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Gastrointestinal Cancer

The Prognostic Impact of *KRAS* G12C Mutation in Patients with Metastatic Colorectal Cancer: A Multicenter Retrospective Observational Study

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. *KRAS* • G12C • Colorectal cancer • Chemotherapy • Prognosis

Abstract

Background. *KRAS* is one of the most frequently mutated oncogenes in colorectal cancer (CRC). Recently, a novel therapy targeting *KRAS* G12C mutation has demonstrated promising activities for corresponding advanced solid tumors, including metastatic CRC (mCRC). However, the prognostic impact of the *KRAS* G12C mutation remains unclear in patients with mCRC.

Materials and Methods. We retrospectively reviewed medical records of patients with mCRC who received first-line chemotherapy between January 2005 and December 2017 at four large oncology facilities in Japan. Survival outcomes were compared between patients with *KRAS* G12C and those with non-G12C mutations.

Results. Among 2,457 patients with mCRC, 1,632 met selection criteria, and of these, 696 had *KRAS* exon 2 mutations, including 45 with *KRAS* G12C mutation tumors. Patient characteristics were not significantly different between the *KRAS* G12C and non-G12C groups. At a median follow-up of 64.8 months, patients with the *KRAS* G12C mutation showed significantly shorter first-line progression-free survival (PFS; median, 9.4 vs. 10.8 months; $p = .015$) and overall survival (OS; median, 21.1 vs. 27.3 months; $p = .015$) than those with non-G12C mutations. Multivariate analysis also showed that *KRAS* G12C mutation was significantly associated with shorter PFS (hazard ratio [HR], 1.43; 95% confidence interval [CI], 1.04–1.96, $p = .030$) and OS (HR, 1.42; 95% CI, 1.01–2.00; $p = .044$).

Conclusion. We demonstrate that, compared with non-G12C mutations, *KRAS* G12C mutation is significantly correlated with shorter first-line PFS and OS. These findings indicate the relevance of a stratified treatment targeting *KRAS* G12C mutation in mCRC. ***The Oncologist*** 2021;26:845–853

Implications for Practice: Among patients with *KRAS* exon 2 mutated metastatic colorectal cancer (mCRC), median progression-free survival (PFS) and overall survival (OS) were 9.4 and 21.1 months, respectively, for G12C mutation and 10.8 and 27.3 months, respectively, for patients with non-G12C mutations, indicating significantly shorter PFS (hazard ratio [HR], 1.47; 95% confidence interval [CI], 1.08–2.01; $p = .015$) and OS (HR, 1.50; 95% CI, 1.08–2.08; $p = .015$) in patients with G12C mutation than in those with non-G12C mutations. Furthermore, multivariate analysis showed that *KRAS* G12C mutation was independently associated with shorter first-line PFS and OS. Thus, these findings underscore the relevance of a stratified treatment targeting *KRAS* G12C mutation in mCRC.

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Introduction

The rat sarcoma (*RAS)* family of proto-oncogenes, including Kirsten rat sarcoma (*KRAS*), neuroblastoma rat sarcoma (*NRAS*), and Harvey sarcoma, plays a central role in many human cancers [1], and *KRAS* is one of the most frequently mutated oncogenes in colorectal cancer (CRC). The various *RAS* mutation subtypes show specific functional profiles, and in cell lines, these mutation subtypes exhibit different patterns of transformation, aggressiveness, and/or drug response [2–5]. *RAS* mutations are undruggable targets because of the presence of large, deep-seated hydrophobic pockets in their molecular structure that are difficult to target with small-molecule chemistry [6]; however, the development of small-molecule inhibitors that selectively bind to a newly discovered allosteric regulatory site in the G12C *KRAS* mutant is underway [7].

A phase I trial of AMG 510, which is the first-in-class *KRAS* G12C inhibitor, achieved a partial response in 30% of patients with non-small cell lung cancer and in 7.1% of patients with CRC [8]. Additionally, an ongoing clinical trial is testing a combination of the *KRAS* G12C inhibitor and anti–epidermal growth factor receptor (EGFR) antibody [9].

Thus, the prognostic impact of *KRAS* G12C mutation in metastatic CRC (mCRC) is important for the development of novel, clinically effective agents; however, there have been few reports on the prognostic impact of *KRAS* G12C mutation in mCRC. Therefore, the aim of this study was to evaluate the prognostic impact of *KRAS* G12C mutation in mCRC using real-world data.

Materials and Methods

Data Acquisition

Data were collected from patients with mCRC who had undergone palliative chemotherapy at four centers from January 2005 to December 2017. Designated participating centers were large oncology facilities in Japan, namely, the National Cancer Center Hospital East (Kashiwa, Chiba, Japan), the Aichi Cancer Center (Nagoya, Aichi, Japan), the Shizuoka Cancer Center (Nagaizumi, Shizuoka, Japan), and the Hokkaido University Hospital (Sapporo, Hokkaido, Japan). All data were retrospectively collected from electronic medical records, and the eligibility criteria were as follows: (a) histologically proven colorectal adenocarcinoma, (b) *RAS* or *BRAF* mutation confirmed by polymerase chain reaction or next-generation sequencing methods, (c) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, and (d) adequate organ function.

First-line backbone chemotherapy regimens were divided into three groups: mono (5-fluorouracil [5-FU]/leucovorin [LV], capecitabine, tegafur-uracil [UFT]/LV, or S-1 monotherapy), doublet (oxaliplatin-based regimens [FOLFOX, CAPOX, or SOX] or irinotecan-based regimens [FOLFIRI, IRIS/SIRB, CAPIRI]), and triplet (FOLFOXIRI). Information on the history of bevacizumab administration was also obtained.

The study protocol was approved by the institutional review board of each institution and was carried out in accordance with the guidelines for biomedical research specified in the Declaration of Helsinki. The requirement for informed consent was waived because of the retrospective design of this study.

RAS/*BRAF*^{V600E} Mutation Assessment

RAS and *BRAF*^{V600E} mutation status were centrally assessed using polymerase chain reaction (PCR) kits, namely, TheraScreen K-RAS Mutation Kit (QIAGEN, Germantown, MD), MuPACK KIT, MEBGEN RASKET KIT, and MEBGEN RASKET-B KIT (Medical & Biological Laboratories, Tokyo, Japan) [10–12], and *BRAF*^{V600E} status was centrally evaluated using a next-generation sequencing method (Oncomine Cancer Research Panel or Oncomine Comprehensive Assay version 3; Thermo Fisher Scientific, Waltham, MA) as well as the PCR methods.

Statistical Analysis

Progression-free survival (PFS) was defined as the time from first-line chemotherapy initiation to disease progression or death from any cause. Overall survival (OS) was defined as the time from study treatment initiation to death from any cause. Both PFS and OS were calculated using the Kaplan-Meier method, and the following pretreatment clinical data and baseline laboratory values were used as covariates, namely, age, gender, ECOG PS, primary tumor site (caecum, ascending colon, or transverse colon were classified as right-sided, whereas those located in the splenic flexure, descending colon, sigmoid colon, or rectum were classified as left-sided), surgery on the primary tumor, time of first metastasis (synchronous or metachronous), histology (well/moderately differentiated adenocarcinoma or poorly differentiated/mucinous adenocarcinoma), white blood cell count, serum albumin level, serum lactate dehydrogenase (LDH) level, serum C-reactive protein level, metastatic tumor site (liver, lung, lymph node, or peritoneal dissemination), number of metastatic sites, and *KRAS* exon 2 mutation subtypes. Survival outcomes were compared between patients with *KRAS* G12C mutation and those with non-G12C mutations.

Quantitative data are expressed as median and range, the cutoff value for LDH was set to the median, and the Glasgow prognostic score (GPS) was calculated based on data from previous reports [13]. The Mann-Whitney *U* test or the Kruskal-Wallis test was used to compare continuous variables, whereas Fisher's exact test or the χ^2-test was performed to compare categorical variables. Survival curves were estimated using the Kaplan-Meier method and differences between the groups were tested by the log-rank test. Hazard ratios (HRs) were estimated using the Cox proportional hazards model. PFS and OS were analyzed using univariate and multivariate Cox regression analyses. The backward method was used to select retained factors ($p < .1$) during multivariate analysis. All values of $p < .05$ were considered statistically significant, and all statistical analyses were performed using the statistical program R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Overview

Among 2,457 patients administered systemic chemotherapy for mCRC, we included 1,717 patients with known *RAS* status and clinical follow-up data. *BRAF*^{V600E} mutations and *KRAS* exon 2 mutations were identified in 43 patients and 702 patients, respectively, and the remaining 972 patients had tumors without *KRAS* exon 2 mutations. Among these, we excluded patients with *KRAS* co-mutations (*KRAS* G13D and G13R [$n = 4$], *KRAS* G12V and G13D [$n = 1$], and *KRAS* G12A and G13D [$n = 1$]), *KRAS* exon 3/4 mutation ($n = 45$), and *NRAS* mutations ($n = 34$). Thus, 43, 893, and 696 patients were present in the *BRAF*^{V600E} mutation, the *KRAS* exon 2 wild-type, and the *KRAS* exon 2 mutation groups, respectively (Fig. 1). The distribution of *KRAS* exon 2 wild-type and each combination of *KRAS* exon 2/*BRAF*^{V600E} mutations is shown in Figure 2. *KRAS* exon 2 wild-type accounted for 54.7% (893/1632), and the following six mutations accounted for the majority of *KRAS* exon 2 mutations: *KRAS* G12D (16.0%, 261/1632), G13D (9.8%,160/1632), G12V (9.3%, 151/1632), G12C (2.8%, 45/1632), G12S (2.2%, 36/1632), and G12A (1.9%, 31/1632). Characteristics of patients with *KRAS* G12C or non-G12C mutations are summarized in Table 1. There was no significant difference between *KRAS* G12C and non-G12C mutations; 5% of difference was observed in the following characteristics: gender, ECOG PS, surgery on primary tumor, time of first metastasis, liver metastasis, peritoneal dissemination, number of metastatic sites, and GPS. Characteristics of patients with each *KRAS* exon 2 mutation subtype are summarized in supplemental online Table 1, and there were no significant differences among the *KRAS* exon 2 mutation subtypes.

Survival in the Entire Population

Median follow-up period was 64.8 months (95% confidence interval [CI], 59.6–71.1 months), and 1,243 (76.2%) patients had died. Median OS for the entire population was 29.4 months (95% CI, 27.9–30.9 months). Compared with patients with wild-type *KRAS* exon 2, median OS was significantly shorter in patients with *KRAS* exon 2 mutations (HR, 1.23 [95% CI, 1.10–1.38], $p < .001$) and in those with *BRAF*^{V600E} mutations (HR, 1.48 [95% CI, 1.25–1.75], $p < .001$) (Fig. 3). Furthermore, PFS and OS were not significantly influenced by genotype subgroups. The median PFS and OS of patients with *KRAS* exon 2 mutation subtypes ranged from 9.4 months (95% CI, 6.4–12.0) to 11.5 months (95% CI, 9.4–13.5) and from 21.1 months (95% CI, 12.8–29.4) to 29.8 months (20.5–41.9), respectively (supplemental online Figs. 1 and 2).

Prognostic Impact of the *KRAS* G12C Mutation and Non-G12C Mutations

Among patients with *KRAS* exon 2 mutations, those with the G12C mutation had significantly shorter PFS and OS than those with non-G12C mutations (median PFS, 9.4 months [95% CI, 6.4–12.0] vs. 10.8 months [95% CI, 10.1–11.5]; HR, 1.47 [95% CI, 1.08–2.01], $p = .015$; median OS, 21.1 months [95% CI, 12.8–27.9] vs. 27.3 months [95% CI, 24.8–28.9]; HR, 1.50 [95% CI, 1.08–2.08], $p = .015$) (Fig. 4).

Table 2 shows the results of univariate and multivariate analyses for PFS in patients with *KRAS* exon 2 mutations. Multivariate analysis identified the following factors as

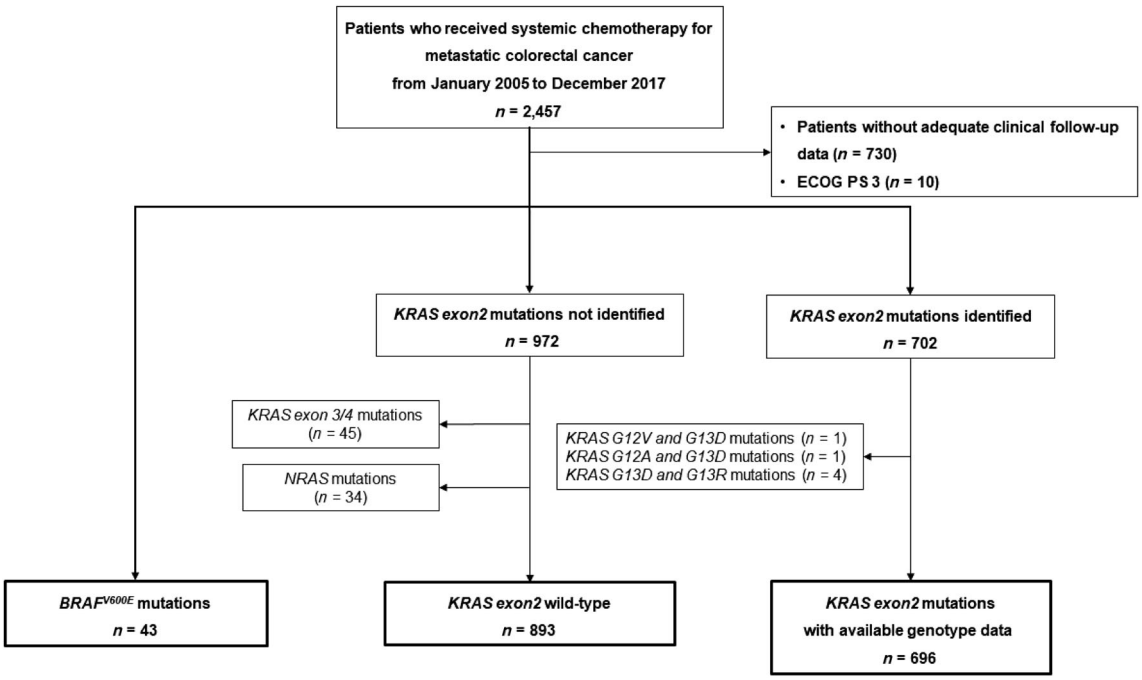

Figure 1. Patient selection flow diagram.
Abbreviations: ECOG PS, Eastern Cooperative Oncology performance status; *KRAS*, Kirsten rat sarcoma; *NRAS*, neuroblastoma rat sarcoma.

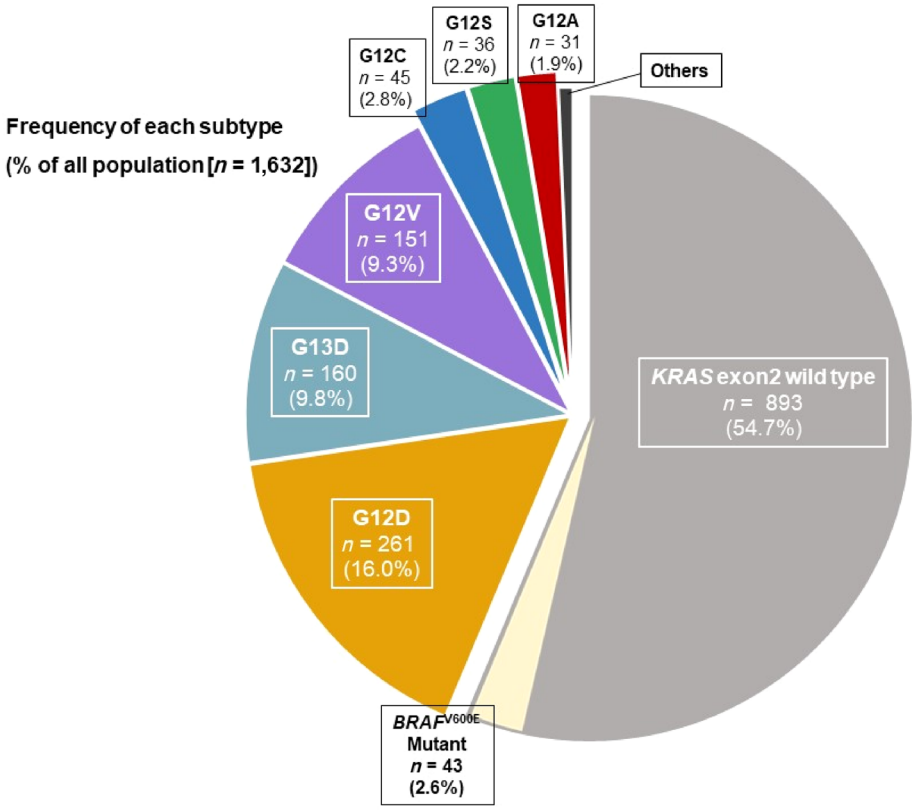

Figure 2. Frequency of each subtype (% of all population). *KRAS* exon 2 wild-type was 56.3%, and the most prevalent mutations in *KRAS* exon 2 were G12D (16.3%), followed by G13D (10.1%), G12V (9.5%), G12C (2.8%), G12S (2.3%), and G12A (1.9%). Abbreviations: *KRAS*, Kirsten rat sarcoma.

significantly associated with PFS: *KRAS* G12C mutation (vs. non-G12C mutation: HR, 1.43; 95% CI, 1.04–1.96; $p = .030$), surgery on primary tumor (yes vs. no: HR, 0.82; 95% CI, 0.69–0.99; $p = .035$), serum LDH (≥210 IU/L [median] vs. <210: HR, 1.24; 95% CI, 1.04–1.47; $p = .014$), GPS (1 or 2 vs. 0: HR, 1.53; 95% CI, 1.21–1.93, $p < .001$), number of metastatic organ sites (≥2 vs. 1: HR, 1.32; 95% CI, 1.12–1.55; $p = .001$), and first-line bevacizumab (yes vs. no: HR, 0.57; 95% CI, 0.45–0.71; $p < .001$) (Table 2).

Table 3 shows the results of univariate and multivariate analyses for OS in patients with *KRAS* exon 2 mutations. Here, multivariate analysis yielded significant association between OS and the following variables: *KRAS* G12C mutation (vs. non-G12C mutation: HR, 1.42; 95% CI, 1.01–2.00; $p = .044$), ECOG PS (1 or 2 vs. 0: HR, 1.25; 95% CI, 1.00–1.57; $p = .049$), surgery on primary tumor (yes vs. no: HR, 0.75; 95% CI, 0.60–0.93; $p = .010$), histology (mucinous or poorly differentiated vs. well or moderately differentiated: HR, 1.44; 95% CI, 1.06–1.95; $p = .021$), serum LDH (≥210 IU/L [median] vs. <210: HR, 1.59; 95% CI, 1.31–1.92; $p < .001$), GPS (1 or 2 vs. 0: HR, 1.64; 95% CI, 1.27–2.12; $p < .001$), and number of metastatic organ sites (≥2 vs. 1: HR, 1.45; 95% CI, 1.21–1.74; $p < .001$) (Table 3).

Furthermore, in the patients who received doublet or triplet chemotherapy, their characteristics were not significantly different between those with *KRAS* G12C and non-G12C mutations (supplemental online Table 2). Also, consistently poor PFS and OS were observed in those with *KRAS* G12C mutation (supplemental online Fig. 3).

Discussion

Our study assessed the prognostic impact of *KRAS* G12C mutation in chemotherapy-naïve patients with mCRC. Median OS for each type of mutation (i.e., *KRAS* exon 2 wild-type, *KRAS* exon 2 mutant, and $BRAF^{V600E}$ mutant) was consistent with that reported previously [14, 15], indicating that our cohort was representative of the mCRC population and that the results presented here reflect prognosis in clinical practice. We modeled real-world distributions of *KRAS* mutation subtypes and reveal poor PFS and OS in patients with *KRAS* G12C mutation compared with patients with non-G12C mutations.

The overall prevalence of *KRAS* exon 2 mutations and that of the three major *KRAS* mutation subtypes, along with the targetable subtype *KRAS* G12C, obtained in this study is consistent with previous reports [16–18]. A recent analysis of the distribution of *KRAS* G12C mutation categorized according to race, gender, and cancer type identified a trend of greater prevalence among female patients, irrespective of their ethnicity; however, *KRAS* G12C mutation was less frequent in CRC compared with non-small cell lung cancer (3.2% vs. 13.8%). This higher proportion of female patients is also consistent with the results from our study [18].

Although several reports have described the prognostic impact of *KRAS* mutation subtypes, most have focused on patients with non-small cell lung cancer and/or nonmetastatic CRC [19, 20], and only a few studies have analyzed the prognostic impact of *KRAS* G12C mutation in mCRC [16, 21]. A

Table 1. Patient characteristics

Characteristic	*KRAS* G12C mutations ($n = 45$), *n* (%)	*KRAS* non-G12C mutations ($n = 651$), *n* (%)	*p* value[a]
Age, years, median (range)	65 (31–79)	65 (24–88)	.709
Age ≥65 years	24 (53.3)	339 (52.1)	.879
Gender			.278
Female	24 (53.3)	287 (44.1)	
Male	21 (46.7)	364 (55.9)	
ECOG PS			.113
0	31 (68.9)	491 (75.4)	
1	9 (20.0)	133 (20.4)	
2	5 (11.1)	27 (4.1)	
Primary tumor location			.776
Right	16 (35.6)	213 (32.7)	
Left	29 (64.4)	436 (67.0)	
Missing	0 (0.0)	2 (0.3)	
Surgery on primary tumor			.205
Yes	21 (46.7)	240 (36.9)	
No	24 (53.3)	411 (63.1)	
Time of first metastasis			.075
Metachronous	10 (22.2)	233 (35.8)	
Synchronous	35 (77.8)	418 (64.2)	
Histology			.706
Well/mod	40 (88.9)	581 (89.2)	
Poor/muc	4 (8.9)	61 (9.4)	
Missing	1 (2.2)	9 (1.4)	
Metastatic sites			
Liver	30 (66.7)	375 (57.6)	.275
Lung	18 (40.0)	274 (42.1)	.876
Peritoneal dissemination	16 (35.6)	150 (23.0)	.070
Number of metastatic sites			.281
1	18 (40.0)	319 (49.0)	
≥2	27 (60.0)	332 (51.0)	
Serum LDH, median (range), IU/L	221 (140–1,459)	210 (75–4,340)	.515
GPS			.763
0	27 (60.0)	427 (65.6)	
1	10 (22.2)	110 (16.9)	
2	7 (15.6)	105 (16.1)	
Missing	1 (2.2)	9 (1.4)	
First-line backbone regimen			.357
Mono[b]	2 (4.4)	32 (4.9)	
Doublet[c]	43 (95.6)	591 (90.8)	
Triplet[d]	0 (0.0)	28 (4.3)	
First-line bevacizumab			.843
Yes	36 (80.0)	531 (81.6)	
No	9 (20.0)	120 (18.5)	

[a]Values of *p* were calculated using Fisher's exact probability test for categorical variables.
[b]Mono indicates 5-fluorouracil (5-FU)/leucovorin (LV), capecitabine, tegafur-uracil (UFT)/LV, or S-1 monotherapy.
[c]Doublet indicates oxaliplatin-based regimens (FOLFOX, CAPOX, and SOX) or irinotecan-based regimens (FOLFIRI, IRIS [SIRB], CAPIRI).
[d]Triplet indicates FOLFOXIRI.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; GPS, Glasgow prognostic score; *KRAS*, Kirsten rat sarcoma; LDH, lactate dehydrogenase; mod, moderately differentiated; muc, mucinous adenocarcinoma; por, poorly differentiated; well, well differentiated.

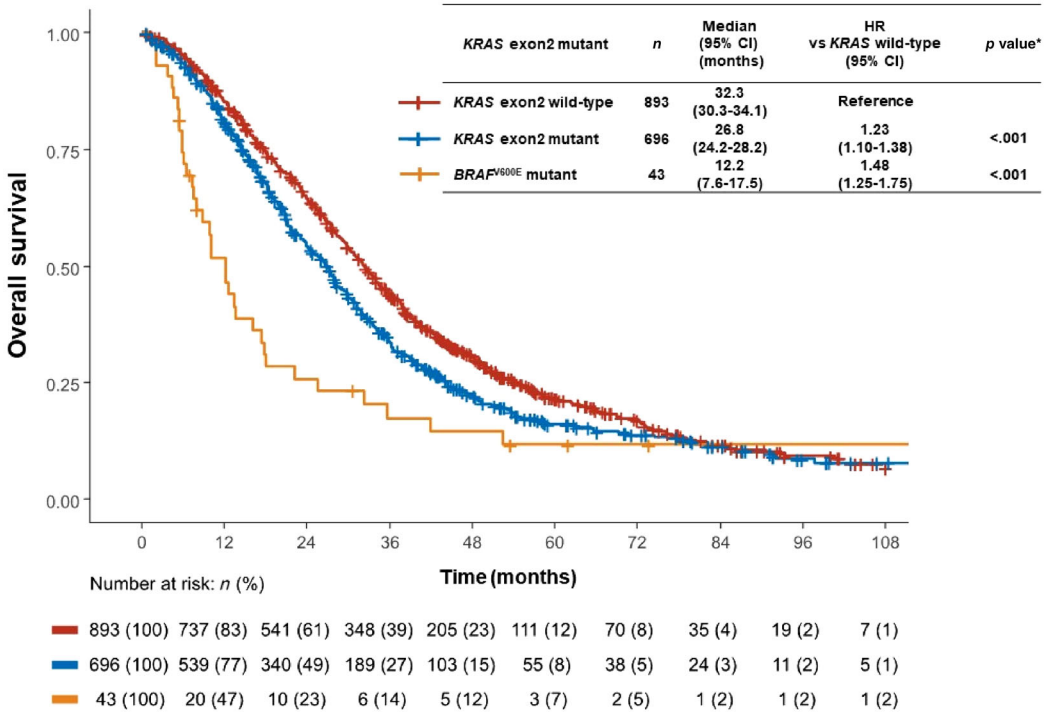

Figure 3. Kaplan-Meier curves for overall survival (OS) in patients with *KRAS* wild-type, *KRAS* exon 2 mutations, and *BRAF*^{V600E} mutations. Compared with *KRAS* exon 2 wild-type, the median OS was significantly shorter in patients with *KRAS* exon 2 mutations (HR, 1.23 [95% CI, 1.10–1.38], $p < .001$) and for those with *BRAF*^{V600E} mutations (HR, 1.48 [95% CI, 1.25–1.75], $p < .001$).
Abbreviations: CI, confidence interval; *KRAS*, Kirsten rat sarcoma; HR, hazard ratio.

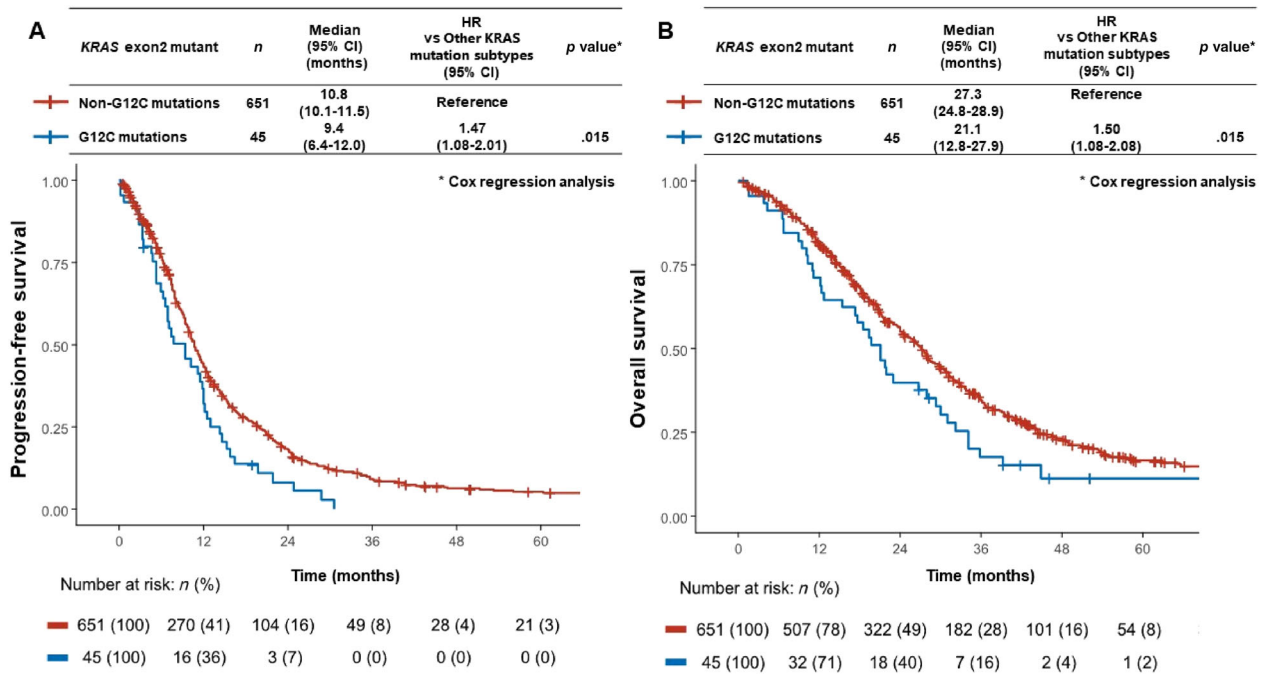

Figure 4. Kaplan-Meier curves for progression-free survival (PFS) and overall survival (OS) in *KRAS* G12C mutation versus non-G12C mutations. **(A):** Median PFS in patients with *KRAS* G12C mutation was significantly shorter than that in patients with non-G12C mutations (9.4 months [95% CI, 6.4–12.0] vs. 10.8 months [95% CI, 10.1–11.8]; HR, 1.47 [95% CI, 1.08–2.01], $p = .015$). **(B):** Median OS in patients with *KRAS* G12C mutation was significantly shorter than that in patients with non-G12C mutations (21.1 months [95% CI, 12.8–27.9] vs. 27.3 months [95% CI, 24.8–28.9]; HR, 1.50 [95% CI, 1.08–2.08], $p = .015$).
Abbreviations: CI, confidence interval; *KRAS*, Kirsten rat sarcoma; HR, hazard ratio.

Table 2. Univariate and multivariate analysis for progression-free survival

	Univariate		Multivariate	
Category	**HR (95% CI)**	***p* value[a]**	**HR (95% CI)**	***p* value[a]**
KRAS exon 2 mutation: G12C vs. non-G12C	1.47 (1.08–2.01)	.015	1.43 (1.04–1.96)	.030
Age: ≥65 vs. <65 years	0.97 (0.83–1.14)	.724		
Gender: Male vs. female	0.98 (0.83–1.15)	.794		
ECOG PS: 1 or 2 vs. 0	1.48 (1.24–1.78)	<.001	1.08 (0.88–1.33)	.443
Primary tumor site: left vs. right	0.93 (0.79–1.10)	.417		
Surgery on primary tumor: Yes vs. No	0.69 (0.59–0.81)	<.001	0.82 (0.69–0.99)	.035
Time of first metastasis: Synchronous vs. metachronous	1.15 (0.97–1.35)	.113		
Histology: Poor/muc vs. well/mod	1.17 (0.89–1.54)	.258		
Serum LDH, IU/L: ≥210 (median) vs. <210	1.50 (1.28–1.76)	<.001	1.24 (1.04–1.47)	.014
GPS: 1 or 2 vs. 0	1.96 (1.58–2.44)	<.001	1.53 (1.21–1.93)	<.001
Number of metastatic organ sites: ≥2 vs. 1	1.46 (1.25–1.71)	<.001	1.32 (1.12–1.55)	.001
First-line backbone regimen: Doublet[b] or triplet[c] vs. mono[d]	0.84 (0.57–1.22)	.355		
First-line bevacizumab: Yes vs. no	0.51 (0.42–0.63)	<.001	0.57 (0.45–0.71)	<.001

[a]Values of *p* were calculated using the Cox proportional hazard model.
[b]Doublet indicates oxaliplatin-based regimens (FOLFOX, CAPOX, and SOX) or irinotecan-based regimens (FOLFIRI, IRIS [SIRB], CAPIRI).
[c]Triplet indicates FOLFOXIRI.
[d]Mono indicates 5-fluorouracil (5-FU)/leucovorin (LV), capecitabine, tegafur-uracil (UFT)/LV, or S-1 monotherapy.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GPS, Glasgow prognostic score; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma; LDH, lactate dehydrogenase; mod, moderately differentiated; muc, mucinous adenocarcinoma; poor, poorly differentiated; well, well differentiated.

Table 3. Univariate and multivariate analysis for overall survival

	Univariate		Multivariate	
Category	**HR (95% CI)**	***p* value[a]**	**HR (95% CI)**	***p* value[a]**
KRAS exon 2 mutation: G12C vs. non-G12C	1.50 (1.08–2.08)	.015	1.42 (1.01–2.00)	.044
Age: ≥65 vs. <65 years	1.03 (0.87–1.22)	.725		
Gender: Male vs. female	0.90 (0.76–1.07)	.219		
ECOG PS: 1 or 2 vs. 0	1.78 (1.46–2.17)	<.001	1.25 (1.00–1.57)	.049
Primary tumor site: left vs. right	0.82 (0.68–0.98)	.028	0.99 (0.82–1.21)	.976
Surgery on primary tumor: Yes vs. no	0.58 (0.48–0.69)	<.001	0.75 (0.60–0.93)	.010
Time of first metastasis: Synchronous vs. metachronous	1.47 (1.23–1.77)	<.001	0.95 (0.76–1.19)	.647
Histology: por/muc vs. well/mod	1.44 (1.07–1.94)	.016	1.44 (1.06–1.95)	.021
Serum LDH, IU/L: ≥210 (median) vs. <210	1.93 (1.62–2.30)	<.001	1.59 (1.31–1.92)	<.001
GPS: 1 or 2 vs. 0	2.31 (1.83–2.90)	<.001	1.64 (1.27–2.12)	<.001
Number of metastatic organ site: ≥2 vs. 1	1.63 (1.37–1.94)	<.001	1.45 (1.21–1.74)	<.001
First-line backbone regimen: Doublet[b] or triplet[c] vs. mono[d]	0.60 (0.41–0.90)	.012	0.76 (0.50–1.17)	.219
First-line bevacizumab: Yes vs. no	0.69 (0.55–0.86)	<.001	0.84 (0.66–1.08)	.174

[a]Values of *p* were calculated using the Cox proportional hazard model.
[b]Doublet indicates oxaliplatin-based regimens (FOLFOX, CAPOX, and SOX) or irinotecan-based regimens (FOLFIRI, IRIS [SIRB], CAPIRI).
[c]Triplet indicates FOLFOXIRI.
[d]Mono indicates 5-fluorouracil (5-FU)/leucovorin (LV), capecitabine, tegafur-uracil (UFT)/LV, or S-1 monotherapy.
Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; GPS, Glasgow prognostic score; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma; LDH, lactate dehydrogenase; mod, moderately differentiated; muc, mucinous adenocarcinoma; poor, poorly differentiated; well, well differentiated.

pooled analysis by the Arbeitsgemeinschaft Internistische Onkologie [AIO] study group revealed that *KRAS* G12C mutation was significantly associated with lower OS compared with tumors with no *KRAS* mutations [16]; however, it must be noted here that this pooled analysis also included patients who had received a nonstandard treatment regimen, including FUFIRI, FUFOX, and mIROX as induction chemotherapies and bevacizumab monotherapy or observation alone as maintenance therapies in clinical trials [22, 23]. Schirripa et al. have recently reported poor prognosis in patients with mCRC and

KRAS G12C mutation; however, the prevalence of *KRAS* G12C mutation was relatively high at 17.3%, and favorable outcomes, such as median OS greater than 35 months in patients with *KRAS* non-G12C mutations, might not reflect real-world clinical practice [21]. The strength of our study lies in validating poor prognosis in the presence of the *KRAS* G12C mutation with respect to PFS and OS using real-world data obtained outside a clinical trial setting. We also included data from patients with mCRC receiving standard chemotherapies by performing a multivariate analysis that included important covariate factors.

A preclinical study has shown specific differences in intrinsic or GTPase Activating Protein-mediated GTP hydrolysis among the *KRAS* mutation subtypes that result in differential activation of downstream effectors, such as the mitogen-activated protein kinase [MAPK]/extracellular signal-regulated kinase [ERK] pathway [24, 25]. Profiles of biochemical properties of *KRAS* mutations and G12C, G12D, and G13D mutants showed a high level of intrinsic GTPase activity compared with those of other *KRAS* mutations, such as G12A and G12V [5]. However, there are insufficient data on the reasons for the *KRAS* G12C mutation leading to poorer prognosis than non-G12C mutations in mCRC; therefore, further investigations are needed to identify the precise mechanism underlying the observed poor prognosis.

Recently, two *KRAS* G12C inhibitors, AMG 510 and MRTX849, have been developed; both specifically bind to the mutant cysteine residue [7]. The first two trials with AMG 510 and MRTX849 revealed promising clinical results in non-small cell lung cancer; however, the response in patients with CRC was unexpectedly limited [8, 26]. Indeed, rapid heterogeneous adaptation to conformation-specific *KRAS* G12C inhibition has been pointed out as a mechanism of resistance to the *KRAS* G12C inhibitor, and importantly, this phenomenon could be reverted when therapy was combined with the EGFR inhibitor [27, 28]. Furthermore, a phase I study of a combination of AMG 510 plus EGFR inhibitor with or without chemotherapy is ongoing in patients with *KRAS* G12 mutant mCRC. Given the development and trial of novel targeted agents, our data would be an important source of reference on the real-world distribution and prognostic impact of the *KRAS* G12C mutation in patients with mCRC.

Limitations to the present study need to be considered when interpreting these results. First, as previously noted, this was a nonrandomized retrospective study. Second, although our study included 1,632 patients with mCRC, the number of patients with the *KRAS* G12C mutation in tumors was limited. Nevertheless, taking into consideration that there are only a few reports that provide a detailed prognosis in *KRAS* G12C mutation, the data presented here can play an important role in the clinical development of *KRAS* G12C inhibitors. Third, all patients in our study were Asian. However, a recent report has revealed no difference in the distribution of *KRAS* G12C mutation in CRC between Asian and Western populations, unlike non-small cell lung cancer [18]. Therefore, our result may be applied to Western populations as well as Asian populations.

Conclusion

We demonstrate that the *KRAS* G12C mutation is significantly correlated with a shorter PFS and OS compared with *KRAS* non-G12C mutations in chemotherapy-naïve patients with mCRC. These findings indicate the importance of individualized treatment that targets the *KRAS* G12C mutation.

Acknowledgments

The authors thank all patients and families for participation in the studies, as well as all involved study centers, colleagues, and nurses. The authors also would like to thank Enago (www.enago.jp) for the English language review.

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Disclosures

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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