



Clinical trial results:

Randomized, controlled, open label, multicenter, phase II study to evaluate the efficacy and safety of CetuGEX plus chemotherapy in comparison to cetuximab plus chemotherapy for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2013-003695-13 |
| Trial protocol | DE ES IT BE PL |
| Global end of trial date | 04 October 2017 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 16 December 2020 |
| First version publication date | 16 December 2020 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | GEXMab52201 |
|-----------------------|-------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02052960 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Glycotope GmbH |
| Sponsor organisation address | Robert-Roessle-Str.10, Berlin, Germany, 13125 |
| Public contact | Dr. Isabelle Ahrens-Fath, Glycotope GmbH, +49 30 94892610, Isabelle.Ahrens-Fath@glycotope.com |
| Scientific contact | Dr. Isabelle Ahrens-Fath, Glycotope GmbH, +49 30 94892610, Isabelle.Ahrens-Fath@glycotope.com |
| Sponsor organisation name | Glycotope GmbH |
| Sponsor organisation address | Robert Roessle St 10, Berlin, Germany, 13125 |
| Public contact | Reception desk, Glycotope GmbH, +49 3094892600, Trials@glycotope.com |
| Scientific contact | Reception desk, Glycotope GmbH, +49 3094892600, Trials@glycotope.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 | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 May 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 28 August 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 October 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the efficacy of CetuGEX™ for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) as compared to cetuximab (both in combination with platinum-based chemotherapy) in terms of progression-free survival (PFS).

Protection of trial subjects:

An independent DSMB was established, whose task was to review periodically the relevant safety data and provide advice on the continuation, modification or termination of the study. The DSMB comprised 3 members, 2 of them being oncologists and 1 of them a statistician. A study-specific charter defined in detail the composition, responsibilities, and procedures of the DSMB (Appendix 16.1.1). As soon as at least 10 patients per treatment arm had completed the second cycle of first line treatment, a first meeting of DSMB was scheduled to review the patient safety data. After this, regular 6-monthly meetings were scheduled until all ongoing patients had been treated for at least 6 months. Starting at the second DSMB meeting, in addition to review of patient safety data a descriptive analysis on progression and survival was included to monitor a potential detrimental effect of the IMP. For important reasons, additional meetings could be scheduled by the coordinating investigator, sponsor, medical monitor, or DSMB members for as long as patients were at risk.

Background therapy:

Eligible patients were randomized to receive as first line treatment either CetuGEX™ or cetuximab in combination with chemotherapy (5-FU and cisplatin) for the maximum duration of 6 cycles of combined treatment. In case of toxicity, chemotherapy could be dose reduced, discontinued or, if later than the first cycle, switched to carboplatin.

Single-agent maintenance therapy was continued with an unchanged dosing schedule until progression of disease or limiting toxicity

Evidence for comparator:

Cetuximab (Erbix®) is a chimeric immunoglobulin G (IgG) 1 mouse-human antibody targeted against the extracellular domain of the epidermal growth factor receptor (EGFR) with high specificity and affinity and is produced in the murine myeloma cell line SP2/0.

Cetuximab is approved for use in combination with radiation therapy for treating squamous cell carcinoma of the head and neck (SCCHN) or in combination with platinum-based chemotherapy and 5-fluorouracil (5-FU) for the treatment of recurrent and/or metastatic SCCHN.

| | |
|---|------------------|
| Actual start date of recruitment | 27 February 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 24 Months |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Poland: 58 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | France: 44 |
| Country: Number of subjects enrolled | Germany: 62 |
| Country: Number of subjects enrolled | Italy: 8 |
| Country: Number of subjects enrolled | Romania: 43 |
| Worldwide total number of subjects | 240 |
| EEA total number of subjects | 240 |

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) | 177 |
| From 65 to 84 years | 63 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Between 27 Feb 2014 and 25 Jan 2016 a total of 321 patients (100.0%) were screened.

Date of first enrollment: 27 Feb 2014

Pre-assignment

Screening details:

Patients aged at least 18 years, with histologically confirmed recurrent and/or metastatic SCCHN not eligible for local treatment were enrolled in this study.

Period 1

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

Blinding implementation details:

No blinding

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | CetuGEX |

Arm description:

CetuGEX™, chimeric monoclonal immunoglobulin G (IgG) antibody with fully human glycosylation; solution for intravenous infusion, provided in single-use vials.

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

Dosage and administration details:

The IMP CetuGEX™ was administered as infusion to all patients randomized to the CetuGEX™ arm, once weekly, starting with Day 0. Starting with the second infusion (Day 8 of Cycle 1), a time window of ± 1 day was allowed for the weekly infusions (calculated from the previous infusion).

The initial dose was 990 mg and subsequent doses were 720 mg once weekly. The initial loading dose was given as split-dose over 2 days with a priming dose of 60 mg on Day 0 diluted to a total volume of 100 mL (administered over 2 hours with a 30-minute break) and the remaining dose of 930 mg on Day 1 diluted to a total volume 500 mL (the intravenous infusion lasted for approximately 4 hours).

| | |
|------------------|-----------|
| Arm title | Cetuximab |
|------------------|-----------|

Arm description:

Cetuximab, chimeric monoclonal IgG antibody; solution for intravenous infusion, provided in single-use vials.

| | |
|--|---------------------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Cetuximab |
| Investigational medicinal product code | SUB31982 |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Cetuximab was administered once weekly as infusion to all patients randomized to the cetuximab arm.

Starting with the second infusion (Day 8 of Cycle 1), a time window of ± 1 day was allowed for the weekly infusions (calculated from the previous infusion). The initial dose was 400 mg/m² body surface area (BSA) and each subsequent dose was 250 mg/m² BSA. The maximum Infusion rate for the initial dose could not exceed 5 mg/min. The maximum infusion rate for subsequent doses could not exceed 10 mg/min. The BSA was calculated using the Mosteller formula:

$$\text{BSA [m}^2\text{]} = (\text{Weight [kg]} \times \text{Height [cm]}/3600)^{1/2}$$

| Number of subjects in period 1 | CetuGEX | Cetuximab |
|---------------------------------------|---------|-----------|
| Started | 117 | 123 |
| Completed | 59 | 74 |
| Not completed | 58 | 49 |
| Consent withdrawn by subject | 6 | 11 |
| Adverse event, non-fatal | 19 | 17 |
| still on treatment | 4 | 3 |
| unspecified | 25 | 15 |
| Protocol deviation | 4 | 3 |

Baseline characteristics

Reporting groups

| | |
|--|-----------|
| Reporting group title | CetuGEX |
| Reporting group description: CetuGEX™, chimeric monoclonal immunoglobulin G (IgG) antibody with fully human glycosylation; solution for intravenous infusion, provided in single-use vials. | |
| Reporting group title | Cetuximab |
| Reporting group description: Cetuximab, chimeric monoclonal IgG antibody; solution for intravenous infusion, provided in single-use vials. | |

| Reporting group values | CetuGEX | Cetuximab | Total |
|---------------------------------------|---------|-----------|-------|
| Number of subjects | 117 | 123 | 240 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 88 | 89 | 177 |
| From 65-84 years | 29 | 34 | 63 |
| Age continuous Units: years | | | |
| arithmetic mean | 59.8 | 59.8 | |
| standard deviation | ± 7.54 | ± 7.91 | - |
| Gender categorical Units: Subjects | | | |
| Female | 18 | 17 | 35 |
| Male | 99 | 106 | 205 |

Subject analysis sets

| | |
|--|----------------------------|
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population (SAF) included all patients who received at least one dose of trial medication. This population was used for safety analyses. | |
| Subject analysis set title | Intent to treat population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT population consisted of all randomized patients. The ITT population was the primary population for the efficacy analysis. | |

| Reporting group values | Safety population | Intent to treat population | |
|------------------------------------|-------------------|----------------------------|--|
| Number of subjects | 237 | 240 | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | | 177 | |
| From 65-84 years | | 63 | |
| Age continuous Units: years | | | |
| arithmetic mean | | 59.8 | |

| | | | |
|--------------------|---|--------|--|
| standard deviation | ± | ± 7.72 | |
|--------------------|---|--------|--|

| | | | |
|--------------------|--|-----|--|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | | 35 | |
| Male | | 205 | |

End points

End points reporting groups

| | |
|--|----------------------------|
| Reporting group title | CetuGEX |
| Reporting group description: CetuGEX™, chimeric monoclonal immunoglobulin G (IgG) antibody with fully human glycosylation; solution for intravenous infusion, provided in single-use vials. | |
| Reporting group title | Cetuximab |
| Reporting group description: Cetuximab, chimeric monoclonal IgG antibody; solution for intravenous infusion, provided in single-use vials. | |
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population (SAF) included all patients who received at least one dose of trial medication. This population was used for safety analyses. | |
| Subject analysis set title | Intent to treat population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The ITT population consisted of all randomized patients. The ITT population was the primary population for the efficacy analysis. | |

Primary: Progression free survival

| | |
|---|---------------------------|
| End point title | Progression free survival |
| End point description: The primary objective of the study was to evaluate the efficacy of CetuGEX™ for the treatment of patients with stage III/IV recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN) as compared to cetuximab (both in combination with platinum-based chemotherapy) in terms of progression-free survival (PFS). | |
| End point type | Primary |
| End point timeframe: The PFS was defined as time from randomization until disease progression or death of any cause. | |

| End point values | CetuGEX | Cetuximab | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 123 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 27.571 (23.429 to 33.571) | 26.429 (24.714 to 31.286) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Log-Rank Test and Kaplan-Meier Analysis |
| Comparison groups | CetuGEX v Cetuximab |

| | |
|---|---------------|
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8167 |
| Method | Logrank |
| Confidence interval | |
| sides | 2-sided |

Secondary: Objective response rate

| | |
|---|-------------------------|
| End point title | Objective response rate |
| End point description: | |
| Objective response rate is the portion of patients with a tumor size reduction of a predefined amount for a minimum time period and it is defined as the sum of partial responses and complete responses. | |
| End point type | Secondary |
| End point timeframe: | |
| Time from randomization until disease progression or death, whichever occurs first | |

| End point values | CetuGEX | Cetuximab | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 123 | | |
| Units: patients | 52 | 57 | | |

Statistical analyses

| | |
|---|---------------------|
| Statistical analysis title | Chi-square test |
| Comparison groups | CetuGEX v Cetuximab |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.768 |
| Method | Chi-squared |
| Parameter estimate | rate difference |
| Point estimate | -1.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -14.5 |
| upper limit | 10.7 |

Secondary: Clinical Benefit Rate

| | |
|-----------------|-----------------------|
| End point title | Clinical Benefit Rate |
|-----------------|-----------------------|

End point description:

The clinical benefit rate is the portion of patients with an objective response or stable disease.

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

End point timeframe:

Time from randomization until disease progression or death, whichever occurs first.

SD: follow-up measurements must have met the SD criteria at least once after randomization at a minimum interval of 8 weeks

| End point values | CetuGEX | Cetuximab | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 123 | | |
| Units: Subjects | 88 | 94 | | |

Statistical analyses

| | |
|---|---------------------|
| Statistical analysis title | Chi-square test |
| Comparison groups | Cetuximab v CetuGEX |
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8269 |
| Method | Chi-squared |
| Parameter estimate | rate difference |
| Point estimate | -1.21 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.05 |
| upper limit | 9.63 |

Secondary: Response duration

| | |
|-----------------|-------------------|
| End point title | Response duration |
|-----------------|-------------------|

End point description:

Duration of response, defined as the interval between the date of first response and the date of first progression (modified irRC) or death

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

End point timeframe:

Response duration is measured from the time of initial response until documented tumor progression.

| End point values | CetuGEX | Cetuximab | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 52 | 57 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 26.143 (21.571 to 34.857) | 30.143 (24.286 to 37.000) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Log-Rank Test and Kaplan-Meier Analysis |
| Comparison groups | CetuGEX v Cetuximab |
| Number of subjects included in analysis | 109 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.8663 |
| Method | Logrank |

Secondary: Overall survival

| | |
|------------------------|--|
| End point title | Overall survival |
| End point description: | The overall survival is defined as the duration of time from randomization to the time of death. |
| End point type | Secondary |
| End point timeframe: | Duration of time from randomization to the time of death. |

| End point values | CetuGEX | Cetuximab | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 117 | 123 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 49.714 (40.714 to 73.857) | 59.000 (52.857 to 70.286) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Log-Rank Test and Kaplan-Meier Analysis |
| Comparison groups | CetuGEX v Cetuximab |

| | |
|---|---------------|
| Number of subjects included in analysis | 240 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.9616 |
| Method | Logrank |

Secondary: Time to treatment failure

| | |
|--|---------------------------|
| End point title | Time to treatment failure |
| End point description: Time to treatment failure is defined as the time from randomization to treatment discontinuation for any reason, including disease progression, treatment toxicity, patient preference, or death | |
| End point type | Secondary |
| End point timeframe: Time to treatment failure, defined as the interval between the date of randomization and the date of treatment discontinuation for any reason | |

| End point values | CetuGEX | Cetuximab | | |
|----------------------------------|---------------------------|---------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 116 | 123 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 22.143 (17.000 to 25.714) | 23.286 (16.143 to 25.571) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Log-Rank Test and Kaplan-Meier Analysis |
| Comparison groups | CetuGEX v Cetuximab |
| Number of subjects included in analysis | 239 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7038 |
| Method | Logrank |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of signing the ICF through the Safety Follow-Up Visit performed for all patients at 28 days (+ 2 days) after the last dose administered.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Safety population |
|-----------------------|-------------------|

Reporting group description:

The safety population included all patients who received at least 1 dose of trial medication. This population was used for safety analyses.

| | |
|-----------------------|---------------------------|
| Reporting group title | CetuGEX Safety population |
|-----------------------|---------------------------|

Reporting group description: -

| | |
|-----------------------|-----------------------------|
| Reporting group title | Cetuximab Safety population |
|-----------------------|-----------------------------|

Reporting group description: -

| Serious adverse events | Safety population | CetuGEX Safety population | Cetuximab Safety population |
|---|--------------------|---------------------------|-----------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 148 / 237 (62.45%) | 70 / 115 (60.87%) | 78 / 122 (63.93%) |
| number of deaths (all causes) | 34 | 20 | 14 |
| number of deaths resulting from adverse events | 34 | 20 | 14 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 2 / 115 (1.74%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 3 / 115 (2.61%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 3 / 5 | 3 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 2 / 115 (1.74%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |

| | | | |
|--|------------------|-----------------|-----------------|
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 2 / 115 (1.74%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 18 / 237 (7.59%) | 9 / 115 (7.83%) | 9 / 122 (7.38%) |
| occurrences causally related to treatment / all | 0 / 22 | 0 / 10 | 0 / 12 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 15 / 237 (6.33%) | 8 / 115 (6.96%) | 7 / 122 (5.74%) |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 8 | 0 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 237 (2.53%) | 2 / 115 (1.74%) | 4 / 122 (3.28%) |
| occurrences causally related to treatment / all | 5 / 9 | 2 / 2 | 3 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 3 / 115 (2.61%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leukopenia | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 1 / 115 (0.87%) | 4 / 122 (3.28%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 1 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Death | | | |
| subjects affected / exposed | 4 / 237 (1.69%) | 2 / 115 (1.74%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 1 / 4 | 1 / 2 | 0 / 2 |
| General physical health deterioration | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 237 (1.69%) | 2 / 115 (1.74%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 4 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Device dislocation | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 1 / 115 (0.87%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 2 / 115 (1.74%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 3 / 115 (2.61%) | 0 / 122 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 3 / 115 (2.61%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 2 / 5 | 1 / 3 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 3 / 115 (2.61%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 3 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 4 / 237 (1.69%) | 2 / 115 (1.74%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 2 / 115 (1.74%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 4 / 5 | 2 / 2 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|------------------|-------------------|-----------------|
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 2 / 115 (1.74%) | 1 / 122 (0.82%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 1 / 115 (0.87%) | 2 / 122 (1.64%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 21 / 237 (8.86%) | 12 / 115 (10.43%) | 9 / 122 (7.38%) |
| occurrences causally related to treatment / all | 10 / 25 | 6 / 15 | 4 / 10 |
| deaths causally related to treatment / all | 0 / 8 | 0 / 6 | 0 / 2 |
| Sepsis | | | |
| subjects affected / exposed | 10 / 237 (4.22%) | 3 / 115 (2.61%) | 7 / 122 (5.74%) |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 3 | 1 / 7 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 2 |
| Device related infection | | | |
| subjects affected / exposed | 9 / 237 (3.80%) | 5 / 115 (4.35%) | 4 / 122 (3.28%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 5 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung abscess | | | |
| subjects affected / exposed | 3 / 237 (1.27%) | 0 / 115 (0.00%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 9 / 237 (3.80%) | 4 / 115 (3.48%) | 5 / 122 (4.10%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypomagnesaemia | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 9 / 237 (3.80%) | 4 / 115 (3.48%) | 5 / 122 (4.10%) |
| occurrences causally related to treatment / all | 8 / 9 | 0 / 4 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 237 (2.95%) | 3 / 115 (2.61%) | 4 / 122 (3.28%) |
| occurrences causally related to treatment / all | 4 / 10 | 1 / 5 | 3 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 5 / 237 (2.11%) | 2 / 115 (1.74%) | 3 / 122 (2.46%) |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 2 | 1 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Safety population | CetuGEX Safety population | Cetuximab Safety population |
|---|--------------------|---------------------------|-----------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 235 / 237 (99.16%) | 114 / 115 (99.13%) | 121 / 122 (99.18%) |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 32 / 237 (13.50%) | 16 / 115 (13.91%) | 16 / 122 (13.11%) |
| occurrences (all) | 44 | 20 | 24 |
| Hypertension | | | |
| subjects affected / exposed | 19 / 237 (8.02%) | 11 / 115 (9.57%) | 8 / 122 (6.56%) |
| occurrences (all) | 43 | 30 | 13 |
| General disorders and administration site conditions | | | |
| Fatigue | | | |
| subjects affected / exposed | 79 / 237 (33.33%) | 41 / 115 (35.65%) | 38 / 122 (31.15%) |
| occurrences (all) | 163 | 82 | 81 |
| Asthenia | | | |
| subjects affected / exposed | 71 / 237 (29.96%) | 34 / 115 (29.57%) | 37 / 122 (30.33%) |
| occurrences (all) | 135 | 60 | 75 |
| Mucosal inflammation | | | |
| subjects affected / exposed | 60 / 237 (25.32%) | 24 / 115 (20.87%) | 36 / 122 (29.51%) |
| occurrences (all) | 108 | 45 | 63 |
| Pyrexia | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 40 / 237 (16.88%) | 16 / 115 (13.91%) | 24 / 122 (19.67%) |
| occurrences (all) | 47 | 17 | 30 |
| Chills | | | |
| subjects affected / exposed | 32 / 237 (13.50%) | 26 / 115 (22.61%) | 6 / 122 (4.92%) |
| occurrences (all) | 34 | 28 | 6 |
| General physical health deterioration | | | |
| subjects affected / exposed | 13 / 237 (5.49%) | 7 / 115 (6.09%) | 6 / 122 (4.92%) |
| occurrences (all) | 16 | 10 | 6 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 25 / 237 (10.55%) | 10 / 115 (8.70%) | 15 / 122 (12.30%) |
| occurrences (all) | 31 | 10 | 21 |
| Dyspnoea | | | |
| subjects affected / exposed | 25 / 237 (10.55%) | 11 / 115 (9.57%) | 14 / 122 (11.48%) |
| occurrences (all) | 33 | 17 | 16 |
| Epistaxis | | | |
| subjects affected / exposed | 16 / 237 (6.75%) | 6 / 115 (5.22%) | 10 / 122 (8.20%) |
| occurrences (all) | 20 | 7 | 13 |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 12 / 237 (5.06%) | 8 / 115 (6.96%) | 4 / 122 (3.28%) |
| occurrences (all) | 18 | 13 | 5 |
| Investigations | | | |
| Weight decreased | | | |
| subjects affected / exposed | 81 / 237 (34.18%) | 42 / 115 (36.52%) | 39 / 122 (31.97%) |
| occurrences (all) | 155 | 83 | 72 |
| Blood creatinine increased | | | |
| subjects affected / exposed | 19 / 237 (8.02%) | 11 / 115 (9.57%) | 8 / 122 (6.56%) |
| occurrences (all) | 34 | 19 | 15 |
| Platelet count decreased | | | |
| subjects affected / exposed | 13 / 237 (5.49%) | 7 / 115 (6.09%) | 6 / 122 (4.92%) |
| occurrences (all) | 19 | 13 | 6 |
| Cardiac disorders | | | |
| Tachycardia | | | |
| subjects affected / exposed | 13 / 237 (5.49%) | 10 / 115 (8.70%) | 3 / 122 (2.46%) |
| occurrences (all) | 14 | 11 | 3 |

| | | | |
|--------------------------------------|--------------------|-------------------|-------------------|
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 29 / 237 (12.24%) | 14 / 115 (12.17%) | 15 / 122 (12.30%) |
| occurrences (all) | 36 | 16 | 20 |
| Headache | | | |
| subjects affected / exposed | 26 / 237 (10.97%) | 13 / 115 (11.30%) | 13 / 122 (10.66%) |
| occurrences (all) | 35 | 16 | 19 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 12 / 237 (5.06%) | 3 / 115 (2.61%) | 9 / 122 (7.38%) |
| occurrences (all) | 23 | 4 | 19 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 100 / 237 (42.19%) | 44 / 115 (38.26%) | 56 / 122 (45.90%) |
| occurrences (all) | 256 | 104 | 152 |
| Neutropenia | | | |
| subjects affected / exposed | 98 / 237 (41.35%) | 47 / 115 (40.87%) | 51 / 122 (41.80%) |
| occurrences (all) | 229 | 105 | 124 |
| Leukopenia | | | |
| subjects affected / exposed | 70 / 237 (29.54%) | 33 / 115 (28.70%) | 37 / 122 (30.33%) |
| occurrences (all) | 188 | 98 | 90 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 47 / 237 (19.83%) | 21 / 115 (18.26%) | 26 / 122 (21.31%) |
| occurrences (all) | 117 | 48 | 69 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 23 / 237 (9.70%) | 11 / 115 (9.57%) | 12 / 122 (9.84%) |
| occurrences (all) | 25 | 13 | 12 |
| Tinnitus | | | |
| subjects affected / exposed | 14 / 237 (5.91%) | 8 / 115 (6.96%) | 6 / 122 (4.92%) |
| occurrences (all) | 17 | 10 | 7 |
| Hearing impaired | | | |
| subjects affected / exposed | 13 / 237 (5.49%) | 6 / 115 (5.22%) | 7 / 122 (5.74%) |
| occurrences (all) | 14 | 6 | 8 |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 19 / 237 (8.02%) | 10 / 115 (8.70%) | 9 / 122 (7.38%) |
| occurrences (all) | 28 | 16 | 12 |

| | | | |
|--|--------------------|-------------------|-------------------|
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 121 / 237 (51.05%) | 58 / 115 (50.43%) | 63 / 122 (51.64%) |
| occurrences (all) | 284 | 122 | 162 |
| Diarrhoea | | | |
| subjects affected / exposed | 79 / 237 (33.33%) | 38 / 115 (33.04%) | 41 / 122 (33.61%) |
| occurrences (all) | 157 | 73 | 84 |
| Vomiting | | | |
| subjects affected / exposed | 76 / 237 (32.07%) | 35 / 115 (30.43%) | 41 / 122 (33.61%) |
| occurrences (all) | 150 | 67 | 83 |
| Constipation | | | |
| subjects affected / exposed | 57 / 237 (24.05%) | 34 / 115 (29.57%) | 23 / 122 (18.85%) |
| occurrences (all) | 87 | 47 | 40 |
| Stomatitis | | | |
| subjects affected / exposed | 38 / 237 (16.03%) | 26 / 115 (22.61%) | 12 / 122 (9.84%) |
| occurrences (all) | 87 | 66 | 21 |
| Dysphagia | | | |
| subjects affected / exposed | 31 / 237 (13.08%) | 15 / 115 (13.04%) | 16 / 122 (13.11%) |
| occurrences (all) | 42 | 20 | 22 |
| Dyspepsia | | | |
| subjects affected / exposed | 28 / 237 (11.81%) | 15 / 115 (13.04%) | 13 / 122 (10.66%) |
| occurrences (all) | 42 | 23 | 19 |
| Abdominal pain | | | |
| subjects affected / exposed | 19 / 237 (8.02%) | 7 / 115 (6.09%) | 12 / 122 (9.84%) |
| occurrences (all) | 30 | 17 | 13 |
| Abdominal pain upper | | | |
| subjects affected / exposed | 15 / 237 (6.33%) | 9 / 115 (7.83%) | 6 / 122 (4.92%) |
| occurrences (all) | 17 | 11 | 6 |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 91 / 237 (38.40%) | 44 / 115 (38.26%) | 47 / 122 (38.52%) |
| occurrences (all) | 243 | 116 | 127 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 51 / 237 (21.52%) | 30 / 115 (26.09%) | 21 / 122 (17.21%) |
| occurrences (all) | 170 | 106 | 64 |
| Dry skin | | | |

| | | | |
|---|-------------------|-------------------|-------------------|
| subjects affected / exposed | 43 / 237 (18.14%) | 20 / 115 (17.39%) | 23 / 122 (18.85%) |
| occurrences (all) | 49 | 23 | 26 |
| Skin fissures | | | |
| subjects affected / exposed | 36 / 237 (15.19%) | 19 / 115 (16.52%) | 17 / 122 (13.93%) |
| occurrences (all) | 74 | 38 | 36 |
| Acne | | | |
| subjects affected / exposed | 21 / 237 (8.86%) | 10 / 115 (8.70%) | 11 / 122 (9.02%) |
| occurrences (all) | 63 | 23 | 40 |
| Alopecia | | | |
| subjects affected / exposed | 20 / 237 (8.44%) | 9 / 115 (7.83%) | 11 / 122 (9.02%) |
| occurrences (all) | 23 | 10 | 13 |
| Erythema | | | |
| subjects affected / exposed | 16 / 237 (6.75%) | 8 / 115 (6.96%) | 8 / 122 (6.56%) |
| occurrences (all) | 18 | 8 | 10 |
| Pruritus | | | |
| subjects affected / exposed | 14 / 237 (5.91%) | 10 / 115 (8.70%) | 4 / 122 (3.28%) |
| occurrences (all) | 22 | 16 | 6 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 16 / 237 (6.75%) | 5 / 115 (4.35%) | 11 / 122 (9.02%) |
| occurrences (all) | 23 | 7 | 16 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 13 / 237 (5.49%) | 6 / 115 (5.22%) | 7 / 122 (5.74%) |
| occurrences (all) | 17 | 9 | 8 |
| Infections and infestations | | | |
| Paronychia | | | |
| subjects affected / exposed | 28 / 237 (11.81%) | 16 / 115 (13.91%) | 12 / 122 (9.84%) |
| occurrences (all) | 55 | 36 | 19 |
| Pneumonia | | | |
| subjects affected / exposed | 25 / 237 (10.55%) | 13 / 115 (11.30%) | 12 / 122 (9.84%) |
| occurrences (all) | 31 | 17 | 14 |
| Urinary tract infection | | | |
| subjects affected / exposed | 13 / 237 (5.49%) | 7 / 115 (6.09%) | 6 / 122 (4.92%) |
| occurrences (all) | 19 | 12 | 7 |
| Bronchitis | | | |

| | | | |
|--|---------------------------|--------------------------|--------------------------|
| subjects affected / exposed occurrences (all) | 12 / 237 (5.06%) 17 | 3 / 115 (2.61%) 3 | 9 / 122 (7.38%) 14 |
| Device related infection subjects affected / exposed occurrences (all) | 12 / 237 (5.06%) 13 | 8 / 115 (6.96%) 8 | 4 / 122 (3.28%) 5 |
| Sepsis subjects affected / exposed occurrences (all) | 12 / 237 (5.06%) 12 | 4 / 115 (3.48%) 4 | 8 / 122 (6.56%) 8 |
| Metabolism and nutrition disorders | | | |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 104 / 237 (43.88%) 327 | 53 / 115 (46.09%) 146 | 51 / 122 (41.80%) 181 |
| Decreased appetite subjects affected / exposed occurrences (all) | 66 / 237 (27.85%) 95 | 36 / 115 (31.30%) 47 | 30 / 122 (24.59%) 48 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 42 / 237 (17.72%) 88 | 20 / 115 (17.39%) 35 | 22 / 122 (18.03%) 53 |
| Dehydration subjects affected / exposed occurrences (all) | 23 / 237 (9.70%) 25 | 10 / 115 (8.70%) 11 | 13 / 122 (10.66%) 14 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 23 / 237 (9.70%) 39 | 10 / 115 (8.70%) 19 | 13 / 122 (10.66%) 20 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 20 / 237 (8.44%) 23 | 11 / 115 (9.57%) 14 | 9 / 122 (7.38%) 9 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 06 February 2015 | Modification to the inclusion criteria such that patients with squamous cell carcinoma of the head and neck could be included irrespective of their EGFR status, rather than restricting inclusion to EGFR-positive patients. In addition, patients' p16 status was removed from the stratification criteria. The EGFR status was added as a subgroup for analysis of secondary endpoints, and an exploration of the effects of both EGFR status and p16 status was added to the sensitivity analyses. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported