



Clinical trial results:

A Randomized Phase II Multicenter, Open-label Study Evaluating the Efficacy and Safety of IMAB362 in Combination with the EOX (Epirubicin, Oxaliplatin, Capecitabine) Regimen as First-line Treatment of Patients with CLDN18.2-positive Advanced Adenocarcinomas of the Stomach, the Esophagus or the Gastroesophageal Junction (FAST)

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2011-005285-38 |
| Trial protocol | DE CZ LV BG |
| Global end of trial date | 31 January 2019 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 04 January 2020 |
| First version publication date | 04 January 2020 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | GM-IMAB-001-03 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01630083 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Acronym: FAST, Other study number: 8951-CL-0202 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Astellas Pharma Global Development, Inc. |
| Sponsor organisation address | 1 Astellas Way, Northbrook, IL, United States, 60062 |
| Public contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.com |
| Scientific contact | Clinical Trial Disclosure, Astellas Pharma Global Development, Inc., astellas.resultsdisclosure@astellas.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 | 31 January 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 January 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the efficacy of zolbetuximab in combination with EOX as determined by progression-free survival (PFS) and to determine the safety and tolerability of zolbetuximab in combination with EOX.

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy: -

Evidence for comparator: -

| | |
|---|--------------|
| Actual start date of recruitment | 19 July 2012 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| 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 | Bulgaria: 18 |
| Country: Number of subjects enrolled | Czech Republic: 4 |
| Country: Number of subjects enrolled | Germany: 23 |
| Country: Number of subjects enrolled | Latvia: 25 |
| Country: Number of subjects enrolled | Russian Federation: 105 |
| Country: Number of subjects enrolled | Ukraine: 77 |
| Worldwide total number of subjects | 252 |
| EEA total number of subjects | 70 |

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) | 199 |
| From 65 to 84 years | 53 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Male & female participants with CLDN18.2-positive advanced adenocarcinomas of the stomach, esophagus or gastroesophageal junction were enrolled in this multinational, multicenter study. Participants who had a tumor with 2+ or 3+ CLDN18.2 staining intensity in at least 40% of the tumor cells based on immunohistochemical testing were eligible.

Pre-assignment

Screening details:

Participants were randomized in two arms in a 1:1 ratio which was later adjusted to 1:1:7 to allow recruitment in Arm 3 which was added at a later date, to catch up with arms 1 & 2. Randomization was later adjusted to 1:1:1 and stratified by CLDN18.2 positivity and presence of nonmeasurable vs measurable disease at baseline.

Pre-assignment period milestones

| | |
|--|--------------------|
| Number of subjects started | 730 ^[1] |
| Intermediate milestone: Number of subjects | Screen failed: 478 |
| Number of subjects completed | 252 |

Pre-assignment subject non-completion reasons

| | |
|----------------------------|--|
| Reason: Number of subjects | Claudin-18 splice variant 2 (CLDN18.2) negative: 352 |
| Reason: Number of subjects | CLDN18.2 positive but other criteria not fulfilled: 82 |
| Reason: Number of subjects | CLDN18.2 not assessable: 44 |

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number includes all randomized participants, the pre-assignment period includes participants in the screening period.

Period 1

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

Arms

| | |
|------------------------------|---------------|
| Are arms mutually exclusive? | Yes |
| Arm title | EOX Treatment |

Arm description:

Participants received up to 8 cycles of epirubicin, oxaliplatin and capecitabine (EOX) chemotherapy treatment alone (50 mg/m² epirubicin intravenously on day 1 of each cycle, 130 mg/m² oxaliplatin intravenously on day 1 of each cycle, 625 mg/m² capecitabine orally twice daily on days 1 to 21 of each cycle). The first dose of capecitabine taken in the evening of day 1.

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

Dosage and administration details:

Epirubicin was administered at a dose of 50 mg/m² as a 15-minute intravenous infusion on day 1 of each cycle.

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

Dosage and administration details:

The daily dose of capecitabine was 1250 mg/m². Capecitabine tablets were given once daily at a dose of 625 mg/m² orally in the evening of day 1 of each cycle and twice daily at a dose of 625 mg/m² orally on days 2 to 21 of each cycle; the morning dose of capecitabine on day 1 of each cycle was omitted due to administration of zolbetuximab, epirubicin and oxaliplatin.

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

Dosage and administration details:

Oxaliplatin was administered at a dose of 130 mg/m² as a 2-hour intravenous infusion on day 1 of each cycle.

| | |
|------------------|--|
| Arm title | EOX+zolbetuximab 800/600 mg/m ² |
|------------------|--|

Arm description:

Participants received up to 8 cycles of EOX chemotherapy treatment in combination with zolbetuximab administered as loading dose of 800 mg/m² intravenously on day 1 of cycle 1 followed by 600 mg/m² intravenously on day 1 of each subsequent cycle. Zolbetuximab was administered prior to EOX chemotherapy. After completion of the EOX treatment phase, participants were permitted to continue zolbetuximab monotherapy (600 mg/m² every 3 weeks administered intravenously as a 2-hour infusion) until progressive disease (PD), withdrawal of consent or unacceptable toxicity. PD per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study, an absolute increase of at least 5mm must also be demonstrated, unequivocal progression of existing non-target lesions and appearance of one or more new lesions was considered progression.

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

Dosage and administration details:

Epirubicin was administered at a dose of 50 mg/m² as a 15-minute intravenous infusion on day 1 of each cycle.

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

Dosage and administration details:

The daily dose of capecitabine was 1250 mg/m². Capecitabine tablets were given once daily at a dose of 625 mg/m² orally in the evening of day 1 of each cycle and twice daily at a dose of 625 mg/m² orally on days 2 to 21 of each cycle; the morning dose of capecitabine on day 1 of each cycle was omitted due to administration of zolbetuximab, epirubicin and oxaliplatin.

| | |
|--|--|
| Investigational medicinal product name | zolbetuximab |
| Investigational medicinal product code | IMAB362 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Two different formats of zolbetuximab, comprising different strengths, were provided. Vials contained 22

mg or 105 mg of zolbetuximab. Prior to administration, zolbetuximab was reconstituted with 1.1 mL (22 mg zolbetuximab vials) or 5.0 mL (105 mg zolbetuximab vials) water for injection, which resulted in a concentration of 20 mg/mL zolbetuximab. The extractable volume per vial was 1 mL (for 22 mg zolbetuximab vials) or 5 mL (for 105 mg zolbetuximab vials). The reconstituted solution was further diluted with sodium chloride 0.9% to a final concentration of 2 mg/mL zolbetuximab. Zolbetuximab was administered as an intravenous infusion over 2 to 3 hours.

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

Dosage and administration details:

Oxaliplatin was administered at a dose of 130 mg/m² as a 2-hour intravenous infusion on day 1 of each cycle.

| | |
|------------------|---|
| Arm title | EOX+zolbetuximab 1000 mg/m ² |
|------------------|---|

Arm description:

Participants received up to 8 cycles of EOX chemotherapy treatment in combination with zolbetuximab 1000 mg/m² intravenously on day 1 of each cycle. Zolbetuximab was administered prior to EOX chemotherapy. After completion of the EOX treatment phase, participants were permitted to continue zolbetuximab monotherapy (1000 mg/m² every 3 weeks administered intravenously as a 2-hour infusion) until PD, withdrawal of consent or unacceptable toxicity.

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

Dosage and administration details:

Epirubicin was administered at a dose of 50 mg/m² as a 15-minute intravenous infusion on day 1 of each cycle.

| | |
|--|--|
| Investigational medicinal product name | zolbetuximab |
| Investigational medicinal product code | IMAB362 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for concentrate for solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Two different formats of zolbetuximab, comprising different strengths, were provided. Vials contained 22 mg or 105 mg of zolbetuximab. Prior to administration, zolbetuximab was reconstituted with 1.1 mL (22 mg zolbetuximab vials) or 5.0 mL (105 mg zolbetuximab vials) water for injection, which resulted in a concentration of 20 mg/mL zolbetuximab. The extractable volume per vial was 1 mL (for 22 mg zolbetuximab vials) or 5 mL (for 105 mg zolbetuximab vials). The reconstituted solution was further diluted with sodium chloride 0.9% to a final concentration of 2 mg/mL zolbetuximab. Zolbetuximab was administered as an intravenous infusion over 2 to 3 hours.

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

Dosage and administration details:

The daily dose of capecitabine was 1250 mg/m². Capecitabine tablets were given once daily at a dose of 625 mg/m² orally in the evening of day 1 of each cycle and twice daily at a dose of 625 mg/m² orally on days 2 to 21 of each cycle; the morning dose of capecitabine on day 1 of each cycle was omitted due to administration of zolbetuximab, epirubicin and oxaliplatin.

| | |
|--|-----------------------|
| Investigational medicinal product name | oxaliplatin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Solution for infusion |

| | |
|--------------------------|-----------------|
| Routes of administration | Intravenous use |
|--------------------------|-----------------|

Dosage and administration details:

Oxaliplatin was administered at a dose of 130 mg/m² as a 2-hour intravenous infusion on day 1 of each cycle.

| Number of subjects in period 1 | EOX Treatment | EOX+zolbetuximab 800/600 mg/m ² | EOX+zolbetuximab 1000 mg/m ² |
|--|------------------|---|--|
| Started | 85 | 79 | 88 |
| Treated | 84 | 77 | 85 |
| Discontinued within 8 cycles | 52 | 42 | 45 |
| Continued zolbetuximab monotherapy | 0 ^[2] | 32 ^[3] | 27 ^[4] |
| Completed | 32 | 34 | 38 |
| Not completed | 53 | 45 | 50 |
| Clinical progression | 8 | 1 | 2 |
| Adverse event (AE)/Serious Adverse Event (SAE) | 3 | 4 | 3 |
| EOX not completed cont. zolbetuximab | - | 1 | 2 |
| Randomized but not treated | 1 | 2 | 3 |
| Significant protocol violation | 2 | - | 1 |
| Miscellaneous | 4 | 4 | 1 |
| Withdrawal of consent | 8 | 10 | 11 |
| Confirmed progression per RECIST v1.1 | 21 | 19 | 21 |
| Lost to follow-up | - | 1 | - |
| Change in patient's condition | 6 | 3 | 6 |

Notes:

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: No participants in Arm 1 continued on to receive zolbetuximab as a single-agent maintenance treatment after the EOX phase.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A total of 32 participants in Arm 2 continued to receive zolbetuximab as a single-agent maintenance treatment after the EOX phase.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A total of 27 participants in Arm 3 continued to receive zolbetuximab as a single-agent maintenance treatment after the EOX phase.

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | EOX Treatment |
| Reporting group description: | |
| Participants received up to 8 cycles of epirubicin, oxaliplatin and capecitabine (EOX) chemotherapy treatment alone (50 mg/m ² epirubicin intravenously on day 1 of each cycle, 130 mg/m ² oxaliplatin intravenously on day 1 of each cycle, 625 mg/m ² capecitabine orally twice daily on days 1 to 21 of each cycle). The first dose of capecitabine taken in the evening of day 1. | |
| Reporting group title | EOX+zolbetuximab 800/600 mg/m ² |
| Reporting group description: | |
| Participants received up to 8 cycles of EOX chemotherapy treatment in combination with zolbetuximab administered as loading dose of 800 mg/m ² intravenously on day 1 of cycle 1 followed by 600 mg/m ² intravenously on day 1 of each subsequent cycle. Zolbetuximab was administered prior to EOX chemotherapy. After completion of the EOX treatment phase, participants were permitted to continue zolbetuximab monotherapy (600 mg/m ² every 3 weeks administered intravenously as a 2-hour infusion) until progressive disease (PD), withdrawal of consent or unacceptable toxicity. PD per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study, an absolute increase of at least 5mm must also be demonstrated, unequivocal progression of existing non-target lesions and appearance of one or more new lesions was considered progression. | |
| Reporting group title | EOX+zolbetuximab 1000 mg/m ² |
| Reporting group description: | |
| Participants received up to 8 cycles of EOX chemotherapy treatment in combination with zolbetuximab 1000 mg/m ² intravenously on day 1 of each cycle. Zolbetuximab was administered prior to EOX chemotherapy. After completion of the EOX treatment phase, participants were permitted to continue zolbetuximab monotherapy (1000 mg/m ² every 3 weeks administered intravenously as a 2-hour infusion) until PD, withdrawal of consent or unacceptable toxicity. | |

| Reporting group values | EOX Treatment | EOX+zolbetuximab 800/600 mg/m ² | EOX+zolbetuximab 1000 mg/m ² |
|--|---------------|--|---|
| Number of subjects | 85 | 79 | 88 |
| Age categorical Units: Subjects | | | |
| Age continuous | | | |
| The baseline characteristics consisted of the all randomized population. | | | |
| Units: years | | | |
| arithmetic mean | 55.9 | 56.8 | 57.4 |
| standard deviation | ± 10.5 | ± 11.8 | ± 9.8 |
| Gender categorical Units: Subjects | | | |
| M | 57 | 48 | 59 |
| F | 28 | 31 | 29 |
| Location of Tumor at First Diagnosis Units: Subjects | | | |
| ESOPHAGUS | 4 | 2 | 0 |
| GASTROESOPHAGEAL JUNCTION | 12 | 14 | 8 |
| STOMACH | 69 | 63 | 80 |
| Measurable Disease Units: Subjects | | | |
| MEASURABLE | 67 | 66 | 61 |
| NON-MEASURABLE | 18 | 13 | 27 |

| | | | |
|-------------------------------------|-------|--------|--------|
| Race | | | |
| Units: Subjects | | | |
| WHITE | 81 | 75 | 86 |
| OTHER | 4 | 4 | 2 |
| Result of CLDN18.2 IHC Test | | | |
| Units: Subjects | | | |
| 2+ | 35 | 26 | 43 |
| 3+ | 50 | 53 | 45 |
| Time since First Diagnosis (months) | | | |
| Units: Year | | | |
| arithmetic mean | 4.3 | 8.2 | 6.4 |
| standard deviation | ± 6.4 | ± 16.3 | ± 11.8 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 252 | | |
| Age categorical | | | |
| Units: Subjects | | | |

| | | | |
|--|-----|--|--|
| Age continuous | | | |
| The baseline characteristics consisted of the all randomized population. | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| M | 164 | | |
| F | 88 | | |
| Location of Tumor at First Diagnosis | | | |
| Units: Subjects | | | |
| ESOPHAGUS | 6 | | |
| GASTROESOPHAGEAL JUNCTION | 34 | | |
| STOMACH | 212 | | |
| Measurable Disease | | | |
| Units: Subjects | | | |
| MEASURABLE | 194 | | |
| NON-MEASURABLE | 58 | | |
| Race | | | |
| Units: Subjects | | | |
| WHITE | 242 | | |
| OTHER | 10 | | |
| Result of CLDN18.2 IHC Test | | | |
| Units: Subjects | | | |
| 2+ | 104 | | |
| 3+ | 148 | | |
| Time since First Diagnosis (months) | | | |
| Units: Year | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | EOX Treatment |
| Reporting group description: Participants received up to 8 cycles of epirubicin, oxaliplatin and capecitabine (EOX) chemotherapy treatment alone (50 mg/m ² epirubicin intravenously on day 1 of each cycle, 130 mg/m ² oxaliplatin intravenously on day 1 of each cycle, 625 mg/m ² capecitabine orally twice daily on days 1 to 21 of each cycle). The first dose of capecitabine taken in the evening of day 1. | |
| Reporting group title | EOX+zolbetuximab 800/600 mg/m ² |
| Reporting group description: Participants received up to 8 cycles of EOX chemotherapy treatment in combination with zolbetuximab administered as loading dose of 800 mg/m ² intravenously on day 1 of cycle 1 followed by 600 mg/m ² intravenously on day 1 of each subsequent cycle. Zolbetuximab was administered prior to EOX chemotherapy. After completion of the EOX treatment phase, participants were permitted to continue zolbetuximab monotherapy (600 mg/m ² every 3 weeks administered intravenously as a 2-hour infusion) until progressive disease (PD), withdrawal of consent or unacceptable toxicity. PD per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 was defined as at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum on study, an absolute increase of at least 5mm must also be demonstrated, unequivocal progression of existing non-target lesions and appearance of one or more new lesions was considered progression. | |
| Reporting group title | EOX+zolbetuximab 1000 mg/m ² |
| Reporting group description: Participants received up to 8 cycles of EOX chemotherapy treatment in combination with zolbetuximab 1000 mg/m ² intravenously on day 1 of each cycle. Zolbetuximab was administered prior to EOX chemotherapy. After completion of the EOX treatment phase, participants were permitted to continue zolbetuximab monotherapy (1000 mg/m ² every 3 weeks administered intravenously as a 2-hour infusion) until PD, withdrawal of consent or unacceptable toxicity. | |

Primary: Progression-free Survival (PFS)

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|---|---------------------------------|
| End point title | Progression-free Survival (PFS) |
| End point description: PFS was defined as the time from randomization to the first observation of disease progression (based on central reading) or death from any cause (as assessed by the independent reviewer). Participants without documented progression or death were censored as of the last tumor evaluation determining lack of progression. The analysis population consisted of the full analysis set (FAS) which consisted of all participants who were randomized and received at least 1 dose of any study medication. | |
| End point type | Primary |
| End point timeframe: From randomization to the data cut-off date of 31JAN2019; maximum time on follow-up was, 68.2, 47.2 & 59.6 months in the EOX, EOX+Zolbetuximab 600 mg, and EOX+Zolbetuximab 1000 mg treatment groups respectively. | |

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|----------------------------------|------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.3 (4.1 to 7.1) | 7.5 (5.6 to 11.3) | 7.1 (5.6 to 8.0) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | PFS Treatment Comparison (Arm 1 versus Arm 2) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 800/600 mg/m ² |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | < 0.0005 ^[2] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.67 |

Notes:

[1] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[2] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|---|---|
| Statistical analysis title | PFS Treatment Comparison (Arm 1 versus Arm 3) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[3] |
| P-value | = 0.0114 ^[4] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.58 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 0.85 |

Notes:

[3] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[4] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|-----------------------------------|---|
| Statistical analysis title | PFS Treatment Comparison (Arm 3 versus Arm 2) |
| Comparison groups | EOX+zolbetuximab 800/600 mg/m ² v EOX+zolbetuximab |

| | |
|---|----------------------------|
| | 1000 mg/m ² |
| Number of subjects included in analysis | 162 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[5] |
| P-value | = 0.2842 ^[6] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.18 |

Notes:

[5] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[6] - The analyses were performed using a 2-sided test at the 5% significance level for the comparison of Arm 3 vs Arm 2.

Primary: Number of Participants with Adverse Events (AEs)

| | |
|-----------------|---|
| End point title | Number of Participants with Adverse Events (AEs) ^[7] |
|-----------------|---|

End point description:

An AE was defined as any unintended or undesirable, noxious or pathological change, compared to pre-existing conditions, experienced by a participant during a clinical study or the follow-up period, regardless of relationship to study medication. Treatment-emergent adverse event (TEAE) were those AEs that started or worsened after the first dose of study medication. The analysis population consisted of the safety analysis set (SAF) which consisted of all participants who received at least 1 dose of any study medication.

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

End point timeframe:

From the first dose of study drug administration up to 30 days after the last study medication administration (up to 1791 days).

Notes:

[7] - 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: Statistical analyses not applicable, only descriptive statistics data applicable for this endpoint.

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|--|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: participants | | | | |
| Any TEAE | 84 | 74 | 85 | |
| Grade ≥ 3 TEAEs | 54 | 54 | 58 | |
| Serious TEAEs | 27 | 19 | 17 | |
| Study drug-related TEAEs | 80 | 74 | 83 | |
| Study drug-related TEAEs - zolbetuximab | 0 | 64 | 73 | |
| Study drug-related TEAEs - epirubicin | 76 | 70 | 77 | |
| Study drug-related TEAEs - oxaliplatin | 76 | 71 | 74 | |
| Study drug-related TEAEs - capecitabine | 78 | 70 | 75 | |
| Study drug-related serious TEAEs | 5 | 8 | 5 | |

| | | | | |
|---|----|----|----|--|
| Study drug-related serious TEAEs - zolbetuximab | 0 | 1 | 0 | |
| Study drug-related serious TEAEs - epirubicin | 4 | 6 | 3 | |
| Study drug-related serious TEAEs - oxaliplatin | 4 | 7 | 3 | |
| Study drug-related serious TEAEs - capecitabine | 5 | 8 | 5 | |
| TEAEs leading to withdrawal of zolbetuximab | 0 | 10 | 11 | |
| Fatal TEAEs | 15 | 8 | 9 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical PFS

| | |
|-----------------|--------------|
| End point title | Clinical PFS |
|-----------------|--------------|

End point description:

Clinical PFS (CPFS) was defined as the time from randomization to the first observation of disease progression, either confirmed by CT scans or by clinical evaluation, or death from any cause (as assessed by the independent reviewer with clinical PD considered as an event). Participants without documented progression or death were censored as of the last tumor evaluation determining lack of progression. The analysis population consisted of the FAS.

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

End point timeframe:

From randomization to the data cut-off date of 31JAN2019; maximum time on follow-up was, 68.2, 47.2 & 59.6 months in the EOX, EOX+Zolbetuximab 600 mg, and EOX+Zolbetuximab 1000 mg treatment groups respectively.

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|----------------------------------|------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: months | | | | |
| median (confidence interval 95%) | 4.6 (4.0 to 7.1) | 7.5 (5.6 to 11.3) | 7.1 (5.6 to 8.0) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | CPFS Treatment Comparison (Arm 1 versus Arm 2) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 800/600 mg/m ² |

| | |
|---|----------------------------|
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[8] |
| P-value | < 0.0005 ^[9] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.43 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 0.65 |

Notes:

[8] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs

≥ 70%.

[9] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|---|---|
| Statistical analysis title | CPFS Treatment Comparison (Arm 1 versus Arm 3) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[10] |
| P-value | = 0.0085 ^[11] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.38 |
| upper limit | 0.83 |

Notes:

[10] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs

≥ 70%.

[11] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|---|--|
| Statistical analysis title | CPFS Treatment Comparison (Arm 3 versus Arm 2) |
| Comparison groups | EOX+zolbetuximab 800/600 mg/m ² v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 162 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.2904 ^[12] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.5 |
| upper limit | 1.18 |

Notes:

[12] - The analyses were performed using a 2-sided test at the 5% significance level for the comparison of Arm 3 vs Arm 2.

Secondary: Overall Survival Rate at 12 Months

| | |
|-----------------|------------------------------------|
| End point title | Overall Survival Rate at 12 Months |
|-----------------|------------------------------------|

End point description:

Overall survival rate at 12 months after therapy initiation was defined as a proportion of participants alive after 12 months from first dose of any study drug. The analysis population consisted of the FAS.

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

End point timeframe:

Up to 12 months

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|-----------------------------------|------------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 27.4 (18.2 to 37.4) | 52.9 (40.8 to 63.6) | 37.4 (27.0 to 47.8) | |

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 randomization to death from any cause or last contact (if alive). The analysis population consisted of the FAS.

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

End point timeframe:

From randomization to the data cut-off date of 31JAN2019; maximum time on follow-up was, 68.2, 47.2 & 59.6 months in the EOX, EOX+Zolbetuximab 600 mg, and EOX+Zolbetuximab 1000 mg treatment groups respectively.

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|----------------------------------|----------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.3 (6.9 to 10.2) | 13.0 (9.7 to 18.7) | 9.6 (8.3 to 11.4) | |

Statistical analyses

| Statistical analysis title | OS Treatment Comparison (Arm 1 versus Arm 2) |
|---|--|
| Comparison groups | EOX Treatment v EOX+zolbetuximab 800/600 mg/m ² |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[13] |
| P-value | < 0.0005 ^[14] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.55 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 0.77 |

Notes:

[13] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[14] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| Statistical analysis title | OS Treatment Comparison (Arm 1 versus Arm) |
|---|---|
| Comparison groups | EOX Treatment v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[15] |
| P-value | = 0.1292 ^[16] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.75 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.55 |
| upper limit | 1.04 |

Notes:

[15] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs

≥ 70%.

[16] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|---|--|
| Statistical analysis title | OS Treatment Comparison (Arm 3 versus Arm 2) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 800/600 mg/m ² |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[17] |
| P-value | = 0.128 ^[18] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.73 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.52 |
| upper limit | 1.02 |

Notes:

[17] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[18] - The analyses were performed using a 2-sided test at the 5% significance level for the comparison of Arm 3 vs Arm 2.

Secondary: Time to Progression (TTP)

| | |
|--|---------------------------|
| End point title | Time to Progression (TTP) |
| End point description: | |
| TTP was defined as the time from randomization to the first observation of disease progression (based on central reading as assessed by the investigator reviewer). Participants without documented progression were censored as of the last tumor evaluation determining lack of progression. The analysis population consisted of the FAS. | |
| End point type | Secondary |

End point timeframe:

From randomization to the data cut-off date of 31JAN2019; maximum time on follow-up was, 68.2, 47.2 & 59.6 months in the EOX, EOX+Zolbetuximab 600 mg, and EOX+Zolbetuximab 1000 mg treatment groups respectively.

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|----------------------------------|------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: months | | | | |
| median (confidence interval 95%) | 7.0 (5.7 to 7.7) | 9.0 (6.1 to 11.6) | 6.9 (5.6 to 8.4) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | TTP Treatment Comparison (Arm 1 versus Arm 2) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 800/600 mg/m ² |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[19] |
| P-value | = 0.0076 ^[20] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.54 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 0.83 |

Notes:

[19] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[20] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|---|--|
| Statistical analysis title | TTP Treatment Comparison (Arm 3 versus Arm 2) |
| Comparison groups | EOX+zolbetuximab 800/600 mg/m ² v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 162 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[21] |
| P-value | = 0.0997 ^[22] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.71 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.47 |
| upper limit | 1.06 |

Notes:

[21] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[22] - The analyses were performed using a 2-sided test at the 5% significance level for the comparison of Arm 3 vs Arm 2.

| | |
|---|---|
| Statistical analysis title | TTP Treatment Comparison (Arm 1 versus Arm 3) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[23] |
| P-value | = 0.183 ^[24] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.77 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.51 |
| upper limit | 1.15 |

Notes:

[23] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[24] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

Secondary: Objective Tumor Response Rate (ORR)

| | |
|-----------------|-------------------------------------|
| End point title | Objective Tumor Response Rate (ORR) |
|-----------------|-------------------------------------|

End point description:

ORR was defined as the fraction of participants with a complete response (CR) or partial response (PR), according to RECIST v1.1 (as assessed by the investigator reviewer). CR according to RECIST v1.1 was defined as the disappearance of all target lesions, any pathological lymph node must have had reduction in short axis to < 10 mm, disappearance of all non-target lesions and normalization of tumor marker level should have occurred as well as no simultaneous appearance of new lesions. PR according to RECIST v1.1 was defined as at least 30% decrease in the sum of the longest diameter of target lesions, taking as reference the screening sum longest diameter and no simultaneous increase in the size of any lesion or the appearance of new lesions should have occurred. The analysis population consisted of the FAS. N is the number of participants with available data.

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

End point timeframe:

Up to week 94

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|--|--------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 21 ^[25] | 30 ^[26] | 26 ^[27] | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Based on best response (confirmed) | 25.0 | 39.0 | 30.6 | |
| Based on best response (confirmed and unconfirmed) | 33.3 | 49.4 | 41.2 | |

Notes:

[25] - N=28 for confirmed and unconfirmed

[26] - N=38 for confirmed and unconfirmed

[27] - N=35 for confirmed and unconfirmed

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control Rate (DCR)

| | |
|-----------------|----------------------------|
| End point title | Disease Control Rate (DCR) |
|-----------------|----------------------------|

End point description:

DCR was defined as the fraction of participants with CR or PR or stable disease (SD) according to RECIST v1.1 (as assessed by the investigator reviewer). SD according to RECIST v1.1 was defined as neither sufficient shrinkage to qualify for PR or CR nor sufficient increase to qualify for PD, taking as

reference the smallest sum longest diameter recorded since treatment started, measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks, no simultaneous increase in the size of any lesion or the appearance of new lesions should have occurred, evaluable lesions must have remained stable or regressed for this category. The analysis population consisted of the FAS. N is the number of participants with available data.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Up to week 94 | |

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|--|-----------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 64 | 64 | 67 ^[28] | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| Based on best response (confirmed) | 76.2 | 83.1 | 78.8 | |
| Based on best response (confirmed and unconfirmed) | 76.2 | 83.1 | 80.0 | |

Notes:

[28] - N=68 for confirmed and unconfirmed

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

| | |
|--|----------------------------|
| End point title | Duration of Response (DOR) |
| End point description: | |
| DOR was determined as the time when criteria for CR or PR were first met until the first date that recurrent or progressive disease or death occurred (as assessed by the independent reviewer). The analysis population consisted of the FAS. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization to the data cut-off date of 31JAN2019; maximum time on follow-up was, 68.2, 47.2 & 59.6 months in the EOX, EOX+Zolbetuximab 600 mg, and EOX+Zolbetuximab 1000 mg treatment groups respectively. | |

| End point values | EOX Treatment | EOX+zolbetuxi mab 800/600 mg/m ² | EOX+zolbetuxi mab 1000 mg/m ² | |
|----------------------------------|------------------|---|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 84 | 77 | 85 | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.0 (3.2 to 6.7) | 7.5 (4.8 to 10.9) | 7.6 (4.5 to 11.7) | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | OS Treatment Comparison (Arm 1 versus Arm 2) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 800/600 mg/m ² |
| Number of subjects included in analysis | 161 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[29] |
| P-value | = 0.0234 ^[30] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.26 |
| upper limit | 0.93 |

Notes:

[29] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[30] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|---|---|
| Statistical analysis title | OS Treatment Comparison (Arm 1 versus Arm 3) |
| Comparison groups | EOX Treatment v EOX+zolbetuximab 1000 mg/m ² |
| Number of subjects included in analysis | 169 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[31] |
| P-value | = 0.0854 ^[32] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.56 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.29 |
| upper limit | 1.09 |

Notes:

[31] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs ≥ 70%.

[32] - The analyses were performed using 1-sided tests at the 2.5% significance level for comparisons vs Arm 1.

| | |
|-----------------------------------|--|
| Statistical analysis title | OS Treatment Comparison (Arm 3 versus Arm 2) |
| Comparison groups | EOX+zolbetuximab 800/600 mg/m ² v EOX+zolbetuximab 1000 mg/m ² |

| | |
|---|-----------------------------|
| Number of subjects included in analysis | 162 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[33] |
| P-value | = 0.5781 ^[34] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.88 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 1.57 |

Notes:

[33] - Hazard ratios were based on a Cox proportional hazard model stratified by presence of measurable vs nonmeasurable disease at baseline and by the number of CLDN18.2 stained cells categorized as < 70% vs \geq 70%.

[34] - The analyses were performed using a 2-sided test at the 5% significance level for the comparison of Arm 3 vs Arm 2.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug administration up to 30 days after the last study medication administration (up to 1791 days).

Adverse event reporting additional description:

The total number of deaths (all causes) includes deaths reported after the time frame above.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------------|
| Reporting group title | EOX Treatment |
|-----------------------|---------------|

Reporting group description:

Reporting group 1 description

| | |
|-----------------------|---|
| Reporting group title | EOX+zolbetuximab 1000 mg/m ² |
|-----------------------|---|

Reporting group description:

Reporting group 3 description

| | |
|-----------------------|--|
| Reporting group title | EOX+zolbetuximab 800/600 mg/m ² |
|-----------------------|--|

Reporting group description:

Reporting group 2 description

| Serious adverse events | EOX Treatment | EOX+zolbetuximab 1000 mg/m ² | EOX+zolbetuximab 800/600 mg/m ² |
|---|------------------|--|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 84 (32.14%) | 17 / 85 (20.00%) | 19 / 77 (24.68%) |
| number of deaths (all causes) | 79 | 77 | 63 |
| number of deaths resulting from adverse events | 15 | 9 | 8 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Breast cancer recurrent | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neoplasm malignant | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | 4 / 85 (4.71%) | 3 / 77 (3.90%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 3 |
| Neoplasm progression | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Oesophageal adenocarcinoma | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Injury, poisoning and procedural complications | | | |
| Remnant gastritis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Pyloric stenosis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Arterial thrombosis limb | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Embolism | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vena cava thrombosis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Cardiac failure | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Coronary artery insufficiency | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Disseminated intravascular coagulation | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 0 / 85 (0.00%) | 2 / 77 (2.60%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|--|----------------|----------------|----------------|
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Death | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Disease progression | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Multi-organ failure | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |

| | | | |
|---|----------------|----------------|----------------|
| Gastrointestinal disorders | | | |
| Ascites | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Obstruction gastric | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatitis | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 0 / 85 (0.00%) | 1 / 77 (1.30%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary artery thrombosis | | | |
| subjects affected / exposed | 1 / 84 (1.19%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 2 / 85 (2.35%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 0 / 85 (0.00%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 84 (0.00%) | 1 / 85 (1.18%) | 0 / 77 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |

| | | | |
|--|--------------------------------------|--------------------------------------|--------------------------------------|
| Infections and infestations Abscess soft tissue subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 84 (1.19%) 0 / 1 0 / 0 | 0 / 85 (0.00%) 0 / 0 0 / 0 | 0 / 77 (0.00%) 0 / 0 0 / 0 |
| Lobar pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 84 (0.00%) 0 / 0 0 / 0 | 0 / 85 (0.00%) 0 / 0 0 / 0 | 1 / 77 (1.30%) 0 / 2 0 / 0 |
| Pneumonia subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 84 (0.00%) 0 / 0 0 / 0 | 1 / 85 (1.18%) 0 / 1 0 / 0 | 2 / 77 (2.60%) 0 / 2 0 / 0 |
| Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 84 (0.00%) 0 / 0 0 / 0 | 1 / 85 (1.18%) 0 / 1 0 / 1 | 0 / 77 (0.00%) 0 / 0 0 / 0 |

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

| Non-serious adverse events | EOX Treatment | EOX+zolbetuximab 1000 mg/m ² | EOX+zolbetuximab 800/600 mg/m ² |
|---|------------------|--|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 82 / 84 (97.62%) | 83 / 85 (97.65%) | 74 / 77 (96.10%) |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 9 / 84 (10.71%) | 1 / 85 (1.18%) | 6 / 77 (7.79%) |
| occurrences (all) | 11 | 1 | 13 |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 11 / 84 (13.10%) | 6 / 85 (7.06%) | 7 / 77 (9.09%) |
| occurrences (all) | 14 | 6 | 14 |
| Body temperature increased | | | |
| subjects affected / exposed | 7 / 84 (8.33%) | 4 / 85 (4.71%) | 3 / 77 (3.90%) |
| occurrences (all) | 12 | 10 | 14 |
| C-reactive protein increased | | | |

| | | | |
|--------------------------------------|------------------|------------------|------------------|
| subjects affected / exposed | 3 / 84 (3.57%) | 5 / 85 (5.88%) | 3 / 77 (3.90%) |
| occurrences (all) | 3 | 6 | 3 |
| Gamma-glutamyltransferase increased | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 8 / 85 (9.41%) | 9 / 77 (11.69%) |
| occurrences (all) | 7 | 12 | 11 |
| Lipase increased | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 3 / 85 (3.53%) | 4 / 77 (5.19%) |
| occurrences (all) | 3 | 3 | 4 |
| Weight decreased | | | |
| subjects affected / exposed | 26 / 84 (30.95%) | 25 / 85 (29.41%) | 25 / 77 (32.47%) |
| occurrences (all) | 27 | 28 | 25 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 5 / 85 (5.88%) | 6 / 77 (7.79%) |
| occurrences (all) | 7 | 5 | 18 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 8 / 84 (9.52%) | 4 / 85 (4.71%) | 4 / 77 (5.19%) |
| occurrences (all) | 30 | 4 | 15 |
| Headache | | | |
| subjects affected / exposed | 18 / 84 (21.43%) | 13 / 85 (15.29%) | 12 / 77 (15.58%) |
| occurrences (all) | 56 | 31 | 68 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 0 / 85 (0.00%) | 6 / 77 (7.79%) |
| occurrences (all) | 8 | 0 | 10 |
| Paraesthesia | | | |
| subjects affected / exposed | 9 / 84 (10.71%) | 12 / 85 (14.12%) | 10 / 77 (12.99%) |
| occurrences (all) | 26 | 15 | 18 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 10 / 85 (11.76%) | 5 / 77 (6.49%) |
| occurrences (all) | 16 | 13 | 10 |
| Polyneuropathy | | | |
| subjects affected / exposed | 4 / 84 (4.76%) | 0 / 85 (0.00%) | 4 / 77 (5.19%) |
| occurrences (all) | 4 | 0 | 5 |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|------------------|------------------|------------------|
| Anaemia | | | |
| subjects affected / exposed | 30 / 84 (35.71%) | 40 / 85 (47.06%) | 35 / 77 (45.45%) |
| occurrences (all) | 35 | 59 | 59 |
| Leukopenia | | | |
| subjects affected / exposed | 14 / 84 (16.67%) | 14 / 85 (16.47%) | 12 / 77 (15.58%) |
| occurrences (all) | 19 | 28 | 23 |
| Lymphopenia | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 8 / 85 (9.41%) | 3 / 77 (3.90%) |
| occurrences (all) | 8 | 15 | 6 |
| Neutropenia | | | |
| subjects affected / exposed | 28 / 84 (33.33%) | 40 / 85 (47.06%) | 33 / 77 (42.86%) |
| occurrences (all) | 48 | 85 | 70 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 9 / 84 (10.71%) | 8 / 85 (9.41%) | 11 / 77 (14.29%) |
| occurrences (all) | 11 | 8 | 14 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 19 / 84 (22.62%) | 17 / 85 (20.00%) | 18 / 77 (23.38%) |
| occurrences (all) | 36 | 37 | 34 |
| Chills | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 3 / 85 (3.53%) | 4 / 77 (5.19%) |
| occurrences (all) | 3 | 3 | 5 |
| Fatigue | | | |
| subjects affected / exposed | 17 / 84 (20.24%) | 21 / 85 (24.71%) | 24 / 77 (31.17%) |
| occurrences (all) | 31 | 32 | 47 |
| Oedema peripheral | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 12 / 85 (14.12%) | 10 / 77 (12.99%) |
| occurrences (all) | 11 | 14 | 14 |
| Pyrexia | | | |
| subjects affected / exposed | 16 / 84 (19.05%) | 9 / 85 (10.59%) | 9 / 77 (11.69%) |
| occurrences (all) | 28 | 12 | 12 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 10 / 84 (11.90%) | 9 / 85 (10.59%) | 14 / 77 (18.18%) |
| occurrences (all) | 17 | 17 | 24 |
| Abdominal pain upper | | | |

| | | | |
|---|------------------|------------------|------------------|
| subjects affected / exposed | 18 / 84 (21.43%) | 8 / 85 (9.41%) | 7 / 77 (9.09%) |
| occurrences (all) | 26 | 10 | 9 |
| Ascites | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 4 / 85 (4.71%) | 2 / 77 (2.60%) |
| occurrences (all) | 14 | 5 | 5 |
| Constipation | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 3 / 85 (3.53%) | 4 / 77 (5.19%) |
| occurrences (all) | 15 | 7 | 6 |
| Diarrhoea | | | |
| subjects affected / exposed | 31 / 84 (36.90%) | 16 / 85 (18.82%) | 13 / 77 (16.88%) |
| occurrences (all) | 100 | 30 | 32 |
| Dyspepsia | | | |
| subjects affected / exposed | 3 / 84 (3.57%) | 4 / 85 (4.71%) | 4 / 77 (5.19%) |
| occurrences (all) | 9 | 4 | 5 |
| Dysphagia | | | |
| subjects affected / exposed | 6 / 84 (7.14%) | 2 / 85 (2.35%) | 4 / 77 (5.19%) |
| occurrences (all) | 7 | 2 | 6 |
| Nausea | | | |
| subjects affected / exposed | 64 / 84 (76.19%) | 70 / 85 (82.35%) | 63 / 77 (81.82%) |
| occurrences (all) | 301 | 389 | 305 |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 8 / 85 (9.41%) | 5 / 77 (6.49%) |
| occurrences (all) | 3 | 20 | 8 |
| Stomatitis | | | |
| subjects affected / exposed | 5 / 84 (5.95%) | 1 / 85 (1.18%) | 3 / 77 (3.90%) |
| occurrences (all) | 5 | 1 | 3 |
| Vomiting | | | |
| subjects affected / exposed | 46 / 84 (54.76%) | 66 / 85 (77.65%) | 52 / 77 (67.53%) |
| occurrences (all) | 159 | 348 | 292 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 2 / 84 (2.38%) | 4 / 85 (4.71%) | 5 / 77 (6.49%) |
| occurrences (all) | 4 | 8 | 5 |
| Dyspnoea | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 4 / 84 (4.76%) 6 | 4 / 85 (4.71%) 7 | 4 / 77 (5.19%) 4 |
| Epistaxis subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 7 | 1 / 85 (1.18%) 1 | 2 / 77 (2.60%) 3 |
| Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all) | 17 / 84 (20.24%) 18 | 22 / 85 (25.88%) 22 | 22 / 77 (28.57%) 23 |
| Palmar-plantar erythrodysaesthesia syndrome subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 6 | 3 / 85 (3.53%) 3 | 10 / 77 (12.99%) 11 |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 3 / 84 (3.57%) 6 | 5 / 85 (5.88%) 7 | 3 / 77 (3.90%) 3 |
| Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all) | 6 / 84 (7.14%) 7 | 1 / 85 (1.18%) 1 | 2 / 77 (2.60%) 3 |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 19 / 84 (22.62%) 26 | 16 / 85 (18.82%) 31 | 15 / 77 (19.48%) 19 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 5 / 84 (5.95%) 5 | 8 / 85 (9.41%) 9 | 5 / 77 (6.49%) 7 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 01 June 2012 | The changes included: Amendment 1 was issued before the first patient was enrolled into the study. The amendment revised the inclusion criterion related to CLDN18.2 expression in tumor cells. |
| 12 June 2013 | The changes included: Amendment 2 was issued after approximately 60 patients had been enrolled into each of Arms 1 and 2. This amendment specified the addition of Arm 3 |
| 26 May 2014 | The changes included: Amendment 3 was issued after 248 patients had been enrolled into the study. The amendment clarified the analysis parameters. |
| 04 November 2014 | The changes included: Amendment 4 was issued after 252 patients had been enrolled into the study. The amendment specified the addition of the interim analysis. |
| 28 July 2015 | The changes included: Amendment 5 added a single additional blood draw for patients receiving zolbetuximab for > 12 months to allow for an assessment of adaptive immunity. |
| 26 January 2016 | The changes included: Amendment 6 condensed the schedule of procedures to facilitate the longer-term follow-up of patients including prolonging the imaging intervals from 6 to 12 weeks and simplifying the follow-up procedures. |
| 11 September 2017 | The changes included: Amendment 7 changed the study sponsor from Ganymed Pharmaceuticals, Ag to Astellas Pharma Global Development, Inc. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

The study was conducted by Ganymed AG, a company that was acquired by Astellas in Dec 2016.

Notes: