The COMET Open-label Phase II Study of Neoadjuvant FOLFOX or XELOX Treatment Combined with Molecular Targeting Monoclonal Antibodies in Patients with Resectable Liver Metastasis of Colorectal Cancer

Running head: Therapy of Colorectal Liver Metastasis

Masato Kataoka,[1*] MD, Mitsuro Kanda,[2*] MD, Kiyoshi Ishigure,[3] MD, Hiroshi Matsuoka,[4] MD, Yusuke Sato,[5] MD, Takao Takahashi,[6] MD, Chihiro Tanaka,[7] MD, Tomohiro Deguchi,[8] MD, Yoshihisa Shibata,[9] MD, Mikinori Sato,[10] MD, Hitoshi Inagaki,[11] MD, Takanori Matsui,[12] MD, Akinori Kondo,[13] MD, Nao Takano,[2] MD, Haruyoshi Tanaka,[2] MD, Junichi Sakamoto,[14] MD, Koji Oba,[15, 16] MD, and Ken Kondo[1] MD

[1]Department of Surgery, Nagoya National Hospital, Nagoya, Japan; [2]Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, Nagoya, Japan; [3]Department of Surgery, Konan Kosei Hospital, Konan, Japan; [4]Department of Surgery, Fujita Health University School of Medicine, Aichi, Japan; [5]Department of Surgery, Tosei Hospital, Seto, Japan; [6]Department of Surgical Oncology, Gifu University Graduate School of Medicine, Gifu, Japan; [7]Department of Surgery, Gifu Prefectural General Medical Center, Gifu, Japan; [8]Department of Surgery, Gifu Prefectural Tajimi Hospital, Tajimi, Japan; [9]Department of Surgery, Toyohashi

Municipal Hospital, Toyohashi, Japan; [10]Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan; [11]Department of Surgery, Yokoyama Hospital for Gastroenterological Diseases, Nagoya, Japan; [12]Department of Gastroenterological Surgery, Aichi Cancer Center Aichi Hospital, Okazaki, Japan; [13]Department of Surgery, Saiseikai Matsusaka General Hospital, Matsusaka, Japan; [14]Director, Tokai Central Hospital, Gifu, Japan; [15]Department of Biostatistics, School of Public Health, Tokyo University Graduate School of Medicine, Tokyo, Japan; [16]Interfaculty Initiative in Information Studies, Tokyo University, Tokyo, Japan

Correspondence and requests for reprints to: Mitsuro Kanda, MD, PhD, FACS, Department of Gastroenterological Surgery (Surgery II), Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.

Tel: +81-52-744-2249, fax: +81-52-744-2255, e-mail: m-kanda@med.nagoya-u.ac.jp

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*Masato Kataoka and Mitsuro Kanda contributed equally to this work.

Synopsis

A phase II trial of patients with resectable and untreated liver metastasis of colorectal cancer demonstrated that neoadjuvant therapy using FOLFOX/XELOX combined with molecular targeting monoclonal antibodies was well-tolerated but did not improve progression-free survival.

ABSTRACT

Background; Advantages of neoadjuvant chemotherapy combined with monoclonal antibodies for treating patients with resectable colorectal cancer liver metastasis (CLM) have not been established. The aim of this study was to evaluate the efficacy and safety of oxaliplatin-based regimen (FOLFOX or XELOX) plus monoclonal antibodies (cetuximab or bevacizumab) treatment in patients with resectable CLM.

Methods; A single-arm, open label multicenter phase II trial was conducted for patients aged ≥20 years with resectable and untreated CLM. Patients received preoperative FOLFOX (six cycles) or XELOX (four cycles). Cetuximab or bevacizumab was administered to patients with wild-type or mutated *KRAS* codons 12 and 13, respectively. The primary endpoint was progression-free survival (PFS).

Results; Between January 2010 and June 2012, 47 patients were enrolled from 12 institutions. Wild-type or mutant *KRAS* sequences were examined in 32 and 15 patients, respectively. Twenty-one (45%) patients experienced Grades 3/4 adverse events, and 55% of all patients responded to therapy. The sizes of tumors of patients in the wild-type *KRAS* group were significantly reduced compared with those of the mutant *KRAS* group. The overall rates of liver resection and postoperative morbidity were 83% and 14%, respectively, and the median PFS was 15.6 months. The median PFS times of the *KRAS* wild-type and mutant groups were 22.5 months and 10.5 months, respectively.

Conclusion; Neoadjuvant therapy using FOLFOX/XELOX combined with monoclonal antibodies

did not improve PFS, though it was administered safely and had less adverse effects after liver resection.

INTRODUCTION

The liver is the most common site of colorectal cancer (CRC) metastasis and recurrences.[1] Improvements in surgical techniques and liver resectability criteria as well as encouraging increases in the probability of 5-year survival following resection with curative intent, approaching 45%–60%, have led physicians to consider liver resection as a mainstay treatment component for managing patients with CRC.[2,3] However, the frequency of recurrent disease after resection of colorectal cancer liver metastasis (CLM) is disappointingly high and has generated much interest in administering adjunct chemotherapy to manage such patients.[4]

Several clinical trials have been conducted to evaluate the efficacy of postoperative adjuvant chemotherapy administered to patients with CLM; however, they failed to demonstrate a survival benefit.[5-7] More recently, current trends in care indicate increased administration of neoadjuvant chemotherapy to patients with resectable CLM. Neoadjuvant therapy may facilitate and enhance better tolerability, permit technically easier liver resection and decreased operative time by simplifying the procedure through reduction of number, size and contact to the vessels, target occult metastases, or exclude patients who have a disease progression during chemotherapy.[8] The EORTC intergroup trial 4098310 that compared perioperative FOLFOX4 with surgery alone is the largest randomized double-blind trial to investigate the role of neoadjuvant chemotherapy in this context.[9] Although 3-year progression-free survival (PFS) was prolonged by preoperative FOLFOX4 in

eligible and resected patients, reversible complications occurred more frequently in the chemotherapy group (25% vs 16%) and the long-term follow-up data revealed that there was no difference in overall survival (OS) between the perioperative chemotherapy group and surgery alone group (51.2% vs 47.8%).[10] The New EPOC evaluated the benefit of including cetuximab in the standard perioperative chemotherapy regimen administered to patients with resectable CLM and wild-type *KRAS*.[11] Surprisingly, PFS was significantly shorter for patients who received chemotherapy plus cetuximab compared with those who received only chemotherapy (14.1 months vs 20.5 months), although the incidence of grade 3/4 adverse effects (AEs) and R0 resection rates were comparable.[11] Still, little evidence is available on the effects of neoadjuvant chemotherapy combined with monoclonal antibodies, particularly in the Asian population.

To address these gaps in knowledge, we conducted a prospective single-arm open label multicenter phase II trial designed to test our hypothesis that the proper use of monoclonal antibodies to preoperative FOLFOX according to *KRAS* status leads to improved postoperative outcome compared to perioperative FOLFOX (EORTC-40983 trial) without increasing postoperative morbidity in Japanese patients with resectable CLM.

METHODS

Patient eligibility

This study was conducted in accordance with the Declaration of Helsinki (2008) and registered with the University Hospital Medical Information Network (UMIN) Clinical Trial Registry as UMIN000003796 (http://www.umin.ac.jp/ctr/index.htm). Signed, written informed consent was obtained from each patient.

Patients from 12 institutes were included if they met the eligibility criteria as follows: (1) histologically confirmed colorectal adenocarcinoma; (2) confirmed *KRAS* status of primary or metastatic lesions; (3) resectable metastasis confined to the liver; (4) no prior chemotherapy or radiation therapy for CLM; (5) Eastern Cooperative Oncology Group Performance Status 0 or 1; (6) age ≥20 years; (7) adequate function of vital organs. Key exclusion criteria included adjuvant chemotherapy for colorectal carcinoma administered <6 months before detection of liver metastasis, uncontrolled pleural effusion or ascites, other active malignancies, liver cirrhosis, hepatitis virus infection, and impaired peripheral nerve function. The nucleotide sequences of *KRAS* codons 12 and 13 were determined using direct sequence analysis as described previously.[12]

Treatment

Oxaliplatin-based regimen (FOLFOX or XELOX) plus cetuximab was administered to patients with wild-type *KRAS* codon 12 or 13, and oxaliplatin-based regimen (FOLFOX or XELOX) plus

bevacizumab was administrated to those with a mutated *KRAS* codon. On the first day of the 14-day treatment cycle, patients received cetuximab (initial dose 400 mg/m^2 infused for 2 h and 250 mg/m^2 weekly for 1 h) or 5 mg/kg bevacizumab followed 1 h later by FOLFOX (oxaliplatin 85 mg/m^2 on day 1, infused for 2 h; leucovorin [LV] 200 mg/m^2, infused for 2 h followed by a 400 mg/m^2 intravenous bolus of 5-fluorouracil [FU] and then a 2400 mg/m^2 infusion of FU for 46 h starting on day 1). The XELOX plus bevacizumab group was administered intravenous (i.v.) oxaliplatin (130 mg/m^2) and bevacizumab (7.5 mg/kg) on day 1 and every 3 weeks thereafter. Oral capecitabine (2000 mg/m^2/day) was divided into two doses that were administered for 14 days, discontinued for 7 days, and this schedule was repeated every 3 weeks. The XELOX plus cetuximab group received 130 mg/m^2 of i.v. oxaliplatin on day 1 of each cycle combined with 1700 mg/m^2 of oral capecitabine per day on days 1–14 of each cycle and cetuximab on day 1 (initial dose 400 mg/m^2 and 250 mg/m^2 weekly thereafter). The planned courses were six for FOLFOX (14-day treatment cycle) and four for XELOX (21-day treatment cycle). When patients exhibited AEs, the dose of each drug was reduced as specified in the study protocol that provided detailed algorithms for managing drug-specific toxicities as previously described.[13]

A patient's ability to undergo surgery was reassessed using computed tomography (CT) after protocol chemotherapy was completed. Patients were judged resectable if they had a sufficient volume of liver and if resection would likely remove residual lesions (R0) regardless of tumor regression or growth. Such patients were scheduled for surgery 3 (5 for patients who received

bevacizumab) to approximately 8 weeks after the last dose of chemotherapy. The study protocol did not provide for treatment after hepatectomy.

Study parameters

During treatment, CT scans were performed every 6 to approximately 8 weeks to assess tumor status. Response Evaluation Criteria In Solid Tumors (RECIST) ver. 1.1 was used to evaluate tumor shrinkage rate, responses and determine disease progression; complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). Response-rate assessment (measurement of the size of target lesions) was performed by radiologists of each institution in a blinded manner. Toxicities, which were graded according to the criteria of the National Cancer Institute “Common Terminology for Adverse Events” (version 4.0), were evaluated during chemotherapy, according to the findings of physical examinations and laboratory tests (hematology, chemistry, electrolytes, and urinalysis).

Statistical analysis

Our primary objective was to determine PFS. In case our approach achieved a longer PFS compared with the previous pivotal trial of perioperative FOLFOX (EORTC-40983 trial), it can be

considered as a promising treatment strategy enough to be recommended for a large phase III trial. Considering a threshold PFS of 11.7 months and an estimated median PFS of 18.7 months as well as referring to data from the EORTC-40983 trial, we determined that a significance level = 95%, α-error = 0.05, β-error = 0.2, power = 80%, and 40 patients were required to detect important differences. Forty-five patients were required to estimate a loss as high as 10% of the final subject population. The Kaplan–Meier method was used to estimate survival, and the Cox proportional hazards model was used to calculate confidence intervals (CI).[14] The qualitative χ^2 and quantitative Mann–Whitney tests were used to compare the differences between groups.[15] A statistically significant difference was defined as $p<0.05$.

RESULTS

Patients' characteristics

Participating physicians strictly checked the eligibility criteria before patient screening. Fifty patients treated between January 2010 and June 2012 at 12 institutions were screened, and 47 patients met all eligibility requirements and received at least one course of the planned treatment. Baseline patient characteristics are shown in Table 1. Wild-type or mutated *KRAS* codons 12 or 13 were detected in DNAs prepared from the tumor tissues of 32 and 15 patients, respectively.

Toxicities of neoadjuvant chemotherapy

Patients with wild-type *KRAS* received regimens with cetuximab as follows: FOLFOX, *n*=26 (81%) and XELOX, *n*=6 (19%). Patients with mutant *KRAS* received regimens with bevacizumab as follows: FOLFOX, *n*=10 (67%) and XELOX, *n*=5 (33%). Thirty-four (72%) patients completed neoadjuvant therapy. The reasons for discontinuing neoadjuvant chemotherapy were disease progression (*n*=3), AEs (*n*=6), and patient withdrawal (*n*=4). Overall treatment-related toxicities were as follows: 47 (100%) and 21 (45%) of patients experienced at least one grade of an AE or grade-3 AEs or higher, respectively (Table 2). Frequent AEs grade 3 or higher were neutropenia (23%), leucopenia (11%), and nausea (9%) (Table 2).

Treatment profiles

The best radiographic response of each patient is presented in Fig. 1a. Patients in the wild-type *KRAS* group had significantly increased tumor shrinkage compared with that of the mutant *KRAS* group (median 59% and 8%, respectively, $p<0.001$). The overall rates of CR, PR, SD, and PD were 2%, 53%, 30%, and 9%, respectively, and the response and disease control rates were 55% and 85%, respectively (Table 3).

Thirty-nine (83%) patients underwent liver resection following neoadjuvant chemotherapy. The seasons for not performing liver resection were CR (*n*=1), PD (*n*=2), nephrotic syndrome (*n*=1), and patient refusal (*n*=4). Detailed surgical information available for 36 patients revealed that 11%, 25%, and 64% underwent lobectomy, segmental resection, and partial resection, respectively. According to resection margins, the R0 resection rate was 82%. Median operative time was 250 min (range 76–805 min), and the median estimated blood loss was 499 ml (range 4–2270 ml). The morbidity rate was 14% (Clavien-Dindo classification grade II-IV), including pneumonia (*n*=1), infectious endocarditis (*n*=1), cholangitis (*n*=1), and wound infection (*n*=3). The mean duration of postoperative hospitalization was 16.4 days (± 12.3, standard deviation). There were two postoperative death within 90 days after liver resection, one died from aspiration pneumonia and the other died from infectious endocarditis. The median follow-up period was 39.4 months or until death. The median PFS was 15.6 months (Fig. 1b). The data for OS are presented in Fig. 1c. In the subgroup analysis performed according to *KRAS* status, the wild-type *KRAS* group included one patient with a CR, and there was a significantly higher response rate (CR + PR) compared with the mutant *KRAS* group (72% vs 20%). The liver resection rates were 88% and 73% for the wild-type and mutant *KRAS* groups, respectively. Median durations of PFS of the *KRAS* wild-type and mutant groups were 22.5 and 10.5 months, respectively, $p = 0.235$ (Fig. 2a). Patients who underwent liver resection (*n*=39) experienced significantly longer PFS compared with those who did not (*n*=8) (median 6.4 and 25.7 months, respectively, $p<0.001$) (Fig. 2b).

DISCUSSION

Although liver resection is the most effective treatment option for patients with CLM, the high incidence of disease recurrence must be resolved.[3,16,17] Here, we designed the COMET trial to evaluate the efficacy and safety for patients with resectable CLM of neoadjuvant chemotherapy that included either one of the two molecular targeting monoclonal antibodies. The reasons for applying these treatment regimens were follows: 1) Postoperative adjuvant FOLFOX/XELOX therapy of CLM failed to demonstrate any advantages.[16,18] 2) The EORTC-40983 trial showed that perioperative FOLFOX prolonged 3-year PFS, though there was no difference in overall survival after long-term follow-up.[9] 3) We expected a beneficial effect of monoclonal antibodies according to the findings of large clinical trials in a palliative setting.[19,20]

Here we report the results of the COMET trial. The primary endpoint PFS of our study was 15.6 months and we failed to fulfill the estimated median PFS (18.7 months) from the results of the EORTC-40983 trial.[9] Accordingly, we have to say that our treatment strategy is unworthy of being evaluated in a future large-scale phase III trial. The possible reasons for the difference include the estimation of expected PFS from survival data of patients who underwent perioperative chemotherapy, heterogeneous tumor types and stages, treatment regimens, *KRAS* status, no provision for postoperative treatment, and the refusal of four patients regardless of their ability to undergo surgery. In particular, a patient's refusal to undergo liver resection might influence the primary

endpoint of the present trial, because the median PFS of patients who underwent liver resection was 25.7 months.

The pivotal CELIM trial evaluated the survival benefit of FOLFOX/cetuximab or FOLFIRI/cetuximab for patients with initially unresectable CLM.[21] The median durations of PFS of patients treated with FOLFOX/cetuximab or FOLFIRI/cetuximab were 10.8 months and 11.2 months, respectively, and patients who achieved R0 resection survived longer.[21] However, the second pivotal trial, the New EPOC trial, failed to demonstrate survival benefit of including cetuximab in the standard perioperative chemotherapy regimen administered to patients with resectable CLM and wild-type *KRAS*.[11] Therefore, we are unable to conclude that neoadjuvant-monoclonal antibody therapy offers a benefit for patients with CLM. Future clinical trials enhanced by including imaging techniques such as gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging as well as contrast-enhanced ultrasonography that can detect small lesions are expected. Further, the identification of molecular biomarkers that predict treatment efficacy will likely improve our ability to manage these patients.[22]

It is important to note that the outcome of the COMET trial is highly significant because of its data regarding safety and influence on PFS after liver resection. For example, the overall frequency of grade 3/4 AEs, including hematologic and non-hematologic events, was 45%, which is generally consistent that of the New EPOC trial (preoperative cetuximab plus chemotherapy, 40%) and an earlier clinical trial conducted in the United Kingdom.[11,17] The preoperative response rate (CR + PR)

of the present study was 55% compared with 43% and 70% achieved by the EORTC-40983 and New EPOC trials, respectively.[9,11] The liver resection rate in the present study was 83%, which is comparable with that of patients who underwent preoperative therapy in the latter two trials (87% each).[9,11] There have been concerns that preoperative administration of molecular targeting agents including bevacizumab results in impaired wound healing.[23] With respect to liver resection for CLM, it has been reported that an interval for 5 to 8 weeks between the last administration of bevacizumab and elective surgery resulted in complication rates equivalent to those in patients who received chemotherapy without bevacizumab.[24-26] Although the sample size was limited, our perioperative result (median blood loss 499 ml, morbidity rate 14% and no mortality) was comparable to previous reports including the New EPOC trial (23% and 16% for the chemotherapy-alone and chemotherapy plus cetuximab groups).[11,24-26] Thus, it provided a supportive data for safety of preoperative administration of molecular targeting agents when appropriate interval was provided before liver resection.

Another important finding of the present study was the influence of the sequences of *KRAS* codons on response to treatment and prognosis. Although the molecular targeting agents were different (cetuximab and bevacizumab for the wild-type and mutant *KRAS* groups, respectively), the former tended to have a favorable PFS and exhibited significantly increased tumor shrinkage as their best responses. The possible explanations of the difference was as follows; 1) CRCs with mutant *KRAS* are known to have more aggressive characteristics compared to those with wild-type *KRAS*,

[1,27] 2) The survival benefit of addition of cetuximab to FOLFOX/XELOX has been demonstrated in patients with metastatic CRCs, whereas bevacizumab has not.[19,28,29] Nevertheless, our findings may provide a foundation for future studies designed to compare the advantages of neoadjuvant chemotherapy plus monoclonal antibodies according to the *KRAS* mutational status. The OPUS trial revealed that patients with *RAS*-mutant metastatic CRC, as defined by mutations in *KRAS* and *NRAS* exons 2-4, derive no benefit and may be harmed by the addition of cetuximab to FOLFOX4.[30] Unfortunately, information of *KRAS* codon 61, *NRAS* and *BRAF* status were unavailable this time. Evaluation of all *RAS* and *BRAF* status enable us to provide further information and deepen the discussion in the neoadjuvant setting.[31]

The small sample size of the COMET trial, inequality of patient allocation into cetuximab or bevacizumab and the refusal of four (9%) patients to undergo liver resection potentially biased the survival analysis. Exclusion of patients who received adjuvant chemotherapy for colorectal carcinoma administered <6 months before detection of liver metastasis would make a potential selection bias by excluding patients who experienced early recurrences predicting poor prognosis. The lack of a provision for postoperative adjuvant treatment may have influenced outcomes. Moreover, because this was a single-arm study, we were unable to determine the survival benefit of neoadjuvant FOLFOX or XELOX combined with monoclonal antibodies.

In conclusion, neoadjuvant therapy using FOLFOX/XELOX combined with monoclonal antibodies did not improve PFS of patients with resectable CLM, though it was administered safely

and had less adverse effects after liver resection.

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FIGURE LEGENDS

FIG. 1 (**a**) Waterfall plot of the maximum percentage tumor shrinkage. (**b**) The median progression-free survival time was 15.6 months. NA, not available. (**c**) Overall survival included 14 deaths.

FIG. 2 Kaplan–Meier curves of PFS according to (**a**) *KRAS* status and (**b**) liver resection.

TABLE 1 Patients' baseline characteristics

Clinical characteristic	**Overall (n = 47)**	***KRAS* status**		***P Value****
		Wild type (n = 32)	**Mutant (n = 15)**	
Sex				
Male (%)	28 (60%)	19 (59%)	9 (60%)	0.968
Female (%)	19 (40%)	13 (41%)	6 (40%)	
Age (years)				
Median (range)	67 (49-85)	66 (53-85)	71 (49-82)	0.064
ECOG performance status				
0	44 (94%)	29 (91%)	15 (100%)	0.121
1	3 (6%)	3 (9%)	0 (0%)	
Primary sites				
Colon	30 (64%)	19 (59%)	11 (73%)	0.347
Rectum	17 (36%)	13 (41%)	4 (27%)	
Primary tumor resection				
Performed	45 (96%)	31 (97%)	14 (93%)	0.588
Not performed	2 (4%)	1 (3%)	1 (7%)	
Appearance of metastasis				
Synchronous	31 (66%)	22 (69%)	9 (60%)	0.558
Metachronous	16 (34%)	10 (31%)	6 (40%)	
Number of metastatic sites				
1	24 (51%)	17 (53%)	7 (47%)	
2	9 (19%)	5 (16%)	4 (27%)	0.042
3	2 (4%)	0 (0%)	2 (13%)	
4	6 (13%)	4 (12%)	2 (13%)	
5 or more	6 (13%)	6 (19%)	0 (0%)	
Maximum tumor size (mm), Median (range)	29 (10 -75)	29 (10 -58)	29 (13 -75)	0.706

*Comparison between the wild-type and mutant *KRAS* groups. *ECOG*, Eastern Cooperative Oncology Group

TABLE 2 Treatment-related adverse events

	Grade 1/2	Grade 3	Grade 4	All grades (%)	Grade 3/4 (%)
Overall	-	-	-	47 (100%)	21 (45%)
Hematologic AEs					
Leucopenia	25	4	1	30 (64%)	5 (11%)
Neutropenia	15	7	4	26 (55%)	11 (23%)
Anemia	24	0	0	24 (51%)	0 (0%)
Thrombocytopenia	24	2	1	27 (57%)	3 (6%)
Non-hematologic AEs					
Elevated AST	20	0	0	20 (43%)	0 (0%)
Elevated ALT	17	0	0	17 (36%)	0 (0%)
Elevated creatinine	7	0	0	7 (15%)	0 (0%)
Hyperbilirubinemia	7	3	0	10 (21%)	3 (6%)
Fatigue	17	1	0	18 (38%)	1 (2%)
Anorexia	30	1	0	31 (66%)	1 (2%)
Nausea	19	4	0	23 (49%)	4 (9%)
Vomiting	13	1	0	14 (30%)	1 (2%)
Diarrhea	9	2	1	12 (26%)	3 (6%)
Stomatitis	17	2	0	19 (40%)	2 (4%)
Hand–foot syndrome	14	0	1	15 (32%)	1 (2%)
Febrile neutropenia	0	2	0	2 (4%)	2 (4%)
Neuropathy (sensory)	31	1	0	32 (68%)	1 (2%)
Allergy	0	0	1	1 (2%)	1 (2%)
Cetuximab-associated AE					
Hypomagnesemia	5	0	0	5 (11%)	0 (%)
Rash	23	1	0	24 (51%)	1 (2%)
Bevacizumab-associated AEs					
Hypertension	4	1	0	5 (11%)	1 (2%)
Proteinuria	3	0	0	3 (6%)	0 (%)
Thrombosis	0	0	0	0 (0%)	0 (%)
Bleeding	0	1	0	1 (2%)	1 (2%)

AE, adverse event

TABLE 3 Treatment profiles

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease

	Overall (n=47)	***KRAS* status**	
		Wild type (n=32)	**Mutant (n=15)**
CR	1 (2%)	1 (3%)	0 (0%)
PR	25 (53%)	22 (69%)	3 (20%)
SD	14 (30%)	5 (16%)	9 (60%)
PD	4 (9%)	2 (6%)	2 (13%)
Not evaluated	3 (6%)	2 (6%)	1 (7%)
Response rate (CR + PR)	55%	72%	20%
Disease control rate (CR + PR + SD)	85%	88%	80%
Liver resection rate	83%	88%	73%

FIG 1.

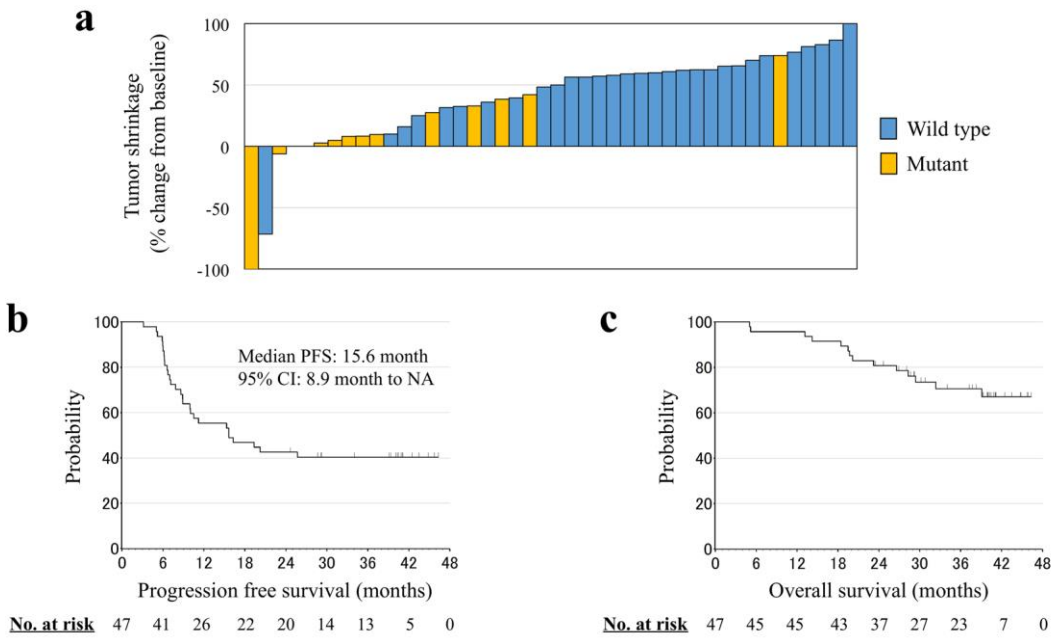
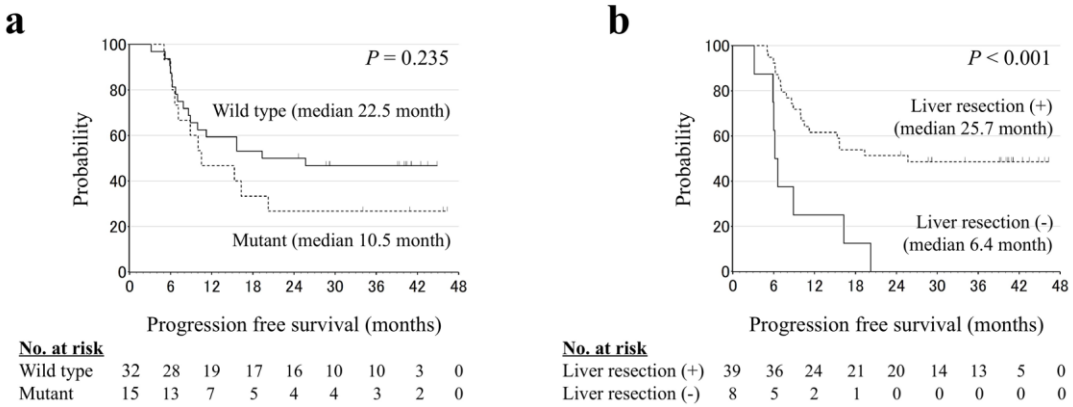

a
Tumor shrinkage
(% change from baseline)
100
50
0
-50
-100
Wild type
Mutant
b
Probability
Median PFS: 15.6 month
95% CI: 8.9 month to NA
Progression free survival (months)
No. at risk 47 41 26 22 20 14 13 5 0
c
Probability
Overall survival (months)
No. at risk 47 45 45 43 37 27 23 7 0

FIG 2.


a
P = 0.235
Wild type (median 22.5 month)
Mutant (median 10.5 month)
Probability
Progression free survival (months)
No. at risk
Wild type 32 28 19 17 16 10 10 3 0
Mutant 15 13 7 5 4 4 3 2 0
b
P < 0.001
Liver resection (+) (median 25.7 month)
Liver resection (-) (median 6.4 month)
Probability
Progression free survival (months)
No. at risk
Liver resection (+) 39 36 24 21 20 14 13 5 0
Liver resection (-) 8 5 2 1 0 0 0 0 0