



## Clinical trial results:

**Randomized, controlled trial of Platinum-Cetuximab combined either with Docetaxel (TPEx) or with 5FU (Extreme) in patients with recurrent/metastatic squamous cell cancer of the head and neck**

### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-000048-14   |
| Trial protocol           | ES DE            |
| Global end of trial date | 31 December 2021 |

### Results information

|                                   |   |
|-----------------------------------|---|
| Result version number             | v1 (current)  |
| This version publication date     | 19 November 2023  |
| First version publication date    | 19 November 2023  |
| Summary attachment (see zip file) | summary of report (2014-000048-14_Résumé rapport_TPextreme.pdf) |

### Trial information

#### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | TPEXTREME |
|-----------------------|-----------|

#### Additional study identifiers

|                                    |                           |
|------------------------------------|---------------------------|
| ISRCTN number                      | -                         |
| ClinicalTrials.gov id (NCT number) | NCT02268695               |
| WHO universal trial number (UTN)   | -                         |
| Other trial identifiers            | TPExtreme: GORTEC 2014-01 |

Notes:

### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | GORTEC   |
| Sponsor organisation address | 4 Bis Rue Emile Zola, TOURS, France, 37000           |
| Public contact               | Laura Sinigaglia, GORTEC, laura.sinigaglia@gortec.fr |
| Scientific contact           | Pr Joël GUIGAY, GORTEC, joel.guigay@gortec.fr        |

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                       | 20 December 2022 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 31 December 2021 |
| Was the trial ended prematurely?                     | Yes              |

Notes:

## General information about the trial

Main objective of the trial:

to compare in terms of overall survival the TPEx and EXTREME regimens as first line treatment of patients with recurrent / metastatic HN SCC

Protection of trial subjects:

Follow-up of patients according to the protocol calendar, adaptation of treatment or discontinuation of treatment according to toxicities

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 10 October 2014  |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 12 Months        |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Spain: 68   |
| Country: Number of subjects enrolled | France: 409 |
| Country: Number of subjects enrolled | Germany: 64 |
| Worldwide total number of subjects   | 541         |
| EEA total number of subjects         | 541         |

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)                      | 438 |
| From 65 to 84 years                       | 103 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

The study is presented to patients during a standard visit by the investigator. If the patient agrees to participate and meets the eligibility criteria, then they can be included in the trial.

### Pre-assignment

Screening details:

- Histologically confirmed diagnosis squamous cell carcinoma of head and neck: oral cavity, oropharynx, hypopharynx, larynx (histological confirmation is mandatory at least for initial diagnosis).
- Recurrence and/or metastatic disease not suitable for local therapy.
- At least one measurable lesion (RECIST) by CT or MRI.

### Period 1

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

### Arms

|                              |                              |
|------------------------------|------------------------------|
| Are arms mutually exclusive? | Yes                          |
| <b>Arm title</b>             | Standard treatment (EXTREME) |

Arm description:

6 cycles every 3 weeks

- Cisplatin: 100 mg/m<sup>2</sup> iv on Day1
- 5FU: 4000 mg/m<sup>2</sup> total dose starting on day 1 and during 96h in continuous infusion
- Cetuximab: 400 mg/m<sup>2</sup> iv on Day1 (loading dose), then 250 mg/m<sup>2</sup> iv weekly.
- If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m<sup>2</sup>, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor.

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

Dosage and administration details:

100 mg/m<sup>2</sup> iv on Day1

|  |   |
|--|---|
| Investigational medicinal product name | 5-Fluorouracil  |
| Investigational medicinal product code |   |
| Other name                             |   |
| Pharmaceutical forms                   | Concentrate for solution for infusion, Concentrate for solution for injection |
| Routes of administration               | Infusion , Injection  |

Dosage and administration details:

4000 mg/m<sup>2</sup> total dose starting on day 1 and during 96h in continuous infusion

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

Dosage and administration details:

400 mg/m<sup>2</sup> iv on Day1 (loading dose), then 250 mg/m<sup>2</sup> iv weekly.

|                  |                               |
|------------------|-------------------------------|
| <b>Arm title</b> | Experimental treatment (TPEX) |
|------------------|-------------------------------|

Arm description:

- 4 cycles every 3 weeks
- Cisplatin: 75 mg/m<sup>2</sup> iv on Day1
- Docetaxel: 75 mg/m<sup>2</sup> iv on Day1
- Cetuximab: 400 mg/m<sup>2</sup> iv on Day1 (loading dose) then 250 mg/m<sup>2</sup> iv weekly.
- If cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. Primary prophylactic administration of GCSF was administered systematically after each cycle of chemotherapy.

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

Dosage and administration details:

75mg/m<sup>2</sup> iv on Day1

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

Dosage and administration details:

75 mg/m<sup>2</sup> iv on Day1

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

Dosage and administration details:

400 mg/m<sup>2</sup> iv on Day1 (loading dose) then 250 mg/m<sup>2</sup> iv weekly.

| <b>Number of subjects in period 1</b> | Standard treatment (EXTREME) | Experimental treatment (TPEX) |
|---------------------------------------|------------------------------|-------------------------------|
| Started                               | 270                          | 271                           |
| Completed                             | 118                          | 191                           |
| Not completed                         | 152                          | 80                            |
| Adverse event, serious fatal          | 21                           | 10                            |
| Physician decision                    | 4                            | 2                             |
| Consent withdrawn by subject          | 17                           | 6                             |
| Adverse event, non-fatal              | 36                           | 20                            |
| no treatment received                 | 6                            | 8                             |
| other toxicity                        | -                            | 17                            |
| Lost to follow-up                     | 2                            | 1                             |
| missing reason                        | -                            | 1                             |
| Tumor progression                     | 34                           | 13                            |
| other reason                          | 32                           | 2                             |



## Baseline characteristics

### Reporting groups

|                       |                              |
|-----------------------|------------------------------|
| Reporting group title | Standard treatment (EXTREME) |
|-----------------------|------------------------------|

Reporting group description:

6 cycles every 3 weeks

- Cisplatin: 100 mg/m<sup>2</sup> iv on Day1
- 5FU: 4000 mg/m<sup>2</sup> total dose starting on day 1 and during 96h in continuous infusion
- Cetuximab: 400 mg/m<sup>2</sup> iv on Day1 (loading dose), then 250 mg/m<sup>2</sup> iv weekly.
- If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m<sup>2</sup>, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor.

|                       |                               |
|-----------------------|-------------------------------|
| Reporting group title | Experimental treatment (TPEX) |
|-----------------------|-------------------------------|

Reporting group description:

- 4 cycles every 3 weeks
- Cisplatin: 75 mg/m<sup>2</sup> iv on Day1
- Docetaxel: 75 mg/m<sup>2</sup> iv on Day1
- Cetuximab: 400 mg/m<sup>2</sup> iv on Day1 (loading dose) then 250 mg/m<sup>2</sup> iv weekly.
- If cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. Primary prophylactic administration of GCSF was administered systematically after each cycle of chemotherapy.

| Reporting group values         | Standard treatment (EXTREME) | Experimental treatment (TPEX) | Total |
|--------------------------------|------------------------------|-------------------------------|-------|
| Number of subjects             | 270                          | 271                           | 541   |
| Age categorical                |                              |                               |       |
| Age ≥ 18 years and < 71 years. |                              |                               |       |
| Units: Subjects                |                              |                               |       |
| Adults (18-64 years)           | 223                          | 215                           | 438   |
| From 65-71 years               | 47                           | 56                            | 103   |
| Age continuous                 |                              |                               |       |
| Units: years                   |                              |                               |       |
| median                         | 60                           | 60                            |       |
| full range (min-max)           | 23 to 71                     | 38 to 70                      | -     |
| Gender categorical             |                              |                               |       |
| Units: Subjects                |                              |                               |       |
| Female                         | 39                           | 31                            | 70    |
| Male                           | 231                          | 240                           | 471   |

## End points

### End points reporting groups

|   |                               |
|---|-------------------------------|
| Reporting group title   | Standard treatment (EXTREME)  |
| Reporting group description:<br>6 cycles every 3 weeks<br>- Cisplatin: 100 mg/m <sup>2</sup> iv on Day1<br>- 5FU: 4000 mg/m <sup>2</sup> total dose starting on day 1 and during 96h in continuous infusion<br>- Cetuximab: 400 mg/m <sup>2</sup> iv on Day1 (loading dose), then 250 mg/m <sup>2</sup> iv weekly.<br>- If Cisplatin is not tolerated and/or when the total cumulative dose of cisplatin (including prior administration) reaches 600 mg/m <sup>2</sup> , cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. |                               |
| Reporting group title   | Experimental treatment (TPEX) |
| Reporting group description:<br>- 4 cycles every 3 weeks<br>- Cisplatin: 75 mg/m <sup>2</sup> iv on Day1<br>- Docetaxel: 75 mg/m <sup>2</sup> iv on Day1<br>- Cetuximab: 400 mg/m <sup>2</sup> iv on Day1 (loading dose) then 250 mg/m <sup>2</sup> iv weekly.<br>- If cisplatin is not tolerated, cisplatin has to be replaced by carboplatin, AUC 5, except in the case of bleeding tumor. Primary prophylactic administration of GCSF was administered systematically after each cycle of chemotherapy.  |                               |

### Primary: Overall survival

|  |                                 |
|--|---------------------------------|
| End point title  | Overall survival <sup>[1]</sup> |
| End point description:<br>Overall survival (OS): defined as the time to death from any cause measured from randomization. Patients with disease progression may be treated with off protocol therapy but will be followed for overall survival evaluation. |                                 |
| End point type   | Primary                         |
| End point timeframe:<br>At the end of study  |                                 |

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 analysis of efficacy endpoints was done in the Intent to Treat (ITT) population. The toxicity analysis was done in the population of patients who received at least one administration of chemotherapy or cetuximab.

| End point values                 | Standard treatment (EXTREME) | Experimental treatment (TPEX) |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 243                          | 234                           |  |  |
| Units: Survival rate             |                              |                               |  |  |
| number (confidence interval 95%) | 13.4 (12.2 to 15.8)          | 14.5 (12.5 to 15.8)           |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Objective response rate



|   |                         |
|---|-------------------------|
| End point title   | Objective response rate |
| End point description:<br>Objective response rate (complete response (CR) or partial response (PR) according to RECIST 1.1 criteria and assessed by central imaging review) at 12 weeks, by local assessment and by centralized review. |                         |
| End point type  | Secondary               |
| End point timeframe:<br>At the end of trial   |                         |

| End point values                 | Standard treatment (EXTREME) | Experimental treatment (TPEX) |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 270                          | 269                           |  |  |
| Units: Survival rate             |                              |                               |  |  |
| number (confidence interval 95%) | 5.9 (5.3 to 6.3)             | 5.1 (4.6 to 6.6)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Best overall tumor response rate

|   |                                  |
|---|----------------------------------|
| End point title   | Best overall tumor response rate |
| End point description:<br>Best overall tumor response rate (RECIST v.1.1 criteria) during treatment by local assessment |                                  |
| End point type  | Secondary                        |
| End point timeframe:<br>During the treatment  |                                  |

| End point values                 | Standard treatment (EXTREME) | Experimental treatment (TPEX) |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 270                          | 269                           |  |  |
| Units: Survival rate             |                              |                               |  |  |
| number (confidence interval 95%) | 5.9 (5.3 to 6.3)             | 5.1 (4.6 to 6.6)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Progression free survival (PFS)

|                 |                                 |
|-----------------|---------------------------------|
| End point title | Progression free survival (PFS) |
|-----------------|---------------------------------|

End point description:

Progression free survival (PFS): minimum time from randomization to progression as defined by RECIST v. 1.1 criteria or to death from any cause. Patients who did not have any of these events were censored at the date of last follow-up.

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

End point timeframe:

from randomization until progression

| End point values                 | Standard treatment (EXTREME) | Experimental treatment (TPEX) |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 255                          | 248                           |  |  |
| Units: Survival rate             |                              |                               |  |  |
| number (confidence interval 95%) | 6.2 (5.8 to 6.7)             | 6.0 (5.7 to 6.4)              |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Time to Progression (TTP)

|                 |                           |
|-----------------|---------------------------|
| End point title | Time to Progression (TTP) |
|-----------------|---------------------------|

End point description:

Time to Progression (TTP): minimum time from randomization to progression as defined by RECIST v.1.1 criteria. In case of death from other cause than cancer and no prior progression, the patient was censored at the time of death. In case of death related to cancer without an accurate date of progression before death, the patient was considered in progression at the time of death. In the event of no progression and no death, the patient was censored at the date of last follow-up.

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

End point timeframe:

from randomization to progression

| End point values                 | Standard treatment (EXTREME) | Experimental treatment (TPEX) |  |  |
|----------------------------------|------------------------------|-------------------------------|--|--|
| Subject group type               | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed      | 235                          | 232                           |  |  |
| Units: Survival rate             |                              |                               |  |  |
| median (confidence interval 95%) | 6.6 (6.1 to 7.3)             | 6.2 (5.9 to 7.4)              |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Health related quality of life (QoL)**

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|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Health related quality of life (QoL) |
|-----------------|--------------------------------------|

End point description:

Health related quality of life (QoL) assessed by EORTC QLQ-C30. The primary endpoint of the QoL study was the global health status/quality of-life scale of the QLQ-C30 questionnaire.

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

End point timeframe:

During the treatment

---

| End point values                          | Standard treatment (EXTREME) | Experimental treatment (TPEX) |  |  |
|---|------------------------------|-------------------------------|--|--|
| Subject group type                        | Reporting group              | Reporting group               |  |  |
| Number of subjects analysed               | 270                          | 269                           |  |  |
| Units: Survival rate                      |                              |                               |  |  |
| arithmetic mean (confidence interval 95%) | 57 (55 to 60)                | 60 (57 to 63)                 |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were described during chemotherapy and during maintenance

Adverse event reporting additional description:

Any SAE which occurs or comes to the attention of the investigator at any time during the study, since study treatment is started and within 30 days after the last administration of study drugs independent of the circumstances or suspected cause, must be reported immediately, within 24 hours of knowledge (at latest on the next working day).

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 17.1   |

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | EXTREME |
|-----------------------|---------|

Reporting group description: -

|                       |      |
|-----------------------|------|
| Reporting group title | TPEX |
|-----------------------|------|

Reporting group description: -

| Serious adverse events                               | EXTREME            | TPEX               |  |
|--|--------------------|--------------------|--|
| Total subjects affected by serious adverse events    |                    |                    |  |
| subjects affected / exposed                          | 143 / 265 (53.96%) | 118 / 263 (44.87%) |  |
| number of deaths (all causes)                        | 243                | 234                |  |
| number of deaths resulting from adverse events       | 23                 | 16                 |  |
| Blood and lymphatic system disorders                 |                    |                    |  |
| Febrile neutropenia                                  |                    |                    |  |
| subjects affected / exposed                          | 10 / 265 (3.77%)   | 21 / 263 (7.98%)   |  |
| occurrences causally related to treatment / all      | 10 / 10            | 21 / 21            |  |
| deaths causally related to treatment / all           | 6 / 6              | 3 / 3              |  |
| General disorders and administration site conditions |                    |                    |  |
| General physical health deterioration                |                    |                    |  |
| subjects affected / exposed                          | 17 / 265 (6.42%)   | 10 / 263 (3.80%)   |  |
| occurrences causally related to treatment / all      | 17 / 17            | 10 / 10            |  |
| deaths causally related to treatment / all           | 3 / 3              | 2 / 2              |  |
| Allergic reaction                                    |                    |                    |  |
| subjects affected / exposed                          | 10 / 265 (3.77%)   | 5 / 263 (1.90%)    |  |
| occurrences causally related to treatment / all      | 10 / 10            | 5 / 5              |  |
| deaths causally related to treatment / all           | 3 / 3              | 2 / 2              |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Fever   |                  |                 |  |
| subjects affected / exposed                     | 6 / 265 (2.26%)  | 7 / 263 (2.66%) |  |
| occurrences causally related to treatment / all | 6 / 6            | 7 / 7           |  |
| deaths causally related to treatment / all      | 2 / 2            | 1 / 1           |  |
| Fatigue   |                  |                 |  |
| subjects affected / exposed                     | 8 / 265 (3.02%)  | 3 / 263 (1.14%) |  |
| occurrences causally related to treatment / all | 8 / 8            | 3 / 3           |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0           |  |
| Gastrointestinal disorders                      |                  |                 |  |
| Vomiting  |                  |                 |  |
| subjects affected / exposed                     | 20 / 265 (7.55%) | 7 / 263 (2.66%) |  |
| occurrences causally related to treatment / all | 20 / 20          | 7 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Mucositis oral                                  |                  |                 |  |
| subjects affected / exposed                     | 9 / 265 (3.40%)  | 8 / 263 (3.04%) |  |
| occurrences causally related to treatment / all | 9 / 9            | 8 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Nausea  |                  |                 |  |
| subjects affected / exposed                     | 8 / 265 (3.02%)  | 4 / 263 (1.52%) |  |
| occurrences causally related to treatment / all | 8 / 8            | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea                                       |                  |                 |  |
| subjects affected / exposed                     | 4 / 265 (1.51%)  | 8 / 263 (3.04%) |  |
| occurrences causally related to treatment / all | 4 / 4            | 8 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                  |                 |  |
| Dyspnea   |                  |                 |  |
| subjects affected / exposed                     | 2 / 265 (0.75%)  | 7 / 263 (2.66%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 7 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Infections and infestations                     |                  |                 |  |
| Infection (any type)                            |                  |                 |  |

|   |                   |                   |
|---|-------------------|-------------------|
| subjects affected / exposed                     | 41 / 265 (15.47%) | 37 / 263 (14.07%) |
| occurrences causally related to treatment / all | 41 / 41           | 37 / 37           |
| deaths causally related to treatment / all      | 9 / 9             | 8 / 8             |

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

| <b>Non-serious adverse events</b>                     | EXTREME            | TPEX                |  |
|---|--------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                    |                     |  |
| subjects affected / exposed                           | 264 / 265 (99.62%) | 263 / 263 (100.00%) |  |
| Investigations  |                    |                     |  |
| Gamma glutamyl transferase increased                  |                    |                     |  |
| subjects affected / exposed                           | 135 / 265 (50.94%) | 115 / 263 (43.73%)  |  |
| occurrences (all)                                     | 135                | 115                 |  |
| Serum albumine decreased                              |                    |                     |  |
| subjects affected / exposed                           | 133 / 265 (50.19%) | 137 / 263 (52.09%)  |  |
| occurrences (all)                                     | 133                | 137                 |  |
| Alcaline phosphatase increased                        |                    |                     |  |
| subjects affected / exposed                           | 66 / 265 (24.91%)  | 64 / 263 (24.33%)   |  |
| occurrences (all)                                     | 66                 | 64                  |  |
| Alanine aminotransferase increased                    |                    |                     |  |
| subjects affected / exposed                           | 57 / 265 (21.51%)  | 58 / 263 (22.05%)   |  |
| occurrences (all)                                     | 57                 | 58                  |  |
| Aspartate aminotransferase increased                  |                    |                     |  |
| subjects affected / exposed                           | 52 / 265 (19.62%)  | 56 / 263 (21.29%)   |  |
| occurrences (all)                                     | 52                 | 56                  |  |
| Creatinine renal clearance increased                  |                    |                     |  |
| subjects affected / exposed                           | 115 / 265 (43.40%) | 64 / 263 (24.33%)   |  |
| occurrences (all)                                     | 115                | 64                  |  |
| Blood and lymphatic system disorders                  |                    |                     |  |
| Anemia  |                    |                     |  |
| subjects affected / exposed                           | 214 / 265 (80.75%) | 201 / 263 (76.43%)  |  |
| occurrences (all)                                     | 214                | 201                 |  |
| Neutropenia   |                    |                     |  |

|   |                           |                           |  |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 121 / 265 (45.66%)<br>121 | 67 / 263 (25.48%)<br>67   |  |
| Leucopenia<br>subjects affected / exposed<br>occurrences (all)                            | 148 / 265 (55.85%)<br>148 | 96 / 263 (36.50%)<br>96   |  |
| Febrile leucopenia<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 265 (3.02%)<br>8      | 15 / 263 (5.70%)<br>15    |  |
| Trombocytopenia<br>subjects affected / exposed<br>occurrences (all)                       | 148 / 265 (55.85%)<br>148 | 96 / 263 (36.50%)<br>96   |  |
| General disorders and administration<br>site conditions                                   |                           |                           |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)                               | 194 / 265 (73.21%)<br>194 | 178 / 263 (67.68%)<br>178 |  |
| Fever<br>subjects affected / exposed<br>occurrences (all)                                 | 31 / 265 (11.70%)<br>31   | 30 / 263 (11.41%)<br>30   |  |
| General physical health deterioration<br>subjects affected / exposed<br>occurrences (all) | 19 / 265 (7.17%)<br>19    | 11 / 263 (4.18%)<br>11    |  |
| Allergic reaction<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 265 (0.38%)<br>1      | 9 / 263 (3.42%)<br>9      |  |
| Ear and labyrinth disorders   |                           |                           |  |
| Tinnitus<br>subjects affected / exposed<br>occurrences (all)                              | 33 / 265 (12.45%)<br>33   | 14 / 263 (5.32%)<br>14    |  |
| Hearing impairment or hypoacusia<br>subjects affected / exposed<br>occurrences (all)      | 30 / 265 (11.32%)<br>30   | 10 / 263 (3.80%)<br>10    |  |
| Gastrointestinal disorders  |                           |                           |  |
| Mucositis oral<br>subjects affected / exposed<br>occurrences (all)                        | 152 / 265 (57.36%)<br>152 | 118 / 263 (44.87%)<br>118 |  |
| Nausea  |                           |                           |  |

|   |                           |                           |  |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 173 / 265 (65.28%)<br>173 | 135 / 263 (51.33%)<br>135 |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 116 / 265 (43.77%)<br>116 | 83 / 263 (31.56%)<br>83   |  |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 93 / 265 (35.09%)<br>93   | 116 / 263 (44.11%)<br>116 |  |
| Constipation<br>subjects affected / exposed<br>occurrences (all)  | 76 / 265 (28.68%)<br>76   | 61 / 263 (23.19%)<br>61   |  |
| Dysphagia<br>subjects affected / exposed<br>occurrences (all)   | 48 / 265 (18.11%)<br>48   | 33 / 263 (12.55%)<br>33   |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all) | 30 / 265 (11.32%)<br>30   | 21 / 263 (7.98%)<br>21    |  |
| Skin and subcutaneous tissue disorders<br>Rash acneiform<br>subjects affected / exposed<br>occurrences (all)    | 166 / 265 (62.64%)<br>166 | 167 / 263 (63.50%)<br>167 |  |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)  | 72 / 265 (27.17%)<br>72   | 74 / 263 (28.14%)<br>74   |  |
| Palmar-plantar erythrodysesthesia syndrome<br>subjects affected / exposed<br>occurrences (all)                  | 36 / 265 (13.58%)<br>36   | 28 / 263 (10.65%)<br>28   |  |
| Alopecia<br>subjects affected / exposed<br>occurrences (all)  | 31 / 265 (11.70%)<br>31   | 59 / 263 (22.43%)<br>59   |  |
| Infections and infestations<br>Infection any type<br>subjects affected / exposed<br>occurrences (all)           | 72 / 265 (27.17%)<br>72   | 77 / 263 (29.28%)<br>77   |  |
| Metabolism and nutrition disorders  |                           |                           |  |



|  |                           |                           |
|--|---------------------------|---------------------------|
| Magnesium metabolism disorder<br>subjects affected / exposed<br>occurrences (all)  | 161 / 265 (60.75%)<br>161 | 147 / 263 (55.89%)<br>147 |
| Potassium disorders<br>subjects affected / exposed<br>occurrences (all)            | 162 / 265 (61.13%)<br>162 | 129 / 263 (49.05%)<br>129 |
| Calcium disorders<br>subjects affected / exposed<br>occurrences (all)              | 144 / 265 (54.34%)<br>144 | 145 / 263 (55.13%)<br>145 |
| Sodium disorders<br>subjects affected / exposed<br>occurrences (all)               | 139 / 265 (52.45%)<br>139 | 125 / 263 (47.53%)<br>125 |
| Phosphorus metabolism disorder<br>subjects affected / exposed<br>occurrences (all) | 137 / 265 (51.70%)<br>137 | 127 / 263 (48.29%)<br>127 |
| Hyperglycaemia<br>subjects affected / exposed<br>occurrences (all)                 | 61 / 265 (23.02%)<br>61   | 48 / 263 (18.25%)<br>48   |
| Anorexia<br>subjects affected / exposed<br>occurrences (all)                       | 84 / 265 (31.70%)<br>84   | 86 / 263 (32.70%)<br>86   |
| Weight loss<br>subjects affected / exposed<br>occurrences (all)                    | 58 / 265 (21.89%)<br>58   | 52 / 263 (19.77%)<br>52   |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 08 August 2014  | <ul style="list-style-type: none"><li>- Change of principal investigator</li><li>- Addition of further investigational sites in France</li></ul>  |
| 14 January 2015 | <ul style="list-style-type: none"><li>- Addition of an exclusion criterion concerning concomitant malignancies</li><li>- Addition of details concerning the commercially availability of the study treatments, premedications, concomitant treatments, and GCSF</li><li>- Adjustment of the General Guidelines for the cetuximab administration both during chemotherapy and maintenance</li><li>- Addition of details concerning the cisplatin administration both in the EXTREME arm and in the TPEx arm</li><li>- Addition of details concerning the 5FUand docetaxel administration</li><li>- Addition of details concerning the assessments to be performed during the study</li><li>- Addition of details concerning the QoL assessments to be performed during the study follow-up if a patient was withdrawn from study treatment</li><li>- Addition of details concerning the QoL assessments to be performed during the study follow-up if a patient was withdrawn from study treatment</li><li>- Clarification on the definition of the G1 hypercreatinemia according to the NCI CTCAE V4.03 and on the actions to be taken concerning the chemotherapy administration</li></ul> |
| 09 June 2015    | <ul style="list-style-type: none"><li>- Modification of the Exclusion Criterion concerning the concomitant radiotherapy within 6 weeks before study entry</li><li>- Addition of two Exclusion Criteria</li><li>- Addition in the section 2.2 of details concerning the EMR 62202-008 phase I/II study and EXTREME study on standard treatment in recurrent and/or metastatic HNSCC.</li><li>- Clarification on the use of carboplatin (as part of the EXTREME regimen) for patients not able to receive cisplatin.</li><li>- Clarifications on the medical, financial, or ethical reasons for study discontinuation</li><li>- Addition of note in the Flow-Chart clarifying the coagulation tests to be done(Prothrombin time, INR, and aPTT).</li><li>- Clarification that deaths caused by disease progression more than 30 days after the end ofstudy treatment were not considered as SAEs and were excluded from expedited reporting.</li><li>-Update of the bibliographic references.</li></ul>   |
| 17 January 2017 | <ul style="list-style-type: none"><li>- Addition of a statistical analysis of futility.</li><li>-Addition of further 124 patients to be included in the study in order to increase the powerof study from 80% to 88% as consequence of the addition of a statistical analysis of futility</li></ul>   |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|------|--------------|--------------|
|------|--------------|--------------|

|                  |   |   |
|------------------|---|---|
| 31 December 2021 | <p>The sponsor has decided to set the LPLV at 31/12/2021 and to censor the last patients still undergoing treatment on this date.</p> <p>Indeed, the protocol provided for a maintenance period continuing until toxicity or progression. Also, 5 patients were still being treated at this date, making it impossible to perform the final analysis of this trial. The management of these patients continues according to a standard protocol. They will therefore be considered as "long survivors" for this analysis. In addition, the last patient was included in the trial on 13/11/2017, the chosen LPLV therefore ensures a sufficiently long follow-up period, i.e. 4 years. post last inclusion. Furthermore, during this decision, the sponsor was aware that more than 80% of the patients included in the trial had died.</p> <p>The vital status of all patients will be collected on 31/12/2021</p> | - |
|------------------|---|---|

Notes:

## Limitations and caveats

None reported