Reduced Dose of Salvage-line Regorafenib Monotherapy for Metastatic Colorectal Cancer in Japan

GEN HIRANO[1], AKITAKA MAKIYAMA[1], CHINATSU MAKIYAMA[1], TAITO ESAKI[2], HISANOBU ODA[2], KEITA UCHINO[3], MASATO KOMODA[3], RISA TANAKA[4], YUZO MATSUSHITA[4], KENJI MITSUGI[4], YOSHIHIRO SHIBATA[5], HOZUMI KUMAGAI[6], SHUJI ARITA[6,7], HIROSHI ARIYAMA[6], HITOSHI KUSABA[6], KOICHI AKASHI[6] and EISHI BABA[7]

[1]*Department of Hematology and Oncology, Japan Community Health Care Organization Kyushu Hospital, Kitakyushu, Japan;*
[2]*Department of Gastrointestinal and Medical Oncology, National Kyushu Cancer Center, Fukuoka, Japan;*
[3]*Department of Medical Oncology, Clinical Research Institute, National Hospital Organization Kyushu Medical Center, Fukuoka, Japan;*
[4]*Department of Oncology, Hamanomachi Hospital, Fukuoka, Japan;*
[5]*Department of Chemotherapy, Miyazaki Prefectural Miyazaki Hospital, Miyazaki, Japan;*
[6]*Department of Hematology and Oncology of Kyushu University Hospital, Fukuoka, Japan;*
[7]*Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, Fukuoka, Japan*

Abstract. *Background: Salvage-line regorafenib monotherapy exhibited a marked survival benefit for metastatic colorectal cancer (mCRC). However, the toxicity of this regimen has resulted in the clinical use of a reduced dose of regorafenib. Patients and Methods: Thirty-two Japanese mCRC patients (median age=61 years) who had been treated with regorafenib were retrospectively examined. Results: Best objective response rate was 0% and stable disease (SD) was 31%. Median progression-free survival was 81 days and median overall survival was 233 days. Adverse events of any grade were observed in all patients: 17 (53%) patients suffered grade 3 or 4 adverse events including fatigue (13%), anorexia (13%), hand-foot skin reaction (22%) and elevations of alanine aminotransferase/aspartate aminotransferase (19%/16%). One patient with grade 5 liver dysfunction was identified (3%). Twenty-nine (91%) patients required treatment dose reduction or a delay in treatment. The relative dose intensity was 59%. Regorafenib treatments were terminated because of disease progression (59%) or adverse events (34%). Conclusion: Despite a decrease in the intensity of regorafenib treatment, because of severe adverse events, a fairly favorable efficacy was achieved in Japanese patients.*

Correspondence to: Eishi Baba, MD, Ph.D., Department of Comprehensive Clinical Oncology, Faculty of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. Tel: +81 926426921, Fax: +81 926426922, e-mail: e-baba@c-oncology.med.kyushu-u.ac.jp

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Colorectal cancer (CRC) is the third most common cancer and the fourth most common cause of death in the world (1). In Japan, CRC is the third most common cause of death and the number of annual deaths continues to increase (2). While surgical treatments are performed for patients with localized disease, at least 50% of CRC patients will develop distant metastases and are, therefore, inoperable (3). Systemic chemotherapy has been developed as a standard therapy against metastatic CRC (mCRC), and therapeutic outcomes have since improved. Combination chemotherapy regimens with cytotoxic drugs, such as oxaliplatin, irinotecan and fluoropyrimidine, and with molecular-targeting drugs, such as anti-vascular endothelial growth factor (VEGF) and anti-epidermal growth factor receptor (EGFR) antibodies, can extend survival time in mCRC patients. Recent clinical studies showed that a median overall survival of 30 months was achieved in mCRC patients (4). However, tumors often become resistant to these agents and show disease progression despite chemotherapies. Therefore, further therapeutic options are required.

Regorafenib is an oral multi-kinase inhibitor that interferes with multiple signaling pathways that participate in the proliferation and survival of CRC cells, including those mediating angiogenesis, oncogenesis and maintenance of tumor microenvironment (5). The global phase 3 CORRECT study (Regorafenib Monotherapy for Previously Treated

Metastatic Colorectal Cancer) assessed the efficacy and safety of regorafenib monotherapy *vs*. placebo for mCRC patients after failure of standard chemotherapy that included oxaliplatin, irinotecan, fluoropyrimidine, bevacizumab and anti-EGFR antibodies in case of *KRAS* wild-type status (6). A total of 760 patients (83% from Western countries in 83%, 14% from Asian countries, 3% from Eastern Europe countries) were randomly assigned to a regorafenib arm or a placebo arm at the rate of 2 to 1. The CORRECT study demonstrated that overall survival (OS) was significantly better in the regorafenib group than in the placebo group and, thus, regorafenib monotherapy was subsequently approved as an agent for salvage-line chemotherapy of mCRC in 2012 in the United States and the European Union and in 2013 in Japan. Additionally, regorafenib was proven to be effective for patients with metastatic gastrointestinal stromal tumors, as demonstrated in a phase III clinical study (GRID study) (7).

In the CORRECT study, Common Terminology Criteria for Adverse Events (CTC-AE) grade 3 and higher toxicity occurred in 14% of the placebo group and in 54% in the regorafenib group. Hand-foot skin reaction, fatigue, diarrhea, hypertension and rash or desquamation was frequently observed and, thus, intensive maintenance for these adverse events was required. In terms of adverse events related to anti-angiogenic activity, grade 5 cerebrovascular events and bleeding from the lung, rectum and vagina were reported. One death also occurred due to liver dysfunction. While the toxicity of this regimen has resulted in the clinical use of a reduced dose of regorafenib, the actual efficacy and safety profiles of this reduced-dose regimen has not yet been studied. Therefore, the goal of the present study was to investigate the efficacy and safety of reduced-dose regorafenib for treatment of mCRC in Japan.

Patients and Methods

Patients. The present study retrospectively investigated 32 patients with pathohistologically-proven unresectable, recurrent or metastatic colorectal adenocarcinoma. All patients received regorafenib monotherapy from February 1, 2011 to January 8, 2014 at one of the following six Institutions: Department of Hematology and Oncology, Japan Community Health Care Organization Kyushu Hospital; Department of Gastrointestinal and Medical Oncology of National Kyushu Cancer Center; Department of Medical Oncology in Hamanomachi Hospital; Department of Medical Oncology, National Hospital Organization Kyushu Medical Center; Department of Chemotherapy, Miyazaki Prefectural Miyazaki Hospital; Department of Hematology and Oncology of Kyushu University Hospital, Fukuoka, Japan. Information regarding all cases was obtained from medical records from each institution. Patient background characteristics were recorded and included age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), primary site of the tumor, *KRAS* mutational status and history of prior chemotherapies. In patients who were treated with regorafenib during this survey period, administration doses and schedule, best therapeutic effects and adverse events were investigated. Progression-free survival (PFS) was defined as the period from the initiation of the therapy to the day of tumor progression or the day of any caused death. OS was defined as the period from initiation of the therapy to the day of any caused death. Each reason for therapeutic dose reduction before and during regorafenib administration was also examined. The present study was carried out according to the regulations of local ethics committee of each institution and according to the Declaration of Helsinki.

Treatment. All patients had been treated with one or more regimens of systemic chemotherapy and found non-responsive or did not tolerate the regimen. The study treatment of regorafenib was administered until disease progression, unacceptable toxicity or the decision to discontinue by the patient or the investigator. The treatment dose of regorafenib was 160 mg/day *per os* (*p.o.*) for the first 21 days of each 28-day cycle. In cases of adverse events, the dose was reduced to 120 mg/day or 80 mg/day; otherwise, administration of regorafenib was suspended until recovery from the adverse events. Therapeutic dose reduction and treatment delay were performed according to the dose modification/interruption protocol of the CORRECT study (6). Additional modification of therapy was carried-out based on the investigators' decisions considering symptoms and laboratory data of patients.

Assessments. In the first treatment cycle, patients were hospitalized or visited the outpatient office weekly. Patients were assessed for adverse events by physical examination, urinalysis, blood cell counts and serum chemistry at every visit. All adverse events were evaluated according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0. The most severe grades of adverse events during chemotherapy were recorded. Assessment of tumor regions was performed by computed tomography (CT) scan, gastrointestinal endoscopy and magnetic resonance imaging (MRI) every 4-12 weeks.

Statistics. Sub-groups based on the patients characteristics or the relative dose-intensity of regorafenib in terms of OS were separately analyzed by the log-rank test.

Results

Patients' background and treatments. Thirty-two patients were treated with regorafenib monotherapy during the observation period. Their median age was 61 years (range=30-78 years) and the population included 18 (56%) males (Table I). ECOG PS was 0 in eight cases (25%), 1 in 21 cases (66%) and 2 in three cases (9%). The primary affected organ was the colon in 19 cases (59%) and the rectum in 13 cases (41%). The primary site was resected in 21 cases. All cases were histologically diagnosed as adenocarcinoma. Wild-type *KRAS* exon 2 was identified in 22 cases (69%) and mutated *KRAS* type was identified in nine cases (28%). One case had uncertain *KRAS* exon 2 status, whereas other kinds of gene alterations of the tumors were not examined. Two regimens of prior chemotherapy were performed in 15 cases (47%), three regimens of prior chemotherapy were performed in 10 cases (31%) and more

Table I. *Baseline patients' characteristics*.

Characteristic	No.	%
Gender		
Male	18	56
Female	14	44
Age		
Median (range), years	61	(30-78)
Performance status		
0	8	25
1	21	66
2	3	9
Primary tumor		
Colon	19	59
Rectum	13	41
Resected	21	66
Remaining	11	34
Histology		
Adenocarcinoma	32	100
Others	0	0
KRAS mutational status		
Wild-type	22	69
Mutant-type	9	28
Not tested	1	3
Prior chemotherapy (regimens)		
2	15	47
3	10	31
4 or more	7	22
Prior bevacizumab therapy	25	78
Prior EGFR antibody	23	72

EGFR, Epithelial growth factor receptor.

Table II. *Efficacy of regorafenib monotherapy.*

Best objective response	No.	%
CR	0	0
PR	0	0
SD	10	31
non-CR/non-PD	1	3
PD	17	53
NE	4	13
Response rate	0	0
Disease control rate	11	34

CR, Complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable.

than four regimens of prior chemotherapy were performed in seven cases (22%). Twenty-five cases (78%) had prior bevacizumab therapy and the other seven cases had no history of bevacizumab treatment even though they did not have any complications, which were contraindicated to anti-angiogenesis inhibitors. Anti-EGFR antibodies were administered in 22 cases (69%) with wild-type *KRAS* exon 2 and in one case (3%) with unknown *KRAS* status.

Table III. *Characteristics of regorafenib monotherapy.*

Characteristics	No.	%
Duration of therapy		
Median weeks (range)	10.9	(0.6-51.9)
Relative dose intensity (%)	59	(24-100)
Dose reduction or interrupt dose		
Total	29	91
Dose reduction prior to the therapy	7	22
Dose reduction during therapy	22	69
Reasons for the dose reduction prior to the therapy		
Complication other than liver disease	1	
Complication of liver disease	1	
Poor performance status	1	
Predicted adverse events	2	
Reasons for the dose reduction during therapy		
Adverse events	22	
Reasons for the termination of therapy		
Progressive disease	19	59
Adverse events	11	34
Others	2	6

Treatment. The median regorafenib treatment period was 10.9 weeks (range=0.6-51.9 weeks) and the median relative dose intensity was 59% (range=24-100%) (Table III). In this study, patients were followed until July 8, 2014. At that point, administration of regorafenib was terminated in all cases. Twenty-two patients had died, six patients remained alive and four patients were lost to follow-up. In the present study, dose modification and treatment delay of regorafenib were performed in 29 cases (91%). Reduced-dose administration of regorafenib in the initial cycle of the therapy was observed in seven cases (22%) (120 mg/day in five cases, and 80 mg/day in two cases). The reasons for the initial dose reduction included liver dysfunction in three cases, complications other than liver dysfunction in one, poor PS in one case and suspected severe adverse events in two cases. On the other hand, dose reduction and treatment delay in 22 cases were caused by adverse events. Regorafenib treatment was terminated because of tumor progression in 19 cases (59%), adverse events in 11 cases (34%) and other reasons in two cases (6%).

Efficacy. None of the cases achieved complete response (CR) or partial response (PR). Ten cases (31%) showed stable disease (SD), one case (3%) showed non-CR/non-progressive disease (PD), 17 cases (53%) showed PD and four cases (13%) were not evaluable (NE) (Table II). The objective response rate was 0% and the disease control rate

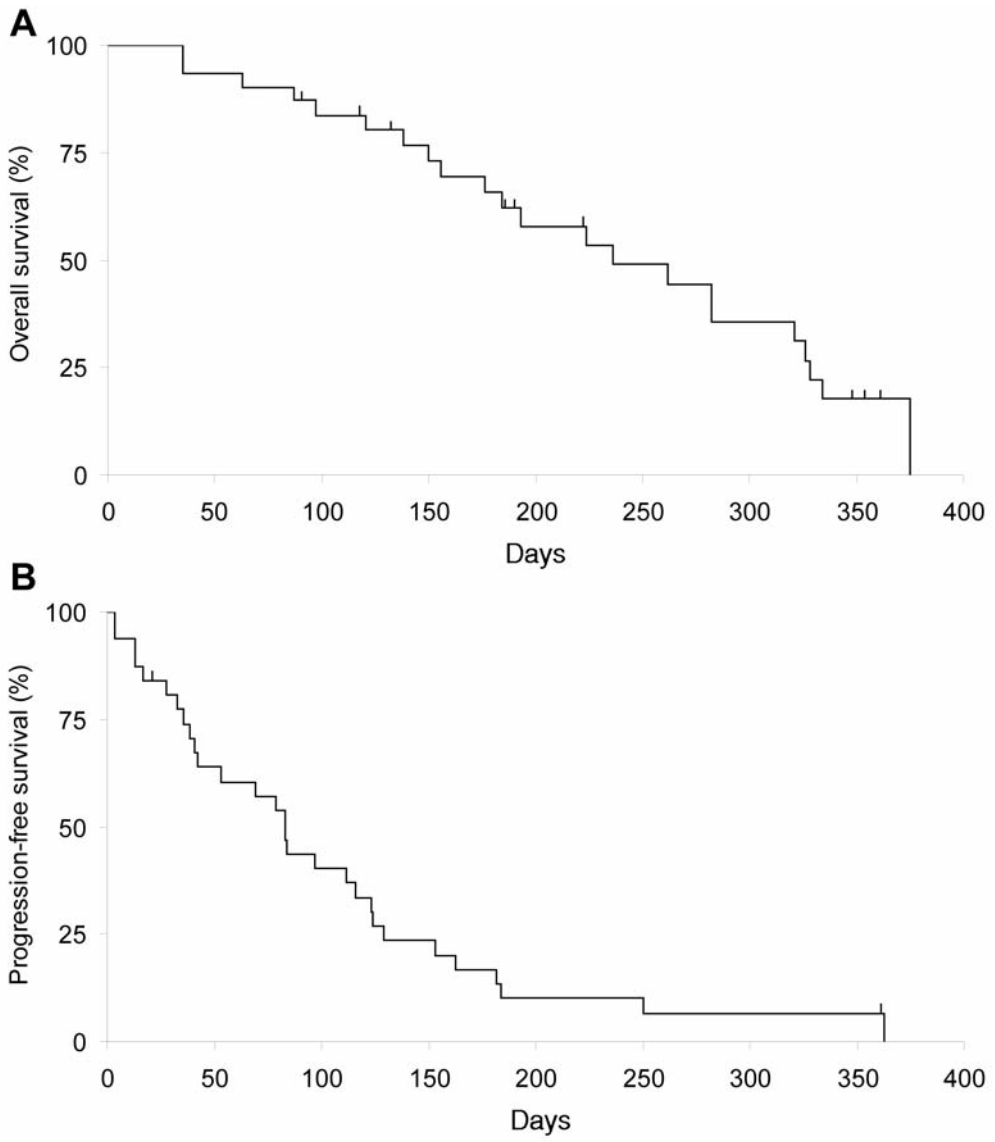

Figure 1. *Overall survival and progression free survivals. Kaplan-Meier estimates for overall survival (A) and progression free survival (B) in the whole examined population (n=32).*

(CR+PR+SD+non-CR/non-PD) was 34%. Median PFS was 81 days (4-363) and median OS was 233 days (32-375) (Figure 1A, B).

Safety. Therapy-related toxicities in the patients were assessed according to CTC-AE version 4.0 and the worst grade is shown in Table IV. Concerning hematological toxicities, thrombocytopenia was observed in 44% (grade 3/4; 6%), anemia in 56% (grade 3/4; 3%) and leukocytopenia in 19% (grade 3/4; 0%). No febrile neutropenia was recorded.

In terms of non-hematological toxicities, fatigue was observed in 47% of patients (grade 3/4; 13%), hand-foot skin reaction in 72% (grade 3/4; 22%), anorexia in 41% (grade 3/4; 13%), stomatitis in 25% (grade 3/4; 3%) and diarrhea in 6% (grade 3/4; 3%). Serum chemistry examination revealed that increments of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and total bilirubin were found in 81%, 59% and 50% of all the patients, respectively (grade 3/4; 19%, 16%, 9%). Unfortunately, grade 5 liver dysfunction occurred in one female patient in her 30s who had sigmoid colon cancer with multiple liver metastases. Her prior chemotherapies consisted of the combination of oxaliplatin and 5-FU (FOLFOX) plus bevacizumab and the combination of irinotecan and 5-FU (FOLFIRI) plus panitumumab. A

Table IV. *Adverse events*.

Adverse event	All grades		Grade 3		Grade 4		Grade 5	
	N	%	N	%	N	%	N	%
Fatigue	15	47	4	13	0	0	0	0
Hand-foot skin reaction	23	72	7	22	0	0	0	0
Hypertension	15	47	3	9	0	0	0	0
Anorexia	13	41	4	13	0	0	0	0
Skin eruption	9	28	2	6	0	0	0	0
Nausea/Vomiting	1	3	1	3	0	0	0	0
Stomatitis	8	25	1	3	0	0	0	0
Diarrhea	2	6	1	3	0	0	0	0
Proteinuria	1	3	1	3	0	0	0	0
Pneumonia	1	3	1	3	0	0	0	0
Stevens-Johnson syndrome	1	3	1	3	0	0	0	0
Hepatic failure	1	3	0	0	0	0	1	3
Leukocytopenia	6	19	0	0	0	0	0	0
Anemia	18	56	1	3	0	0	0	0
Thrombocytopenia	14	44	2	6	0	0	0	0
Albumin decreased	22	69	0	0	0	0	0	0
AST increase	26	81	3	9	3	9	0	0
ALT increase	19	59	2	6	3	9	0	0
LDH increase	22	69	2	6	0	0	0	0
Total bilirubin increase	16	50	1	3	2	6	0	0

AST, Aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase.

slight increase in serum AST and total bilirubin occurred at 22 days after the initiation of standard-dose regorafenib and liver dysfunction progressed even after termination of regorafenib administration on day 22. The patient died on day 35 despite various liver supporting therapies.

Subgroup analysis. Patients were stratified with respect to a broad range of background characteristics and OS was compared between these groups using the log-rank test (Table V). No differences in OS were seen when stratifying patients according to age, sex, primary disease site or prior chemotherapies (including a history of bevacizumab therapy and number of regimens). Patients with PS of 2 showed significantly worse outcomes when compared to those with PS 0 or 1, suggesting that PS 0 or 1 before regorafenib therapy could be a valuable indication to start therapy. Also, patients with *KRAS* wild-type status showed a tendency towards favorable OS when compared with patients with *KRAS* exon 2 mutation (Table V).

Table V. *Sub-group analysis of overall survival*.

Factors	Valuables	No.	p-Value
Age	<65 years	22	0.95
	>66 years	10	
Gender	Male	18	0.94
	Female	14	
PS	0/1	29	<0.001
	2	3	
Primary site	Colon	19	0.21
	Rectum	13	
KRAS	Wild-type	22	0.025
	Mutant-type	9	
Prior regimens	1/2	16	0.17
	3 or more	16	
Prior bevacizumab	Yes	25	0.17
	No	7	
Relative dose intensity	>59%	16	0.22
	<59%	16	

PS, Performance status.

Discussion

The relative dose intensity of regorafenib monotherapy in the present study was 59% when compared to a 78.9% relative dose intensity reported in a previous phase III trial (CORRECT study). The CORRECT study demonstrated a significant survival benefit of salvage-line regorafenib monotherapy over best supportive care for patients with advanced colorectal cancer (6). The decreased relative dose intensity is reflected by dose reduction and treatment delay

of regorafenib therapy, which was observed in 91% of patients in this study. These therapy modifications were performed in 75.6% of the patients in the CORRECT study. The higher ratio of dose modification/interruption in the present study, than that in CORRECT study, might be due to several reasons. First, severe toxicities appeared more often in the present study. Any CTC-AE grades of fatigue and appetite loss were observed in 47% and 41% of the patients in this study, respectively, and grade 3 and higher fatigue and appetite loss were observed in 13% and 13%, respectively. Any grades and grade 3 of hand-foot skin reaction were also seen in 72% and 22%, respectively. Hand-foot skin reaction in this study occurred more frequently than that in the CORRECT study (any grades, 47%; grade 3, 17%). One possible explanation for this toxicity profile might be related to differences in ethnicity of the patient population when comparing the two studies. Since all dose modifications/interruptions during the therapy period were performed because of adverse events, more severe toxicities might lead to lower relative dose intensity. Second, 22% of patients were treated with a decreased dose of regorafenib during the initial cycle of treatment and liver dysfunction occurred in half of the patients. Most adverse events induced by regorafenib are ameliorated by therapeutic dose reduction and treatment delay, which underscores the dose-dependent nature of adverse events. Therefore, the initial dose reduction is inevitable, especially for patients who are at high risk of developing severe adverse events. While this strategy might result in decreased anti-tumor efficacy, outcomes were still good despite initial dose reduction. Four patients (13%) were given the planned dose of regorafenib for more than two cycles suggesting that initial dose reduction does not have a strong impact on efficacy.

OS and PFS were similar when comparing the present study to the CORRECT study, despite the lower relative dose intensity in the present study. The therapeutic dose reduction was performed mainly because of safety; improvements of quality of life (QOL) were not assessed in this study. Regorafenib monotherapy might help to maintain QOL by improving disease status (6). Therefore, salvage-line regorafenib monotherapy with dose reduction might improve survival while maintaining QOL.

Elevations in AST/ALT of grade 3 and higher were more frequently observed in the Japanese subpopulation than in the whole cohort in the CORRECT study (8), and a 62-year-old Asian man suffered grade 5 drug-induced liver dysfunction. In the present study, 19/16% patients had elevation in AST/ALT of grade 3 and higher and one patient died of liver dysfunction. A previous randomized phase III clinical trial of regorafenib monotherapy *vs.* placebo (GRID study) for advanced gastrointestinal stromal tumor demonstrated a survival benefit for regorafenib (7); one quarter of the enrolled patients in this study were Asians. A total of 98.5% of patients in the regorafenib arm had adverse events (grade 3 and higher, 59.8%) and 68.2% of patients in the placebo arm had adverse events (grade 3 and higher, 9.1%). However, the incidence of liver dysfunction was not reported. The pharmacokinetic profiles of regorafenib and its active metabolites, M2 and M5, in a phase I study of Japanese solid tumor patients revealed that the range of regorafenib exposure was similar to those reported in European patients in phase I and II studies (9). These findings suggest that there is a high likelihood of developing liver dysfunction, especially in the Japanese population. Further study is needed to characterize the risk of regorafenib-induced liver dysfunction in Japanese and Asian populations.

Although the present study was a retrospective analysis of a small number of mCRC patients, we believe these data yield important insight into the efficacy adverse events of this therapy in a Japanese population. According to the present findings, uniform dose reduction and treatment delay could not be recommended but dose reduction, based on the toxicity profiles of each patient, should be actively considered. Exploration of biomarkers predicting the efficacy and safety of regorafenib and establishing safer treatment guidelines by clarifying the mechanism of regorafenib-induced liver dysfunction and other adverse events would be of benefit.

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