



Clinical trial results:

A Randomized, Phase III, Multicenter, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of Onartuzumab in Combination With Erlotinib as First-Line Treatment for Patients with Met-Positive Unresectable Stage IIIB or IV Non-Small Cell Lung Cancer (NSCLC) Carrying an Activating EGFR Mutation

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2013-000868-29 |
| Trial protocol | ES DE IT FR |
| Global end of trial date | 05 February 2015 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 07 April 2016 |
| First version publication date | 07 April 2016 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | GO28758 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01887886 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH-4070 |
| Public contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.com |
| Scientific contact | Roche Trial Information Hotline, F. Hoffmann-La Roche AG, +41 61 6878333, global.trial_information@roche.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 | 05 February 2015 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 05 February 2015 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

Participants with previously untreated MET-positive NSCLC carrying an activating epidermal growth factor receptor (EGFR) mutation were treated with onartuzumab plus erlotinib (versus placebo plus erlotinib) to evaluate the safety and efficacy of the two-drug combination. The primary efficacy objective was to compare progression-free survival (PFS) as assessed by the investigator.

Protection of trial subjects:

This study was conducted in full conformance with the International Conference on Harmonisation (ICH) E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research was conducted, whichever afforded the greater protection to the individual. The study has complied with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Study sites in the United States (US) or under a US Investigational New Drug application (IND) complied with US Food and Drug Administration (FDA) regulations and applicable local, state, and federal laws. Studies conducted in the European Union (EU)/European Economic Area (EEA) complied with the EU Clinical Trial Directive (2001/20/EC).

Background therapy: -

Evidence for comparator: -

| | |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment | 16 December 2013 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Korea, Republic of: 1 |
| Country: Number of subjects enrolled | United States: 4 |
| Worldwide total number of subjects | 10 |
| EEA total number of subjects | 5 |

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) | 4 |
| From 65 to 84 years | 6 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Screening tests and evaluations were performed within 28 days prior to Day 1 of Cycle 1. All screening evaluations were required to be completed and reviewed before randomization to confirm that participants met all eligibility criteria.

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Onartuzumab + Erlotinib |

Arm description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received onartuzumab as 15 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 milligrams (mg) orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| | |
|----------------------------------------|--------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1.

| | |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Onartuzumab |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Onartuzumab was given as 15 mg/kg via IV infusion on Day 1 of each 21-day cycle.

| | |
|------------------|---------------------|
| Arm title | Placebo + Erlotinib |
|------------------|---------------------|

Arm description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received placebo (matched to onartuzumab) via IV infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| | |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

| | |
|----------------------------------------|--------------------|
| Investigational medicinal product name | Erlotinib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1.

| | |
|----------------------------------------|---------------------------------------|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo was administered via IV infusion on Day 1 of each 21-day cycle.

| Number of subjects in period 1 | Onartuzumab + Erlotinib | Placebo + Erlotinib |
|---------------------------------------|-------------------------|---------------------|
| Started | 5 | 5 |
| Completed | 0 | 0 |
| Not completed | 5 | 5 |
| Consent withdrawn by subject | 1 | - |
| Study terminated by Sponsor | 3 | 3 |
| Death | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Onartuzumab + Erlotinib |
|-----------------------|-------------------------|

Reporting group description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received onartuzumab as 15 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 milligrams (mg) orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo + Erlotinib |
|-----------------------|---------------------|

Reporting group description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received placebo (matched to onartuzumab) via IV infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| Reporting group values | Onartuzumab + Erlotinib | Placebo + Erlotinib | Total |
|-------------------------------------------------------------------------|-------------------------|---------------------|-------|
| Number of subjects | 5 | 5 | 10 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 71.2 ± 10.8 | 61 ± 9.1 | - |
| Gender categorical Units: Subjects | | | |
| Female | 4 | 5 | 9 |
| Male | 1 | 0 | 1 |

End points

End points reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Onartuzumab + Erlotinib |
|-----------------------|-------------------------|

Reporting group description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received onartuzumab as 15 milligrams per kilogram (mg/kg) via intravenous (IV) infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 milligrams (mg) orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo + Erlotinib |
|-----------------------|---------------------|

Reporting group description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received placebo (matched to onartuzumab) via IV infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

Primary: PFS

| | |
|-----------------|--------------------|
| End point title | PFS ^[1] |
|-----------------|--------------------|

End point description:

PFS was defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using Response Evaluation Criteria in Solid Tumors (RECIST v1.1) or death. Disease progression was defined as greater than or equal to (\geq) 20 percent (%) increase in the sum of diameters of target lesions, taking as reference the smallest sum on study including Baseline. Endpoint data were to be analyzed using Kaplan-Meier methodology.

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

End point timeframe:

Tumor assessments every 6 weeks for the first year, then every 9 weeks until disease progression (up to 14 months overall)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The data were not analyzed because the development program was terminated by the Sponsor.

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|-------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[2] | 0 ^[3] | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[2] - The data were not analyzed because the development program was terminated by the Sponsor.

[3] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|-----------------|-----------------------|
| End point title | Overall Survival (OS) |
|-----------------|-----------------------|

End point description:

OS was defined as the time from date of randomization until death from any cause. Endpoint data were to be analyzed using Kaplan-Meier methodology.

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

End point timeframe:

Continuously during treatment (up to 14 months) and every 3 months until withdrawal, death, or study end (up to 14 months overall)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|-------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[4] - The data were not analyzed because the development program was terminated by the Sponsor.

[5] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Partial or Complete Response According to RECIST v1.1

| | |
|-----------------|---------------------------------------------------------------------------------------|
| End point title | Percentage of Participants with Partial or Complete Response According to RECIST v1.1 |
|-----------------|---------------------------------------------------------------------------------------|

End point description:

Partial response was defined as $\geq 30\%$ decrease in the sum of diameters of target lesions, taking as reference the Baseline sum of diameters. Complete response was defined as disappearance of all target lesions. The overall response rate (ORR) was to be determined as the percentage of participants with meeting either set of criteria during the study.

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

End point timeframe:

Tumor assessments every 6 weeks for the first year, then every 9 weeks until disease progression (up to 14 months overall)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|-----------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[6] - The data were not analyzed because the development program was terminated by the Sponsor.

[7] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Deterioration (TTD) in Lung Cancer Symptoms

| | |
|-----------------|-----------------------------------------------------|
| End point title | Time to Deterioration (TTD) in Lung Cancer Symptoms |
|-----------------|-----------------------------------------------------|

End point description:

TTD was defined the time from Baseline to first increase (i.e. worsening) in lung cancer symptoms of cough, dyspnea, chest pain, or arm/shoulder pain. Symptom worsening was defined as a ≥ 10 -point increase in the individual item score on the European Organisation for Research and Treatment of Cancer (EORTC) 30-Item Core Quality of Life Questionnaire (QLQ-C30) or EORTC 13-Item Lung Cancer Module (QLQ-LC13). Most questions from the QLQ-C30 and QLQ-LC13 use a 4-point scale (1 equals [=] 'not at all' to 4 = 'very much') except for two questions from the QLQ-C30 that use a 7-point scale (1 = 'very poor' to 7 = 'excellent'). Regardless, item scores are transformed to a scale from 0 to 100, where higher scores indicate a greater degree of symptoms.

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

End point timeframe:

Baseline, every 3 months during treatment (up to 14 months), within 30 days of last dose, and 3 months after last dose (up to 14 months overall)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|-------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | | |
| Units: months | | | | |
| median (full range (min-max)) | (to) | (to) | | |

Notes:

[8] - The data were not analyzed because the development program was terminated by the Sponsor.

[9] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in EORTC QLQ-C30 Domain Scores

| | |
|-----------------|-----------------------------------------------------|
| End point title | Change from Baseline in EORTC QLQ-C30 Domain Scores |
|-----------------|-----------------------------------------------------|

End point description:

The EORTC QLQ-C30 includes functional scales (physical, role, cognitive, emotional, and social), global health status, symptom scales (fatigue, pain, nausea/vomiting) and single items (dyspnea, appetite loss, insomnia, constipation/diarrhea, and financial difficulties). Most questions use a 4-point scale (1 equals [=] 'not at all' to 4 = 'very much') except for two questions that use a 7-point scale (1 = 'very poor' to 7 = 'excellent'). Regardless, item scores are transformed to a scale from 0 to 100, where higher scores indicate better level of functioning or a greater degree of symptoms.

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

End point timeframe:

Baseline to end of treatment (up to 14 months)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|--------------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[10] - The data were not analyzed because the development program was terminated by the Sponsor.

[11] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline EORTC QLQ-LC13 Domain Scores

| | |
|-----------------|---------------------------------------------------|
| End point title | Change from Baseline EORTC QLQ-LC13 Domain Scores |
|-----------------|---------------------------------------------------|

End point description:

The QLQ-LC13 consists of 13 questions relating to disease symptoms specific to lung cancer and treatment side effects typical of treatment with chemotherapy and radiotherapy. The 13 questions comprise one 3-item scale for dyspnea and ten single-item symptom and side effects scales (cough, hemoptysis, sore mouth, dysphagia, peripheral neuropathy, alopecia, chest pain, arm pain, other pain, and medicine for pain). Participants are asked to recall symptoms within the prior week. Questions use a 4-point scale (1 = 'not at all' to 4 = 'very much'). Item scores are transformed to a scale from 0 to 100, where higher scores indicate a greater degree of symptoms.

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

End point timeframe:

Baseline to end of treatment (up to 14 months)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|--------------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[12] - The data were not analyzed because the development program was terminated by the Sponsor.

[13] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve (AUC) of Onartuzumab

| | |
|-----------------|--------------------------------------------------------------|
| End point title | Area Under the Concentration-Time Curve (AUC) of Onartuzumab |
|-----------------|--------------------------------------------------------------|

End point description:

Serum samples were collected at various timepoints to assess the pharmacokinetics of onartuzumab. The AUC was to be determined for each participant, averaged across all participants, and expressed in micrograms by hours per milliliter (mcg*h/mL).

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

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycles 1, 2, 4; post-dose (1 hour after end of infusion) on Day 1 of Cycle 1; and within 30 days of last dose (up to 14 months overall)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|--------------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | | |
| Units: mcg*h/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[14] - The data were not analyzed because the development program was terminated by the Sponsor.

[15] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Concentration (Cmin) of Onartuzumab

| | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| End point title | Minimum Observed Concentration (Cmin) of Onartuzumab |
| End point description: Serum samples were collected at various timepoints to assess the pharmacokinetics of onartuzumab. The Cmin was to be determined for each participant, averaged across all participants, and expressed in micrograms per milliliter (mcg/mL). | |
| End point type | Secondary |
| End point timeframe: Pre-dose (0 hours) on Day 1 of Cycles 1, 2, 4 | |

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|--------------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[16] | 0 ^[17] | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[16] - The data were not analyzed because the development program was terminated by the Sponsor.

[17] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Concentration (Cmax) of Onartuzumab

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| End point title | Maximum Observed Concentration (Cmax) of Onartuzumab |
| End point description: Serum samples were collected to assess the pharmacokinetics of onartuzumab. The Cmax was to be determined for each participant, averaged across all participants, and expressed in mcg/mL. | |
| End point type | Secondary |
| End point timeframe: Post-dose (1 hour after end of infusion) on Day 1 of Cycle 1 | |

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|--------------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[18] | 0 ^[19] | | |
| Units: mcg/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[18] - The data were not analyzed because the development program was terminated by the Sponsor.

[19] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Onartuzumab

| | |
|-----------------|-----------------------------------------------------------------------------------|
| End point title | Percentage of Participants with Anti-Therapeutic Antibodies (ATAs) to Onartuzumab |
|-----------------|-----------------------------------------------------------------------------------|

End point description:

Serum samples were collected at various timepoints to assess for the presence of ATAs to onartuzumab. The percentage of participants who demonstrated ATAs at any time was to be determined.

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

End point timeframe:

Pre-dose (0 hours) on Day 1 of Cycles 1 and 4 and within 30 days of last dose (up to 14 months overall)

| End point values | Onartuzumab + Erlotinib | Placebo + Erlotinib | | |
|-----------------------------------|-------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[20] | 0 ^[21] | | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |

Notes:

[20] - The data were not analyzed because the development program was terminated by the Sponsor.

[21] - The data were not analyzed because the development program was terminated by the Sponsor.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Continuously during treatment (up to 14 months) and within 30 days of last dose (up to 14 months overall)

Adverse event reporting additional description:

Safety Population: All participants who received at least one dose of study medication.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Onartuzumab + Erlotinib |
|-----------------------|-------------------------|

Reporting group description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received onartuzumab as 15 mg/kg via IV infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| | |
|-----------------------|---------------------|
| Reporting group title | Placebo + Erlotinib |
|-----------------------|---------------------|

Reporting group description:

Participants with MET receptor-positive, unresectable Stage IIIB or Stage IV NSCLC carrying an activating EGFR mutation received placebo (matched to onartuzumab) via IV infusion on Day 1 of each 21-day cycle. Erlotinib tablets were administered as 150 mg orally once daily beginning on Day 1 of Cycle 1. Treatment continued until disease progression, unacceptable toxicity, withdrawal, death, or termination of the study.

| Serious adverse events | Onartuzumab + Erlotinib | Placebo + Erlotinib | |
|---------------------------------------------------|-------------------------|---------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 5 (20.00%) | |
| number of deaths (all causes) | 1 | 2 | |
| number of deaths resulting from adverse events | | | |
| Vascular disorders | | | |
| Raynaud's phenomenon | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Encephalopathy | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Musculoskeletal and connective tissue | | | |

| | | | |
|-------------------------------------------------|----------------|---------------|--|
| disorders | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Onartuzumab + Erlotinib | Placebo + Erlotinib | |
|-------------------------------------------------------|-------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 5 / 5 (100.00%) | 5 / 5 (100.00%) | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 1 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 1 | 1 | |
| Axillary pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Chills | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 1 | 1 | |
| Fatigue | | | |
| subjects affected / exposed | 3 / 5 (60.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 3 | 2 | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 1 | |
| Mucosal inflammation | | | |

| | | | |
|-------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 4 | 0 / 5 (0.00%) 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 2 | 1 / 5 (20.00%) 1 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Dyspnoea exertional subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Haemoptysis subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Pleural effusion subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Wheezing subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Depression | | | |

| | | | |
|--------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Insomnia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Investigations Transaminases increased subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Nervous system disorders Carpal tunnel syndrome subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Headache subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 2 / 5 (40.00%) 2 | |
| Paraesthesia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Tremor subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Visual field defect subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Eye disorders Glaucoma subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Vision blurred subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Abdominal pain | | | |

| | | |
|----------------------------------|----------------|-----------------|
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 |
| Abdominal pain upper | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 |
| Anal fissure | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 |
| Anorectal discomfort | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 |
| Constipation | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 2 |
| Diarrhoea | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 3 / 5 (60.00%) |
| occurrences (all) | 2 | 4 |
| Dry mouth | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 |
| Dysphagia | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 1 |
| Gastrointestinal pain | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gastrooesophageal reflux disease | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nausea | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 5 / 5 (100.00%) |
| occurrences (all) | 2 | 5 |
| Stomatitis | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 0 | 2 |
| Toothache | | |

| | | | |
|--------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Vomiting subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 3 | 1 / 5 (20.00%) 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | 1 / 5 (20.00%) 1 | |
| Alopecia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Dermatitis acneiform subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Dry skin subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 5 (40.00%) 2 | |
| Rash subjects affected / exposed occurrences (all) | 4 / 5 (80.00%) 7 | 3 / 5 (60.00%) 3 | |
| Pruritus subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Endocrine disorders | | | |
| Hypothyroidism subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 2 / 5 (40.00%) 2 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Musculoskeletal chest pain | | | |

| | | | |
|-----------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Infections and infestations | | | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Oral candidiasis subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | |
| Paronychia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Rhinitis subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Tooth infection subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | |
| Urinary tract infection subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 3 | 1 / 5 (20.00%) 3 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 2 / 5 (40.00%) 2 | |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 | |
| Hypocalcaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 1 / 5 (20.00%) | |
| occurrences (all) | 0 | 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 05 February 2015 | The study was terminated following concerns that the addition of onartuzumab to erlotinib could have the potential to shorten survival in previously untreated patients with MET-positive EGFR-mutant locally advanced or metastatic NSCLC. | - |

Notes:

Limitations and caveats

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

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| Because the study was terminated early, the study results were reported in an abbreviated format that did not include analysis of efficacy or pharmacokinetic data. Only safety results are reported herein. |
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Notes: