i.v.

Schedule: days 1q22

Duration: 4 cycles or unacceptable toxicity, patient's request or withdrawal from study

|  |                       |
|--|-----------------------|
| Investigational medicinal product name | CMF                   |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intravenous use       |

Dosage and administration details:

Dose: Cyclophosphamide 500 mg/m<sup>2</sup>; Methotrexate 40mg/m<sup>2</sup>, 5-FU 600 mg/m<sup>2</sup>

Route: i.v.

Schedule: days 1+8 q29

Duration: 6 cycles or unacceptable toxicity, patient's request or withdrawal from study

|           |      |
|-----------|------|
| Arm title | nP-X |
|-----------|------|

**Arm description:**

Experimental treatment with 6 cycles nab-paclitaxel (100 mg/m<sup>2</sup> IV over 30 min, on days weekly in five out of 6 weeks) plus capecitabine (1000 mg/m<sup>2</sup> PO bid on days 1-14 every 3 weeks).

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

**Dosage and administration details:**

100 mg/m<sup>2</sup> IV over 30 min, on days weekly in five out of 6 weeks

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

**Dosage and administration details:**

1000 mg/m<sup>2</sup> PO bid on days 1-14 every 3 weeks

| <b>Number of subjects in period 1</b> | <b>EC/CMF</b> | <b>nP-X</b> |
|---------------------------------------|---------------|-------------|
| Started                               | 198           | 193         |
| Completed                             | 185           | 124         |
| Not completed                         | 13            | 69          |
| Adverse event, serious fatal          | 1             | 5           |
| Physician decision                    | 2             | 9           |
| Consent withdrawn by subject          | 3             | 18          |
| Adverse event, non-fatal              | 7             | 32          |
| other                                 | -             | 5           |

## Baseline characteristics

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | EC/CMF |
|-----------------------|--------|

Reporting group description:

Standard treatment with either 4 cycles EC (epirubicin 90mg/m<sup>2</sup> and cyclophosphamide 600mg/m<sup>2</sup> IV on day 1 every 3 weeks) (N=182 patients) or 6 cycles CMF (cyclophosphamide 500 mg/m<sup>2</sup>, methotrexate 40mg/m<sup>2</sup>, 5-fluorouracil 600 mg/m<sup>2</sup> IV on days 1+8 every 4 weeks) (N=16 patients) based on investigators decision

|                       |      |
|-----------------------|------|
| Reporting group title | nP-X |
|-----------------------|------|

Reporting group description:

Experimental treatment with 6 cycles nab-paclitaxel (100 mg/m<sup>2</sup> IV over 30 min, on days weekly in five out of 6 weeks) plus capecitabine (1000 mg/m<sup>2</sup> PO bid on days 1-14 every 3 weeks).

| Reporting group values                | EC/CMF | nP-X | Total |
|---------------------------------------|--------|------|-------|
| Number of subjects                    | 198    | 193  | 391   |
| Age categorical<br>Units: Subjects    |        |      |       |
| 64-69                                 | 52     | 49   | 101   |
| 70-80                                 | 144    | 143  | 287   |
| >80                                   | 2      | 1    | 3     |
| Gender categorical<br>Units: Subjects |        |      |       |
| Female                                | 196    | 191  | 387   |
| Male                                  | 2      | 2    | 4     |

## End points

### End points reporting groups

|  |        |
|--|--------|
| Reporting group title  | EC/CMF |
| Reporting group description:<br>Standard treatment with either 4 cycles EC (epirubicin 90mg/m <sup>2</sup> and cyclophosphamide 600mg/m <sup>2</sup> IV on day 1 every 3 weeks) (N=182 patients) or 6 cycles CMF (cyclophosphamide 500 mg/m <sup>2</sup> , methotrexate 40mg/m <sup>2</sup> , 5-fluorouracil 600 mg/m <sup>2</sup> IV on days 1+8 every 4 weeks) (N=16 patients) based on investigators decision |        |
| Reporting group title  | nP-X   |
| Reporting group description:<br>Experimental treatment with 6 cycles nab-paclitaxel (100 mg/m <sup>2</sup> IV over 30 min, on days weekly in five out of 6 weeks) plus capecitabine (1000 mg/m <sup>2</sup> PO bid on days 1-14 every 3 weeks).  |        |

### Primary: Compliance

|   |            |
|---|------------|
| End point title   | Compliance |
| End point description:<br>Discontinuations of study treatment |            |
| End point type  | Primary    |
| End point timeframe:<br>during active study treatment         |            |

| End point values            | EC/CMF          | nP-X            |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 198             | 193             |  |  |
| Units: percent              |                 |                 |  |  |
| number (not applicable)     | 13              | 69              |  |  |

### Statistical analyses

|  |                               |
|--|-------------------------------|
| Statistical analysis title   | Discontinuations between arms |
| Statistical analysis description:<br>Treatment groups were compared using Fisher's exact test (for binary Parameters). |                               |
| Comparison groups  | EC/CMF v nP-X                 |
| Number of subjects included in analysis  | 391                           |
| Analysis specification   | Pre-specified                 |
| Analysis type  | superiority                   |
| P-value  | < 0.001                       |
| Method   | Fisher exact                  |

### Primary: Compliance

|   |            |
|---|------------|
| End point title                                       | Compliance |
| End point description:<br>Chemotherapy dose reduction |            |
| End point type  | Primary    |
| End point timeframe:<br>during active study treatment |            |

| End point values            | EC/CMF          | nP-X            |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 198             | 193             |  |  |
| Units: percent              |                 |                 |  |  |
| number (not applicable)     | 9               | 112             |  |  |

### Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Chemotherapy dose reduction between arms |
| Statistical analysis description:<br>Treatment groups were compared using Fisher's exact test (for binary Parameters). |  |
| Comparison groups  | nP-X v EC/CMF                            |
| Number of subjects included in analysis  | 391                                      |
| Analysis specification   | Pre-specified                            |
| Analysis type  | superiority                              |
| P-value  | < 0.001                                  |
| Method   | Fisher exact                             |

### Primary: Compliance

|   |            |
|---|------------|
| End point title                                       | Compliance |
| End point description:<br>Cycle delays                |            |
| End point type  | Primary    |
| End point timeframe:<br>during active study treatment |            |

| End point values            | EC/CMF          | nP-X            |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 198             | 193             |  |  |
| Units: percent              |                 |                 |  |  |
| number (not applicable)     | 35              | 125             |  |  |



## Statistical analyses

|  |                           |
|--|---------------------------|
| <b>Statistical analysis title</b>  | Cycle delays between arms |
| Statistical analysis description:<br>Treatment groups were compared using Fisher`s exact test (for binary Parameters). |                           |
| Comparison groups  | EC/CMF v nP-X             |
| Number of subjects included in analysis  | 391                       |
| Analysis specification   | Pre-specified             |
| Analysis type  | superiority               |
| P-value  | < 0.001                   |
| Method   | Fisher exact              |

## Primary: Compliance

|   |            |
|---|------------|
| End point title                                       | Compliance |
| End point description:<br>RTDI in %                   |            |
| End point type  | Primary    |
| End point timeframe:<br>during active study treatment |            |

|                             |                    |                 |  |  |
|-----------------------------|--------------------|-----------------|--|--|
| <b>End point values</b>     | EC/CMF             | nP-X            |  |  |
| Subject group type          | Reporting group    | Reporting group |  |  |
| Number of subjects analysed | 198 <sup>[1]</sup> | 193             |  |  |
| Units: percent              |                    |                 |  |  |
| number (not applicable)     | 97.5               | 85.4            |  |  |

Notes:

[1] - RTDI EC 100.0%, RTDI CMF 94.9%

## Statistical analyses

|  |                   |
|--|-------------------|
| <b>Statistical analysis title</b>  | RTDI between arms |
| Statistical analysis description:<br>Treatment groups were compared using Fisher`s exact test (for binary Parameters). |                   |
| Comparison groups  | nP-X v EC/CMF     |

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 391                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[2]</sup> |
| P-value                                 | < 0.001                    |
| Method                                  | Fisher exact               |

Notes:

[2] - Median RTDI for EC was 100% (25-103.7), for CMF 94.9 (8.3-100.0)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the study treatment period were reported

Adverse event reporting additional description:

Non-serious AEs are reported per patient; any grade (1-4) during the complete treatment duration for the overall safety population.

Free-text AEs are listed if occurring in >20%

For SAEs relatedness was not tabulated, therefore here we conservatively record all SAEs as related to treatment

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | n.a. |
|--------------------|------|

### Reporting groups

|                       |        |
|-----------------------|--------|
| Reporting group title | EC/CMF |
|-----------------------|--------|

Reporting group description:

Standard treatment with either 4 cycles EC (epirubicin 90mg/m<sup>2</sup> and cyclophosphamide 600mg/m<sup>2</sup> IV on day 1 every 3 weeks) or 6 cycles CMF (cyclophosphamide 500 mg/m<sup>2</sup>, methotrexate 40mg/m<sup>2</sup>, 5-fluorouracil 600 mg/m<sup>2</sup> IV on days 1+8 every 4 weeks) based on investigators decision

|                       |      |
|-----------------------|------|
| Reporting group title | nP-X |
|-----------------------|------|

Reporting group description:

Experimental treatment with 6 cycles nab-paclitaxel (100 mg/m<sup>2</sup> IV over 30 min, on days weekly in five out of 6 weeks) plus capecitabine (1000 mg/m<sup>2</sup> PO bid on days 1-14 every 3 weeks).

| Serious adverse events                               | EC/CMF            | nP-X              |  |
|--|-------------------|-------------------|--|
| Total subjects affected by serious adverse events    |                   |                   |  |
| subjects affected / exposed                          | 38 / 198 (19.19%) | 62 / 193 (32.12%) |  |
| number of deaths (all causes)                        | 1                 | 5                 |  |
| number of deaths resulting from adverse events       | 1                 | 5                 |  |
| Vascular disorders                                   |                   |                   |  |
| Thromboembolic event                                 |                   |                   |  |
| subjects affected / exposed                          | 5 / 198 (2.53%)   | 14 / 193 (7.25%)  |  |
| occurrences causally related to treatment / all      | 5 / 5             | 14 / 14           |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| Other vascular disorders                             |                   |                   |  |
| subjects affected / exposed                          | 1 / 198 (0.51%)   | 3 / 193 (1.55%)   |  |
| occurrences causally related to treatment / all      | 1 / 1             | 3 / 3             |  |
| deaths causally related to treatment / all           | 0 / 0             | 0 / 0             |  |
| General disorders and administration site conditions |                   |                   |  |
| Fatigue  |                   |                   |  |

|   |   |                 |  |
|---|---|-----------------|--|
| subjects affected / exposed                     | 4 / 198 (2.02%)                                   | 8 / 193 (4.15%) |  |
| occurrences causally related to treatment / all | 4 / 4   | 8 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Oedema  |   |                 |  |
| subjects affected / exposed                     | 1 / 198 (0.51%)                                   | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1   | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Fever   | Additional description: Fever without neutropenia |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)                                   | 3 / 193 (1.55%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Other general disorders                         |   |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)                                   | 1 / 193 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 1 / 1           |  |
| Pain  |   |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)                                   | 1 / 193 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Immune system disorders                         |   |                 |  |
| Allergic reactions                              |   |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)                                   | 2 / 193 (1.04%) |  |
| occurrences causally related to treatment / all | 0 / 0   | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0   | 0 / 0           |  |
| Reproductive system and breast disorders        |   |                 |  |
| Other reproductive system disorders             |   |                 |  |
| subjects affected / exposed                     | 1 / 198 (0.51%)                                   | 0 / 193 (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 |   |                 |  |
| Dyspnoea  |   |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 198 (0.00%) | 1 / 193 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%) | 1 / 193 (0.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 198 (0.51%) | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory disorder                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 198 (0.51%) | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Injury, poisoning, procedural complications     |                 |                 |  |
| subjects affected / exposed                     | 3 / 198 (1.52%) | 3 / 193 (1.55%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Other cardiac disease                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%) | 4 / 193 (2.07%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 3 / 3           |  |
| Nervous system disorders                        |                 |                 |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%) | 2 / 193 (1.04%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Other neurological disorders                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 198 (0.51%) | 5 / 193 (2.59%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 5 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 8 / 198 (4.04%) | 1 / 193 (0.52%) |  |
| occurrences causally related to treatment / all | 8 / 8           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile neutropenia                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 198 (1.52%) | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 198 (0.00%) | 2 / 193 (1.04%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Leukopenia                                      |                 |                 |  |
| subjects affected / exposed                     | 5 / 198 (2.53%) | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 5 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Other hematological disorders                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 198 (2.02%) | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Gastrointestinal disorders</b>               |                 |                 |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 198 (0.51%) | 1 / 193 (0.52%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 2 / 198 (1.01%) | 0 / 193 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |

|   |  |                  |  |
|---|--|------------------|--|
| subjects affected / exposed                     | 2 / 198 (1.01%)  | 11 / 193 (5.70%) |  |
| occurrences causally related to treatment / all | 2 / 2  | 11 / 11          |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Mucositis                                       | Additional description: Mucositis, Stomatitis, esophagitis |                  |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)  | 2 / 193 (1.04%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Other gastrointestinal disorders                |  |                  |  |
| subjects affected / exposed                     | 2 / 198 (1.01%)  | 2 / 193 (1.04%)  |  |
| occurrences causally related to treatment / all | 2 / 2  | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Hepatobiliary disorders                         |  |                  |  |
| Other hepatobiliary disorders                   |  |                  |  |
| subjects affected / exposed                     | 1 / 198 (0.51%)  | 0 / 193 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |  |                  |  |
| Hand-foot syndrome                              |  |                  |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)  | 3 / 193 (1.55%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Nail changes                                    |  |                  |  |
| subjects affected / exposed                     | 0 / 198 (0.00%)  | 1 / 193 (0.52%)  |  |
| occurrences causally related to treatment / all | 0 / 0  | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |  |                  |  |
| Other musculo-skeletal disorders                |  |                  |  |
| subjects affected / exposed                     | 1 / 198 (0.51%)  | 0 / 193 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1  | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0  | 0 / 0            |  |
| Infections and infestations                     |  |                  |  |
| Infection                                       |  |                  |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 3 / 198 (1.52%) | 10 / 193 (5.18%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 10 / 10          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Metabolism and nutrition disorders              |                 |                  |  |
| Other metabolic disorders                       |                 |                  |  |
| subjects affected / exposed                     | 0 / 198 (0.00%) | 3 / 193 (1.55%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

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

| Non-serious adverse events                            | EC/CMF              | nP-X                |  |
|---|---------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                     |                     |  |
| subjects affected / exposed                           | 198 / 198 (100.00%) | 193 / 193 (100.00%) |  |
| Investigations  |                     |                     |  |
| Bilirubin   |                     |                     |  |
| subjects affected / exposed                           | 0 / 198 (0.00%)     | 11 / 193 (5.70%)    |  |
| occurrences (all)                                     | 0                   | 11                  |  |
| ASAT  |                     |                     |  |
| subjects affected / exposed                           | 30 / 198 (15.15%)   | 60 / 193 (31.09%)   |  |
| occurrences (all)                                     | 30                  | 60                  |  |
| ALAT  |                     |                     |  |
| subjects affected / exposed                           | 36 / 198 (18.18%)   | 66 / 193 (34.20%)   |  |
| occurrences (all)                                     | 36                  | 66                  |  |
| Alkaline phosphatase                                  |                     |                     |  |
| subjects affected / exposed                           | 30 / 198 (15.15%)   | 43 / 193 (22.28%)   |  |
| occurrences (all)                                     | 30                  | 43                  |  |
| Serum creatinine                                      |                     |                     |  |
| subjects affected / exposed                           | 17 / 198 (8.59%)    | 31 / 193 (16.06%)   |  |
| occurrences (all)                                     | 17                  | 31                  |  |
| Vascular disorders                                    |                     |                     |  |
| Thromboembolic event                                  |                     |                     |  |
| subjects affected / exposed                           | 12 / 198 (6.06%)    | 25 / 193 (12.95%)   |  |
| occurrences (all)                                     | 12                  | 25                  |  |
| Cardiac disorders                                     |                     |                     |  |



|   |   |   |  |
|---|---|---|--|
| <p>Congestive heart failure NYHA subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>1 / 198 (0.51%)</p> <p>1</p>   | <p>6 / 193 (3.11%)</p> <p>6</p>   |  |
| <p>Cardiac except congestive heart failure subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>13 / 198 (6.57%)</p> <p>13</p>   | <p>14 / 193 (7.25%)</p> <p>14</p>   |  |
| <p>Cardiac ischemia subjects affected / exposed</p> <p>occurrences (all)</p>  | <p>0 / 198 (0.00%)</p> <p>0</p>   | <p>19 / 193 (9.84%)</p> <p>1</p>  |  |
| <p>Nervous system disorders</p> <p>Hand-foot syndrome subjects affected / exposed</p> <p>occurrences (all)</p> <p>Dizziness subjects affected / exposed</p> <p>occurrences (all)</p> <p>Sensory neuropathy subjects affected / exposed</p> <p>occurrences (all)</p>   | <p>13 / 198 (6.57%)</p> <p>13</p> <p>41 / 198 (20.71%)</p> <p>41</p> <p>22 / 198 (11.11%)</p> <p>22</p>   | <p>152 / 193 (78.76%)</p> <p>152</p> <p>53 / 193 (27.46%)</p> <p>53</p> <p>115 / 193 (59.59%)</p> <p>115</p>  |  |
| <p>Blood and lymphatic system disorders</p> <p>Leukopenia subjects affected / exposed</p> <p>occurrences (all)</p> <p>Neutropenia subjects affected / exposed</p> <p>occurrences (all)</p> <p>Febrile neutropenia subjects affected / exposed</p> <p>occurrences (all)</p> <p>Anaemia subjects affected / exposed</p> <p>occurrences (all)</p> <p>Thrombopenia subjects affected / exposed</p> <p>occurrences (all)</p> | <p>191 / 198 (96.46%)</p> <p>191</p> <p>164 / 198 (82.83%)</p> <p>164</p> <p>8 / 198 (4.04%)</p> <p>8</p> <p>170 / 198 (85.86%)</p> <p>170</p> <p>98 / 198 (49.49%)</p> <p>98</p> | <p>163 / 193 (84.46%)</p> <p>163</p> <p>120 / 193 (62.18%)</p> <p>120</p> <p>2 / 193 (1.04%)</p> <p>2</p> <p>169 / 193 (87.56%)</p> <p>169</p> <p>33 / 193 (17.10%)</p> <p>33</p> |  |
| <p>General disorders and administration site conditions</p>   |   |   |  |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| Fatigue   |                    |                    |  |
| subjects affected / exposed                     | 139 / 198 (70.20%) | 142 / 193 (73.58%) |  |
| occurrences (all)                               | 139                | 142                |  |
| Oedema  |                    |                    |  |
| subjects affected / exposed                     | 21 / 198 (10.61%)  | 50 / 193 (25.91%)  |  |
| occurrences (all)                               | 21                 | 50                 |  |
| Fever without neutropenia                       |                    |                    |  |
| subjects affected / exposed                     | 7 / 198 (3.54%)    | 12 / 193 (6.22%)   |  |
| occurrences (all)                               | 7                  | 12                 |  |
| Immune system disorders                         |                    |                    |  |
| Allergic reactions                              |                    |                    |  |
| subjects affected / exposed                     | 8 / 198 (4.04%)    | 28 / 193 (14.51%)  |  |
| occurrences (all)                               | 8                  | 28                 |  |
| Gastrointestinal disorders                      |                    |                    |  |
| Nausea  |                    |                    |  |
| subjects affected / exposed                     | 119 / 198 (60.10%) | 101 / 193 (52.33%) |  |
| occurrences (all)                               | 119                | 101                |  |
| Vomiting  |                    |                    |  |
| subjects affected / exposed                     | 33 / 198 (16.67%)  | 41 / 193 (21.24%)  |  |
| occurrences (all)                               | 33                 | 41                 |  |
| Diarrhoea                                       |                    |                    |  |
| subjects affected / exposed                     | 45 / 198 (22.73%)  | 117 / 193 (60.62%) |  |
| occurrences (all)                               | 45                 | 117                |  |
| Mucositis, stomatitis, oesophagitis             |                    |                    |  |
| subjects affected / exposed                     | 93 / 198 (46.97%)  | 107 / 193 (55.44%) |  |
| occurrences (all)                               | 93                 | 107                |  |
| Constipation                                    |                    |                    |  |
| subjects affected / exposed                     | 49 / 198 (24.75%)  | 41 / 193 (21.24%)  |  |
| occurrences (all)                               | 49                 | 41                 |  |
| Respiratory, thoracic and mediastinal disorders |                    |                    |  |
| Dyspnoea  |                    |                    |  |
| subjects affected / exposed                     | 23 / 198 (11.62%)  | 36 / 193 (18.65%)  |  |
| occurrences (all)                               | 23                 | 36                 |  |
| Skin and subcutaneous tissue disorders          |                    |                    |  |
| Alopecia  |                    |                    |  |

|  |                           |                           |  |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)   | 176 / 198 (88.89%)<br>176 | 166 / 193 (86.01%)<br>166 |  |
| Musculoskeletal and connective tissue disorders<br>Joint/muscle pain<br>subjects affected / exposed<br>occurrences (all) | 45 / 198 (22.73%)<br>45   | 53 / 193 (27.46%)<br>53   |  |
| Infections and infestations<br>Infection without neutropenia<br>subjects affected / exposed<br>occurrences (all)         | 11 / 198 (5.56%)<br>11    | 18 / 193 (9.33%)<br>18    |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date         | Amendment   |
|--------------|---|
| 11 June 2010 | <p>The trial protocol was amended once:</p> <p>After 78 patients had been recruited supply of nab-paclitaxel was stopped because of impurities in the drug vials in one German center. At 1st of April 2010 the BfArM issued a temporary suspension of the clinical trial authorization and requested corrective actions from the sponsor and the working supply with nab-Paclitaxel as inevitable for re-initiation of the trial. There was a period of nine months without nab-paclitaxel and patients under treatment received paclitaxel instead. Recruitment was stopped for this period. In its meeting on June 30, 2010 the IDMC recommended that analysis should be performed with and without complete nab-paclitaxel.</p> <p>The provision of the complete nab-Paclitaxel medication required for the entire treatment duration was made mandatory for the start of any new patient via Amendment 1, which also included the introduction of two additional geriatric scores (IADL and G8 score), resulting from a request of the IDMC.</p> |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26111104>