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/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.

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/m^2 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/m^2. Capecitabine tablets were given once daily at a dose of 625 mg/m^2 orally in the evening of day 1 of each cycle and twice daily at a dose of 625 mg/m^2 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/m^2 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/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.

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/m^2 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/m^2. Capecitabine tablets were given once daily at a dose of 625 mg/m^2 orally in the evening of day 1 of each cycle and twice daily at a dose of 625 mg/m^2 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/m^2 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/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.

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/m^2 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/m^2. Capecitabine tablets were given once daily at a dose of 625 mg/m^2 orally in the evening of day 1 of each cycle and twice daily at a dose of 625 mg/m^2 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/m^2 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)

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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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+zolbetuximab 800/600 mg/m^2	EOX+zolbetuximab 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
≥ 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	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
Lobar pneumonia			
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 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 84 (0.00%)	1 / 85 (1.18%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
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

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