Clinical trial results:
Phase IV, multicentric study to evaluate correlation between global objectives response according RECIST v1.1 criteria evaluated by conventional images tecniques with morfologic response by TAC and pathologic response after hepatic metastatic resectability secondary to colorectal cancer in treatment with bevacizumab and XELOX.

Summary

EudraCT number	2011-000143-24
Trial protocol	ES
Global end of trial date	18 December 2017

Results information

Result version number	v1 (current)
This version publication date	20 February 2019
First version publication date	20 February 2019

Trial information

Trial identification

Sponsor protocol code	GEMCAD-10-06

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01493713
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	GEMCAD group
Sponsor organisation address	Secretari Coloma, 64-68, esc. B, entlo. 5ª, Barcelona, Spain, 08024
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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	07 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 December 2017
Global end of trial reached?	Yes
Global end of trial date	18 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Correlation between global objectives response according RECIST v1.1 criteria evaluated by conventional images tecniques with morfologic response by TAC and pathologic response after hepatic metastatic resectability.

Protection of trial subjects:

All patients signed an ICF and all data were properly anonymized to ensure data protection. Data recorded on source documents was transcribed onto a validated data collection instrument (an electronic case report form) provided by Pivotal. The investigator ensured the accuracy and completeness of the data reported, and its consistency with the source documentation.
Data were collected on all subjects who provide written informed consent.
The primary source document for this study was the subject's medical record. If separate research records were maintained by the investigator(s), both the medical record and the research records were monitored/audited for the purposes of the study.
Study documents (including subject records, copies of collected data, study notebook, and pharmacy records) were kept secured in accordance with site practices and applicable regulatory requirements.

Background therapy:

Clinical study of bevacizumab with XELOX in patients with potentially resectable hepatic metastases of CRC, as front-line treatment.

Evidence for comparator:

This was a one arm clinical trial, no comparator was present.

Actual start date of recruitment	15 July 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 83
Worldwide total number of subjects	83
EEA total number of subjects	83

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)	36
From 65 to 84 years	47
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

83 patients were screened and included at 23 Spanish sites

Pre-assignment

Screening details:

Patients with the diagnosis of liver metastasis presenting synchronically or after a disease-free interval. The primary tumor shall have been resected previously although the inverse approach may be acceptable if the tumor is not very symptomatic.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable

Arms

Arm title	Study arm

Arm description:

Firstly, patients received 4 cycles of treatment with bevacizumab + XELOX. Then, depending on a radiologic evaluation with conventional CT and assessment of the patient by a multidisciplinary team consisting of an oncologist and surgeon, patients who were candidates for surgery received another treatment cycle without bevacizumab, i.e., with XELOX alone, and they underwent surgical resection of liver metastases. The rest of the patients, who were not candidates for surgery after this first evaluation, continued with the same schedule of bevacizumab + XELOX treatment until hepatic resection is possible or until progression, the occurrence of unacceptable toxicity, or the patient withdraws informed consent.
Patients in whom liver metastases were resected after the initial treatment (5 treatment cycles) continued later with the same treatment schedule until completing a maximum of 6 cycles. Overall, patients received a maximum of 12 treatment cycles.

Arm type	Experimental
Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	bevacizumab
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab: 7.5 mg/kg on day 1 of every 3-week cycle

Investigational medicinal product name	capecitabine
Investigational medicinal product code	capecitabine
Other name	xeloda
Pharmaceutical forms	Buccal tablet
Routes of administration	Oral use

Dosage and administration details:

Capecitabine: 1000 mg/m2 orally, 2 times a day, days 1 to 14 every 3 weeks

Investigational medicinal product name	oxaliplatin
Investigational medicinal product code	oxaliplatin
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:
Oxaliplatin: 130 mg/m2 i.v. administered in a 2-hour infusion on day 1, every 3 weeks

Number of subjects in period 1	Study arm
Started	83
Completed	59
Not completed	24
Adverse event, non-fatal	24

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description:

All patients had adenocarcinoma histology, and most tumors were located in left colon (58 [69.88%]). Metastatic disease was present at first diagnosis in 58 (69.88%) patients.
Thirteen patients (15.66%) had received previous adjuvant quemotherapy.
KRAS was obtained for 79 patients. Thirty-six patients had mutated KRAS and 43 patients were wild-type KRAS. Besides this characteristic, both subgroups were similar in terms of sex, age and demographics.
ITT population comprised 78 patients as five patients were considered screening failure and did not start treatment.Most patients had an ECOG functional status 0 (64 patients, 77.11%), while 18 (21.69%) were ECOG 1. Thirteen patients had received adjuvant chemotherapy and two patients had previously received radiotherapy.Seventy-two patients had undergone previous surgery, 51 out of them had a radical surgery. In total, 43 patients (51.81%) had wild type KRAS, whereas 36 (43.37%) had KRAS mutated.

Reporting group values	Overall trial	Total	
Number of subjects	83	83	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	36	36	
From 65-84 years	47	47	
85 years and over	0	0	
Age continuous Units: years			
median	66		
standard deviation	± 8	-	
Gender categorical			
Eighty-three patients were included. More men (55 [66.27%]) than women (28 [33.73%]) were treated in the study.			
Units: Subjects			
Female	28	28	
Male	55	55	

End points

End points reporting groups

Reporting group title	Study arm

Reporting group description:

Firstly, patients received 4 cycles of treatment with bevacizumab + XELOX. Then, depending on a radiologic evaluation with conventional CT and assessment of the patient by a multidisciplinary team consisting of an oncologist and surgeon, patients who were candidates for surgery received another treatment cycle without bevacizumab, i.e., with XELOX alone, and they underwent surgical resection of liver metastases. The rest of the patients, who were not candidates for surgery after this first evaluation, continued with the same schedule of bevacizumab + XELOX treatment until hepatic resection is possible or until progression, the occurrence of unacceptable toxicity, or the patient withdraws informed consent.
Patients in whom liver metastases were resected after the initial treatment (5 treatment cycles) continued later with the same treatment schedule until completing a maximum of 6 cycles. Overall, patients received a maximum of 12 treatment cycles.

Subject analysis set title	one arm
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Primary endpoint was the correlation of global objective responses according to RECIST criteria v1.1. evaluated by conventional imaging techniques, with the morphological and the pathological response after resection of liver metastases.
Objective response rate was assessed on the ITT population (83 patients).
Sixty-eight patients were evaluated by RECIST, with 33 patients matching partial response, 30 patients reaching stable disease and five patients progressive disease. Morphological assessment was performed in 67 patients (27 optimal responses, 34 incomplete responses, 6 null responses). Fifty-nine patients underwent surgery and 22 patients completed four post-surgery cycles with bevacizumab + XELOX.

Primary: RECIST versus morphologic and pathologic responses

End point title	RECIST versus morphologic and pathologic responses[1]

End point description:

Primary endpoint was the correlation of global objective responses according to RECIST criteria v1.1. evaluated by conventional imaging techniques, with the morphological and the pathological response after resection of liver metastases.
Objective response rate was assessed on the ITT population (83 patients).
Sixty-eight patients were evaluated by RECIST, with 33 patients matching partial response, 30 patients reaching stable disease and five patients progressive disease. Morphological assessment was performed in 67 patients (27 optimal responses, 34 incomplete responses, 6 null responses). Fifty-nine patients underwent surgery and 22 patients completed four post-surgery cycles with bevacizumab + XELOX.

End point type	Primary

End point timeframe:

along the study

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Primary endpoint was the correlation of global objective responses according to RECIST criteria v1.1. evaluated by conventional imaging techniques, with the morphological and the pathological response after resection of liver metastases.
Objective response rate was assessed on the ITT population (83 patients).
Sixty-eight patients were evaluated by RECIST, with 33 patients matching partial response, 30 patients reaching stable disease and five patients progressive disease.

End point values	one arm			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: responses	83			

Statistical analyses

No statistical analyses for this end point

Secondary: Progression free survival

End point title	Progression free survival

End point description:

Progression free survival (PFS) was defined as the time, calculated in months, elapse from the date when the patient signed the informed consent form and the date of disease progression or death from any cause. For those patients that did not present any event (death/ disease progression), the date of the last visit was considered.
In patients undergoing metastases surgery (R0, R1, R2) PFS was defined as the time from when patient started treatment till any of the following events:
-Recurrence or progressive disase after surgery.
-Death.
In patients who did not undergo metastases surgery, PFS was defined as time from patient started treatment until any of the following:
-Progressive disease (if it happens before or after scheduled surgery).
-Death.
Median PFS in patients with resected metastases was 21.14 months, whereas in those patients with non-resected metastases, median PFS was 4.6 months ($p<0.0001$).

End point type	Secondary

End point timeframe:

Along the study

End point values	one arm			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: months				
median (standard deviation)	4.6 (± 1.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Recurrence Free Survival

End point title	Recurrence Free Survival

End point description:

Those patients with metastases resection have been analyzed for this purpose (n=49), including R0, R1 and R2.

RFS is defined as the interval from surgery to disease progression. Those patients receiving XELOX + bevacizumab post-metastasectomy, or who have changed treatment without prior progressive disease,

were censored at the time of their last prior XELOX + bevacizumab cycle.

Median RFS was 10.32 months.

End point type	Secondary

End point timeframe:

Along the study.

End point values	one arm			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: months				
median (standard deviation)	10.32 (± 3.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival

End point title	Overall survival

End point description:

Overall survival (OS) for the entire study population is included in this section. An event was considered as those patient that died during the study. It was calculated as the time in months since the date when the patient signed the informed consent until death.
For those patient that did not die during the follow-up period of the study, it was considered as the last contact with them. In this graphic, it is included the information of all patients that signed the informed consent form.
Median OS was not reached as 59.82% patients were alive at the time of the analysis.

End point type	Secondary

End point timeframe:

Along the study.

End point values	one arm			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: months				
median (standard deviation)	40.29 (± 4.5)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 30 days after lasto study drugs dose	
Adverse event reporting additional description:	
CTCAE 4.03	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	4.03

Reporting groups	
Reporting group title	Safety population

Reporting group description:

The tolerability analysis was performed in the safety population, i.e. the set of patients who had received at least one dose of the treatment.
The safety analysis was performed by treatment received.

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	34 / 78 (43.59%)		
number of deaths (all causes)	8		
number of deaths resulting from adverse events	3		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
brain stroke			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Anastomotic fistula			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			

Pyrexia				
subjects affected / exposed	1 / 78 (1.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
loss apetite				
subjects affected / exposed	1 / 78 (1.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
lung embolism				
subjects affected / exposed	4 / 78 (5.13%)			
occurrences causally related to treatment / all	3 / 4			
deaths causally related to treatment / all	0 / 0			
thoracic pain				
subjects affected / exposed	2 / 78 (2.56%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
dyspnea				
subjects affected / exposed	1 / 78 (1.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Product issues				
hand foot syndrome				
subjects affected / exposed	1 / 78 (1.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
evisceration				
subjects affected / exposed	1 / 78 (1.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound abscess				

subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
bleeding			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Infusion related reaction			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Heart pain			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
cardiac insuficiency			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neurotoxicity			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
anemia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Neutropenia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
diarrhea			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences causally related to treatment / all	7 / 7		
deaths causally related to treatment / all	0 / 0		
Enteritis			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences causally related to treatment / all	3 / 3		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
bowel obstruction			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
subileum			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
ileum			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Jejunal perforation			

subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
epistaxis			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
renal failure			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
back pain			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
septic syndrome			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	1 / 1		
Liver abscess			

subjects affected / exposed	2 / 78 (2.56%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 1		
Anal abscess			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Abdominal abscess			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
neumonia			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 78 (100.00%)		
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	5		
Nervous system disorders			
neurotoxicity			
subjects affected / exposed	12 / 78 (15.38%)		
occurrences (all)	28		
paresthesia			
subjects affected / exposed	11 / 78 (14.10%)		
occurrences (all)	26		
peripheral neuropathy			
subjects affected / exposed	7 / 78 (8.97%)		
occurrences (all)	14		

dysesthesia subjects affected / exposed occurrences (all) sensitive peripheral neuropathy subjects affected / exposed occurrences (all) hypoalbuminemia subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 8 6 / 78 (7.69%) 6 2 / 78 (2.56%) 4		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all) loss apetite subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) dry mouth subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all)	19 / 78 (24.36%) 45 13 / 78 (16.67%) 23 8 / 78 (10.26%) 8 6 / 78 (7.69%) 7 6 / 78 (7.69%) 6		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all) Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all)	9 / 78 (11.54%) 10 6 / 78 (7.69%) 9 5 / 78 (6.41%) 6		
Gastrointestinal disorders			

diarrhea subjects affected / exposed occurrences (all)	39 / 78 (50.00%) 51			
nausea subjects affected / exposed occurrences (all)	18 / 78 (23.08%) 31			
Vomiting subjects affected / exposed occurrences (all)	15 / 78 (19.23%) 24			
Abdominal pain subjects affected / exposed occurrences (all)	8 / 78 (10.26%) 12			
Constipation subjects affected / exposed occurrences (all)	5 / 78 (6.41%) 6			
Enteritis subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 5			
upper abdominal pain subjects affected / exposed occurrences (all)	3 / 78 (3.85%) 5			
rectal bleeding subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 4			
dispepsia subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 4			
dysgeusia subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 4			
Odynophagia subjects affected / exposed occurrences (all)	4 / 78 (5.13%) 4			
Respiratory, thoracic and mediastinal disorders				

Epistaxis subjects affected / exposed occurrences (all) lung embolism subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 5 4 / 78 (5.13%) 4 4 / 78 (5.13%) 4		
Skin and subcutaneous tissue disorders mucosal inflammation subjects affected / exposed occurrences (all) hand foot syndrome subjects affected / exposed occurrences (all) Dry skin subjects affected / exposed occurrences (all)	 6 / 78 (7.69%) 13 8 / 78 (10.26%) 11 2 / 78 (2.56%) 4		
Psychiatric disorders Depression subjects affected / exposed occurrences (all) Anxiety subjects affected / exposed occurrences (all)	 2 / 78 (2.56%) 5 2 / 78 (2.56%) 4		
Renal and urinary disorders Proteinuria subjects affected / exposed occurrences (all)	 2 / 78 (2.56%) 4		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	 5 / 78 (6.41%) 5		
Metabolism and nutrition disorders			

hypokalemia subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 June 2011	some typos were clarified and additional information was provided to improve consistency in an exclusion criterion. A prospective translational study was added to look for predictive biomarkers. Additional sites were included.

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 main limitation of this study is the relatively small sample size, such that statistical differences between KRAS mutated and wild-type were not demonstrated for any parameter.

Notes: