



Clinical trial results:

AIPAC (Active Immunotherapy PAClitaxel): A multicentre, Phase IIb, randomised, double blind, placebo-controlled study in hormone receptor-positive metastatic breast carcinoma patients receiving IMP321 (LAG-3lg fusion protein) or placebo as adjunctive to a standard chemotherapy treatment regimen of paclitaxel.

Summary

| | |
|--------------------------|----------------------|
| EudraCT number | 2015-002541-63 |
| Trial protocol | NL BE HU FR DE PL GB |
| Global end of trial date | 14 May 2021 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 09 July 2022 |
| First version publication date | 09 July 2022 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | IMP321-P011 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02614833 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|------------------------------------------------------------------------------------------|
| Sponsor organisation name | Immutep S.A.S |
| Sponsor organisation address | 21 rue Jean Rostand, Orsay Cedex, France, 91893 |
| Public contact | Clinical Trial Disclosure Enquiries, Immutep S.A.S, +33 146835822, enquiries@immutep.com |
| Scientific contact | Clinical Trial Disclosure Enquiries, Immutep S.A.S, +33 146835822, enquiries@immutep.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|------------------------------------------------------|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 28 June 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 10 January 2020 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy of efti combined with weekly paclitaxel compared to weekly paclitaxel plus placebo in hormone receptor-positive metastatic breast cancer subjects.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Throughout the Randomisation stage of the study, an Independent Data Monitoring Committee (IDMC) monitored subject safety, survival rates and demographics at regular intervals and had the possibility to convene ad hoc upon the request of the PI, Medical Monitor or Sponsor and in accordance with the IDMC charter. During the randomised, placebo-controlled stage of this study, the IDMC received tables, listings and figures per treatment arm. The IDMC received reports of all adverse events (AEs) by system organ class. The IDMC had the authority to recommend any dose de-escalation steps, if needed or stopping the study if at any time during the study unacceptable AEs or safety concerns related to the study treatment occurred.

Background therapy:

Paclitaxel was given in both treatment arms.

The Randomisation Stage (Stage 2) was a randomised, placebo-controlled and double-blind stage. The study design and conduct followed the 'Note for Guidance on evaluation of anti-cancer medicinal products in man' (EMA/CHMP/205/95/rev.4). All subjects received standard-of-care weekly paclitaxel to be ethically treated for the disease. Subjects received weekly paclitaxel instead of every three weeks because this has been observed to result in higher efficacy and less toxicity. Weekly Paclitaxel has become a standard of care administration schedule since more than 15 years ago.

Evidence for comparator:

In this study the use of a placebo associated with double blinding greatly improve the quality of the data and its interpretation. It therefore alleviates many of the statistical biases observed in open label phase II studies. It hence also requires that one of the study arms receives placebo rather than just simply prohibiting the use of endocrine therapy subsequently to termination of the chemoimmunotherapy stage in this arm.

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 12 January 2016 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| Long term follow-up duration | 18 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 35 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | United Kingdom: 28 |

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Belgium: 88 |
| Country: Number of subjects enrolled | France: 25 |
| Country: Number of subjects enrolled | Germany: 33 |
| Country: Number of subjects enrolled | Hungary: 12 |
| Worldwide total number of subjects | 226 |
| EEA total number of subjects | 198 |

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) | 147 |
| From 65 to 84 years | 78 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The 1st ICF for the randomisation stage was signed on 06Jan2017.

32 sites in 7 countries.

Number of sites per country: 9 BE, 3 FR, 5 DE, 2 HU, 8 NL, 2 PL, 3 UK

Pre-assignment

Screening details:

Subjects with hormone receptor positive (HR+), HER2 negative metastatic breast cancer eligible to weekly paclitaxel.

Randomisation Stage: 277 subjects screened, 50 subjects screen failures. 1 subject randomised, but subject did not receive drug

Period 1

| | |
|------------------------------|-------------------------------------------------|
| Period 1 title | Randomisation stage (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Carer, Assessor |

Blinding implementation details:

The Randomisation stage used a double-blind design with regard to the subjects and the Investigators, research staff at the site and sponsor staff, in order to eliminate systematic observer or performance bias. Unblinding of the Investigator was only allowed in case of emergency. To avoid unblinding, staff of the ImmuteP S.A.S. lab did not have access to the eCRF nor attended any meeting where subject data were discussed until unblinding for primary analysis occurred.

Arms

| | |
|------------------------------|----------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Paclitaxel + Placebo |

Arm description:

Placebo Arm:

Paclitaxel (80 mg/m² Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion

| | |
|----------------------------------------|------------------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo to IMP321 |
| Investigational medicinal product code | Placebo to IMP321 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Placebo drug product matched the appearance and injection characteristics of efti drug product and comprised efti formulation buffer. The placebo drug product is a single-use, preservative-free, sterile solution for subcutaneous injections. Preparation of study drug was done according to the Investigational Medicinal Product (IMP) Handling Manual. The placebo was administered via subcutaneous injection (single anatomical site) on the anterior face of the thigh.

Repeated s.c. doses of the placebo were administered on Day 2 and Day 16 of each 4-week cycle during the 6 cycles of weekly paclitaxel chemotherapy (chemo-immunotherapy phase). After completion of this chemo-immunotherapy phase, responding or stable subjects received study agent (i.e. without paclitaxel) every 4 weeks during the maintenance phase for an additional 12 injections.

| | |
|------------------|-------------------------|
| Arm title | Paclitaxel + 30 mg efti |
|------------------|-------------------------|

Arm description:

30 mg Efti Arm:

Paclitaxel (80 mg/m² Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + 30 mg Efti

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|------------------------|
| Investigational medicinal product name | IMP321 |
| Investigational medicinal product code | IMP321 |
| Other name | eftilagimod alfa |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Efti drug product is a single-use, preservative-free, sterile solution of efti for subcutaneous injections. Preparation of study drug was done according to the Investigational Medicinal Product (IMP) Handling Manual. The 30 mg dose of efti was administered via subcutaneous injection (single anatomical site) on the anterior face of the thigh.

Repeated s.c. doses of efti were administered on Day 2 and Day 16 of each 4-week cycle during the 6 cycles of weekly paclitaxel chemotherapy (chemo-immunotherapy phase). After completion of this chemo-immunotherapy phase, responding or stable subjects received study agent (i.e. without paclitaxel) every 4 weeks during the maintenance phase for an additional 12 injections.

| Number of subjects in period 1 | Paclitaxel + Placebo | Paclitaxel + 30 mg efti |
|---------------------------------------|-----------------------------|--------------------------------|
| Started | 112 | 114 |
| Randomisation Stage - Maintenance | 54 | 60 |
| Completed | 2 | 2 |
| Not completed | 110 | 112 |
| Adverse event, serious fatal | 1 | 1 |
| Physician decision | 3 | 2 |
| Consent withdrawn by subject | 1 | 3 |
| Adverse event, non-fatal | 9 | 7 |
| Symptomatic deterioration | 5 | 5 |
| 1 Euthanasia + 1 Long Treatment Delay | - | 2 |
| Sponsor's decision | 1 | - |
| Disease Progression | 90 | 92 |

Baseline characteristics

Reporting groups

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Reporting group title | Paclitaxel + Placebo |
| Reporting group description: | |
| Placebo Arm: Paclitaxel (80 mg/m ² Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion | |
| Reporting group title | Paclitaxel + 30 mg efti |
| Reporting group description: | |
| 30 mg Efti Arm: Paclitaxel (80 mg/m ² Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + 30 mg Efti | |

| Reporting group values | Paclitaxel + Placebo | Paclitaxel + 30 mg efti | Total |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|-------------------------|-------|
| Number of subjects | 112 | 114 | 226 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 71 | 76 | 147 |
| From 65-87 years | 41 | 38 | 79 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 59.3 | 58.0 | |
| standard deviation | ± 11.36 | ± 11.93 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 112 | 114 | 226 |
| Male | 0 | 0 | 0 |
| ECOG at Baseline | | | |
| ECOG performance status | | | |
| Units: Subjects | | | |
| ECOG 0 | 70 | 69 | 139 |
| ECOG 1 | 42 | 44 | 86 |
| ECOG 2 | 0 | 1 | 1 |
| Visceral Disease | | | |
| Disease Overview Per Treatment Group at Baseline: Visceral Disease | | | |
| Units: Subjects | | | |
| Visceral Disease - Yes | 104 | 103 | 207 |
| Visceral Disease - No | 8 | 11 | 19 |
| Breast Cancer Subtype | | | |
| Breast Cancer Subtype – Retrospective Central Assessment The central pathology laboratory applied immunohistochemistry to confirm HR positivity, Ki-67 status, and HER2-neu status. Fluorescence in situ hybridisation analysis was performed on samples yielding positive HER2-neu result on immunohistochemistry. | | | |
| Units: Subjects | | | |
| no result | 25 | 32 | 57 |
| Luminal A | 32 | 28 | 60 |
| Luminal B | 43 | 40 | 83 |
| Luminal undefined | 4 | 8 | 12 |
| Triple negative | 1 | 1 | 2 |
| Undefined | 6 | 5 | 11 |

| | | | |
|-----------------------------------------------------------------------|--------------|--------------|-----|
| HER2 positive | 1 | 0 | 1 |
| Number of Disease Sites at Screening | | | |
| Number of Disease Sites at Screening | | | |
| Units: Subjects | | | |
| 1-2 disease sites | 34 | 46 | 80 |
| >2 disease sites | 78 | 68 | 146 |
| Location of Disease at Screening Bone | | | |
| Location of Disease at Screening | | | |
| Units: Subjects | | | |
| Bone | 82 | 83 | 165 |
| not Bone | 30 | 31 | 61 |
| Location of Disease at Screening Liver | | | |
| Location of Disease at Screening Liver | | | |
| Units: Subjects | | | |
| Liver | 85 | 80 | 165 |
| not Liver | 27 | 34 | 61 |
| Location of Disease at Screening Lymph Node | | | |
| Location of Disease at Screening Lymph Node | | | |
| Units: Subjects | | | |
| Lymph node | 56 | 57 | 113 |
| not Lymph node | 56 | 57 | 113 |
| Biomarker CA 15-3 | | | |
| Biomarker CA 15-3 | | | |
| Units: Subjects | | | |
| <30 arb units/L | 20 | 19 | 39 |
| ≥30 arb units/L | 88 | 92 | 180 |
| not recorded | 4 | 3 | 7 |
| Lactate Dehydrogenase at Baseline | | | |
| Lactate Dehydrogenase at Baseline | | | |
| Units: Subjects | | | |
| Elevated (>250 U/L) | 81 | 74 | 155 |
| Non-Elevated (≤250 U/L) | 30 | 39 | 69 |
| not recorded | 1 | 1 | 2 |
| Monocytes at Baseline | | | |
| Units: Subjects | | | |
| <0.25 x 10 ⁹ cells/L | 22 | 25 | 47 |
| ≥0.25 x 10 ⁹ cells/L | 89 | 89 | 178 |
| not recorded | 1 | 0 | 1 |
| Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days) | | | |
| Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days) | | | |
| Units: days | | | |
| median | 668.0 | 262.5 | |
| inter-quartile range (Q1-Q3) | 55 to 1070 | 39 to 824 | - |
| Body Mass Index | | | |
| Units: kg/m ² | | | |
| median | 24.9 | 24.7 | |
| full range (min-max) | 15.4 to 44.5 | 18.1 to 48.1 | - |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |

Subject analysis set description:

The full analysis set (FAS) included all assigned/randomised subjects who received at least one dose of study drug (i.e., one dose of paclitaxel or one dose of efti or placebo). Subjects in this population were analysed according to the treatment to which they were randomised. This population is the primary population for the analyses of efficacy endpoints.

| Reporting group values | Full Analysis Set | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|--|--|
| Number of subjects | 226 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 147 | | |
| From 65-87 years | 79 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 58.0 | | |
| standard deviation | ± 11.93 | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 114 | | |
| Male | 0 | | |
| ECOG at Baseline | | | |
| ECOG performance status | | | |
| Units: Subjects | | | |
| ECOG 0 | 139 | | |
| ECOG 1 | 86 | | |
| ECOG 2 | 1 | | |
| Visceral Disease | | | |
| Disease Overview Per Treatment Group at Baseline: Visceral Disease | | | |
| Units: Subjects | | | |
| Visceral Disease - Yes | 207 | | |
| Visceral Disease - No | 19 | | |
| Breast Cancer Subtype | | | |
| Breast Cancer Subtype – Retrospective Central Assessment | | | |
| The central pathology laboratory applied immunohistochemistry to confirm HR positivity, Ki-67 status, and HER2-neu status. Fluorescence in situ hybridisation analysis was performed on samples yielding positive HER2-neu result on immunohistochemistry. | | | |
| Units: Subjects | | | |
| no result | 57 | | |
| Luminal A | 60 | | |
| Luminal B | 83 | | |
| Luminal undefined | 12 | | |
| Triple negative | 2 | | |
| Undefined | 11 | | |
| HER2 positive | 1 | | |
| Number of Disease Sites at Screening | | | |
| Number of Disease Sites at Screening | | | |
| Units: Subjects | | | |
| 1-2 disease sites | 80 | | |
| >2 disease sites | 146 | | |
| Location of Disease at Screening Bone | | | |

| | | | |
|-----------------------------------------------------------------------|--------------|--|--|
| Location of Disease at Screening | | | |
| Units: Subjects | | | |
| Bone | 165 | | |
| not Bone | 61 | | |
| Location of Disease at Screening Liver | | | |
| Location of Disease at Screening Liver | | | |
| Units: Subjects | | | |
| Liver | 165 | | |
| not Liver | 61 | | |
| Location of Disease at Screening Lymph Node | | | |
| Location of Disease at Screening Lymph Node | | | |
| Units: Subjects | | | |
| Lymph node | 113 | | |
| not Lymph node | 113 | | |
| Biomarker CA 15-3 | | | |
| Biomarker CA 15-3 | | | |
| Units: Subjects | | | |
| <30 arb units/L | 39 | | |
| ≥30 arb units/L | 180 | | |
| not recorded | 7 | | |
| Lactate Dehydrogenase at Baseline | | | |
| Lactate Dehydrogenase at Baseline | | | |
| Units: Subjects | | | |
| Elevated (>250 U/L) | 155 | | |
| Non-Elevated (≤250 U/L) | 69 | | |
| not recorded | 2 | | |
| Monocytes at Baseline | | | |
| Units: Subjects | | | |
| <0.25 x 10 ⁹ cells/L | 47 | | |
| ≥0.25 x 10 ⁹ cells/L | 178 | | |
| not recorded | 1 | | |
| Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days) | | | |
| Time Between Metastatic Stage 4 Diagnosis and Informed Consent (days) | | | |
| Units: days | | | |
| median | 741.8 | | |
| inter-quartile range (Q1-Q3) | 41 to 944 | | |
| Body Mass Index | | | |
| Units: kg/m ² | | | |
| median | 24.7 | | |
| full range (min-max) | 15.4 to 48.1 | | |

End points

End points reporting groups

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Reporting group title | Paclitaxel + Placebo |
| Reporting group description: Placebo Arm: Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion | |
| Reporting group title | Paclitaxel + 30 mg efti |
| Reporting group description: 30 mg Efti Arm: Paclitaxel (80 mg/m2 Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + 30 mg Efti | |
| Subject analysis set title | Full Analysis Set |
| Subject analysis set type | Full analysis |
| Subject analysis set description: The full analysis set (FAS) included all assigned/randomised subjects who received at least one dose of study drug (i.e., one dose of paclitaxel or one dose of efti or placebo). Subjects in this population were analysed according to the treatment to which they were randomised. This population is the primary population for the analyses of efficacy endpoints. | |

Primary: Progression-free survival (PFS) - BICR

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| End point title | Progression-free survival (PFS) - BICR |
| End point description: PFS was defined as the number of days between the start date of Randomisation and the earliest date of documented disease progression, as defined by RECIST V1.1, or death without prior progression. For primary analysis an independent blinded review was performed, i.e., all imaging time points were reviewed by two independent reviewers according to RECIST 1.1. In case of discrepancy, a third reader (adjudicator) reviewed the images. Analysis incl. full analysis set. | |
| End point type | Primary |
| End point timeframe: PFS will be calculated as the time from the date of randomisation to the date of first documentation of disease progression (RECIST1.1) or date of death due to any cause, whichever occurs first. | |

| End point values | Paclitaxel + Placebo | Paclitaxel + 30 mg efti | | |
|----------------------------------|----------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 112 | 114 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 7.29 (5.52 to 7.46) | 7.29 (6.64 to 7.46) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------------------|
| Statistical analysis title | Progression-Free Survival (BICR) |
| Comparison groups | Paclitaxel + Placebo v Paclitaxel + 30 mg efti |

| | |
|-----------------------------------------|------------------------|
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.341 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.93 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.67 |
| upper limit | 1.3 |
| Variability estimate | Standard deviation |

Notes:

[1] - stratified by ECOG (0 versus 1)

Secondary: Overall Survival

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|
| End point title | Overall Survival |
| End point description: | |
| OS was defined as the time between the date of the date of Randomisation and the date of death. For subjects without documentation of death, OS was censored on the last date the subject was known to be alive. | |
| End point type | Secondary |
| End point timeframe: | |
| Overall survival (OS) is defined as the time between the date of randomisation and the date of death from any cause. | |

| End point values | Paclitaxel + Placebo | Paclitaxel + 30 mg efti | | |
|----------------------------------|------------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 112 | 114 | | |
| Units: month | | | | |
| median (confidence interval 95%) | 17.54 (12.91 to 21.85) | 20.37 (14.26 to 25.07) | | |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------------|
| Statistical analysis title | Statistical Analysis OS |
| Comparison groups | Paclitaxel + Placebo v Paclitaxel + 30 mg efti |
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.197 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |

| | |
|----------------------|--------------------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.64 |
| upper limit | 1.19 |
| Variability estimate | Standard deviation |

Secondary: Objective Response Rate

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| End point title | Objective Response Rate |
| End point description: Objective Response Rate (ORR) according to RECIST V1.1 | |
| End point type | Secondary |
| End point timeframe: Radiological assessments according to RECIST 1.1. from screening onwards every 8 weeks until week 73, every 12 weeks thereafter. | |

| End point values | Paclitaxel + Placebo | Paclitaxel + 30 mg efti | | |
|----------------------------------|----------------------|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 112 | 114 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | 40.6 (31 to 51) | 51.4 (42 to 61) | | |

Statistical analyses

| | |
|-----------------------------------------|------------------------------------------------|
| Statistical analysis title | Overall Response Rate |
| Comparison groups | Paclitaxel + 30 mg efti v Paclitaxel + Placebo |
| Number of subjects included in analysis | 226 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.118 |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference in proportion |
| Point estimate | 11 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3 |
| upper limit | 24 |
| Variability estimate | Standard deviation |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Screening and then at each visit until end of PFS and OS follow up (every 12 weeks after end of treatment).

Adverse event reporting additional description:

According to NCI CTCAE V4.03. Reporting from ICF signature until 30 days after last study agent administration. Safety follow-up is to be performed until resolution of AEs/SAEs or for a minimum of 2 months after last study agent administration or until subject is receiving any other anti-cancer therapy or any other investigational therapy.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Paclitaxel + Placebo |
|-----------------------|----------------------|

Reporting group description:

Placebo Arm:

Paclitaxel (80 mg/m² Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + placebo in a double-blinded fashion.

| | |
|-----------------------|-------------------------|
| Reporting group title | Paclitaxel + 30 mg efti |
|-----------------------|-------------------------|

Reporting group description:

30 mg Efti Arm:

Paclitaxel (80 mg/m² Day 1, 8 and 15 every 4 weeks [1 cycle] for maximum of 6 cycles) + efti 30mg in a double-blinded fashion

| Serious adverse events | Paclitaxel + Placebo | Paclitaxel + 30 mg efti | |
|---------------------------------------------------|----------------------|-------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 22 / 112 (19.64%) | 22 / 114 (19.30%) | |
| number of deaths (all causes) | 83 | 81 | |
| number of deaths resulting from adverse events | 3 | 2 | |
| Surgical and medical procedures | | | |
| Thoracic outlet surgery | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Breast reconstruction | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthopaedic procedure | | | |

| | | | |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (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 | | | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 5 / 114 (4.39%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Pelvic pain | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pleural effusion | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 112 (0.89%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Injection related reaction | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Balance disorder | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain stem infarction | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| Headache | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| 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 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Hepatobiliary disease | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatocellular injury | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------|--|
| Infections and infestations Erysipelas subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 2 / 112 (1.79%) 2 / 2 0 / 0 | 1 / 114 (0.88%) 1 / 1 0 / 0 | |
| Lower respiratory tract infection subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 112 (0.00%) 0 / 0 0 / 0 | 1 / 114 (0.88%) 0 / 1 0 / 0 | |
| Urosepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 112 (0.00%) 0 / 0 0 / 0 | 1 / 114 (0.88%) 0 / 1 0 / 0 | |
| Breast cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 112 (0.89%) 0 / 1 0 / 0 | 0 / 114 (0.00%) 0 / 0 0 / 0 | |
| Cellulitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 112 (0.89%) 0 / 1 0 / 0 | 0 / 114 (0.00%) 0 / 0 0 / 0 | |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 112 (0.89%) 0 / 1 0 / 0 | 0 / 114 (0.00%) 0 / 0 0 / 0 | |
| Respiratory tract infection viral subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 112 (0.89%) 0 / 1 0 / 0 | 0 / 114 (0.00%) 0 / 0 0 / 0 | |
| Staphylococcal sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 112 (0.89%) 1 / 1 0 / 0 | 0 / 114 (0.00%) 0 / 0 0 / 0 | |
| Upper respiratory tract infection | | | |

| | | | |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 112 (0.89%) | 0 / 114 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 1 / 114 (0.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Paclitaxel + Placebo | Paclitaxel + 30 mg efti | |
|-------------------------------------------------------|----------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 112 / 112 (100.00%) | 114 / 114 (100.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 11 / 112 (9.82%) | 14 / 114 (12.28%) | |
| occurrences (all) | 47 | 38 | |
| Hot flush | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 6 / 114 (5.26%) | |
| occurrences (all) | 4 | 7 | |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 55 / 112 (49.11%) | 53 / 114 (46.49%) | |
| occurrences (all) | 85 | 104 | |
| Injection site reaction | | | |
| subjects affected / exposed | 4 / 112 (3.57%) | 39 / 114 (34.21%) | |
| occurrences (all) | 8 | 123 | |
| Injection site erythema | | | |
| subjects affected / exposed | 2 / 112 (1.79%) | 35 / 114 (30.70%) | |
| occurrences (all) | 2 | 101 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 19 / 112 (16.96%) | 8 / 114 (7.02%) | |
| occurrences (all) | 29 | 12 | |
| Pyrexia | | | |

| | | | |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 8 / 112 (7.14%) | 17 / 114 (14.91%) | |
| occurrences (all) | 10 | 38 | |
| Injection site pain | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 12 / 114 (10.53%) | |
| occurrences (all) | 10 | 23 | |
| Influenza like illness | | | |
| subjects affected / exposed | 4 / 112 (3.57%) | 10 / 114 (8.77%) | |
| occurrences (all) | 4 | 15 | |
| Injection site induration | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 9 / 114 (7.89%) | |
| occurrences (all) | 0 | 15 | |
| Pain | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 9 / 114 (7.89%) | |
| occurrences (all) | 0 | 11 | |
| Injection site swelling | | | |
| subjects affected / exposed | 0 / 112 (0.00%) | 7 / 114 (6.14%) | |
| occurrences (all) | 0 | 17 | |
| Chest pain | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 6 / 114 (5.26%) | |
| occurrences (all) | 8 | 6 | |
| Chills | | | |
| subjects affected / exposed | 3 / 112 (2.68%) | 6 / 114 (5.26%) | |
| occurrences (all) | 3 | 9 | |
| Malaise | | | |
| subjects affected / exposed | 7 / 112 (6.25%) | 4 / 114 (3.51%) | |
| occurrences (all) | 7 | 5 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 10 / 112 (8.93%) | 16 / 114 (14.04%) | |
| occurrences (all) | 11 | 17 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 22 / 112 (19.64%) | 20 / 114 (17.54%) | |
| occurrences (all) | 24 | 22 | |
| Dyspnoea | | | |

| | | | |
|--------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 20 / 112 (17.86%) | 16 / 114 (14.04%) | |
| occurrences (all) | 31 | 20 | |
| Epistaxis | | | |
| subjects affected / exposed | 8 / 112 (7.14%) | 8 / 114 (7.02%) | |
| occurrences (all) | 11 | 9 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 2 / 114 (1.75%) | |
| occurrences (all) | 6 | 2 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 10 / 112 (8.93%) | 9 / 114 (7.89%) | |
| occurrences (all) | 10 | 11 | |
| Anxiety | | | |
| subjects affected / exposed | 8 / 112 (7.14%) | 4 / 114 (3.51%) | |
| occurrences (all) | 8 | 4 | |
| Investigations | | | |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 34 / 112 (30.36%) | 25 / 114 (21.93%) | |
| occurrences (all) | 56 | 36 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 18 / 112 (16.07%) | 16 / 114 (14.04%) | |
| occurrences (all) | 26 | 39 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 12 / 112 (10.71%) | 10 / 114 (8.77%) | |
| occurrences (all) | 18 | 33 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 14 / 112 (12.50%) | 9 / 114 (7.89%) | |
| occurrences (all) | 15 | 13 | |
| White blood cell count decreased | | | |
| subjects affected / exposed | 11 / 112 (9.82%) | 5 / 114 (4.39%) | |
| occurrences (all) | 28 | 8 | |
| Lymphocyte count decreased | | | |
| subjects affected / exposed | 7 / 112 (6.25%) | 3 / 114 (2.63%) | |
| occurrences (all) | 8 | 5 | |
| Neutrophil count decreased | | | |

| | | | |
|--------------------------------------------------|----------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 112 (5.36%) 9 | 2 / 114 (1.75%) 4 | |
| Nervous system disorders | | | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 28 / 112 (25.00%) | 23 / 114 (20.18%) | |
| occurrences (all) | 53 | 31 | |
| Headache | | | |
| subjects affected / exposed | 17 / 112 (15.18%) | 21 / 114 (18.42%) | |
| occurrences (all) | 19 | 24 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 22 / 112 (19.64%) | 21 / 114 (18.42%) | |
| occurrences (all) | 47 | 36 | |
| Paraesthesia | | | |
| subjects affected / exposed | 16 / 112 (14.29%) | 14 / 114 (12.28%) | |
| occurrences (all) | 27 | 23 | |
| Dysgeusia | | | |
| subjects affected / exposed | 12 / 112 (10.71%) | 7 / 114 (6.14%) | |
| occurrences (all) | 13 | 7 | |
| Dizziness | | | |
| subjects affected / exposed | 7 / 112 (6.25%) | 6 / 114 (5.26%) | |
| occurrences (all) | 9 | 7 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 5 / 112 (4.46%) | 6 / 114 (5.26%) | |
| occurrences (all) | 5 | 8 | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 21 / 112 (18.75%) | 22 / 114 (19.30%) | |
| occurrences (all) | 46 | 39 | |
| Anaemia | | | |
| subjects affected / exposed | 16 / 112 (14.29%) | 18 / 114 (15.79%) | |
| occurrences (all) | 26 | 39 | |
| Leukopenia | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 3 / 114 (2.63%) | |
| occurrences (all) | 10 | 8 | |
| Gastrointestinal disorders | | | |

| | | | |
|----------------------------------------|-------------------|-------------------|--|
| Asthenia | | | |
| subjects affected / exposed | 20 / 112 (17.86%) | 16 / 114 (14.04%) | |
| occurrences (all) | 35 | 29 | |
| Nausea | | | |
| subjects affected / exposed | 40 / 112 (35.71%) | 44 / 114 (38.60%) | |
| occurrences (all) | 55 | 81 | |
| Diarrhoea | | | |
| subjects affected / exposed | 41 / 112 (36.61%) | 33 / 114 (28.95%) | |
| occurrences (all) | 60 | 59 | |
| Constipation | | | |
| subjects affected / exposed | 20 / 112 (17.86%) | 20 / 114 (17.54%) | |
| occurrences (all) | 23 | 26 | |
| Abdominal pain | | | |
| subjects affected / exposed | 11 / 112 (9.82%) | 17 / 114 (14.91%) | |
| occurrences (all) | 14 | 26 | |
| Vomiting | | | |
| subjects affected / exposed | 13 / 112 (11.61%) | 17 / 114 (14.91%) | |
| occurrences (all) | 19 | 23 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 11 / 112 (9.82%) | 10 / 114 (8.77%) | |
| occurrences (all) | 13 | 13 | |
| Stomatitis | | | |
| subjects affected / exposed | 6 / 112 (5.36%) | 8 / 114 (7.02%) | |
| occurrences (all) | 11 | 8 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 2 / 112 (1.79%) | 6 / 114 (5.26%) | |
| occurrences (all) | 3 | 7 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 56 / 112 (50.00%) | 46 / 114 (40.35%) | |
| occurrences (all) | 84 | 67 | |
| Rash | | | |
| subjects affected / exposed | 12 / 112 (10.71%) | 12 / 114 (10.53%) | |
| occurrences (all) | 20 | 16 | |
| Dry skin | | | |

| | | | |
|-----------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 5 / 112 (4.46%) 5 | 8 / 114 (7.02%) 8 | |
| Nail disorder subjects affected / exposed occurrences (all) | 8 / 112 (7.14%) 11 | 8 / 114 (7.02%) 10 | |
| Pruritus subjects affected / exposed occurrences (all) | 7 / 112 (6.25%) 20 | 6 / 114 (5.26%) 6 | |
| Erythema subjects affected / exposed occurrences (all) | 10 / 112 (8.93%) 11 | 5 / 114 (4.39%) 10 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia subjects affected / exposed occurrences (all) | 13 / 112 (11.61%) 18 | 14 / 114 (12.28%) 16 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 8 / 112 (7.14%) 10 | 14 / 114 (12.28%) 22 | |
| Back pain subjects affected / exposed occurrences (all) | 16 / 112 (14.29%) 22 | 13 / 114 (11.40%) 21 | |
| Myalgia subjects affected / exposed occurrences (all) | 12 / 112 (10.71%) 20 | 10 / 114 (8.77%) 14 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 2 | 6 / 114 (5.26%) 7 | |
| Bone pain subjects affected / exposed occurrences (all) | 9 / 112 (8.04%) 10 | 4 / 114 (3.51%) 5 | |
| Infections and infestations | | | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 11 / 112 (9.82%) 13 | 11 / 114 (9.65%) 13 | |
| Nasopharyngitis | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 16 / 112 (14.29%) 18 | 7 / 114 (6.14%) 8 | |
| Rhinitis subjects affected / exposed occurrences (all) | 4 / 112 (3.57%) 4 | 7 / 114 (6.14%) 9 | |
| Cystitis subjects affected / exposed occurrences (all) | 2 / 112 (1.79%) 2 | 6 / 114 (5.26%) 9 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 14 / 112 (12.50%) 16 | 16 / 114 (14.04%) 20 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 07 November 2016 | <ul style="list-style-type: none">• Primary analysis and long-term follow-up for OS was introduced;• Clarification on treatment/study duration, radiological assessments, contraception, subject criteria, safety reporting and dose adjustments of paclitaxel were given to harmonise between participating countries |
| 10 May 2017 | <ul style="list-style-type: none">• Clarification on timing of radiological assessments, contraception method, safety reporting, statistical methods and analyses populations was given. |
| 16 January 2018 | <ul style="list-style-type: none">• General update (contact details, table of content, abbreviations, references, footnotes, appendices linguistic improvements);• Clarification of inclusion and exclusion criteria incl. details on contraception;• Clarifications on study objectives, endpoints and study design including treatment and assessments;• Clarifications on study duration;• Clarification on safety reporting;• Clarification on statistical assumptions, sample size increase and specification of statistical analyses |
| 12 March 2018 | <ul style="list-style-type: none">• General update (typographical corrections, clarifications, vendor contact details, update on clinical data of efti, update of link to RECIST V1.1 guidelines)• Update to study duration• Clarification on HBV screening requirements;• Explanation on the sequence of primary endpoint analysis;• Addition of two hypersensitivity reactions reported from the efti-P011 study added and related risk language updated;• Addition of management and discontinuation guidelines for hypersensitivity reactions;• Inclusion of local best clinical practice into assessment of safety criteria prior to paclitaxel administration |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

EudraCT results platform is not built to accommodate two stage trials. Results of the randomisation stage are presented in EudraCT.
Early conclusion of overall survival follow up due to data maturity.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/30977393>

