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A Multicenter, Randomized Phase II Trial Assessing the Activity of Gemcitabine – Oxaliplatin Chemotherapy Alone or in Combination with Cetuximab in Patients with Advanced Biliary Cancer

EMR 62202-693 – BINGO
(Biliary cancers: EGFR INhibitor, Gemcitabine and Oxaliplatin)

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BINGO

Final analysis of the phase II trial

2012, October 30th

Report prepared by [redacted]

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1 Introduction

The BINGO trial is an open-label, non-comparative, randomized phase II study evaluating the efficacy and tolerance of gemcitabine-oxaliplatin combination chemotherapy (GEMOX regimen) alone or in combination with cetuximab in the first-line treatment of patients with advanced biliary cancers.

All eligible patients were randomized 1:1 to receive:

- Arm A: GEMOX alone every two weeks
- Arm B: GEMOX + cetuximab every two weeks

The primary objective was to evaluate treatment efficacy on progression-free survival (PFS) rate at 4 months. Secondary objectives were to assess treatment toxicity, rate and duration of objective tumor response and tumor control (tumor responses and stabilizations), secondary resection rate, PFS, and overall survival (OS).

An interim analysis was performed in December 2008. The observed PFS rate at 4 months (10/18 patients) in arm B allowed to continue the trial in accordance with the Simon's statistical plan defined in the protocol.

For the 36 first French patients and all the German patients, the forms were monitored before sending them to the data center. The data center queries were sent thereafter to the centers. For the French patients after the 36th patient, the forms were sent to the data center and then monitored with the data center queries to hand.

Analyses of recruitment, baseline description, end of treatment, response to treatment, follow-up and long-term assessment were performed on the database at the date of October 2012. Analyses of description of study treatments, post-study treatments, treatment toxicity, and severe adverse events were performed on the database at the date of April 2011 as new data were very few.

2 Recruitment

To assess treatment efficacy according to the Simon design and to take into account non-assessable patients, 100 patients (50 per arm) had to be enrolled. This accrual was planned to last 18 months. After a suspension of 6 months, the accrual was continued until 150 patients to reach the target number of patients for the subgroup analyses (non-gallbladder localization, wild-type [WT] KRAS tumor status, n=50 patients each). These 150 patients were included between 2007, October 10th and 2009, December 18th. **The cut-off date for the analysis is March 31st, 2011.**

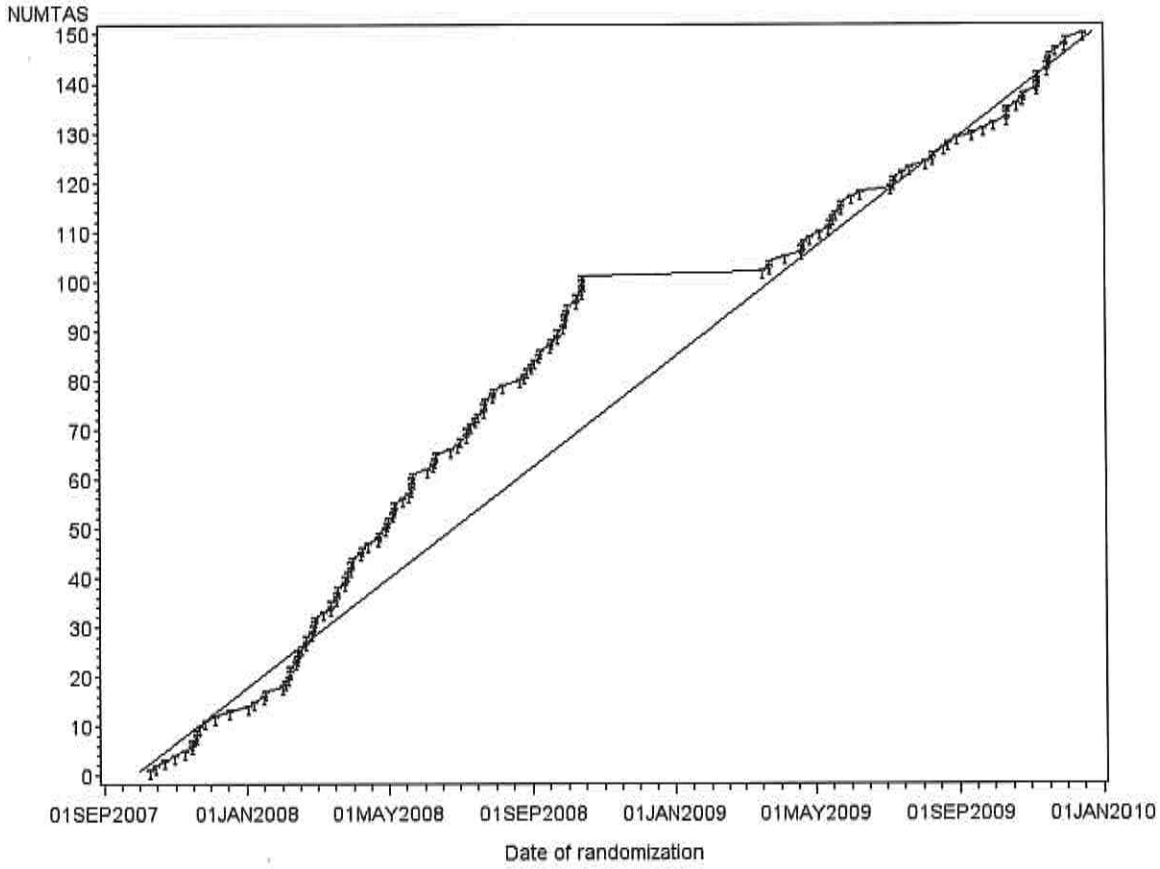

Figure 1: Randomization curve (n=150). Each patient is figured by a tick. The line without tick represents the theoretical accrual.

3 Baseline description of the analysis population

3.1 Centers

The 150 patients were included by 18 centers (France, 11; Germany, 7; Table 1). Four centers included 46% of the patients.

Table 1: Distribution of inclusions by center

	GEMOX + CETUXIMAB n=76		GEMOX n=74		Total n=150	
	N	%	N	%	N	%
Villejuif – Gustave Roussy	5	*7*	5	*7*	10	*7*
Clichy – Hôpital Beaujon	5	*7*	6	*8*	11	*7*
Paris – Hôpital Pitié-Salpétrière	1	*1*	1	*1*	2	*1*
Paris – Hôpital Saint-Antoine	9	*12*	8	*11*	17	*11*
Lyon – Centre Léon Bérard	8	*11*	9	*12*	17	*11*
Montpellier – Centre Val d'Aurelle	3	*4*	4	*5*	7	*5*
Marseille – Institut Paoli Calmettes	5	*7*	4	*5*	9	*6*
Rennes – Centre Eugène Marquis	8	*11*	9	*12*	17	*11*
Bordeaux – Hôpital Saint-André	5	*7*	3	*4*	8	*5*
Créteil – Hôpital Henri Mondor	2	*3*	2	*3*	4	*3*
Pessac – Hôpital Haut Lévêque	2	*3*	1	*1*	3	*2*
Total France	**53**	***70***	**52**	***70***	**105**	***70***
Ulm – Klinik für Innere Medizin	3	*4*	3	*4*	6	*4*
Essen – Klinik Tumorforschung.	9	*12*	9	*12*	18	*12*
Halle – Universitätsklinikum	1	*1*	1	*1*	2	*1*
Hannover – Med. Hochschule	6	*8*	6	*8*	12	*8*
Heidelberg – Nat. Cent. für Tum	3	*4*	1	*1*	4	*3*
München – Klinikum Großhadern	0	*0*	1	*1*	1	*1*
Regensburg – Uniklinik	1	*1*	1	*1*	2	*1*
Total Germany	**23**	***30***	**22**	***30***	**45**	***30***

3.2 Baseline characteristics

Patients were mainly male (85/150, 57%) with a median performance status (PS) equal to 1 (79/142, 56 %). The median age was 62 years (range, 35 to 75). Baseline characteristics were well balanced between the two arms, except for PS status: more patients had PS0 in the GEMOX+CETUXIMAB arm than in the GEMOX alone arm (Table 2).

Table 2: Baseline characteristics

	GEMOX + CETUXIMAB n=76		GEMOX n=74		Total n=150	
	N or median [range]	%	N or median [range]	%	N or median [range]	%
Sex						
Male	43	*57*	42	*57*	85	*57*
Female	33	*43*	32	*43*	65	*43*
Performance status (WHO)						
0	35	*49*	27	*38*	62	*44*
1	36	*51*	43	*61*	79	*56*
2	0	*0*	1	*1*	1	*1*
Missing	*5*	-	*3*	-	*8*	-
Age (years)	61	[35 - 75]	62	[39 - 75]	62	[35 - 75]
Weight (Kg) (2 MD)	70	[38 - 112]	70	[43 - 105]	70	[38 – 112]
Height (cm)	170	[145 - 192]	170	[147 - 190]	170	[145 - 192]
Body Surface Area* (2 MD)	1.79	[1.32 - 2.31]	1.79	[1.41 - 2.32	1.79	[1.32 - 2.32]

MD: Missing Data
*When body surface area (BSA) was not given but weight and height were both available, missing BSA was replaced by their calculated value (n=5).

There was no major difference in baseline biological parameters between the two arms (Table Table 3). Protocol deviations for biological parameters are described in Appendix 1.

Table 3: Baseline biological parameters

	GEMOX + CETUXIMAB n=76		GEMOX n=74		Total n=150	
	Median	[range]	Median	[range]	Median	[range]
Platelets (10^9/L)	278	[110 - 770]	270	[79 - 576]	274	[79 - 770]
Hemoglobin (g/dL)	13	[8 - 17]	13	[8 - 16]	13	[8 - 17]
Neutrophils (10^9/L) (17 MD)	6	[2 - 77]	7	[2 - 299*]	6	[2 - 299]
Bilirubin (µmol/L) (10 MD)	13	[1 - 67]	15	[5 - 91]	13	[1 - 91]
Alk. Phosphatase (UI/L) (3 MD)	164	[1 - 1980]	188	[51 - 1664]	174	[1 - 1980]
AST (UI/L) (4 MD)	37	[14 - 267]	46	[15 - 313]	43	[14 - 313]
ALT (UI/L) (2 MD)	30	[4 - 281]	42	[9 - 174]	36	[4 - 281]
LDH (UI/L) (50 MD)	282	[141 - 2562]	250	[131 - 2325]	263	[131 - 2562]
CA 19-9 (ng/mL) (26 MD)	105	[1 - 50701]	166	[1 - 61883]	120	[1 - 61883]

MD: Missing Data
* Two patients had neutrophil count > 85.10^9/L (266 and 299.10^9/L); queries were sent to centers but not responded.

3.3 Tumor characteristics

Table 4 details the tumor characteristics for the 150 patients. Most patients had metastatic (118/150, 79%) adenocarcinoma (139/143, 97%). The main localization was cholangiocarcinoma. Only one patient had ampulloma, and two patients had multifocal disease.

Table 4: Tumor charactaristics

	GEMOX + CETUXIMAB n=76		GEMOX alone n=74		Total n=150	
	N	%	N	%	N	%
HISTOLOGICAL TYPE						
Adenocarcinoma	71	*99*	68	*96*	139	*97*
Undifferentiated	1	*1*	2	*3*	3	*2*
Unspecified	0		1	*1*	1	*1*
Missing data	*4*	-	*3*	-	*7*	-
TUMOR LOCATION *						
Cholangiocarcinoma	62	*83*	61	*84*	123	*83*
Intrahepatic bile ducts ('peripheral')	49		46		95	
Peri-hilar ('Klatskin-like')	4		7		11	
Extrahepatic bile ducts (distal two-thirds)	3		6		9	
Intrahepatic + peri-hilar bile ducts	0		1		1	
Intrahepatic + extrahepatic bile ducts	1		0		1	
Missing data	5		1		6	
Ampulloma	1	*1*	0	*0*	1	*1*
Gallbladder	11	*15*	11	*15*	22	*15*
Multifocal	1	*1*	1	*1*	2	*1*
Missing data **	*1*		*1*		*2*	
DISEASE STAGE *						
Metastatic	59	*78*	59	*80*	118	*79*
Locally advanced	17	*22*	15	*20*	32	*21*

*See Appendix 2 for comparison with stratification results

** Coded non-gallbladder on the randomization form

3.4 Prior treatments received

The majority of patients (102/150, 68%) did not receive any treatment before the inclusion in the BINGO trial. Among the 48 patients with prior treatment, 34 had undergone curative-intent surgery, 18 had undergone palliative surgery, and two had received adjuvant chemotherapy. Moreover, 32 had undergone biliary stenting.

Table 5: Prior treatments received

	GEMOX + CETUXIMAB n=76		GEMOX alone n=74		Total n=150	
	N	%	N	%	N	%
Curative-intent surgery * (3+2 MD)						
No	55	*75*	56	*78*	111	*77*
Yes	18	*25*	16	*22*	34	*23*
Cholecystectomy	3		8		11	
Partial hepatectomy	6		4		10	
Whipple's procedure	3		2		5	
Other**	5		2		7	
Unspecified	1		0		1	
Palliative surgery (2+ 4 MD)						
No	67	*91*	59	*84*	126	*88*
Yes	7	*9*	11	*16*	18	*13*
Laparotomy without resection	3		9		12	
Biliary bypass	1		0		1	
Other***	3		2		5	
Adjuvant chemotherapy * (1+2 MD)						
No	74	*99*	71	*99*	145	*99*
Yes ****	1	*1*	1	*1*	2	*1*
Biliary stenting (3+3 MD)						
No	58	*79*	54	*76*	112	*78*
Yes	15	*21*	17	*24*	32	*22*
Radiotherapy *						
No	74	*97*	74	*100*	148	*99*
Yes	2	*3*	0	*0*	2	*1*

* see Appendix 2 for comparison with stratification
** pancreaticoduodenectomy, biliary resection + bypass, left lobectomy, lymphadenectomy + hepatectomy + omentectomy, enlarged right hepatectomy
*** Intestinal bypass, exploratory laparotomy, lymphadenectomy + hepatectomy + omentectomy, small bowel resection
**** Patient 15 has received prior adjuvant gemcitabine- and oxaliplatin-based chemotherapy (last cycle, 28/09/2005; BINGO inclusion, 08/01/2008); patient 118 has received prior adjuvant single-agent chemotherapy with capecitabine (last cycle, 02/04/2009; BINGO inclusion, 11/06/2009).

4 Study treatments received

This section is unchanged since previous report, except section 4.3 (the last patient ended his treatment) and section 4.4 which is new.

4.1 Description of cycles given and dose modifications

On December 31st, 2010, information about received treatment was:

- Complete for 138 patients (92%);
- Incomplete for 12 patients (8%): incomplete information includes treatment ongoing and missing cycle forms (according to the end of treatment form).

Only one patient has ongoing treatment on December 31st, 2010 (#149, GEMOX + cetuximab arm). He has received 24 treatment cycles for now.

Among the 147 patients who received treatment, 146 patients ended treatment. For them, 17 cycle forms are missing (in 6 patients) in the GEMOX + cetuximab arm and 19 are missing (4 patients, one having 14 missing forms) in the GEMOX alone arm.

Two patients did not receive any treatment due to early death related to rapid progression (#31 and #75, GEMOX alone arm) and one patient did not receive treatment because he was randomized by error (#127, GEMOX alone arm: violation of the eligibility criteria with elevated bilirubin and alkaline phosphatase levels – 1664 UI/L; ULN=130 UI/L).

To date, 1 601 treatment forms have been received (885 in the GEMOX + cetuximab arm, 716 in the GEMOX alone arm) for 147 patients, including three supplementary cycles which were not analyzed:

- patient #43, cycle 8 (last cycle), received erythropoietin only;
- patient #57, GEMOX cycle 7 (last cycle), given after the date of disease progression;
- patient #86, GEMOX cycle 6 (last cycle), given after the date of disease progression.

Table 6 describes the number of cycles received (i.e., at least one study drug administered). The median number of treatment cycles was similar in the two arms.

Table 6: Number of cycle of treatment received (n=147 treated patients)

	No of cycles received				
Treatment arm	**Minimum**	**10th percentile**	**Median**	**90th percentile**	**Maximum**
GEMOX + cetuximab	2	4	10	23	33
GEMOX alone	1	2	10	18	27
Total	1	3	10	20	33

The administered cycles were as follow.

Table 7: Description of drugs administered per cycle (n=1 598 cycles)

Type of cycles given	GEMOX + cetuximab N=885	%	GEMOX alone N=713	%
Gemcitabine				
As per protocol	827	*93*	651	*91*
Modified	41	*5*	50	*7*
Not given	17	*2*	12 (1)	*2*
Oxaliplatin				
As per protocol	625	*71*	515	*72*
Modified	59	*7*	70	*10*
Not given	201 (27)	*23*	128 (20)	*18*
Cetuximab				
As per protocol	789	*89*	-	-
Modified	25	*3*	-	-
Not given	71 (8)	*8*	713	*100*

In parenthesis: number of courses not given in the last cycle of treatment.

Oxaliplatin was the drug with most modifications: 7% and 10% of oxaliplatin cycles were given with dose reduction in the GEMOX + cetuximab and GEMOX arms, respectively. The planned cycles were not administered in 23% and 18% of the planned cycles respectively, concerning 30 and 25 patients respectively.
For administration of gemcitabine, 2% of cycles in each arm were not administered. Percentages of modifications for these two drugs were similar in the two arms.
No cycle with cetuximab was administered in the GEMOX alone arm; 8% of planned cetuximab cycles were not administered in the GEMOX + cetuximab arm.
The reasons for dose modifications are presented in Table 8.

Table 8: Reasons for drug dose modifications

	Gemcitabine		Oxaliplatin		Cetuximab
Reason for dose reduction	**GEMOX + cetuximab n=41 (%)**	**GEMOX alone n=50 (%)**	**GEMOX + cetuximab n=59**	**GEMOX alone n=70**	**GEMOX + cetuximab n=25**
Hematological toxicity	23 (56)	34 (68)	22 (37)	18 (26)	4 (16)
Non-hematological toxicity	8 (20)	9 (18)	24 (41)	30 (43)	9 (36)
Hematological & non-hematological toxicity	4 (10)	3 (6)	4 (7)	18 (26)	3 (12)
Other	6 (14)	4 (8)	9 (15)	4 (6)	9 (36)
Weight change	*6*	*3*	*5*	*3*	*6*
Personal convenience		*1*		*1*	*1*
Error of administration			*3*		*1*
Physician's decision			*1*		
Not specified					*1*

Reasons for not giving drug were not asked for in the CRF. This information was only available when the form was filled in with a dose 0, and was not frequently reported. Table 9 describes these reasons.

Table 9: Reasons for not giving a drug

Reason for dose reduction	Gemcitabine		Oxaliplatin		Cetuximab
	GEMOX + cetuximab n=17 (%)	GEMOX alone n=12 (%)	GEMOX + cetuximab n=201	GEMOX alone n=128	GEMOX + cetuximab n=71
Not specified	16	12	179	113	65
Hematological toxicity	1	-	-	2	4
Non-hematological toxicity	-	-	21	10	-
Hematological & non-hematological toxicity	-	-	-	1	1
Other	-	-	1	2	1

Duration of treatment and dose-intensity

For each patient, dose-intensity was defined as:

$$DI = \frac{Total.dose.(mg/m^2)}{Total.treatment.duration.(week)}$$

Where the total treatment duration is equal to the time elapsed between the first and the last injection of the considered drug plus 14 days. Thus a drug not administered during the treatment will impact on the dose-intensity, but a drug not administered in the last cycles will not impact on the dose-intensity.
The theoretical dose-intensity was 500 mg/m²/week for gemcitabine, 50 mg/m²/week for oxaliplatin and 250 mg/m²/week for cetuximab. The dose-intensity results are based on the 147 patients who have received study treatment. For patients with missing baseline body surface area value, this information was retrieved from cycle forms.

Table 10: Drug dose-intensity

	GEMOX + cetuximab (n=76 pts)		GEMOX alone (n=71 pts)	
	Median	[range]	Median	[range]
Gemcitabine				
Duration (weeks)	23	[4 - 83]	23	[2 - 72]
Total dose (% of theoretical dose)	99%	[61 - 105]	98%	[71 - 110]
Dose-intensity	434	[228 - 599]	445	[244 - 592]
≥80% of theoretical dose-intensity	52	(68%)	51	(72%)
Oxaliplatin				
Duration (weeks)	19	[4 - 83]	20	[2 - 50]
Total dose (% of theoretical dose)	97%	[60 - 105]	96%	[64 - 108]
Dose-intensity	43	[16 - 60]	44	[14 - 54]
≥80% of theoretical dose-intensity	49	(64%)	41	(58%)
Cetuximab			-	
Duration (weeks)	23	[2 - 83]	-	
Total dose (% of theoretical dose)	100%	[18 - 105]	-	
Dose-intensity	227	[45 - 254]	-	
≥80% of theoretical dose-intensity	49	(64%)		

Dose-intensities of gemcitabine and oxaliplatin were lower than planned, but similar in the two arms.

If the received dose is divided by the overall treatment time and not only the treatment time of the studied drug (74 patients in the GEMOX + cetuximab arm and 70 patients in the GEMOX alone arm), dose-intensities became:

- For gemcitabine, the median dose-intensity became 437 [228 - 599] in the GEMOX + cetuximab arm and 443 [244 - 592] in the GEMOX alone arm; respectively 52 patients (70%) and 51 patients (73%) received ≥80% of theoretical dose-intensity.
- For oxaliplatin, the median dose-intensity became 38 [12 - 60] in the GEMOX + cetuximab arm and 39 [7 - 54] in the GEMOX alone arm; respectively 46 patients (62%) and 46 patients (66%) received ≥80% of theoretical dose-intensity.
- For cetuximab, the median dose intensity became 223 [4 - 254] in the GEMOX + cetuximab arm; 46 patients (42%) received ≥80% of theoretical dose-intensity.

The median duration of treatment was 23 weeks (range, 4 to 83) in the GEMOX + cetuximab arm, and 23 weeks (range, 2 to 58) in the GEMOX alone arm. The only patient with treatment ongoing accounted for until his last received cycle.

4.2 Description of delayed cycles

The duration of a cycle is 14 days. A cycle was defined as delayed if it started more than 7 days after the planned date (as calculated from the previous cycle). Delayed cycles described here are based on calculation rather than declaration. Table 11 presents the number of patients with or without delayed cycles by treatment arm, and the median number (and range) of delayed cycles among the patients with at least one delayed cycle.
Overall, 226 gemcitabine cycles (125 in the GEMOX + cetuximab arm and 101 in the GEMOX alone arm, respectively), 203 oxaliplatin cycles (113 and 90), and 114 cetuximab cycles were delayed.

In the GEMOX + cetuximab arm, the median duration of cycle delays was 8 days (range, 7 to 35) for gemcitabine and cetuximab, and 7 days (range, 7 to 35) for oxaliplatin.
In the GEMOX alone arm, the median duration of cycle delays was 7 days (range, 7 to 28) for gemcitabine, and 7 days (range, 7 to 29) for oxaliplatin.

Table 11: Delayed cycles (n=147 treated patients)

	GEMOX + cetuximab n=76						GEMOX alone n=71					
	Non-delayed cycles	Delayed cycles					Non-delayed cycles	Delayed cycles				
	N	N	Median	Min	90th per.	Max	N	N	Median	Min	90th per.	Max
Gemcitabine	31	45	2	1	4	14*	31	40	2	1	6	10
Oxaliplatin	35	41	2	1	4	14	35	36	2	1	5	9
Cetuximab	34	42	2	1	4	15	-	-	-	-	-	-

* Patient 27 (Rennes): 14 cycles delayed out of 31.

Table 12 describes the reasons for delayed cycles.

Table 12: Reasons for cycle delays

Reasons for cycle delays	Gemcitabine		Oxaliplatin		Cetuximab
	GEMOX + cetuximab n=125 (%)	GEMOX alone n=101 (%)	GEMOX + cetuximab n=113 (%)	GEMOX alone n=90 (%)	GEMOX + cetuximab n=114
Hematological toxicity	36 (29)	30 (30)	34 (30)	27 (30)	29 (25)
Non-hematological toxicity	17 (14)	5 (5)	14 (12)	5 (6)	16 (14)
Hematological and non-hematological toxicity	3 (2)	1 (1)	3 (3)	2 (2)	1 (1)
Personal convenience	16 (13)	10 (10)	14 (12)	8 (9)	16 (14)
Other	10 (8)	12 (12)	8 (7)	10 (11)	10 (9)
Surgery	*1*	*2*		*1*	*1*
Tumor evaluation	*2*	*1*	*1*	*1*	*2*
Logistic reasons	*1*	*6*	*1*	*6*	*1*
Adverse events	*3*	*2*	*2*	*2*	*2*
*Pulmonary infiltration**	*1*		*1*		*1*
not specified	*2*	*1*	*3*		*3*
Not specified**	43 (34)	43 (43)	40 (35)	38 (42)	42 (37)

* To be explored

**The high rate of unspecified reasons is due to the discrepancy between the number of cycles declared as delayed and the number of cycles calculated as delayed (gemcitabine, 86/226; oxaliplatin, 78/203; cetuximab, 42/114). Delay duration did not significantly differ whether delays were declared vs. calculated.

4.3 End of treatment

Among the 150 randomized patients, all have ended their study treatment. Reasons for end of treatment are presented in Table 13.

Table 13: Reasons for end of treatment (n=150 patients)

Reasons for end of treatment	GEMOX + cetuximab n=76	GEMOX alone n=74	Total n=150
Complete response	1	2	3
Curative-intent surgery	1	6	7
Treatment toxicity	9	7	16
Disease progression	47	34	81
Patient's request*	7	8	15
Death**	2	7	9
Other***	9	9	18
Not specified	0	1	1

* None of these patients progressed in the two months following the end of treatment.

** Causes of death: GEMOX + cetuximab arm, disease progression, and catheter infection; GEMOX alone arm, disease progression (n=6), and atypical pneumonia. .

*** GEMOX + cetuximab arm: investigator's decision (n=3), allergic reaction (n=1), treatment delay > 4 weeks (n=2), degradation of general status (n=1), unrelated SAE (n=1), and not specified (n=1); GEMOX alone arm: investigator's decision (n=5), treatment delay > 4 weeks (n=2), jaundice (n=1), randomization by error (n=1) (#127, cf note in paragraph 4.1).
Among these patients, 9 progressed in the two months following the end of treatment (6 in the GEMOX + cetuximab arm and 3 in the GEMOX alone arm).

The patient with unspecified reason of end of treatment (#52, GEMOX alone arm) received 12 cycles of treatment and did not progress or die in the two months following the end of treatment.

Disease progression (with or without death) was the main reason for stopping treatment, accounting for 48 of the 76 patients (63%) in the GEMOX + cetuximab arm and 40 of the 74 patients (54%) in the GEMOX alone arm.

4.4 Description of the patients who underwent secondary curative-intent surgery

Seven patients underwent secondary curative-intent surgery: 6 in the GEMOX alone arm and one in the GEMOX + cetuximab arm. Five patients had intrahepatic cholangiocarcinoma and two patients had gallbladder adenocarcinoma. Curative-intent surgery was attempted for after partial response to GEMOX alone in six patients and in a patient with stabilized disease while receiving GEMOX + cetuximab. Among these seven patients who underwent secondary curative-intent surgery, five died of cancer progression (four in the GEMOX alone arm and one in the GEMOX + cetuximab arm). Each of these patient cases is briefly reported below:

- Patient #9, a 64 year-old man from Hôpital Beaujon (Clichy) was diagnosed with a metastatic gallbladder adenocarcinoma. He underwent biliary stenting and was randomized in the GEMOX alone arm on September 27th, 2007. He received 6 courses of chemotherapy and had a partial response 2.6 months after the beginning of study treatment. He ended the study for curative-intent surgery performed on April 2nd, 2008 (pancreaticoduodenectomy + partial hepatectomy + cholecystectomy, staged as R0). After surgery, GEMOX chemotherapy was resumed. He died 1.7 years after surgery owing to disease progression.
- Patient #33, 51 year-old man from Centre Léon Bérard (Lyon), was diagnosed with a locally advanced intrahepatic cholangiocarcinoma. He was randomized in the GEMOX alone arm on March 7th, 2008 and received 12 courses of chemotherapy. He had a partial response 5.8 months after the beginning of study treatment. A curative-intent surgery was performed on October 21st, 2008 (left hepatectomy, staged as R1). The patient progressed and died 1.1 and 1.7 years after surgery, respectively.
- Patient #46, a 42 year-old woman from Institut Paoli Calmettes (Marseilles) was diagnosed with metastatic intrahepatic cholangiocarcinoma (lymph node metastases). She was randomized in the GEMOX alone arm on April 10th, 2008 and received 16 courses of chemotherapy. She had a partial response 1.8 months after the beginning of treatment, which was maintained for 5 months. She underwent curative-intent surgery (preceded by right portal embolization) on February 24th, 2009 (right lobectomy and cholecystectomy°. Although the procedure was staged as R2, the patient was still alive without evidence of disease 2.8 years after surgery.
- Patient #49, a 66 year-old man from Essen center was diagnosed with a metastatic intrahepatic cholangiocarcinoma. He was randomized in the GEMOX alone arm on April 24th, 2008 and received 21 courses of chemotherapy. He had a partial response 6.1 months after the beginning of treatment, which was maintained for 3.7 months. He underwent a curative-intent surgery (hepatic transplantation with the replacement of the vena cava, staged as R0) on March 16th, 2009. He was still alive without evidence of disease 2.7 years after surgery.
- Patient #92, a 56 year-old man from Centre Eugène Marquis (Rennes) was diagnosed with a gallbladder adenocarcinoma. After failure of right portal

embolization, a biliary stent was placed and the patient was randomized in the GEMOX alone arm on September 30th, 2008. He received 16 courses of chemotherapy. He had a partial response 3.7 months after the beginning of treatment, which was maintained for 4 months. He underwent curative-intent surgery (preceded by successful right portal embolization) on June 18th, 2009 (enlarged right hepatectomy). The patient progressed and died 1.1 and 1.3 years after surgery, respectively.

- Patient #95, a 51 year-old woman from Centre Eugène Marquis (Rennes), was diagnosed with a locally advanced intrahepatic cholangiocarcinoma. She was randomized in the GEMOX alone arm on October 10th, 2008 and received 16 courses of chemotherapy. She had a partial response 3.7 months after the beginning of study treatment which was maintained for 5.3 months. A curative-intent surgery was performed on September 07th, 2009 (left hepatectomy and cholecystectomy staged as R0 but with several doubtful small lesions in the right liver). The patient died 1.2 years after surgery from disease progression.
- Patient #112, a 44 year-old man from Bordeaux center, affected by chronic hepatitis C (liver biopsy, A1F3), was diagnosed with a metastatic intrahepatic cholangiocarcinoma (lymph node metastases). He was randomized in the GEMOX + cetuximab arm on May 15th, 2009 and received 8 courses of chemotherapy. He had stable disease maintained for 3.8 months after the beginning of study treatment. A curative-intent surgery was performed on October 08th, 2009 (right hepatectomy, lymphadenectomy and cholecystectomy staged as R0). The patient progressed and died 4.3 and 5.3 months after surgery, respectively.

5 Toxicities observed during treatment

This section was unchanged since the previous report. For six patients, toxicity was not reported (all in the GEMOX alone arm):

- #31 and #75: no treatment received due to premature death;
- #127: no treatment received due to randomization by error (patient's ineligibility);
- #6 and #98: received one treatment cycle then stopped treatment (patient's request); toxicity not reported;
- #39: received two treatment cycles; toxicity not reported.

5.1 Severe toxicities

For other patients, severe toxicities by patient are detailed in Table 15.

One treatment-related death occurred in the GEMOX alone arm. A 54 year-old woman (#87) died of atypical pneumonia. The local investigator assessed the event as possibly related to study drugs. The very limited information provided to date precluded an adequate assessment of the case. However, a causal relationship between the reported event and study drugs was not ruled out by the sponsor and assessed as possible. So far, no other causes were identified.
Fourteen deaths unrelated to cancer and unrelated to study treatment occurred (Table 14).

Table 14: Deaths unrelated to cancer and unrelated to treatment (n=14)

N°	Treatment arm	Centre	Age	Sex	Total number of cycles	Survival time (months)	2nd line of post-study CT	Progression	Reason of end of treatment	Cause of death
6	GEMOX	IGR	59	Male	1	13.9	.	Yes	Patient's request	NA
20	GEMOX	Ulm	60	Male	16	12.4	Yes	Yes	Disease progression	Unknown
32	GEMOX	Hannover	67	Female	1	5.0	Yes	No	Other	Pneumonia
42	GEMOX + CETUXIMAB	Hannover	64	Female	29	27.6	No	No	Other	Renal failure, sepsis
47	GEMOX + CETUXIMAB	Heidelberg	55	Male	7	16.7	Yes	Yes	Disease progression	NA
61	GEMOX	Essen	73	Male	4	8.8	Yes	Yes	Disease progression	NA
67	GEMOX	Ulm	72	Female	8	13.7	.	No	Patient's request	Unknown, lost to follow-up
79	GEMOX + CETUXIMAB	Lyon	67	Male	6	7.8	.	Yes	Treatment toxicity	NA
80	GEMOX	Marseille	62	Male	16	14.9	Yes	Yes	Other	NA
87	GEMOX	Essen	53	Female	12	5.7	No	No	Death	Atypical pneumonia
89	GEMOX + CETUXIMAB	Ulm	68	Male	10	5.0	.	No	Death	Catheter infection
98	GEMOX	Montpellier	58	Male	1	22.4	.	No	Patient's request	NA
120	GEMOX	Rennes	58	Male	3	2.6	.	Yes	Treatment toxicity	Disease progression
125	GEMOX	Beaujon	71	Male	9	7.8	No	Yes	Other	Cholangitis

Highest grades of toxicities by patient are detailed in Appendix 3.

Table 15: Severe toxicities by patient (n=144 patients)

	GEMOX + CETUXIMAB		GEMOX		All	
	N=76	%	N=68	%	N=144	%
At least one severe (grade ≥3) toxicity*	**63**	**83**	**57**	**84**	**120**	**83**
Hematological toxicity	**27**	**36**	**25**	**37**	**52**	**36**
Hemoglobin	7	9	5	7	12	8
Platelets	8	11	13	19	21	15
White blood cells	7	9	2	3	9	6
ANC	17	22	11	16	28	19
Constitutional / infection	**17**	**22**	**12**	**18**	**29**	**20**
Fatigue	13	17	9	13	22	15
Fever	0	0	1	1	1	1
Infection with ANC <gr 1 (1 MD)	5	7	0	0	5	3
Infection with ANC >gr 1 (1 MD)	1	1	2	3	3	2
Infection with unkn. ANC (1 MD)	0	0	2	3	2	1
Febrile neutropenia (1 MD)	2	3	0	0	2	1
LAB toxicity	**45**	**59**	**45**	**66**	**90**	**63**
ALT/AST	17	22	10	15	27	19
ALP	15	20	15	22	30	21
GGT	44	58	44	65	88	61
Bilirubin	9	12	4	6	13	9
Creatinin	1	1	0	0	1	1
Mg (12 MD)	0	0	0	0	0	0
Gastrointestinal toxicity	**10**	**13**	**10**	**15**	**20**	**14**
Anorexia	3	4	3	4	6	4
Nausea	2	3	2	3	4	3
Vomiting	3	4	2	3	5	3
Diarrhea	6	8	3	4	9	6
Constipation	0	0	0	0	0	0
Mucositis	1	1	0	0	1	1
Skin toxicity	**12**	**16**	**1**	**1**	**13**	**9**
Allergic reaction/hypersensitivity	6	8	1	1	7	5
Alopecia	0	0	0	0	0	0
Acneiform rash	5	7	0	0	5	3
Conjunctivitis	1	1	0	0	1	1
Nail changes	0	0	0	0	0	0
Neuropathy (Levi scale, grade 2 or 3)**	**37**	**49**	**31**	**46**	**68**	**47**
Other toxicity (14 MD)	**15**	**20**	**12**	**18**	**27**	**19**

* and neuropathy grade ≥ 2 using Levi scale; MD=Missing data

** see appendix 3 for results by grade

Table 16: Severe toxicities by treatment cycle (n=1 562 cycles)

	GEMOX + CETUXIMAB		GEMOX		All	
	N=865	%	N=697	%	N=1 562	%
At least one severe toxicity*	**464**	**54**	**385**	**55**	**849**	**54**
Hematological toxicity (10 MD)	**46**	**5**	**41**	**6**	**87**	**6**
Hemoglobin (11 MD)	12	1	6	1	18	1
Platelets (15 MD)	10	1	16	2	26	2
White blood cells (13 MD)	11	1	2	0	13	1
ANC (19 MD)	28	3	22	3	50	3
Constitutional / infection (14 MD)	**26**	**3**	**20**	**3**	**46**	**3**
Fatigue (18 MD)	18	2	14	2	32	2
Fever (24 MD)	0	0	1	0	1	0
Infection with ANC <1 (31 MD)	6	1	0	0	6	0
Infection with ANC >1 (31 MD)	1	0	4	1	5	0
Infection with unknown ANC (31 MD)	0	0	2	0	2	0
Febrile neutropenia (26 MD)	2	0	0	0	2	0
LAB toxicity (32 MD)	**265**	**31**	**295**	**42**	**560**	**36**
ALT/AST (47 MD)	39	5	12	2	51	3
ALP (81 MD)	71	8	55	8	126	8
GGT (52 MD)	256	30	293	42	549	35
Bilirubin (47 MD)	17	2	4	1	21	1
Creatinin (44 MD)	1	0	.	.	1	0
Mg (463 MD)	0	0	0	0	0	0
Gastrointestinal toxicity (15 MD)	**14**	**2**	**10**	**1**	**24**	**2**
Anorexia (24 MD)	4	0	3	0	7	0
Nausea (27 MD)	2	0	2	0	4	0
Vomiting (29 MD)	4	0	2	0	6	0
Diarrhea (27 MD)	8	1	3	0	11	1
Constipation (24 MD)	0	0	0	0	0	0
Mucositis (22 MD)	1	0	0	0	1	0
Skin toxicity (16 MD)	13	2	1	0	14	1
Allergic reaction/hypersensitivity (28 MD)	6	1	1	0	7	0
Alopecia (24 MD)	0	0	0	0	0	0
Acneiform rash (25 MD)	6	1	0	0	6	0
Conjunctivitis (30 MD)	1	0	0	0	1	0
Nail changes (31 MD)	0	0	0	0	0	0
Neuropathy (Levi scale, grade 2 or 3) (32 MD)	**213**	**25**	**125**	**18**	**338**	**22**
Other toxicity (40 MD)	**21**	**2**	**16**	**2**	**37**	**2**

MD: Missing data; queries ongoing to determine whether unfilled items on a same form correspond or not to unknown data. Toxicity was not reported in 12 last cycles (7 in the GEMOX + Cetuximab arm and 5 in the GEMOX alone arm).

Other grade 3-4 toxicities are presented in Table 17.

Table 17: Other severe toxicities

Patient number	Treatment arm	Cycle	Toxicity 'other'	Grade
7	GEMOX alone	6	Performance status deterioration	3
7	GEMOX alone	6	Cholangitis	4
8	GEMOX + cetuximab	4	Dizziness	3
8	GEMOX + cetuximab	4	Performance status deterioration	4
12	GEMOX alone	5	Performance status deterioration	3
12	GEMOX alone	5	Neurological troubles	3
12	GEMOX alone	5	Hypercalcemia	4
12	GEMOX alone	6	Hypercalcemia	3
12	GEMOX alone	6	Neurological troubles	3
18	GEMOX alone	8	Cholangitis	3
25	GEMOX + cetuximab	2	Tumor necrosis	3
25	GEMOX + cetuximab	3	Port site infection	3
26	GEMOX alone	4	Stenosis	3
27	GEMOX + cetuximab	4	Hematemesis	3
32	GEMOX alone	1	Dysphonia (pulmonary)	3
43	GEMOX alone	4	Ascites	3
43	GEMOX alone	5	Ascites	3
43	GEMOX alone	6	Ascites	3
51	GEMOX + cetuximab	5	Hypokalemia	3
53	GEMOX + cetuximab	3	Abdominal cramps	3
53	GEMOX + cetuximab	18	Shoulder calcification	3
55	GEMOX alone	2	Dehydration	3
60	GEMOX + cetuximab	2	Deep vein thrombosis	3
60	GEMOX + cetuximab	8	Sepsis	3
60	GEMOX + cetuximab	8	Arterial hypertension	3
62	GEMOX alone	10	Deep vein thrombosis (upper limb)	3
68	GEMOX + cetuximab	3	Acute pancreatitis	3
68	GEMOX + cetuximab	4	Acute pancreatitis	3
68	GEMOX + cetuximab	5	Acute pancreatitis	3
70	GEMOX + cetuximab	12	Abdominal pain	3
85	GEMOX alone	4	Abdominal pain	3
97	GEMOX + cetuximab	3	Hypokalemia	3
101	GEMOX + cetuximab	4	Hepatic encephalopathy	3
103	GEMOX alone	1	Infectious pneumonia	4
105	GEMOX + cetuximab	6	Infection	3
109	GEMOX + cetuximab	1	Abdominal pain	3
110	GEMOX alone	3	Pain	3
110	GEMOX alone	4	Abdominal pain	3
113	GEMOX + cetuximab	5	Asthenia	3
119	GEMOX + cetuximab	7	Abdominal pain	3
141	GEMOX alone	10	Articular pains (jaws)	3
149	GEMOX + cetuximab	9	Dyspnea	3
149	GEMOX + cetuximab	9	CHAP (meaning??)	3
149	GEMOX + cetuximab	10	Dyspnea	3

Multiple toxicities occurring in a given patient during the same cycle (in grey) account for one case of 'other toxicity' in the previous table. In the GEMOX + Cetuximab arm, 4 patients had abdominal pain/cramps and in the GEMOX alone arm, 2 patients had abdominal pain/cramps.

The rate of severe toxicity did not differ according to treatment arm (54% of cycles in GEMOX + Cetuximab arm vs. 55% in the GEMOX arm, p=0.53) but differed according to the country: 60% of the cycles in French centers vs. 42% of the cycles in German centers (p<0.0001). The rate of severe toxicity according to the center is given in Table 18. Three German centers have a percentage of cycles with severe toxicity of 15% or less.

Table 18: Rate of severe toxicity according to the center

Country	Center	Number of patients	Number of cycles with toxicity information	Number of cycles with severe toxicity	Percentage of cycles with severe toxicity
France	Institut Gustave Roussy - Villejuif	9	107	54	50
France	Hôpital Beaujon - Clichy	10	139	66	47
France	Pitié Salpétrière - Paris	2	8	4	50
France	Hôpital St Antoine - Paris	16	195	117	60
France	Centre Léon Bérard - Lyon	17	196	147	75
France	CRLC Val d'Aurelle - Montpellier	6	68	42	62
France	Institut Paoli Calmettes - Marseille	9	78	49	63
France	Centre Eugène Marquis- Rennes	17	168	119	71
France	Hôpital St André - Bordeaux	8	65	21	32
France	Henri Mondor - Créteil	4	37	15	41
France	Hôpital Bordeaux Haut Lévêque - Pessac	2	29	24	83
Germany	Ulm	6	70	38	54
Germany	Essen	17	187	28	**15**
Germany	Halle	2	14	0	**0**
Germany	Hannover	12	142	103	73
Germany	Heidelberg	4	32	21	66
Germany	München	1	20	10	50
Germany	Regensburg	2	8	1	**13**

5.2 Details on infectious toxicities

5.2.1 Cholangitis

After consulting drug safety and clinical databases, 8 bile duct infections have been identified in 7 patients (considering 2 infections for patient #125): 4 patients in the GEMOX arm and 3 in the GEMOX + Cetuximab arm. They are described below.

Patient (center) Sex/age	PS	Disease (location/ stage)	Arm (cycles received)	Event	Date (days since the last cycle)	SAE	Status
#7 (8) M/66	1	GB/M+	GEMOX (6)	Grade 4 cholangitis	01-feb-08 (17)	Unrelated	Died 14-apr-08 (PD)
#18 (5) F/52	1	CC/M+	GEMOX (8)	Grade 3 cholangitis	22-may-08 (11)	Unrelated	Died 27-oct-10 (PD)
#114 (19) M/55	0	CC/LA	GEMOX (12)	Grade 3 cholangitis	Cycle 6	Unrelated	Alive 08-jul-10
#125 (3) M/71	1	CC/M+	GEMOX (9)	Grade 2 cholangitis	Cycle 5	Unrelated	Died 06-apr-2010 (cholangitis)
#106 (19) F/58	0	CC/M+	GEMOX-cetuximab (13)	Grade 3 cholangitis	Cycle 8	Unrelated	Died 15-feb-10 (PD)
#113 (20) M/72	0	CC/LA	GEMOX-cetuximab (5)	Cholangitis	03-sep-09 (18)	Unrelated	Died 5-oct-10 (PD)
#126 (5) M/53	NA	CC/M+	GEMOX-cetuximab (13)	Grade 3 cholecystitis	Cycle 6	Unrelated	Died 20-oct-10 (PD)

CC, cholangiocarcinoma. GB, gallbladder. LA, locally advanced. M+, metastatic. NA, not available. PD, progressive disease. PS, performance status at study entry.

5.2.2 Other infections

27 infections in 22 patients are described in the next table: 11 infections in 9 patients in the GEMOX arm and 16 infections in 13 patients in the GEMOX + cetuximab arm. Two infections, one in each arm, had a fatal outcome.

Numtas	CT	Trait	Sex	Age	Tumor location	Disease status	PS	During study treatment	Date of Infection	Toxicity descxription	Grade	SAE	Related	Tt relation	Follow_up	Status
13	5	GEMOX + CET	M	75	Cholangiocarcinoma	Metastatic	1	Yes	28-août-08	Dental abscess	2	0			27-nov-10	Death
14	8	GEMOX + CET	M	60	Cholangiocarcinoma	Metastatic	1	Yes	09-janv-08	Urinary infection	2	0			16-oct-08	Death
14	8	GEMOX + CET	M	60	Cholangiocarcinoma	Metastatic	1	Yes	13-févr-08	Urinary infection	1	0			16-oct-08	Death
17	5	GEMOX + CET	M	72	Multifocal	Metastatic	1	Yes	04-févr-08	Central venous catheter infection (anc<1)	3	0			05-avr-08	Death
25	7	GEMOX + CET	M	64	Cholangiocarcinoma	Metastatic	0	Yes	26-mars-08	Septicemia staphylococcal /catheter related	3	1	Unrelated		11-nov-08	Death
25	7	GEMOX + CET	M	64	Cholangiocarcinoma	Metastatic	0	Yes	16-mai-08	Sepsis/catheter related infection	3	1	Unrelated		11-nov-08	Death
42	13	GEMOX + CET	F	64	Cholangiocarcinoma	Metastatic	1	No	21-juil-10	**Renal failure/sepsis**	5	0			21-juil-10	Death
51	11	GEMOX + CET	F	62	Gallbladder	Locally advanced	0	Yes	19-mai-08	Infection (ANC<1)	2	0			16-août-08	Death
51	11	GEMOX + CET	F	62	Gallbladder	Locally advanced	0	Yes	12-juin-08	Infection (ANC<1)	2	0			16-août-08	Death
59	18	GEMOX + CET	M	56	Cholangiocarcinoma	Metastatic	0	Yes	22-mai-08	Bronchitis	1	0			24-mai-10	Death
60	9	GEMOX + CET	F	70	Gallbladder	Metastatic	0	Yes	08-sept-08	Biliary sepsis/renal failure /dyspnea	2	1	Unrelated		08-nov-08	Death
77	6	GEMOX + CET	M	36	Cholangiocarcinoma	Metastatic	1	Yes	26-août-08	Catheter infection	2	1	Unrelated		25-sept-08	Death
89	10	GEMOX + CET	M	68	Cholangiocarcinoma	Metastatic	1	Yes	24-févr-09	Catheter related septicemia	5	1	Unrelated		24-févr-09	Death

105	9	GEMOX + CET	M	61	Cholangiocarcinoma	Locally advanced	1	Yes	15-mai-09	Infection with normal anc /hypothermia	3	1	Unrelated		04-sept-09	Death
109	9	GEMOX + CET	M	55	Cholangiocarcinoma	Locally advanced	1	Yes	28-avr-09	Infection (ANC<1)	3	0			23-mai-10	Death
150	6	GEMOX + CET	F	67	Cholangiocarcinoma	Locally advanced	1	Yes	07-sept-10	Stent related infection /stent placement	3	1	Unrelated		29-déc-10	Alive
11	5	GEMOX alone	F	59	Cholangiocarcinoma	Metastatic	1	Yes	10-oct-08	Clostridium colitis	3	1	Related	GEMCITABINE	29-nov-10	Alive
36	6	GEMOX alone	F	52	Cholangiocarcinoma	Locally advanced	1	Yes	07-juin-08	Septicemia	2	1	Unrelated		03-mars-09	Death
52	7	GEMOX alone	M	42	Cholangiocarcinoma	Metastatic	0	Yes	21-août-08	Sinusitis	2	0			06-sept-10	Death
52	7	GEMOX alone	M	42	Cholangiocarcinoma	Metastatic	0	Yes	11-sept-08	Sinusitis	2	0			06-sept-10	Death
64	8	GEMOX alone	M	65	Cholangiocarcinoma	Metastatic	1	Yes	19-juin-08	Urinary infection	1	0			19-juil-09	Death
85	18	GEMOX alone	F	51	Cholangiocarcinoma	Metastatic	1	Yes	09-sept-08	Infection ANC >=1)	3	0			22-nov-08	Death
87	11	GEMOX alone	F	53	Cholangiocarcinoma	Metastatic	0	Yes	10-mars-09	**Atypical pneumonia**	**5**	1	Related	GEMOX	10-mars-09	Death
95	9	GEMOX alone	F	51	Cholangiocarcinoma	Locally advanced	0	Yes	27-nov-08	Sinusitis	2	0			22-nov-10	Death
95	9	GEMOX alone	F	51	Cholangiocarcinoma	Locally advanced	0	Yes	19-févr-09	Sinusitis	1	0			22-nov-10	Death
103	9	GEMOX alone	M	72	Cholangiocarcinoma	Metastatic	0	Yes	20-avr-09	Lung infection	4	1	Related	GEMOX	05-mai-09	Death
139	6	GEMOX alone	F	62	Cholangiocarcinoma	Metastatic	1	Yes	23-nov-09	Infection ANC unknown	3	0			26-janv-10	Death

6 Serious adverse events

This section was unchanged since the previous report. Data presented here have been reconciled with the drug safety database. The safety reports are based on all included patients (150 patients).

Table 19 lists the serious adverse events (SAE) declared to the drug safety unit:
- In the GEMOX + cetuximab arm, 68 SAE were declared in 38 patients;
- In the GEMOX alone arm, 40 SAE were declared in 24 patients.

The number of declared SAE was 74 in France and 34 in Germany, among 105 and 45 randomized patients, respectively.
Overall, 54 SAE were deemed related to treatment:
- 20 SAE in 12 patients in the GEMOX alone arm,
- 34 SAE in 19 patients in the GEMOX+CETUXIMAB arm.

Additionally, five SAE in three patients were registered in the clinical database but not reported to the drug safety unit: #22, elevated serum bilirubin level; #85 and #139: infection.

Table 19: SAE

Patient number	Arm (A=without, B=WITH CETUX)	Country	serious adverse event	Related	Date of onset	Outcome
2	B	France	prosthesis implantation	Unrelated	17/04/2008	Resolved
7	A	France	cholangitis	Unrelated	18/02/2008	Resolved
8	B	France	nausea post chemotherapy	Related	03/01/2008	Resolved
8	B	France	fatigue	Related	03/01/2008	Resolved
8	B	France	dizziness on standing up	Related	03/01/2008	Resolved
8	B	France	vomiting/weight loss/general physical health deterioration	Unrelated	09/01/2008	Resolved
11	A	France	clostridium colitis	Related	10/10/2008	Resolved
12	A	France	hypercalcemia of malignancy/confusion/general health deterioration/disorientation	Unrelated	27/02/2008	Resolved
12	A	France	humerus fracture	Unrelated	20/03/2008	Resolved
12	A	France	hypercalcemia of malignancy/confusion	Unrelated	20/03/2008	Resolved
13	B	France	allergic reaction	Related	12/07/2008	Resolved
14	B	France	burning micturition	Unrelated	21/02/2008	Resolved
17	B	France	malnutrition	Related	17/03/2008	Resolved
17	B	France	Death (documented disease progression)	Unrelated	04/04/2008	Death
18	A	France	neutropenia	Related	01/03/2008	Resolved
18	A	France	thrombocytopenia	Related	01/03/2008	Resolved
18	A	France	anemia post chemotherapy	Related	01/03/2008	Resolved
18	A	France	cholangitis acute	Unrelated	02/06/2008	Resolved
22	B	France	biliary drainage	Unrelated	16/01/2008	Resolved
22	B	France	drain placement	Unrelated	14/03/2008	Resolved
25	B	France	melaena	Related	03/03/2008	Resolved

25	B	France	septicemia staphylococcal/catheter related infection	Unrelated	26/03/2008	Resolved
25	B	France	sepsis/catheter related infection	Unrelated	16/05/2008	Resolved
26	A	France	duodenal stenosis	Unrelated	17/04/2008	Resolved
27	B	France	bleeding esophageal varices	Unrelated	14/04/2008	Resolved
30	B	Germany	general physical health deterioration	Related	14/04/2008	Resolved
31	A	France	Death (documented disease progression)	Unrelated	27/03/2008	Death
35	B	France	prosthesis implantation	Unrelated	11/09/2008	Resolved
35	B	France	bile duct stenosis/biliary drainage	Unrelated	30/10/2008	Resolved
36	A	France	septicemia	Unrelated	07/06/2008	Resolved
36	A	France	prosthesis implantation	Unrelated	03/07/2008	Resolved
38	A	Germany	allergic reaction	Related	07/08/2008	Resolved
41	B	Germany	nausea post chemotherapy	Related	09/04/2008	Resolved
41	B	Germany	fatigue	Related	05/05/2008	Resolved
45	A	France	Death (Possible etiological factors include the underlying malignancy and the concurrent infrarenal aortic aneurysm)	Unrelated	20/09/2008	Death
47	B	Germany	allergic reaction	Related	17/04/2008	
48	B	France	neutropenia	Related	22/09/2008	Resolved
48	B	France	prosthesis implantation	Unrelated	22/10/2008	Resolved
48	B	France	prosthesis implantation	Unrelated	25/11/2008	Resolved
51	B	Germany	fever of unknown origin	Related	15/05/2008	Resolved
51	B	Germany	abdominal pain	Related	18/06/2008	Resolved
51	B	Germany	fever of unknown origin	Related	18/06/2008	Resolved
51	B	Germany	abdominal pain	Related	19/07/2008	Resolved
52	A	France	fever of unknown origin	Related	06/08/2008	Resolved
52	A	France	catheter placement	Unrelated	02/10/2008	Resolved
53	B	France	nausea post chemotherapy	Related	11/06/2008	Resolved
53	B	France	vomiting post chemotherapy	Related	11/06/2008	Resolved
53	B	France	diarrhea post chemotherapy	Related	08/11/2008	Resolved
55	A	Germany	nausea post chemotherapy	Related	16/05/2008	Resolved
55	A	Germany	vomiting post chemotherapy	Related	16/05/2008	Resolved
55	A	Germany	dehydration	Related	04/06/2008	Resolved
55	A	Germany	fever of unknown origin	Related	04/06/2008	Resolved
55	A	Germany	hypotension	Related	04/06/2008	Resolved
56	B	Germany	thrombocytopenia	Related	18/06/2008	Resolved
56	B	Germany	colitis	Related	18/06/2008	Resolved
60	B	France	biliary sepsis/renal failure/dyspnea	Unrelated	08/09/2008	Resolved
62	A	France	thrombophlebitis arm	Related	12/10/2008	Resolved
63	B	Germany	fever of unknown origin	Related	28/08/2008	Resolved
63	B	Germany	chills	Related	28/08/2008	Resolved
67	A	Germany	cytokine release syndrome	Related	27/08/2008	Resolved
68	B	France	neutropenia	Related	21/07/2008	Resolved
68	B	France	acute pancreatitis	Related	09/08/2008	Resolved
68	B	France	acute pancreatitis	Related	01/09/2008	Resolved
68	B	France	allergic reaction	Related	10/09/2008	Resolved
71	A	France	allergic reaction	Related	03/12/2008	Resolved
75	A	Germany	Death (documented disease progression)	Unrelated	21/08/2008	Death
76	A	Germany	general physical health deterioration	Unrelated	19/08/2008	Resolved

77	B	France	general physical health deterioration/ascites/malnutrition/catheter infection/acute renal insufficiency	Unrelated	26/08/2008	Resolved
78	B	Germany	oropharyngeal dysesthesia	Related	14/08/2008	Resolved
78	B	Germany	pulmonary embolism	Unrelated	29/09/2008	Resolved
78	B	Germany	diarrhoea	Unrelated	15/10/2008	Resolved
79	B	France	bile duct obstruction/general physical health deterioration/asthenia	Unrelated	02/11/2008	Resolved
82	B	Germany	fever of unknown origin	Related	20/09/2008	Resolved
87	A	Germany	abdominal pain	Related	04/02/2009	Resolved
87	A	Germany	atypical pneumonia	Related	10/03/2009	Death
89	B	Germany	tendovaginitis	Unrelated	27/12/2008	Resolved
89	B	Germany	catheter related septicemia	Unrelated	24/02/2009	Death
93	B	Germany	diarrhea post chemotherapy	Related	31/12/2008	Resolved
93	B	Germany	fever of unknown origin	Related	31/12/2008	Resolved
93	B	Germany	cholestasis	Unrelated	12/02/2009	Unknown
96	A	Germany	general physical health deterioration	Unrelated	24/05/2009	Death
100	B	France	allergic reaction	Unrelated	01/07/2009	Resolved
101	B	France	Death (disease progression)	Unrelated	22/12/2008	Death
103	A	France	lung infection	Related	20/04/2009	Unknown
105	B	France	infection with normal anc/hypothermia	Unrelated	15/05/2009	Resolved
106	B	France	cholangitis	Unrelated	27/08/2009	Resolved
109	B	France	fever/abdominal pain	Unrelated	12/05/2009	Resolved
110	B	France	extrahepatic biliary obstruction	Unrelated	13/05/2009	Resolved
113	B	France	hyperthermia	Unrelated	24/08/2009	Resolved
113	B	France	choledochitis	Unrelated	21/09/2009	Resolved
114	A	France	abdominal pain	Unrelated	14/06/2009	Resolved
114	A	France	hematemesis	Unrelated	10/08/2009	Resolved
114	A	France	cholangiolitis	Unrelated	03/09/2009	Resolved
119	B	France	anemia post chemotherapy	Related	13/08/2009	Resolved
121	A	France	gastroenteritis viral	Unrelated	23/12/2009	Resolved
123	A	France	abdominal pain/leg oedema/dyspnea/anorexia/general physical health deterioration	Unrelated	22/10/2009	Resolved
123	A	France	anemia post chemotherapy	Related	22/10/2009	Resolved
123	A	France	thrombopenia	Related	22/10/2009	Resolved
125	A	France	cholangitis	Unrelated	15/10/2009	Resolved
126	B	France	cholecystitis/sepsis/abdominal abscess	Unrelated	10/12/2009	Resolved
126	B	France	device migration	Unrelated	06/01/2010	Resolved
131	A	France	fever of unknown origin	Related	14/10/2009	Resolved
137	B	France	allergic reaction	Related	19/11/2009	Resolved
138	B	Germany	pneumothorax	Unrelated	06/11/2009	Resolved
145	B	France	allergic reaction	Related	19/11/2009	Resolved
145	B	France	neutropenia	Related	04/12/2009	Resolved
150	B	France	acute renal insufficiency	Unrelated	05/01/2010	Resolved
150	B	France	stent related infection/stent placement	Unrelated	07/09/2010	Resolved

7 Response to treatment

7.1 4-month PFS rate

The 4-month PFS rate is defined by the rate of patients whose disease has not progressed at 4 months and during the 30 days thereafter, as judged by the investigator.

7.1.1 Overall population

Two patients changed their main endpoint status for progression after the answer to queries that were received after the previous report.

Among the 76 patients randomized in the GEMOX + cetuximab arm, 27 had progressed at 4 months. One patient was censored before 4 months (#122, censored at 46 days when he went to another hospital). A sensitivity analysis is done for this patient response:

- If patient #122 is considered as a failure, the 4-month PFS rate is equal to 48/76 (63%, 95% CI: 52 to 74%);
- If patient #122 is not considered as a failure, the 4-month PFS rate is equal to 49/76 (64%, 95% CI: 54 to 75%).

On the evaluable population (n=75 patients), the 4-month PFS rate is equal to 48/75 (64%, 95% CI: 53 to 75%).

In the protocol, at least 22 patients out of 46 (48%) should not have progressed to conclude that the GEMOX + cetuximab combination regimen is effective. As 32 out of 50 patients (64%) had not progressed at 4 months, it could be concluded that the GEMOX + cetuximab combination regimen was effective.

Among the 74 patients randomized in the GEMOX alone arm, 34 had progressed at 4 months. No patient was censored at this time. All patients were considered as evaluable at 4 months.
The 4-month PFS rate was equal to 40/74 (54%, 95% CI: 43% to 65%).

Among the first 51 patients, the 4-month PFS rate was equal to 28/51 (55%, 95% CI: 41 to 69%). When non-treated patients were excluded, the 4-month PFS rate was of 28/49 (57%, 95% CI: 43 to 71%).

7.1.2 Subgroup analysis

7.1.2.1 Primary tumor location

Among the 150 patients, 65/76 patients in the GEMOX + cetuximab arm and 63/74 patients in the GEMOX arm had a non-gallbladder tumor.

Reminder: In the protocol, at least 22 patients out of 46 (48%) should not have progressed to conclude that the GEMOX + cetuximab combination regimen is effective.

Among the 65 patients with **non-gallbladder tumor randomized in the GEMOX + cetuximab arm**, 22 had progressed at 4 months. One patient was censored before 4 months (#122, censored at 46 days). A sensitivity analysis is done for this patient response:

- If patient #122 is considered as a failure, the 4-month PFS rate is equal to 42/65 (65%, 95% CI: 53 to 76%);
- If patient #122 is not considered as failure, the 4-month PFS rate is equal to 43/65 (66%, 95% CI: 55 to 78%).

On the evaluable population (n=64 patients), the 4-month PFS rate is equal to 42/64 (66%, 95% CI: 54 to 77%).
Whatever the scenario, the strategy was considered effective in this localization subgroup.

In this arm, 6 patients out of 11 with gallbladder tumor had not progressed at 4 months (55%, 95% CI: 25 to 84). The 4-month PFS rate did not differ between the two localization groups (Fisher exact test, p=0.51).

Among the 63 patients with non-gallbladder tumor randomized in the GEMOX alone arm, 29 had progressed at 4 months. No patient was censored at this time. All patients were considered as evaluable at 4 months. The 4-month PFS rate was equal to 34/63 (54%, 95% CI: 42 to 66%)
In this arm, 6 patients out of 11 with gallbladder tumor had not progressed at 4 months (55% 95% CI: 25 to 84). The 4-month PFS rate did not differ between the two localization groups (Fisher exact test, p=1.00).

7.2 Tumor response and disease control rates

Objective tumor responses include complete responses and partial responses. Disease control is defined as complete response, partial response or stable disease.

7.2.1 At two months

At two months, patients not evaluated have been considered as non-responses.
In the GEMOX + cetuximab arm, the objective tumor response rate (ORR) was 17% (13/76) and the disease control rate (DCR) was 80% (61/76). In this arm, the median time between randomization and this evaluation was 1.8 months (range, 1.1 to 3.3).
In the GEMOX alone arm, ORR was 7% (5/74) and DCR was 65% (48/74). In this arm, the median time between randomization and this evaluation was 1.8 months (range, 1.1 to 2.6).

Table 20: Tumor response at the 2-month assessment

Global response at 2 months	GEMOX + CETUXIMAB n=76	GEMOX alone n=74	Total n=150
Complete Response	1	0	1
Partial Response	12	5	17
Stable Disease	48	43	91
Progressive Disease	8	15	23
Not evaluated (=failure)	7	11	18

Among the 18 patients without evaluation, one was evaluated in subsequent evaluations: #124 had stable disease at six months. All other patients were not evaluated at the subsequent evaluations. At any time, they were considered as non-responders. Consequently, none of the patients, except one (#124), who were considered as failures because of no evaluation, had stable disease or objective response after the missing evaluation.

Table 21: Patients without evaluation at 2 months (n=18)

NUMTAS	Treatment arm	Date of random.	Date of 1st day of last cycle	Total number of cycles	Prog.	Date of event	Survival status	Cause of death
6	GEMOX alone	16/11/2007	19/11/2007	1	1	30/01/2008	1	Progression
8	GEMOX + CETUXIMAB	19/11/2007	02/01/2008	4	1	09/01/2008	1	Progression
31	GEMOX alone	29/02/2008.		0	1	27/03/2008	1	Progression
39	GEMOX alone	25/03/2008	14/04/2008	2	1	30/04/2008	1	Progression
75	GEMOX alone	22/07/2008		0	1	21/08/2008	1	Progression
76	GEMOX alone	24/07/2008	11/08/2008	2	1	19/08/2008	1	Progression
98	GEMOX alone	14/10/2008	14/10/2008	1	1	29/08/2010	1	Other
101	GEMOX + CETUXIMAB	15/10/2008	02/12/2008	4	1	16/12/2008	1	Progression
103	GEMOX alone	24/03/2009	08/04/2009	2	1	20/04/2009	1	Progression
114	GEMOX alone	20/05/2009	25/11/2009	12	0		0	NA
115	GEMOX alone	25/05/2009	22/06/2009	3	1	30/06/2009	1	Progression
120	GEMOX alone	09/07/2009	06/08/2009	3	1	16/09/2009	1	Other
122	GEMOX + CETUXIMAB	17/07/2009	10/08/2009	2	0		0	NA
124	GEMOX + CETUXIMAB	05/08/2009	12/01/2010	12	0		0	NA
127	GEMOX alone	21/08/2009		0	1	20/11/2009	1	Progression
130	GEMOX + CETUXIMAB	14/09/2009	08/02/2010	8	1	14/03/2011	0	NA
138	GEMOX + CETUXIMAB	28/10/2009	17/12/2009	4	1	28/11/2010	1	Progression
146	GEMOX + CETUXIMAB	20/11/2009	08/12/2009	2	1	08/02/2010	1	Progression

NA = not applicable

Notes:
-#124 (Beaujon), evaluation form received with no response specified but obviously stable.
#114 (Mondor) and #130 (Bordeaux), no evaluation form received.

For patients from Henri Mondor, imaging exams have been performed in private clinics that refused to send us the exams. Radiologist from Mondor was not able to conclude with only the exam reports.

7.2.2 At four months

At 4 months, patients progressing or not evaluated at 2 months were considered as non-responses (failure) at 4 months. Patients not evaluated at four months were considered as non-responses.
In the GEMOX + cetuximab arm, ORR was 14% (11/76) and DCR was 62% (47/76). In this arm, the median time between randomization and this evaluation was 3.7 months (range, 2.9 to 5.5).
In the GEMOX alone arm, ORR was 18% (13/74) and DCR was 50% (37/74). In this arm, the median time between randomization and this evaluation was 3.7 months (range, 3.2 to 5.0).

Table 22: Tumor response at the 4-month evaluation

Global response at 4 months	GEMOX + CETUXIMAB n=76	GEMOX alone n=74	Total n=150
Complete Response	1	0	1
Not evaluated but considered as response (#9, see below)	0	1	1
Not evaluated at 2 and 4 months (=failure) but evaluated at 6 months (#124)	1	0	1
Partial Response	10	12	22
Stable Disease	36	24	60
Progressive Disease	9	7	16
Not evaluated (=failure)	5	4	9
Precedent failure	14	26	40

The 9 patients without evaluation are listed in table 23. Additionally, patient #9 (GEMOX alone arm) was not evaluated at 4 months because he stopped treatment to undergo curative-intent surgery. He was considered as objective response.

Table 23: Patients without evaluation at 4 months (n=9)

NUMTAS	Treatment arm	Date of randomization	Number of cycle	Progression	Date of progression/ death	Survival status	Cause of death
7	GEMOX alone	16/11/2007	6	1	14/04/2008	1	Progression
17	GEMOX + Cetuximab	18/01/2008	5	1	05/04/2008	1	Progression
43	GEMOX alone	31/03/2008	8	1	22/07/2008	1	Progression
55	GEMOX alone	07/05/2008	3	1	27/08/2008	1	Progression
60	GEMOX + Cetuximab	21/05/2008	8	1	08/09/2008	1	Progression
67	GEMOX alone	30/06/2008	8	1	23/08/2009	1	Other
68	GEMOX + Cetuximab	03/07/2008	5	1	13/01/2009	1	Progression
78	GEMOX + Cetuximab	31/07/2008	5	1	17/12/2008	1	Progression
105	GEMOX + Cetuximab	07/04/2009	6	1	30/08/2009	1	Progression

Notes:
- #7 (Marseille), #67 (Ulm) stopped treatment for personal convenience before the 4-month tumor evaluation.
- #68 (St Antoine) stopped for treatment toxicity after 5 cycles (09/2008) before 4-month tumor evaluation.
- #55 and 78 (Regensburg) stopped for treatment delay before 4-month tumor evaluation.
- #105 (Rennes) stopped for deterioration of general status before 4 month tumor evaluation.

7.2.3 After four months

Among the 85 patients still having disease control at 4 months or not evaluated at 4 months but evaluated after (#124):

- 17 were not evaluated after this time (9 in the GEMOX + cetuximab arm; 8 in the GEMOX alone arm);
- 32 were progressive at subsequent evaluations (21 in the GEMOX + cetuximab arm; 11 in the GEMOX alone arm);
- 19 had a stable disease (11 in GEMOX + cetuximab arm; 8 in the GEMOX alone arm);
- 17 had an objective tumor response (7 in GEMOX + cetuximab arm; 10 in the GEMOX alone arm), including 3 patient with a complete response (1 and 2 respectively).

For patients evaluated after 4 months (n=68), the median number of evaluations after 4 months was 2 (range, 1 to 7); 28 patients had 3 evaluations or more.

7.2.4 Best response and response duration

Considering the overall best response for the 133 evaluated patients (see Table 24), the **objective tumor response rate** was **26%** (18/70) in the GEMOX + cetuximab arm and **27%** (17/63) in the GEMOX alone arm.
The **disease control rate** in each arm was equal to **89%** (62/70) and **76%** (48/63) respectively.

On intent-to-treat analysis and for the overall best response, the objective tumor response rate was 24% (18/76) in the GEMOX + cetuximab arm and 23% (17/74) in the GEMOX alone arm.
The disease control rate in each arm was equal to 82% (62/76) and 65% (48/74) respectively.

Table 24: Overall best response and validated best response (n=133 evaluated patients)

Best response	GEMOX + cetuximab n=70 N (N validated)	GEMOX alone n=63 N (N validated)	Total n=133
Complete Response	1 (1)	2 (2)	3 (3)
Partial Response	17 (14)	15 (11)	32 (25)
Stable Disease	44 (31)	31 (20)	75 (51)
Progressive Disease	8	15	23

For the 18 patients with objective response (complete response or partial response) in the GEMOX + cetuximab arm, the median duration of response was 5.7 months (range, 1.7 to 26 months). For the 44 patients with stable disease, the median duration of response was 6.1 months (range, 2.4 to 19.6 months).

For the 17 patients with objective response (complete response or partial response) in the GEMOX alone arm, the median duration of response was 8.4 months (range, 2.1 to 33.8 months).
For the 31 patients with stable disease, the median duration of response was 5.9 months (range, 2.4 to 23.8 months).

7.3 Results of scanner review

No new review result was collected since the last report. CT scan collection is ongoing, but we already know that CT scan will not be available for around 10 patients. Section unchanged since previous report.

A review of CT scans by external reviewers was planned, first for the 32 patients of the interim analysis and then for the other patients. Among these 32 patients, 3 (2 in the GEMOX arm) were not evaluable by CT-scan. Because of a misunderstanding on the list of CT-scans to review in priority, the CT scans of 9 patients (5 in the GEMOX + cetuximab arm) are not yet reviewed.

For 22 patients, results of the evaluation at 2 months were reviewed. Results are presented in Table 25.

Table 25 : Review of scanner evaluation at 2 months

	REVIEWER				
INVESTIGATOR	CR	PR	SD	PD	Total
CR					
PR		2			2
SD		1	13		14
PD			4	2	6
Total	0	3	17	2	22

For 14 patients, results of the evaluation at 4 months were reviewed. Results are presented in Table 26.

Table 26 : Review of scanner evaluation at 4 months

	REVIEWER				
INVESTIGATOR	CR	PR	SD	PD	Total
CR					
PR	1				1
SD		1	8	1	10
PD			1	2	3
Total	1	1	9	3	14

For 10 patients, results of the evaluation at 6 months were reviewed. Results are presented in Table 27.

Table 27 : Review of scanner evaluation at 6 months

	REVIEWER				
INVESTIGATOR	CR	PR	SD	PD	Total
CR					
PR	1	1			2
SD		1	3	2	6
PD		1		1	2
Total	1	3	3	3	10

Concerning the evaluation for the main endpoint, discordances were observed in 8 (5 in GEMOX arm) out of 20 patients with scans reviewed: one patient in GEMOX arm deemed stable by the investigator was considered in progression; 5 patients (4 in the GEMOX arm) considered as in progression by the investigator was considered as stable after review; one patient in the cetuximab arm considered as stable was considered in partial response and another patient from the same arm, classified in partial response by the investigator was considered in complete response after review. If we consider the dichotomized classification progression yes/no at 4 months used for the interim analysis in the GEMOX + cetuximab arm, only one patient out of 12 patients with review available in this arm has its response changed from progression to stable. This change has no impact on the decision to continue the trial.

8 Follow-up and long-term assessment

8.1 Follow-up

The median follow-up calculated using inverse Kaplan-Meier method was 31.1 months (range, 1.5 to 36.0). The median follow-up was similar in the two arms: 30.3 months in the GEMOX + cetuximab and 34.9 months in the GEMOX alone arm (log-rank test, p=0.67).
Table 28 describes the 10 patients lost to follow-up on March 31st, 2011 (last contact before November 31st, 2010): 3 in the GEMOX + cetuximab arm and 7 in the GEMOX alone arm.

Table 28 : Patients lost to follow-up (last contact > 4 months; n=10)

Patient number	Treatment arm	Date of end of treatment	Progression	Date of progression	Status	Date of last contact	Follow-up time
117	GEMOX + Cetuximab	30/03/2010	1	07/06/2010	0	12/11/2010	17.3
122	GEMOX + Cetuximab	10/08/2009	0		0	01/09/2009	1.5
145	GEMOX + Cetuximab	2/07/2010	0		0	11/10/2010	10.7
11	GEMOX alone	30/09/2008	1	02/04/2010	0	29/11/2010	36.0
50	GEMOX alone	16/02/2009	1	19/11/2009	0	27/10/2010	29.9
90	GEMOX alone	06/05/2009	1	02/09/2009	0	08/11/2010	25.4
114	GEMOX alone	25/11/2009	0		0	08/07/2010	13.6
121	GEMOX alone	11/01/2010	1	14/01/2010	0	05/10/2010	14.9
135	GEMOX alone	17/03/2010	1	08/04/2010	0	15/11/2010	13.0
141	GEMOX alone	13/04/2010	1	19/07/2010	0	18/11/2010	12.3

Overall survival and progression free survival curves are given for the whole population (n=150) in Figure 2.

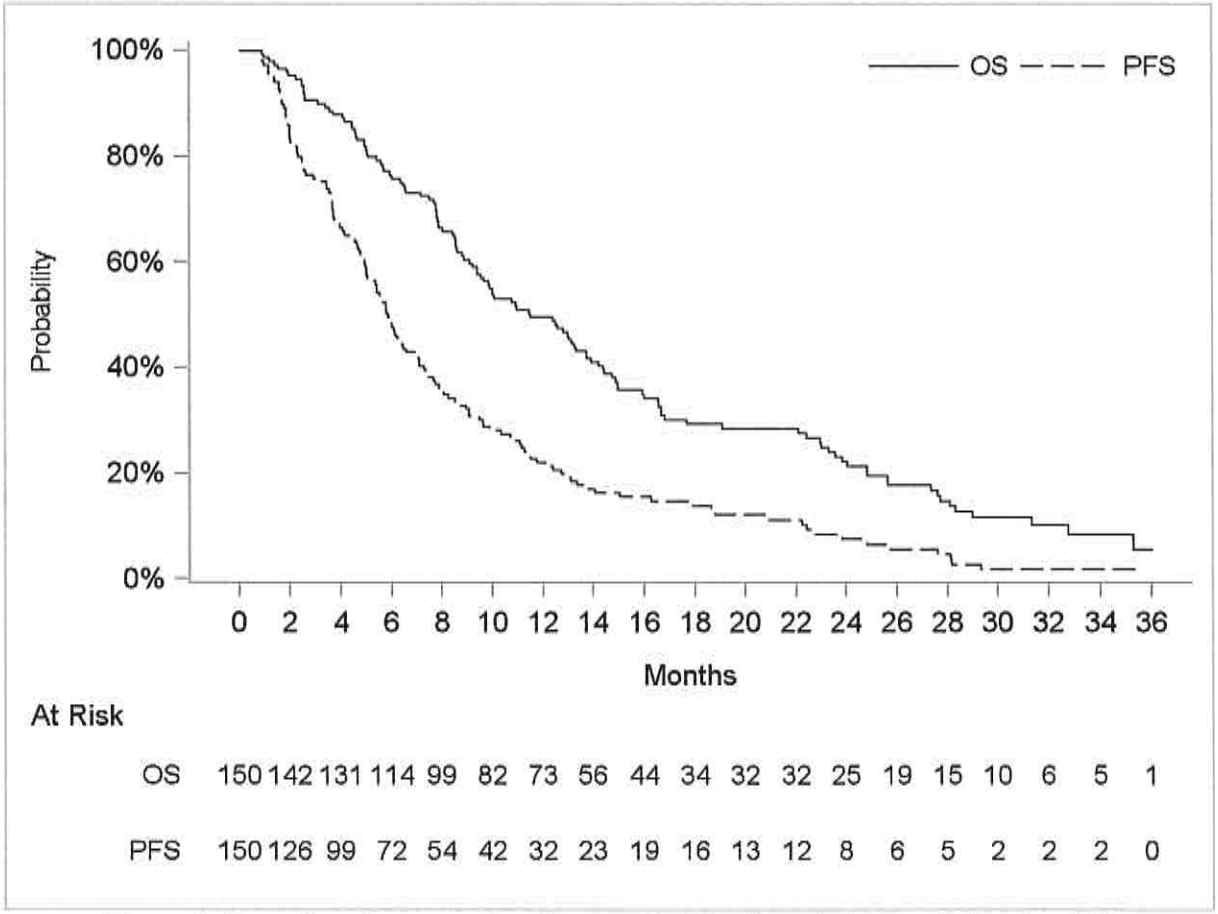

Figure 2: Overall and progression-free survival for the whole population (n=150)

Outcome	No of events	Median (months) [95% CI]	4-month survival [95% CI]	6-month survival [95% CI]	12-month survival [95% CI]	18-month survival [95% CI]
Progression-free survival	140	5.9 [5.0-7.1]	66% [58-73]	48% [39-55]	22% [16-29]	14% [9-20]
Overall survival	124	11.4 [9.4-13.7]	88% [82-92]	76% [68-82]	50% [41-57]	29% [22-37]

Since the last report, two more events occurred for PFS and one more death.

Table 14 in the section on toxicities describes the deaths not related to cancer or treatment.

8.2 Progression-free survival and overall survival in the two arms

Among the 150 patients, 140 patients experienced an event (progression or death), 67 in GEMOX alone arm and 73 in GEMOX + cetuximab arm. The medians [95% confidence interval] of PFS were respectively 5.5 [3.7-6.6] and 6.1 [5.1-7.6] months.

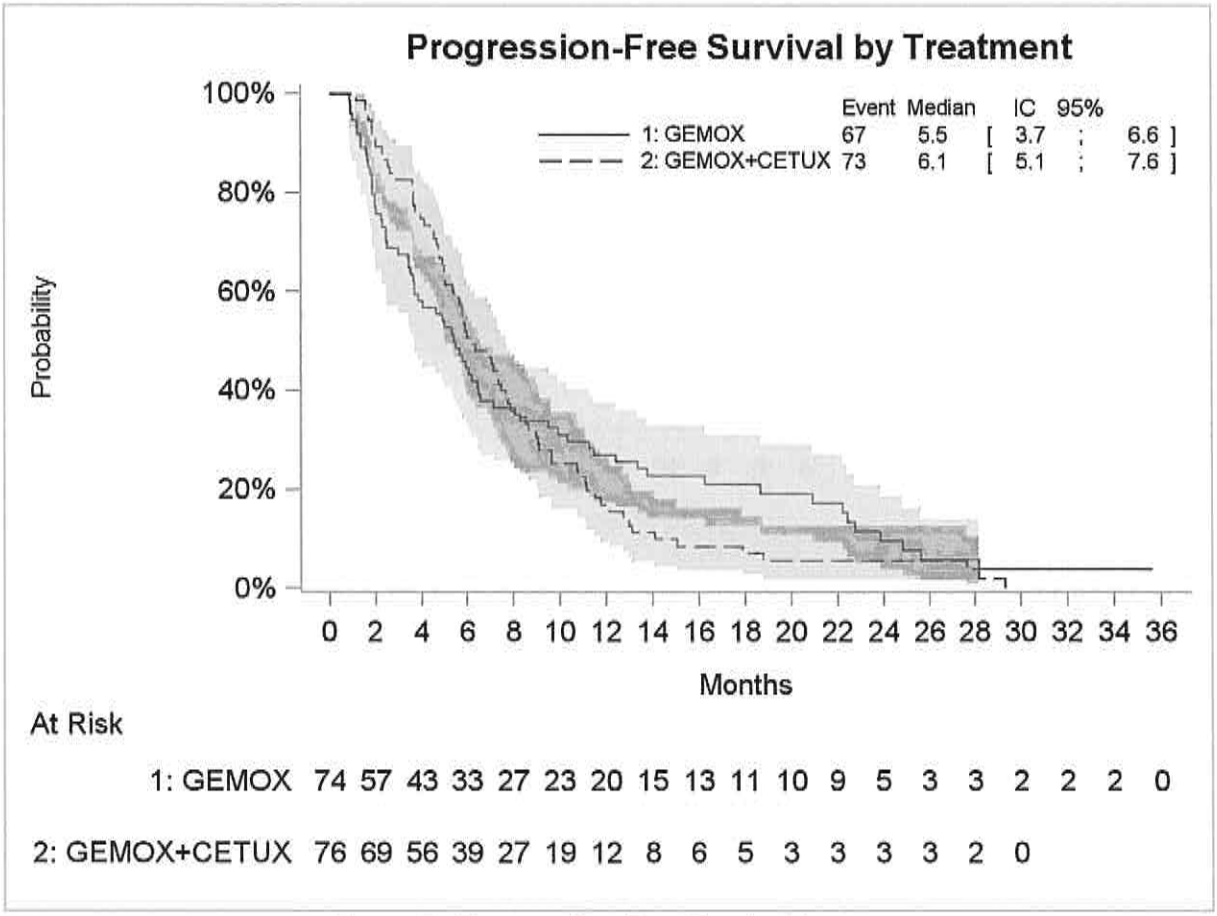

Figure 3 : Progression-Free Survival by arm

Among the 150 patients, 124 patients died, 59 in GEMOX alone arm and 65 in GEMOX + cetuximab arm. The medians [95% confidence interval] of overall survival were respectively 12.4 [8.6-16.0] and 11.0 [9.1-13.7] months.

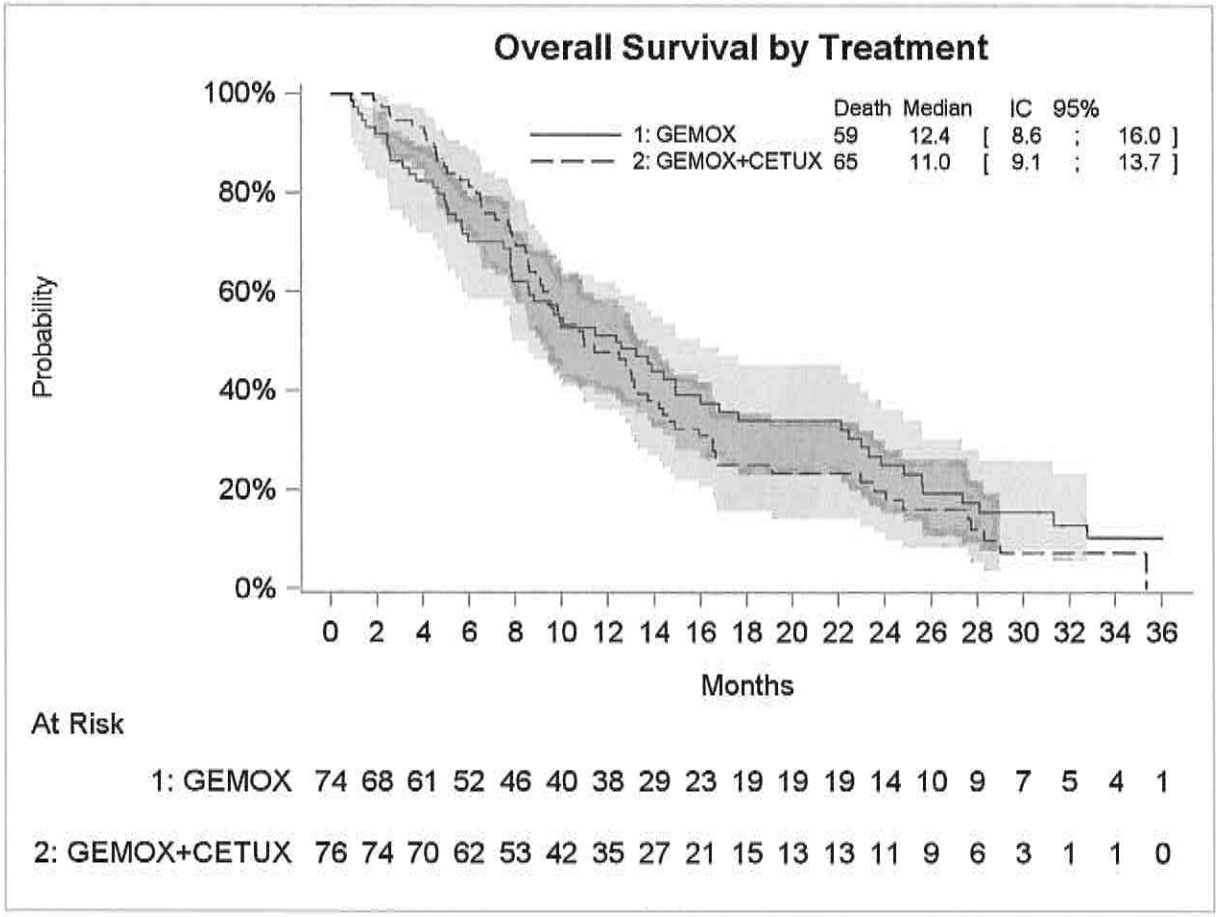

Figure 4 : Overall Survival by arm

8.3 Description of post-study chemotherapy

After stopping study treatment, 60 patients were given a 2nd-line treatment (32 patients in the GEMOX + cetuximab arm and 28 in the GEMOX alone arm), 7 a 3rd-line treatment (5 in the GEMOX + cetuximab arm and 2 in the GEMOX alone arm) and one a 4th-line treatment.
Table 29 details the drug received by the patients in 2nd-line chemotherapy.

Table 29 : Drug received as 2nd-line chemotherapy (n=60)

Drug administrated	GEMOX + cetuximab n=32	GEMOX alone n=28	Total n=60
Capecitabine (CAP)	3	3	6
5 Fluorouracil (FU)	6	1	7
Mitomycin C (MMC)	1	2	3
Gemcitabine (GEM)	2	3	5
Carboplatin		1	
Paclitaxel		1	1
Sunitinib	1	1	2
CAP + Irinotecan (CPT11)	1		1
CAP + GEM	1	3	4
CAP + Carboplatin	1		1
FU + MMC	1		1
FU + CPT11	3	3	6
FU + Folinic Acid + CPT11	1		1
FU + Oxaliplatin	1		1
FU + Cisplatin	2	1	3
FU + Carboplatin		1	1
GEM + Oxaliplatin	1	2	3
GEM + Carboplatin		1	1
GEM + Cetuximab	1		1
CPT11 + Cetuximab		1	1
FOLFIRI	2		2
FOLFIRI + Sunitinib	1		1
Not specified	3	4	7

9 Exploratory analyses according to tumor KRAS/BRAF mutations and EGFR expression

9.1 Laboratory methods

EGFR tumor status was assessed by immunohistochemistry on tissue collected by biopsy or surgery prior to study entry. EGFR expression score was generated using the DAKO EGFR kit and the Hirsch scoring system where EGFR IHC H-score = 1 x (% cells 1+) + 2 x (% cells 2+) + 3 x (% cells 3+) *(Hirsch, J Clin Oncol 2003; Cappuzzo, J Natl Cancer Inst, 2005)*. The outcome-based discriminatory threshold H-score for this analysis was set at 200 samples were then classified as either low (H-score < 200; IHC negative) or high (≥200; IHC positive) for EGFR protein expression *(Pirker, Lancet Oncol 2011; Pirker, Lancet Oncol 2012; Mazières, Lung Cancer 2013)*. DNA was extracted from paraffin-embedded tumor tissue using macrodissection. KRAS/BRAF mutations were screened with high-resolution melting (real-time PCR, Light Cycler 480®, Roche) followed by DNA sequencing (Sanger) if positive. Allelic discrimination was carried out in case of doubtful result (Taqman® MX3000, Stratagene).

9.2 Results

9.2.1 KRAS, BRAF mutations and EGFR expression tumor status

Among 91 samples available for biomarker analysis, 75 were suitable for KRAS and BRAF analysis and 77 samples were suitable for EGFR analysis Table 30). 19% of the tumor samples had a KRAS mutation. 5% of the tumor samples had a BRAF mutation. 23% of the tumor samples had a high EGFR H-score.

Table 30 : KRAS, BRAF mutations and EGFR expression tumor status

	Arm GEMOX + CETUXIMAB n (%)	Arm GEMOX alone n (%)	Total N (%)	P value †
KRAS (n=75)				
Wild type	37 (82%)	24 (80%)	61 (81%)	0.81
Mutated	8 (18%)	6 (20%	14 (19%)	
BRAF (n=75)				
Wild type	43 (96%)	28 (93%)	71 (95%)	1.00 ‡
Mutated	2 (4%)	2 (7%)	4 (5%)	
KRAS/BRAF (n=75)				
Wild type	35 (78%)	22 (73%)	57 (76%)	0.66
Mutated	10 (22%)	8 (27%)	18 (24%)	
EGFR H-score (n=77)				
<200	37 (76%)	22 (79%)	59 (77%)	0.76
≥200	12 (24%)	6 (21%)	18 (23%)	

† Chi square test, ‡ Fisher exact test

9.2.2 4-month PFS rate according to KRAS/BRAF/EGFR tumor status

As shown in Table 31, the 4-month PFS rate did not differ according to the KRAS or BRAF mutation status (wild-type vs. mutated) nor according to the EGFR expression status (EGFR H-score <200 vs. EGFR H-score ≥200).

Table 31 : 4-month PFS rate according to KRAS/BRAF/EGFR tumor status

	4-month PFS rate		P value†
	n/N	%	
KRAS (n=75)			0.72
Wild-type	38/61	*62*	
Mutated	8/14	*57*	
BRAF (n=75)			1.00‡
Wild-type	43/71	*61*	
Mutated	3/4	*75*	
KRAS/BRAF (n=75)			0.98
Wild-type	35/57	*61*	
Mutated	11/18	*61*	
EGFR score (n=77)			0.42
<200	39/59	*63*	
≥200	10/18	*56*	

† Chi square test, ‡ Fisher exact test

9.2.3 4-month PFS rate according to KRAS/BRAF/EGFR tumor status and the treatment arm

As shown in Table 32, no significant differences were seen according to the presence or absence of either KRAS mutation or EGFR overexpression between the treatment arms for the 4-month PFS rate.

Table 32 : 4-month PFS rate according to KRAS/BRAF/EGFR tumor status and the treatment arm

	4-month PFS rate		
	Arm GEMOX + CETUXIMAB n/N (%)	**Arm GEMOX alone** n/N (%)	**OR [95% CI]***
KRAS (n=75)			
Wild type (n=61)	24/37 (65%)	14/24 (58%)	1.32 [0.46-3.79]
Mutated (n=14)	5/8 (63%)	3/6 (50%)	1.67 [0.20-14.27]
BRAF (n=75)			
Wild type (n=71)	27/43 (63)	16/28 (57%)	ND
Mutated (n=4)	2/2 (100%)	1/2 (50%)	ND
KRAS/BRAF (n=75)			
Wild type (n=57)	22/35 (63%)	13/22 (59%)	1.17 [0.39-3.49]
Mutated (n=18)	7/10 (70%)	4/8 (50%)	2.33 [0.34-16.18]
EGFR H-score (n=77)			
<200 (n=59)	25/37 (68%)	14/22 (64%)	1.19 [0.39-3.61]
≥200 (n=18)	7/12 (58%)	3/6 (50%)	1.40 [0.20-10.03]

** GEMOX + Cetuximab vs. GEMOX alone. CI, confidence interval. n/N, number of events/total number of patients. ND, not done due to small numbers. OR, odds ratio.*

The OS and PFS curves according to KRAS/BRAF/EGFR tumor status and treatment arm are presented in Appendix 4.

10 Conclusion

Accrual was more rapid than planned. Overall, the quality of data was good with 10 patients (3 in the GEMOX + cetuximab arm, 7 in the GEMOX alone arm) considered lost to follow-up after the end of their treatment, most of them being followed more than 12 months.
Treatment tolerance was good in this population setting, without major differences between the two arms. No unexpected toxicity was observed.
The scheduled analyses of the main endpoint in the GEMOX + cetuximab arm allow concluding to treatment efficacy, according to prespecified statistical hypotheses. However, overall response rates and median PFS and OS were similar in both arms. With the limit of statistical power in exploratory analyses, tumor KRAS/BRAF mutations and EGFR overexpression (found in approximately one-quarter of patients) had no statistically significant prognostic or predictive impact.

Appendix 1: Protocol violations

ULN=Upper Limit of Normal

2.1 ASAT

Table 33: Patients with ASAT ULN > 5

NUMTAS	Center num	TRAIT	ASAT	ULN_ASAT
16	Ulm	Arm GEMOX + CETUXIMAB	238	33
39	Hôpital Beaujon - Paris	Arm GEMOX alone	313	35

Table 34: Patients with ASAT ULN missing

NUMTAS	Center num	TRAIT	ASAT	ULN_ASAT
30	Ulm	Arm GEMOX + CETUXIMAB	97	.
51	Essen	Arm GEMOX + CETUXIMAB	66	.
54	Essen	Arm GEMOX + CETUXIMAB	46	.
56	Essen	Arm GEMOX + CETUXIMAB	**267**	.
63	Essen	Arm GEMOX + CETUXIMAB	19	.
72	Essen	Arm GEMOX + CETUXIMAB	47	.
78	Regensburg	Arm GEMOX + CETUXIMAB	91	.
82	Heidelberg	Arm GEMOX + CETUXIMAB	39	.
88	Essen	Arm GEMOX + CETUXIMAB	32	.
93	Heidelberg	Arm GEMOX + CETUXIMAB	91	.
105	Centre Eugène Marquis- Rennes	Arm GEMOX + CETUXIMAB	28	.
109	Centre Eugène Marquis- Rennes	Arm GEMOX + CETUXIMAB	33	.
136	Essen	Arm GEMOX + CETUXIMAB	69	.
20	Ulm	Arm GEMOX alone	41	.
49	Essen	Arm GEMOX alone	41	.
50	München	Arm GEMOX alone	61	.
55	Regensburg	Arm GEMOX alone	30	.
57	Heidelberg	Arm GEMOX alone	30	.
61	Essen	Arm GEMOX alone	54	.
65	Essen	Arm GEMOX alone	47	.
75	Essen	Arm GEMOX alone	**138**	.
87	Essen	Arm GEMOX alone	111	.
103	Centre Eugène Marquis- Rennes	Arm GEMOX alone	63	.

The lower observed ULN value in the trial database was 25. Then, only the patients 56 (10.7 ULN) and 75 (5.5 ULN) may have an abnormal value. Their corresponding ALAT value was 131 and 99 (4.7 and 3.5 ULN respectively if considering the lower ULN observed in the trial database).

2.2 ALAT

Table 35: Patients with ALAT ULN > 5

NUMTAS	Center num	TRAIT	ALAT	ULN_ALAT
8	Centre Eugène Marquis- Rennes	Arm GEMOX + CETUXIMAB	231	45

NUMTAS	Center num	TRAIT	ALAT	ULN_ALAT
16	Ulm	Arm GEMOX + CETUXIMAB	281	35
107	Centre Eugène Marquis- Rennes	Arm GEMOX + CETUXIMAB	230	45

Table 36: Patients with ALAT ULN missing

NUMTAS	Center num	TRAIT	ALAT	ULN_ALAT
30	Ulm	Arm GEMOX + CETUXIMAB	21	.
51	Essen	Arm GEMOX + CETUXIMAB	134	.
54	Essen	Arm GEMOX + CETUXIMAB	49	.
56	Essen	Arm GEMOX + CETUXIMAB	131	.
63	Essen	Arm GEMOX + CETUXIMAB	12	.
72	Essen	Arm GEMOX + CETUXIMAB	51	.
78	Regensburg	Arm GEMOX + CETUXIMAB	85	.
82	Heidelberg	Arm GEMOX + CETUXIMAB	19	.
88	Essen	Arm GEMOX + CETUXIMAB	17	.
93	Heidelberg	Arm GEMOX + CETUXIMAB	**158**	.
105	Centre Eugène Marquis- Rennes	Arm GEMOX + CETUXIMAB	17	.
109	Centre Eugène Marquis- Rennes	Arm GEMOX + CETUXIMAB	26	.
136	Essen	Arm GEMOX + CETUXIMAB	39	.
20	Ulm	Arm GEMOX alone	18	.
49	Essen	Arm GEMOX alone	26	.
50	München	Arm GEMOX alone	55	.
55	Regensburg	Arm GEMOX alone	47	.
57	Heidelberg	Arm GEMOX alone	18	.
61	Essen	Arm GEMOX alone	33	.
65	Essen	Arm GEMOX alone	36	.
75	Essen	Arm GEMOX alone	99	.
87	Essen	Arm GEMOX alone	87	.
103	Centre Eugène Marquis- Rennes	Arm GEMOX alone	21	.

The lower observed ULN value in the trial database was 28. Then, only the patient 93 (5.6 ULN) may have an abnormal value. Her corresponding ASAT value was 91.

2.3 Bilirubin

Table 37: Patients with bilirubine superior to 3 ULN

NUMTAS	Center num	TRAIT	Bilirubin µmol/L	Normalized Bilirubin*	Alkaline phosphatase UI/L	ULN Alkaline phosphatase
22	Institut Gustave Roussy - Villejuif	Arm GEMOX + CETUXIMAB	67	3.9	1980	290
88	Essen	Arm GEMOX + CETUXIMAB	58	3.4	.	.
7	Institut Paoli Calmettes - Marseille	Arm GEMOX alone	55	3.2	375	207
86	Hôpital St Antoine - Paris	Arm GEMOX alone	59	3.5	545	115.

NUMTAS	Center num	TRAIT	Bilirubin µmol/L	Normalized Bilirubin*	Alkaline phosphatase UI/L	ULN Alkaline phosphatase
111	Centre Eugène Marquis-Rennes	Arm GEMOX alone	54	3.2	432	120
127**	Hôpital Bordeaux Haut Lévêque - Pessac	Arm GEMOX alone	91	**5.4**	**1664**	**130**
148	Centre Eugène Marquis-Rennes	Arm GEMOX alone	54	3.2	270	120

* value observed divided by a ULN value of 17 µmol/L ** Patient no treated

2.3 Neutrophils

Table 38: Patients with neutrophils blood count missing or inferior to 1.5 109 /L

NUMTAS	*Center num*	*TRAIT*	*Neutrophils BC*
13	Hôpital St Antoine - Paris	Arm GEMOX + CETUXIMAB	.
48	Hôpital St Antoine - Paris	Arm GEMOX + CETUXIMAB	.
73	Hannover	Arm GEMOX + CETUXIMAB	.
78	Regensburg	Arm GEMOX + CETUXIMAB	.
91	Hôpital St Antoine - Paris	Arm GEMOX + CETUXIMAB	.
130	Hôpital St André - Bordeaux	Arm GEMOX + CETUXIMAB	.
9	Hôpital Beaujon - Paris	Arm GEMOX alone	.
24	Essen	Arm GEMOX alone	.
31	Hôpital St Antoine - Paris	Arm GEMOX alone	.
50	München	Arm GEMOX alone	.
71	Hôpital St Antoine - Paris	Arm GEMOX alone	.
74	Hannover	Arm GEMOX alone	.
76	Hannover	Arm GEMOX alone	.
83	Ulm	Arm GEMOX alone	.
86	Hôpital St Antoine - Paris	Arm GEMOX alone	.
87	Essen	Arm GEMOX alone	.
144	Hôpital St Antoine - Paris	Arm GEMOX alone	.

2.4 Platelets

Table 39: Patients with platelets inferior to 100 109 /L

NUMTAS	Center num	TRAIT	PLAT
28	Essen	Arm GEMOX alone	79

2.5 Hemoglobin

Table 40: Patients with hemoglobine < 9g/dL

NUMTAS	Center num	TRAIT	Hemoglobin g/dL
13	Hôpital St Antoine - Paris	Arm GEMOX + CETUXIMAB	8.0
63	Essen	Arm GEMOX + CETUXIMAB	8.7
31	Hôpital St Antoine - Paris	Arm GEMOX alone	8.0

Appendix 2: Difference between stratification factors and initial assessment

1.1 Tumor stage

(no change since the previous report)

Table 41: Discrepancies for tumor stage between randomization and baseline characteristics

NUMTAS	*TRAIT*	*Center num*	*Tumor stage**	*Disease status*
19	Arm GEMOX + CETUXIMAB	Halle	Locally advanced	Metastatic
66	Arm GEMOX + CETUXIMAB	Hôpital Beaujon - Paris	Locally advanced	Metastatic
112	Arm GEMOX + CETUXIMAB	Hôpital St André - Bordeaux	Metastatic	*missing*
124	Arm GEMOX + CETUXIMAB	Hôpital Beaujon - Paris	Locally advanced	Metastatic
134	Arm GEMOX + CETUXIMAB	Centre Eugène Marquis-Rennes	Metastatic	Locally advanced
149	Arm GEMOX + CETUXIMAB	Hôpital Bordeaux Haut Lévêque - Pessac	Locally advanced	Metastatic
81	Arm GEMOX alone	Hannover	Locally advanced	Metastatic
96	Arm GEMOX alone	Hannover	Metastatic	Locally advanced
120	Arm GEMOX alone	Centre Eugène Marquis-Rennes	Metastatic	Locally advanced
121	Arm GEMOX alone	Hôpital Beaujon - Paris	Locally advanced	Metastatic
131	Arm GEMOX alone	Hôpital Beaujon - Paris	Locally advanced	Metastatic
133	Arm GEMOX alone	Hôpital St André - Bordeaux	Metastatic	*missing*

* Variable on the randomization form

A discrepancy between randomization form and baseline characteristics forms was observed in 12 patients (6 in each arm): 7 patients with locally advanced stage on the randomization form were considered metastatic on the second one; 3 patients with metastatic stage were considered locally advanced on the baseline characteristics form; 2 patients with metastatic stage have no information on the baseline characteristics forms. The discrepancy came mainly from 4 centers (10 out of 12): 4 for the Beaujon Hospital, and 2 from Bordeaux St Andre, Hannover and Rennes. Eight patients were among the last 50 patients.

1.2 Tumor location

Table 42: Discrepancies for tumor localization between randomization and baseline characteristics

NUMTAS	TRAIT	Center num	LOC*	TUMLOC	If cholangiocarcinoma, tumor location
3	Arm GEMOX + CETUXIMAB	Institut Paoli Calmettes - Marseille	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
25	Arm GEMOX + CETUXIMAB	CRLC Val d Aurelle - Montpellier	Gallbladder	Cholangiocarcinoma	Extrahepatic bile ducts
78	Arm GEMOX + CETUXIMAB	Regensburg	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
93	Arm GEMOX + CETUXIMAB	Heidelberg	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
112	Arm GEMOX + CETUXIMAB	Hôpital St André - Bordeaux	Non gallbladder	*Missing*	
122	Arm GEMOX + CETUXIMAB	Henri Mondor - Créteil	Gallbladder	Cholangiocarcinoma	*Missing*
142	Arm GEMOX + CETUXIMAB	Institut Paoli Calmettes - Marseille	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
5	Arm GEMOX alone	CRLC Val d Aurelle - Montpellier	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
23	Arm GEMOX alone	Essen	Non gallbladder	Gallbladder	
26	Arm GEMOX alone	CRLC Val d Aurelle - Montpellier	Gallbladder	Cholangiocarcinoma	Peri-hilar
39	Arm GEMOX alone	Hôpital Beaujon - Paris	Gallbladder	Cholangiocarcinoma	Peri-hilar ducts
74	Arm GEMOX alone	Hannover	Non gallbladder	Gallbladder	
80	Arm GEMOX alone	Institut Paoli Calmettes - Marseille	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
85	Arm GEMOX alone	Hôpital St André - Bordeaux	Gallbladder	Cholangiocarcinoma	*Missing*
115	Arm GEMOX alone	Centre Eugène Marquis- Rennes	Gallbladder	Multifocal	
121	Arm GEMOX alone	Hôpital Beaujon - Paris	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
128	Arm GEMOX alone	Hôpital Beaujon - Paris	Gallbladder	Cholangiocarcinoma	Intrahepatic bile ducts
133	Arm GEMOX alone	Hôpital St André - Bordeaux	Non gallbladder	*Missing*	

* Variable on the randomization form

A discrepancy between randomization form and baseline characteristics forms was observed in 18 patients (7 in the GEMOX + Cetuximab arm and 11 in the GEMOX alone arm): 13 patients with gallbladder disease on the randomization form had cholangiocarcinoma on the baseline characteristics form; one patients with gallbladder disease on the randomization form had multifocal disease on the baseline characteristics form; 2 patients with non gallbladder disease on the randomization form had gallbladder disease on the baseline characteristics form; 2 patients with non gallbladder disease on the randomization form had missing data on the baseline characteristics form. The discrepancy came mainly from 4 centers (12 out of 18): 3 for the Beaujon Hospital, Bordeaux, Marseilles and Montpellier. Seven patients were among the last 50 patients.

1.3 Prior treatment

Table 43: Discrepancies for prior treatment between randomization and baseline characteristics

(no change since the previous report)

NUMTAS	TRAIT	Center num	PRIOR treatment*	Prior curative surgery	Palliative surgery before inclusion	Prior adjuvant CT	Prior RT
16	Arm GEMOX + CETUXIMAB	Ulm	None	Yes	No	No	No
42	Arm GEMOX + CETUXIMAB	Hannover	None	No	Yes	No	No
51	Arm GEMOX + CETUXIMAB	Essen	None	Yes	No	No	No
100	Arm GEMOX + CETUXIMAB	Institut Gustave Roussy - Villejuif	None	No	Yes	No	No
134	Arm GEMOX + CETUXIMAB	Centre Eugène Marquis- Rennes	None	.	Yes	No	No
26	Arm GEMOX alone	CRLC Val d Aurelle - Montpellier	None	No	Yes	No	No
58	Arm GEMOX alone	Hannover	None	No	Yes	No	No
67	Arm GEMOX alone	Ulm	None	Yes	No	No	No
74	Arm GEMOX alone	Hannover	None	No	Yes	No	No
81	Arm GEMOX alone	Hannover	None	No	Yes	No	No
83	Arm GEMOX alone	Ulm	None	Yes	No	No	No
116	Arm GEMOX alone	Centre Léon Bérard - Lyon	None	Yes	No	No	No
121	Arm GEMOX alone	Hôpital Beaujon - Paris	None	Yes	Yes	No	No
123	Arm GEMOX alone	Institut Gustave Roussy - Villejuif	None	Yes	No	No	No
125	Arm GEMOX alone	Hôpital Beaujon - Paris	Yes	No	No	No	No
141	Arm GEMOX alone	Centre Léon Bérard - Lyon	None	Yes	No	No	No

*Variable on the randomization form

A discrepancy between randomization form and baseline characteristics forms was observed in 16 patients (5 in the GEMOX + Cetuximab arm and 11 in the GEMOX alone arm): 15 patients with no previous treatment on the randomization form had one on baseline characteristics form; one with previous treatment on the randomization form had none on baseline characteristics form. The discrepancy came mainly from 2 centers (7 out of 16): 4 from Hannover, 3 from Ulm. Seven patients were among the last 50 patients.

Appendix 3: Highest toxicity grade by patients

(no change since the previous report)

	Arm GEMOX + CETUXIMAB		Arm GEMOX alone		All	
	N=76	%	N=68	%	N=144	%
Any toxicity						
Gr. 0	0	0	3	4	3	2
Gr. 1	2	3	1	1	3	2
Gr. 2	13	17	7	10	20	14
Gr. 3	38	50	40	59	78	54
Gr. 4	23	30	17	25	40	28
Hematological toxicity						
Gr. 0	4	5	6	9	10	7
Gr. 1	31	41	10	15	41	28
Gr. 2	14	18	27	40	41	28
Gr. 3	20	26	23	34	43	30
Gr. 4	7	9	2	3	9	6
Hemoglobin						
Gr. 0	13	17	9	13	22	15
Gr. 1	39	51	23	34	62	43
Gr. 2	17	22	31	46	48	33
Gr. 3	6	8	5	7	11	8
Gr. 4	1	1	0	0	1	1
Platelets						
Gr. 0	17	22	14	21	31	22
Gr. 1	37	49	26	38	63	44
Gr. 2	14	18	15	22	29	20
Gr. 3	7	9	13	19	20	14
Gr. 4	1	1	0	0	1	1
White blood cells count						
Gr. 0	40	53	41	60	81	56
Gr. 1	17	22	16	24	33	23
Gr. 2	12	16	9	13	21	15
Gr. 3	7	9	2	3	9	6
ANC						
Gr. 0	41	54	46	68	87	60
Gr. 1	11	14	5	7	16	11
Gr. 2	7	9	6	9	13	9
Gr. 3	12	16	9	13	21	15
Gr. 4	5	7	2	3	7	5
Constitutional / infection						
Gr. 0	12	16	12	18	24	17
Gr. 1	20	26	20	29	40	28
Gr. 2	27	36	24	35	51	35
Gr. 3	16	21	12	18	28	19
Gr. 4	1	1	0	0	1	1
Fatigue						
Gr. 0	18	24	15	22	33	23
Gr. 1	23	30	21	31	44	31

	Arm GEMOX + CETUXIMAB		Arm GEMOX alone		All	
	N=76	%	N=68	%	N=144	%
Gr. 2	22	29	23	34	45	31
Gr. 3	13	17	9	13	22	15
Fever						
Gr. 0	45	59	31	46	76	53
Gr. 1	18	24	24	35	42	29
Gr. 2	13	17	12	18	25	17
Gr. 3	0	0	1	1	1	1
Infection with ANC <Gr. 1						
Missing	1	1	0	0	1	1
Gr. 0	68	89	68	100	136	94
Gr. 2	2	3	0	0	2	1
Gr. 3	5	7	0	0	5	3
Infection with ANC >Gr. 1						
Missing	1	1	0	0	1	1
Gr. 0	74	97	66	97	140	97
Gr. 3	1	1	2	3	3	2
Infection with unknown ANC						
Missing	1	1	0	0	1	1
Gr. 0	74	97	66	97	140	97
Gr. 1	1	1	0	0	1	1
Gr. 3	0	0	2	3	2	1
Febrile neutropenia						
Missing	1	1	0	0	1	1
Gr. 0	72	95	68	100	140	97
Gr. 1	1	1	0	0	1	1
Gr. 3	1	1	0	0	1	1
Gr. 4	1	1	0	0	1	1
LAB toxicity						
Gr. 0	13	17	8	12	21	15
Gr. 1	6	8	4	6	10	7
Gr. 2	12	16	11	16	23	16
Gr. 3	27	36	30	44	57	40
Gr. 4	18	24	15	22	33	23
ALT/AST						
Gr. 0	13	17	12	18	25	17
Gr. 1	28	37	19	28	47	33
Gr. 2	18	24	27	40	45	31
Gr. 3	15	20	10	15	25	17
Gr. 4	2	3	0	0	2	1
ALP						
Gr. 0	19	25	14	21	33	23
Gr. 1	25	33	18	26	43	30
Gr. 2	17	22	21	31	38	26
Gr. 3	11	14	15	22	26	18
Gr. 4	4	5	0	0	4	3

	Arm GEMOX + CETUXIMAB		Arm GEMOX alone		All	
	N=76	%	N=68	%	N=144	%
GGT						
Gr. 0	15	20	13	19	28	19
Gr. 1	7	9	3	4	10	7
Gr. 2	10	13	8	12	18	13
Gr. 3	28	37	30	44	58	40
Gr. 4	16	21	14	21	30	21
Bilirubin						
Gr. 0	51	67	37	54	88	61
Gr. 1	12	16	19	28	31	22
Gr. 2	4	5	8	12	12	8
Gr. 3	5	7	3	4	8	6
Gr. 4	4	5	1	1	5	3
Creatinin						
Gr. 0	67	88	61	90	128	89
Gr. 1	7	9	6	9	13	9
Gr. 2	1	1	1	1	2	1
Gr. 4	1	1	0	0	1	1
Mg						
Missing	3	4	9	13	12	8
Gr. 0	48	63	50	74	98	68
Gr. 1	23	30	9	13	32	22
Gr. 2	2	3	0	0	2	1
Gastrointestinal Toxicity						
Gr. 0	11	14	10	15	21	15
Gr. 1	18	24	19	28	37	26
Gr. 2	37	49	29	43	66	46
Gr. 3	10	13	10	15	20	14
Anorexia						
Gr. 0	30	39	25	37	55	38
Gr. 1	21	28	17	25	38	26
Gr. 2	22	29	23	34	45	31
Gr. 3	3	4	3	4	6	4
Nausea						
Gr. 0	28	37	21	31	49	34
Gr. 1	24	32	25	37	49	34
Gr. 2	22	29	20	29	42	29
Gr. 3	2	3	2	3	4	3
Vomiting						
Gr. 0	38	50	34	50	72	50
Gr. 1	17	22	16	24	33	23
Gr. 2	18	24	16	24	34	24
Gr. 3	3	4	2	3	5	3
Diarrhea						
Gr. 0	41	54	39	57	80	56
Gr. 1	18	24	20	29	38	26
Gr. 2	11	14	6	9	17	12

	Arm GEMOX + CETUXIMAB		Arm GEMOX alone		All	
	N=76	%	N=68	%	N=144	%
Gr. 3	6	8	3	4	9	6
Constipation						
Gr. 0	50	66	36	53	86	60
Gr. 1	20	26	25	37	45	31
Gr. 2	6	8	7	10	13	9
Mucositis						
Gr. 0	47	62	55	81	102	71
Gr. 1	22	29	13	19	35	24
Gr. 2	6	8	0	0	6	4
Gr. 3	1	1	0	0	1	1
Skin toxicity						
Gr. 0	6	8	38	56	44	31
Gr. 1	14	18	22	32	36	25
Gr. 2	44	58	7	10	51	35
Gr. 3	11	14	1	1	12	8
Gr. 4	1	1	0	0	1	1
Allergic reaction / Hypersensitivity						
Gr. 0	45	59	51	75	96	67
Gr. 1	13	17	11	16	24	17
Gr. 2	12	16	5	7	17	12
Gr. 3	5	7	1	1	6	4
Gr. 4	1	1	0	0	1	1
Alopecia						
Gr. 0	49	64	52	76	101	70
Gr. 1	22	29	15	22	37	26
Gr. 2	5	7	1	1	6	4
Acneiform rash						
Gr. 0	12	16	64	94	76	53
Gr. 1	22	29	3	4	25	17
Gr. 2	37	49	1	1	38	26
Gr. 3	5	7	0	0	5	3
Conjunctivitis						
Gr. 0	67	88	65	96	132	92
Gr. 1	7	9	3	4	10	7
Gr. 2	1	1	0	0	1	1
Gr. 3	1	1	0	0	1	1
Nail changes						
Gr. 0	65	86	67	99	132	92
Gr. 1	6	8	1	1	7	5
Gr. 2	5	7	0	0	5	3
Neuropathy (Levi scale)						
Gr. 0	10	13	15	22	25	17
Gr. 1	29	38	22	32	51	35
Gr. 2	19	25	21	31	40	28
Gr. 3	18	24	10	15	28	19

	Arm GEMOX + CETUXIMAB		Arm GEMOX alone		All	
	N=76	%	N=68	%	N=144	%
Other toxicity						
Missing	6	8	8	12	14	10
Gr. 1	28	37	22	32	50	35
Gr. 2	27	36	26	38	53	37
Gr. 3	14	18	9	13	23	16
Gr. 4	1	1	3	4	4	3

Appendix 4: Exploratory analyses: Overall Survival and Progression Free Survival curves according to KRAS/BRAF/EGFR tumor status and treatment arm

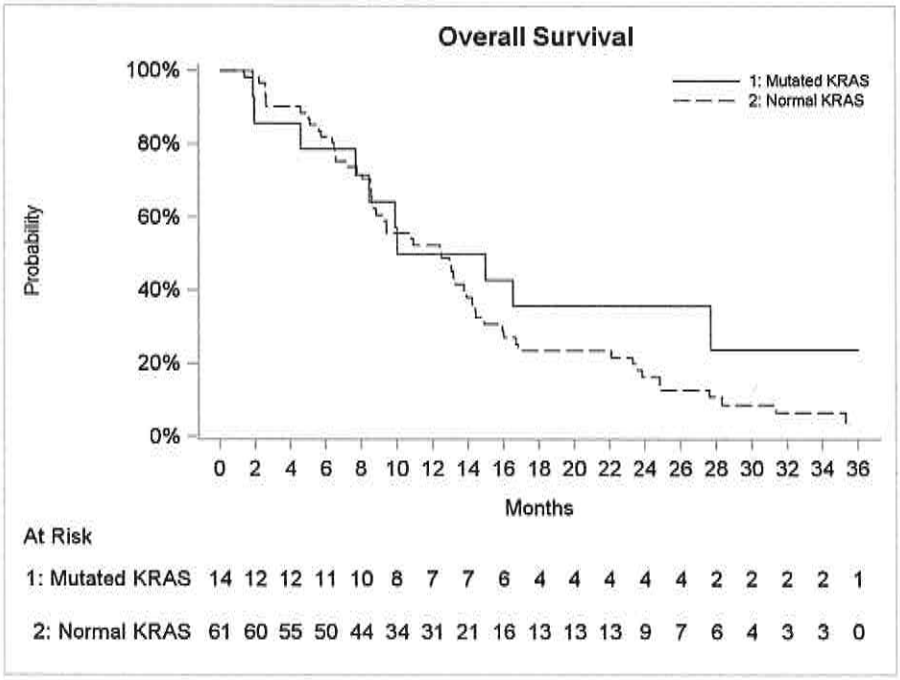

Figure 5 Overall Survival according to KRAS tumor status

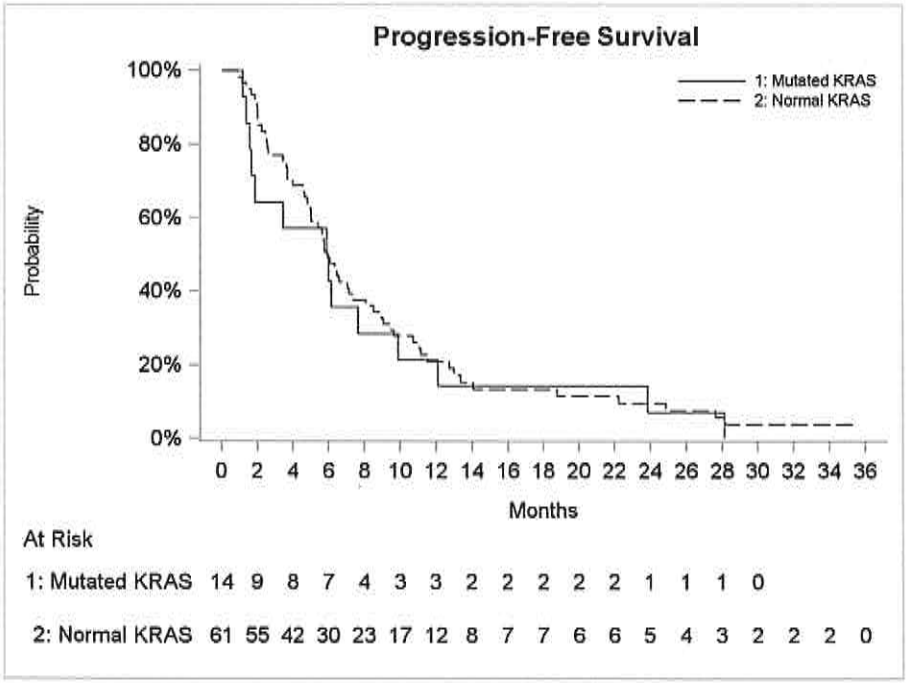

Figure 6 Progression Free Survival according to KRAS tumor status

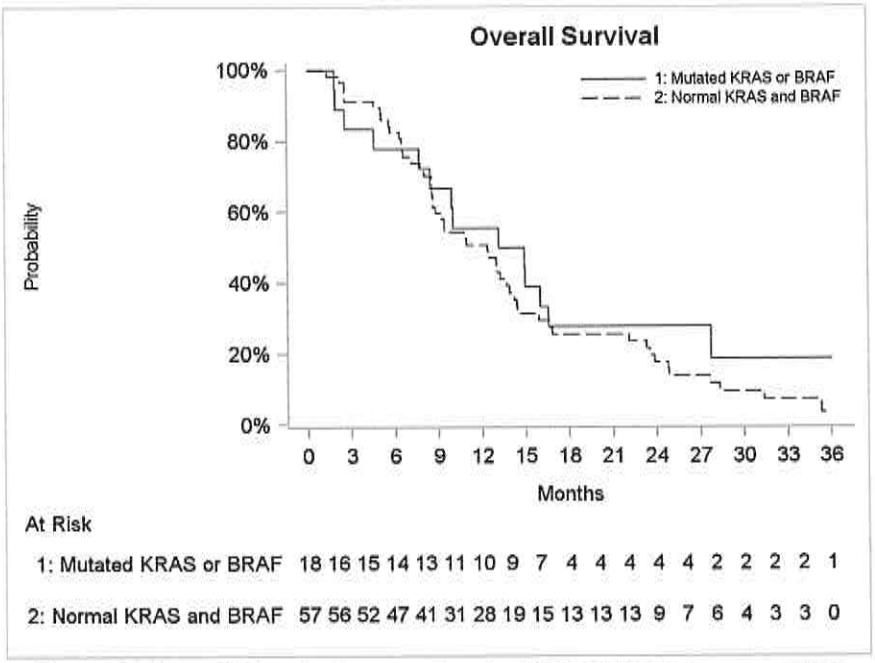

Figure 7 Overall Survival according to KRAS/BRAF tumor status

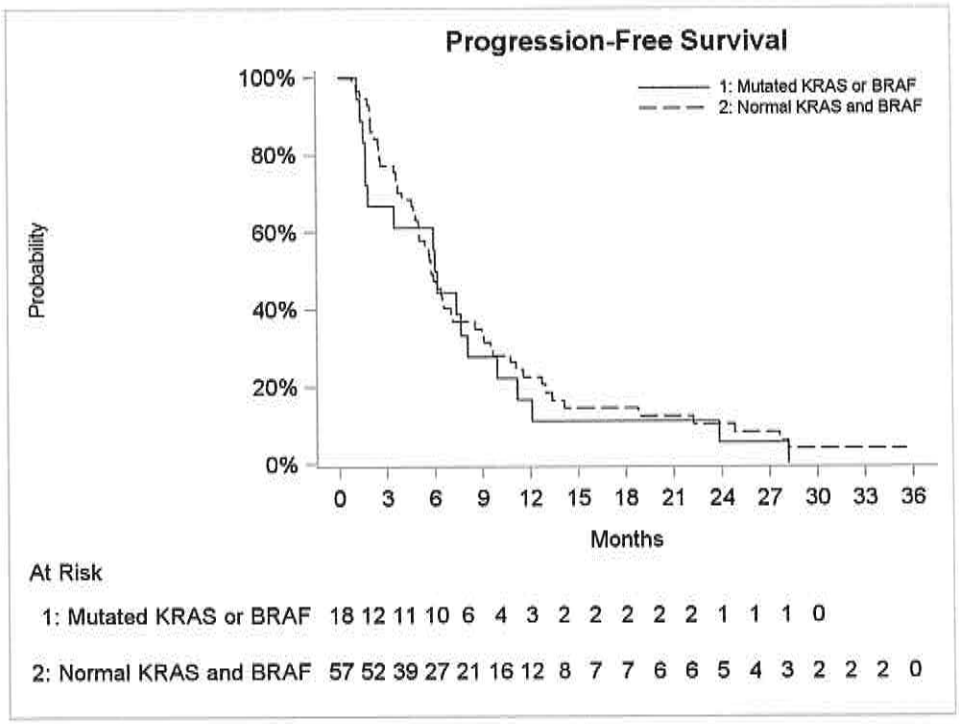

Figure 8 Progression Free Survival according to KRAS/BRAF tumor status

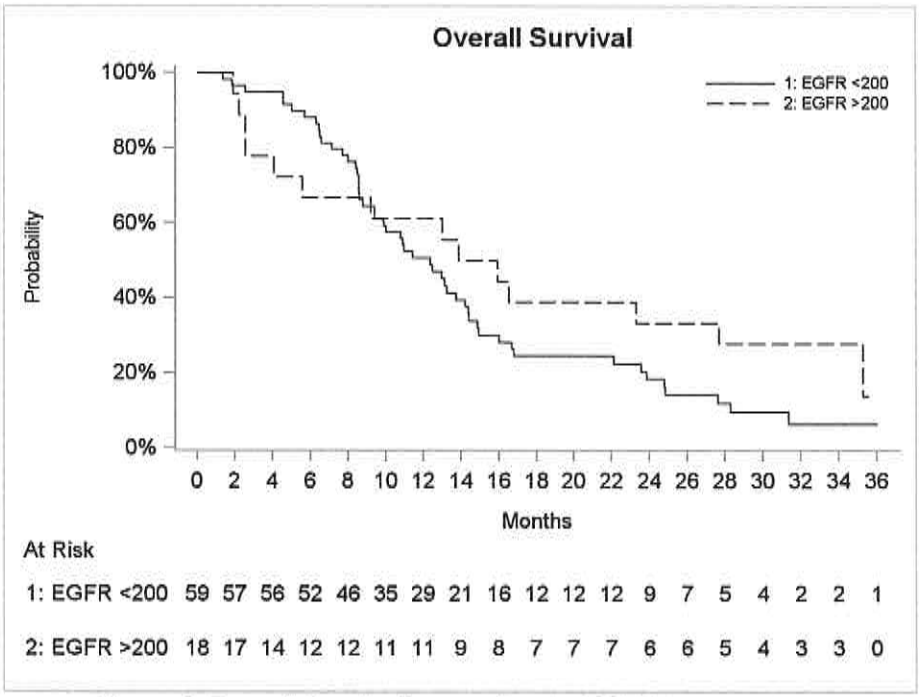

Figure 9 Overall Survival according to EGFR tumor status

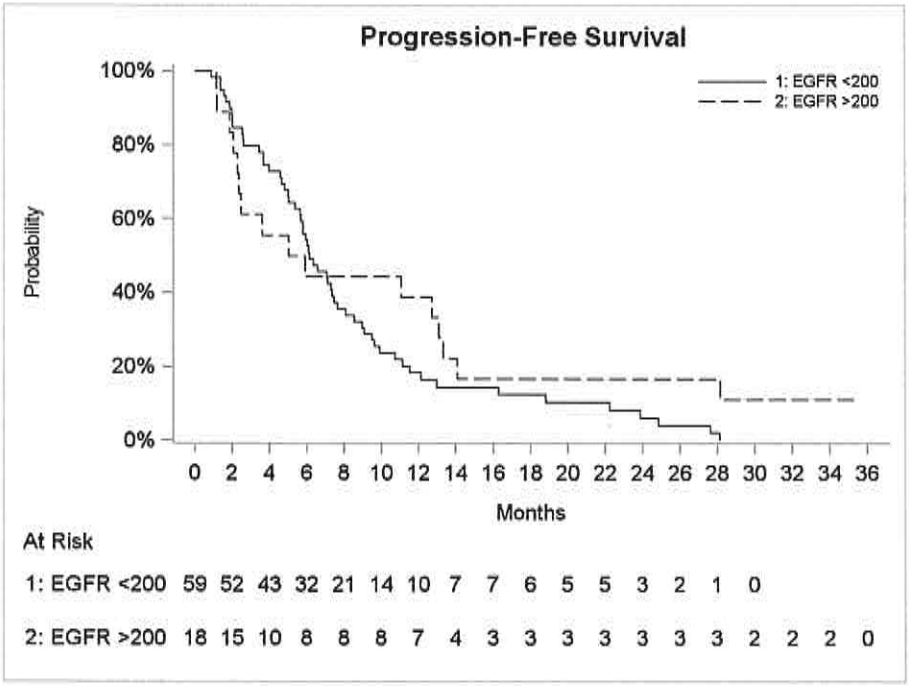

Figure 10 Progression Free Survival according to EGFR tumor status

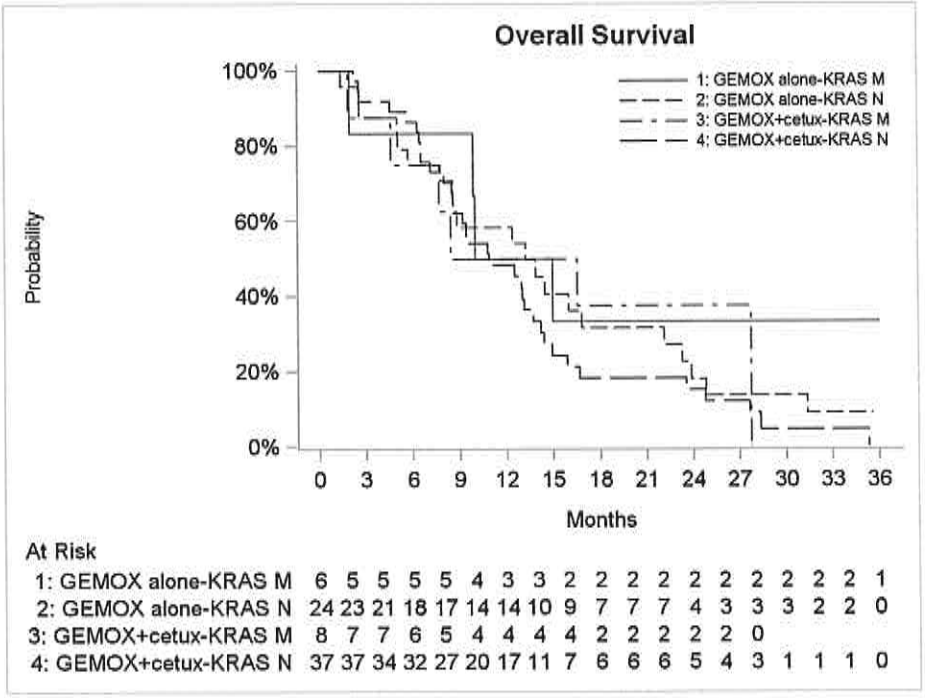

Figure 11 Overall Survival according to KRAS tumor status and treatment arm

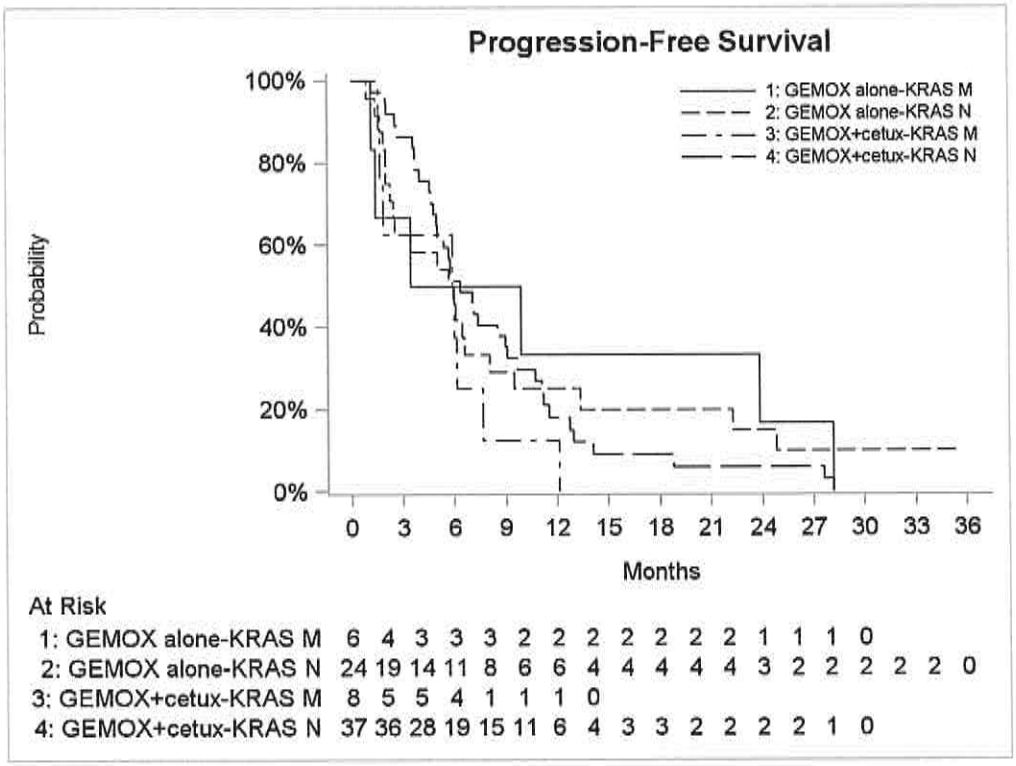

Figure 12 Progression Free Survival according to KRAS tumor status and treatment arm

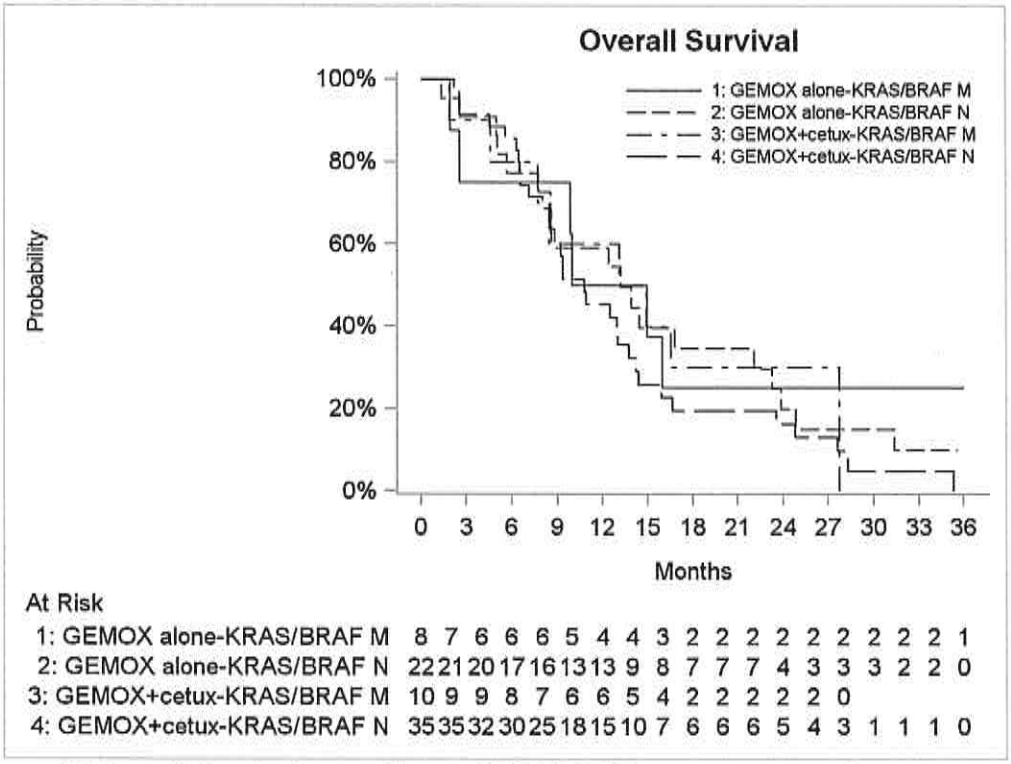

Figure 13 Overall Survival according to KRAS/BRAF tumor status and treatment arm

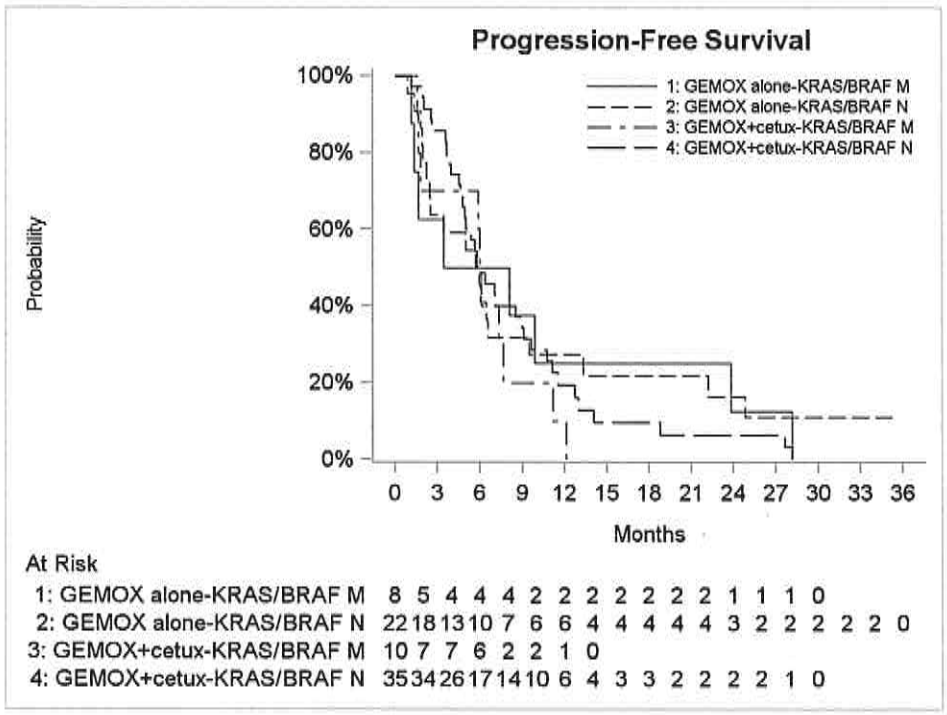

Figure 14 Progression Free Survival according to KRAS/BRAF tumor status and treatment arm

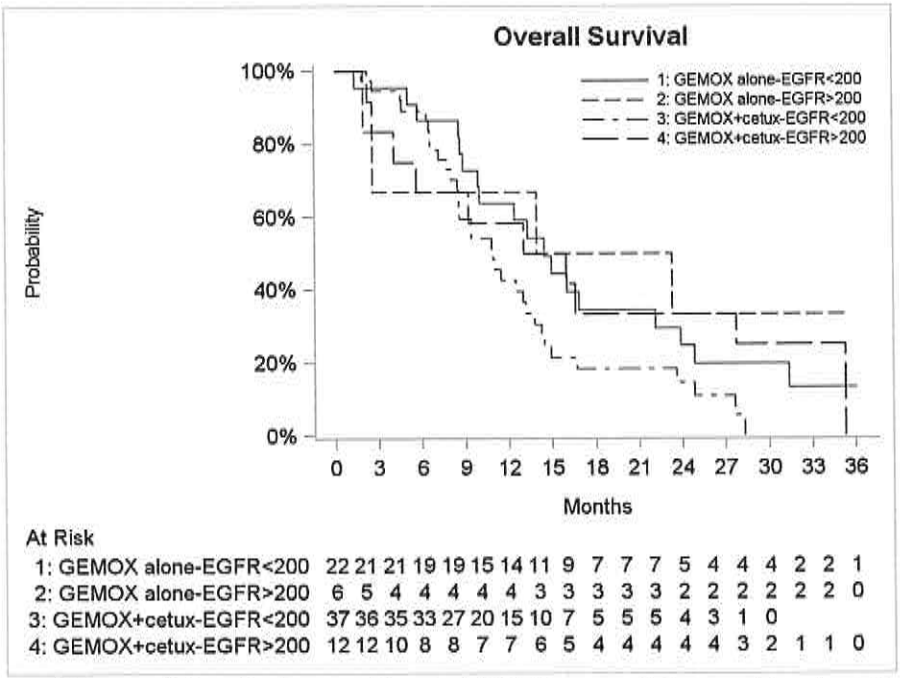

Figure 15 Overall Survival according to EGFR tumor status and treatment arm

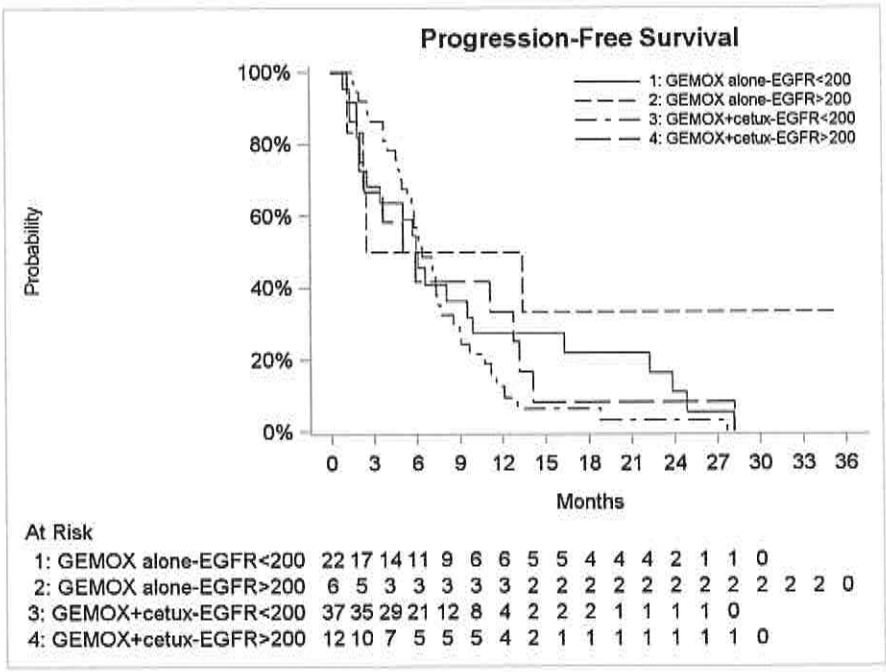

Figure 16 Progression Free Survival according to EGFR tumor status and treatment arm