



Safety data from the phase III Japanese ACHIEVE trial: part of an international, prospective, planned pooled analysis of six phase III trials comparing 3 versus 6 months of oxaliplatin-based adjuvant chemotherapy for stage III colon cancer

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ABSTRACT

Background The International Duration Evaluation of Adjuvant chemotherapy project investigated whether a shorter duration of oxaliplatin-based adjuvant chemotherapy was as effective as 6 months of identical chemotherapy for resected stage III colon cancer. As part of this project, we report safety data from the Japanese ACHIEVE study (JFMC47-1202-C3).

Patients and methods ACHIEVE was an open-label, multicentre trial randomising patients with stage III colon cancer to receive 3 m or 6 m of mFOLFOX6/CAPOX after surgery. Choice of regimen was declared before randomisation by a site investigator.

Results Between August 2012 and June 2014, 1313 patients were enrolled and, of those, 1277 were analysed for the safety analysis, with 635 in arm 6 (mFOLFOX6, n=158; CAPOX, n=477) and 642 in arm 3 (mFOLFOX6, n=161; CAPOX, n=481). Grade 3 or worse peripheral sensory neuropathy (PSN) developed in 5%/0.6% of patients receiving mFOLFOX6 in arm 6/3 (p=0.019) and 6%/1% of those receiving CAPOX in arm 6/3 (p<0.001). Similarly, grade 2 or worse PSN developed in 36%/11% of patients receiving mFOLFOX6 in arm 6/3 (p<0.001) and 37%/14% of those receiving CAPOX in arm 6/3 (p<0.001). An association between baseline creatinine clearance (CCr) and adverse events (AEs) was found that patients with CAPOX were significantly more likely to develop AEs ≥grade 3 when they had a CCr ≤50 (OR 1.67; p=0.048).

Conclusions We confirmed in the Japanese population that the shorter duration of adjuvant chemotherapy resulted in a significant reduction of PSN. In patients with CAPOX, renal function was significantly related to severe AEs.

Trial registration number UMIN000008543, Results.

INTRODUCTION

Colorectal cancer is the third most frequent cancer worldwide and the third highest cause

Key questions

What is already known about this subject?

- ▶ Six months of FOLFOX or CAPOX are positioned as the standard adjuvant chemotherapy regimens for treatment of stage III colon cancer.
- ▶ Peripheral sensory neuropathy (PSN) is an important dose-limiting toxicity of oxaliplatin therapy, so shorter duration of adjuvant FOLFOX or CAPOX therapy would be beneficial for patients if efficacy was not reduced.

What does this study add?

- ▶ We have demonstrated that shorter duration of adjuvant chemotherapy resulted in a significant reduction of PSN.
- ▶ This study was the only investigation in the International Duration Evaluation of Adjuvant chemotherapy (IDEA) project performed for the Asian population. There was a somewhat lower incidence of PSN related to oxaliplatin therapy in Asian patients, but a level of reduction in PSN frequency was consistent among the IDEA studies.
- ▶ We have demonstrated that in patients with CAPOX, renal function was significantly related to severe adverse events.

How might this impact on clinical practice?

- ▶ Our data support the importance of careful selection of starting dose of capecitabine in patients with a renal impairment receiving CAPOX therapy.

of cancer-related deaths.¹ Surgical resection is the only curative treatment for colorectal cancer and postoperative adjuvant chemotherapy, including oxaliplatin-based therapy,

has played an important role in improving outcomes since 2004. Two standard adjuvant chemotherapy regimens for stage III colon cancer, which are FOLFOX (leucovorin (LV), 5-fluorouracil (5-FU) and oxaliplatin) and CAPOX (oxaliplatin and capecitabine), have been established as through the MOSAIC study^{2,3} comparing LV5-FU2 therapy with FOLFOX4 therapy and the XELOXA (NO16968) study⁴ comparing CAPOX with bolus 5-FU/LV, respectively.

Peripheral sensory neuropathy (PSN) is an important dose-limiting toxicity of oxaliplatin therapy. In the MOSAIC study, the incidence of grade 2 and 3 PSN was 31.4% and 12.5%, respectively, and 15.5% of patients had residual PSN (any grade) at 4 years after completing FOLFOX4 therapy.³ Similarly, the Japanese JOIN study found residual PSN (any grade) in about 20% of patients at 3 years after completing mFOLFOX6 therapy.⁵ The JOIN study also revealed that patients with lower grade PSN were more likely to show early recovery, indicating the importance of avoiding grade 2 or higher PSN.⁶

Oxaliplatin-related PSN is likely to progress to higher grades as the total dose of oxaliplatin increases.² Accordingly, a shorter duration of adjuvant FOLFOX or CAPOX therapy would be beneficial for patients if efficacy was not reduced. Therefore, we performed the phase III ACHIEVE study to compare 3 months of current standard adjuvant chemotherapy using mFOLFOX6 or CAPOX (arm 3) with 6 months of chemotherapy (arm 6). This study was part of the International Duration Evaluation of Adjuvant chemotherapy colon cancer (IDEA) project.⁷

Here, we report the safety data from the ACHIEVE study. Each trial in the IDEA project had a different proportion of patients receiving CAPOX therapy (0% to 75%) and our study had the highest proportion; therefore, we have focused on exploring the relationship between severe toxicity of CAPOX and renal dysfunction. Furthermore, our study was the only investigation in the IDEA project performed for the Asian population in which a somewhat different PSN frequency has been reported and will be useful to determine whether the same balance of risk and benefit for oxaliplatin-based adjuvant chemotherapy is observed as in the Western population.^{5,8}

PATIENTS AND METHODS

Patients

Eligibility criteria for our study were as follows: (1) age ≥ 20 years; (2) Eastern Cooperative Oncology Group performance status of 0–1; (3) primary cancer of the caecum, colon or rectosigmoid region diagnosed from operative findings and examination of the resected specimen; (4) complete curative resection including D2 or D3 lymphadenectomy; (5) stage III disease (T any, N1/2/3, M0); and (6) adequate function of vital organs. All patients provided written informed consent before enrolment. The exclusion criteria were (1) cancer of the appendix, (2) a history of other malignancy, (3) PSN of grade 1 or higher and (4) prior treatment with oxaliplatin. The

institutional review board at each study centre approved the protocol.

This trial was registered with University Hospital Medical Information Network (UMIN) Clinical Trials Registry (Trial Identifier, UMIN000008543). This trial was conducted by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC), a non-commercial organisation for investigator-initiated cancer trials, and undertaken in accordance with the Helsinki Declaration.

Treatment schedule

Selection of mFOLFOX6 or CAPOX was decided by the attending physician at registration of each patient. Switching to another regimen was not permitted after enrolment. If continuation of treatment was difficult owing to adverse events (AEs) caused by oxaliplatin, mFOLFOX6 was switched to sLV5-FU2 therapy and CAPOX was switched to capecitabine monotherapy. Dose escalation of 5-FU was not permitted. A single course of mFOLFOX6 therapy involved intravenous administration of oxaliplatin (2-hour infusion: 85 mg/m²), 5-FU (bolus: 400 mg/m²) and LV (200 mg/m²) on day 1, followed by infusion of 5-FU over 46 hours (2400 mg/m²) from day 1 to day 3. This was repeated after 2 weeks (14 days), with a maximum of 12 courses and 6 courses being given in arm 6 and arm 3, respectively. A single course of CAPOX therapy consisted of intravenous oxaliplatin (2-hour infusion: 130 mg/m²) on day 1 and oral capecitabine (2000 mg/m²/day) from the evening of day 1 to the morning of day 15. Capecitabine (1000 mg/m²) was administered twice a day within 30 min after the morning and evening meals for a total of 28 doses. This treatment was repeated after 3 weeks (21 days), with a maximum of eight courses and four courses being given in arm 6 and arm 3, respectively. After the study regimen was completed, further adjuvant chemotherapy was prohibited.

Protocol amendment

Central monitoring by the data centre revealed that discontinuation of CAPOX therapy was more frequent than expected. Therefore, the protocol was amended and a creatinine clearance (CCr) ≥ 30 mL/min was added to the eligibility criteria. In addition, the CAPOX regimen was initiated with a lower dose of capecitabine (1500 mg/m² per day) in patients with a CCr of 30–50 mL/min and/or >70 years old. One patient with a CCr <30 mL/min was enrolled before amendment of the protocol on 25 October 2013.

Statistical analysis

The ACHIEVE study was a multicentre, open-label, randomised phase III study, in which patients who had undergone curative resection of stage III colon cancer were randomly allocated to either arm 6 or arm 3 of adjuvant chemotherapy (mFOLFOX6 or CAPOX) at a 1:1 ratio. Stratification was performed by the N factor (N1 or N2), regimen (mFOLFOX6 or CAPOX), tumour site (colon, rectosigmoid or multiple), age (<70 years or ≥ 70

years) and study institution. Masking was not done for either patients or investigators. Primary endpoint of the study was disease-free survival and key secondary endpoints included overall survival and safety. This study was part of the International Duration Evaluation of Adjuvant chemotherapy colon cancer project (IDEA project). In brief, the IDEA project was a prospective pooled analysis of six randomised trials performed around the world to investigate the non-inferiority of 3 months of FOLFOX or CAPOX versus 6 months of the same regimens for resectable stage III colon cancer with a non-inferiority margin of 1.12.

AEs were reported based on the National Cancer Institute Common Terminology Criteria for Adverse Events V.4.0. Categorical variable (\geq grade 3, <grade 3) was compared between the two groups by Fisher's exact tests. Multivariable analyses for adverse events were done by the logistic regression model with adjusted by treatment duration (3 or 6 months) and age. All p values were two-sided and $p < 0.05$ was considered statistically significant. All analyses were done by SAS V.9.3 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Between August 2012 and June 2014, 1313 patients were enrolled at 244 centres in Japan. The CONSORT diagram is shown in [figure 1](#). Twenty-two patients did not receive the study treatment. Of 1291 patients who started the treatment, 14 were excluded due to the availability of safety data or ineligibility affecting the safety assessment. The safety analysis thus consisted of 1277 patients, with 635 patients in arm 6 (mFOLFOX6, $n=158$; CAPOX, $n=477$) and 642 patients in arm 3 (mFOLFOX6, $n=161$; CAPOX, $n=481$). Patient characteristics were well balanced between both arms ([table 1](#)). Among

patients receiving CAPOX therapy, there were 156/149 patients in arm 6/3 who had a CCr of 30–50 mL/min or were aged ≥ 70 at enrolment. Before amendment of the protocol as explained above, 105/101 patients receiving CAPOX in arm 6/3 started capecitabine at 2000 mg/m²/day, while 51/48 patients in arm 6/3 started capecitabine at 1500 mg/m²/day after protocol amendment.

Treatment compliance in each arm

The relative dose intensity of oxaliplatin and infusional 5-FU achieved with 12/6 cycles of mFOLFOX6 in arm 6/3 was 72/86% and 76/86%, while the relative dose intensity of oxaliplatin and capecitabine for 8/4 cycles of CAPOX in arm 6/3 was 78/92% and 78/88%. The discontinuation rate of mFOLFOX6 in arm 6/3 was 29%/13%, with 23%/10% being related to AEs. In addition, the discontinuation rate of CAPOX in arm 6/3 was 40%/14%, with 31%/12% being related to AEs.

Peripheral sensory neuropathy by oxaliplatin

PSN developed in 5%/0.6% of patients receiving mFOLFOX6 in arm 6/3 ($p=0.019$) and 6%/1% of those receiving CAPOX in arm 6/3 ($p<0.001$). Similarly, grade 2 or worse PSN developed in 36%/11% of patients receiving mFOLFOX6 in arm 6/3 ($p<0.001$) and 37%/14% of those receiving CAPOX in arm 6/3 ($p<0.001$). It was notable that a difference in the 5-FU backbone did not influence the incidence of PSN caused by oxaliplatin. Grade 3 or worse PSN developed in 5% of patients receiving mFOLFOX6 and 6% of patients receiving CAPOX in arm 6 ($p=0.70$), while it was noted in 0.6% with mFOLFOX6 and 1.0% with CAPOX in arm 3 ($p=1.00$). Similarly, grade 2 or worse PSN occurred in 36% of patients receiving mFOLFOX6 and 37% of patients receiving CAPOX in arm 6 ($p=0.92$), while it was

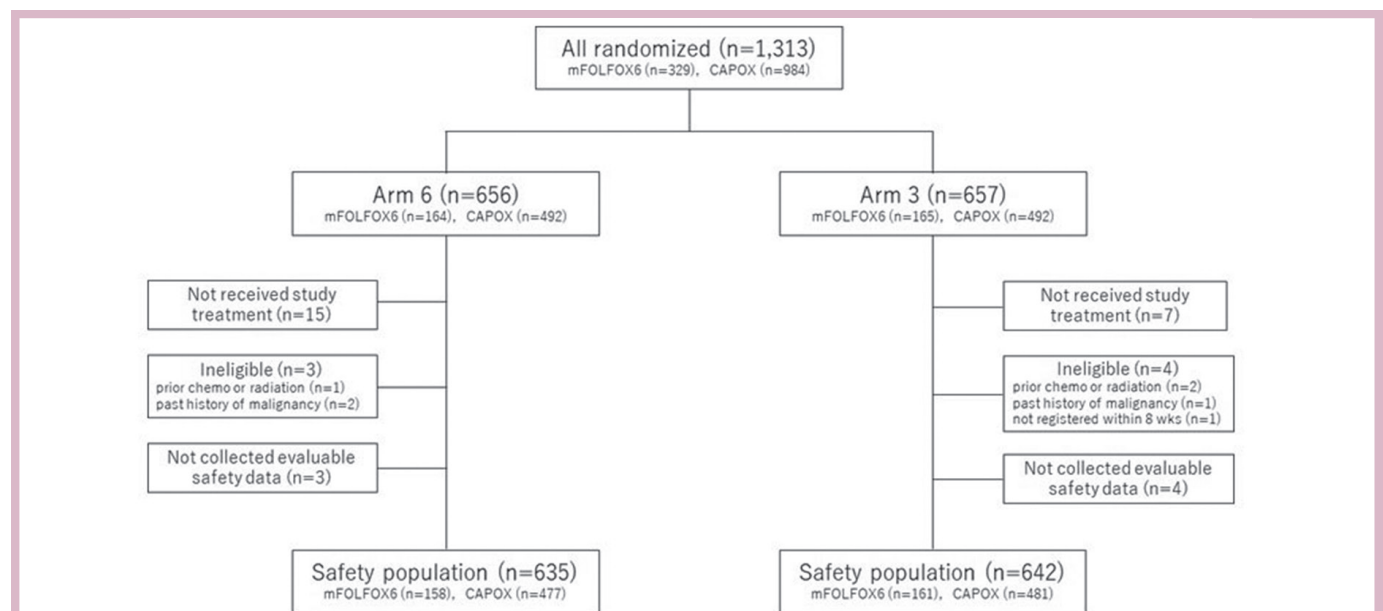


Figure 1 CONSORT diagram for the ACHIEVE study.

Table 1 Characteristics of the patients

| n (%) | Arm 6 | | Arm 3 | |
|----------------------------|-------------------|----------------|-------------------|----------------|
| | mFOLFOX6 n=158 | CAPOX n=477 | mFOLFOX6 n=161 | CAPOX n=481 |
| Sex | | | | |
| Male | 80 (51) | 237 (50) | 77 (48) | 249 (52) |
| Female | 78(49) | 240(50) | 84(52) | 232(48) |
| Age (years) | | | | |
| Median | 67.5 | 65 | 69 | 65 |
| Range | 34–82 | 28–85 | 31–85 | 29–83 |
| ECOG PS | | | | |
| 0 | 154 (97.5) | 462 (97) | 154 (96) | 461 (96) |
| 1 | 4 (2.5) | 15 (3) | 7 (4) | 20 (4) |
| CCr (mL/min) | | | | |
| ≤50 | 13 (8) | 34 (7) | 11 (7) | 31 (6) |
| >50 | 145 (92) | 443 (93) | 150 (93) | 450 (94) |
| BSA (m²) | | | | |
| ≤1.45 | 48 (30) | 118 (25) | 39 (24) | 114 (24) |
| 1.45–1.70 | 68 (43) | 255 (54) | 83 (52) | 231 (48) |
| >1.70 | 42 (27) | 104 (22) | 39 (24) | 136 (28) |
| Tumour site | | | | |
| Colon | 117 (74) | 367 (77) | 121 (75) | 370 (77) |
| Rectosigmoid | 40 (25) | 95 (20) | 35 (22) | 99 (21) |
| Multiple | 1 (1) | 15 (3) | 5 (3) | 12 (3) |
| pT* | | | | |
| T1–2 | 21 (13) | 69 (14.5) | 16 (10) | 84 (17.5) |
| T3–4 | 137 (87) | 408 (85.5) | 145 (90) | 397 (82.5) |
| pN* | | | | |
| N1 | 113 (71.5) | 357 (75) | 118 (73) | 359 (75) |
| N2–3 | 45 (28.5) | 120 (25) | 43 (27) | 122 (25) |

*International Union Against Cancer (UICC) tumour–node–metastasis classification, 7th ed.

BSA, body surface area; CCr, creatinine clearance calculated by the formula of Cockcroft and Gault; ECOG PS, Eastern Cooperative Oncology Group performance status.

seen in 11% with mFOLFOX6 and 14% with CAPOX in arm 3 ($p=0.35$).

Safety profile

Grade 3 or greater AEs occurred in 272 patients (43%) from arm 6 and 184 patients (29%) from arm 3 ($p<0.0001$, [table 2](#)). AEs with a significantly lower incidence in arm 3 compared with arm 6 were neutropenia, hand–foot syndrome and PSN ([table 2](#)), while other AEs had a similar incidence in both arms.

Association of creatinine clearance with severe AEs

We evaluated the relationship between a baseline CCr and grade 3 or greater AEs in patients receiving mFOLFOX6 or CAPOX therapy. [Figure 2](#) shows the frequency of grade 3 or greater AEs stratified by treatment duration and regimen. Multivariable logistic regression analysis

showed that patients receiving CAPOX were significantly more likely to develop grade 3 or greater AEs when they had a CCr ≤ 50 ([table 3](#)), with an adjusted OR of 1.67 (95% CI 1.01 to 2.78; $p=0.048$). Thus, renal impairment was related to the severity of toxicity in patients receiving CAPOX therapy. Although a similar OR (1.49; 95% CI 0.63 to 3.57; $p=0.36$) was seen in patients receiving mFOLFOX6 therapy, the association was not statistically significant.

DISCUSSION

This analysis of safety data from the ACHIEVE study involved the comparison of patients receiving short-term and long-term oxaliplatin-containing adjuvant chemotherapy for stage III colon cancer. Compared with patients in arm 6, those in arm 3 had a significantly lower

Table 2 Summary of grade 3 or higher adverse events stratified by treatment duration and regimen

| n (%) | Arm 6 | | | Arm 3 | | | P value* |
|---------------------------|----------|----------|----------|----------|----------|----------|----------|
| | mFOLFOX6 | CAPOX | Total | mFOLFOX6 | CAPOX | Total | |
| All events ≥grade 3 | 76 (48) | 196 (41) | 272 (43) | 56 (35) | 128 (27) | 184 (29) | <0.001 |
| Haematological | | | | | | | |
| Leucopenia | 9 (6) | 12 (3) | 21 (3) | 12 (8) | 7 (2) | 19 (3) | 0.75 |
| Neutropenia | 54 (34) | 73 (15) | 127 (20) | 43 (27) | 46 (10) | 89 (14) | 0.004 |
| Anaemia | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 (0.4) | 2 (0.3) | 0.50 |
| Thrombocytopenia | 0 (0) | 26 (6) | 26 (4) | 3 (2) | 16 (3) | 19 (3) | 0.29 |
| Non-haematological | | | | | | | |
| Anorexia | 2 (1) | 25 (5) | 27 (4) | 4 (3) | 24 (5) | 28 (4) | 1.00 |
| Diarrhoea | 1 (1) | 26 (6) | 27 (4) | 3 (2) | 27 (6) | 30 (5) | 0.79 |
| Nausea | 1 (1) | 14 (3) | 15 (2) | 2 (1) | 14 (3) | 16 (3) | 1.00 |
| Vomiting | 1 (1) | 4 (1) | 5 (1) | 0 (0) | 10 (2) | 10 (2) | 0.30 |
| HFS | 0 (0) | 15 (3.1) | 15 (2.4) | 0 (0) | 4 (0.8) | 4 (0.6) | 0.011 |
| HFS (≥grade 2) | 4 (3) | 70 (15) | 74 (12) | 2 (1) | 35 (7) | 37 (6) | <0.001 |
| PSN | 8 (5.1) | 30 (6.3) | 38(6) | 1 (0.6) | 5 (1.0) | 6 (0.9) | <0.001 |
| PSN (≥grade 2) | 57 (36) | 175 (37) | 232 (37) | 18 (11) | 69 (14) | 87 (14) | <0.001 |

*Fisher's exact test for comparison of all AEs ≥grade 3 between arm 6 and arm 3.
AE, adverse event; HFS, hand-foot syndrome; PSN, peripheral sensory neuropathy.

incidence of several key AEs, which included PSN, hand-foot syndrome and neutropenia. Among these AEs, PSN is the greatest concern for patients receiving oxaliplatin-containing chemotherapy, and it was noteworthy that the frequency of ≥grade 2 or ≥grade 3 PSN was significantly reduced by decreasing the number of chemotherapy courses irrespective of the 5-FU backbone. A 25% decrease in grade 2 or greater PSN for mFOLFOX6 and a 23% decrease in that for CAPOX were achieved by the short-term therapy. Among other trials participating in the IDEA project, the incidence of PSN ≥grade 2 in arm 6/arm 3 was 56%/24% in the SCOT study⁹ and 66%/36% in the IDEA France study,¹⁰ indicating about 30% decrease in ≥grade 2 PSN by the shorter duration

of treatment. Similarly, the TOSCA study¹¹ showed the incidence of PSN ≥grade 3 in arm 6/arm 3 was 31%/9%. Thus, there was a somewhat lower incidence of PSN related to oxaliplatin therapy in Asian patients, but a level of reduction in PSN frequency was consistent among the IDEA studies.

It has been previously reported that the starting dose of capecitabine monotherapy for metastatic colorectal cancer should be reduced to avoid severe toxicity when CCr is 30–50 mL/min, and that capecitabine may be contraindicated when CCr is <30 mL/min.¹² However, there are insufficient safety data for oxaliplatin-containing regimens in patients with renal impairment

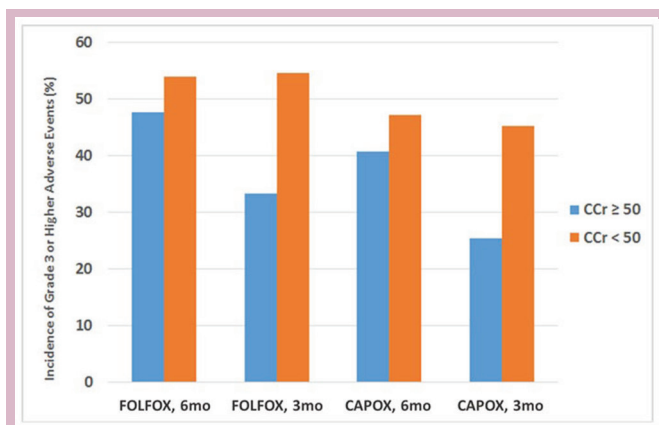


Figure 2 Incidence of grade 3 or higher adverse events by regimen, treatment duration and baseline creatinine clearance. CCr, creatinine clearance; mo, months.

Table 3 Impact of low creatinine clearance (≤50) on AEs ≥grade 3 due to oxaliplatin-containing adjuvant chemotherapy

| | OR | 95% CI | P value |
|------------------------------------|------|--------------|---------|
| FOLFOX | | | |
| Treatment duration (3 vs 6 months) | 0.56 | 0.36 to 0.89 | 0.014 |
| Age (/10 years) | 1.18 | 0.92 to 1.51 | 0.20 |
| CCr (≤50 vs >50) | 1.49 | 0.63 to 3.57 | 0.36 |
| CAPOX | | | |
| Treatment duration (3 vs 6 months) | 0.52 | 0.40 to 0.68 | <0.001 |
| Age (/10 years) | 1.04 | 0.89 to 1.2 | 0.64 |
| CCr (≤50 vs >50) | 1.67 | 1.01 to 2.78 | 0.048 |

AE, adverse event; CCr, creatinine clearance.

or elderly patients because clinical trials are often limited to patients with an adequate renal function (eg, $\text{CCr} > 50 \text{ mL/min}$), especially are the studies of adjuvant chemotherapy. In the present study, multivariable analysis showed that AEs \geq grade 3 were significantly more frequent in patients receiving CAPOX when the baseline CCr was $\leq 50 \text{ mL/min}$ than when it was $> 50 \text{ mL/min}$. Thus, CCr was an independent risk factor for severe AEs associated with CAPOX therapy, suggesting that the starting dose of capecitabine needs to be reduced in patients with a renal impairment receiving CAPOX therapy. Currently, a randomised phase III study (ACHIEVE-2 Trial; Trial Identifier, UMIN000013036) is underway to investigate the optimum duration (6 or 3 months) of mFOLFOX6 or CAPOX therapy after curative resection of high-risk stage II colon cancer, where high-risk patients are defined as those with either T4 tumour, bowel obstruction, perforation/penetration, less than 12 lymph nodes examined, poorly differentiated adenocarcinoma or lymphovascular invasion, and it has employed the same dose reduction schedule for capecitabine. When efficacy data (including disease-free survival and overall survival) are available for both the ACHIEVE and ACHIEVE-2 studies, we will be able to evaluate the efficacy impact of reducing the starting dose of capecitabine for CAPOX therapy in patients with kidney dysfunction or in elderly patients.

From the IDEA project, disease-free survival among patients with stage III colon cancer receiving adjuvant therapy with FOLFOX or CAPOX, noninferiority of 3 months of therapy, as compared with 6 months, was not confirmed in the overall population (HR 1.07; 95% CI 1.00 to 1.15). However, prespecified subgroup analyses showed that among the patients who received CAPOX, the HR for disease-free survival for 3 months versus 6 months was 0.95 (95% CI 0.85 to 1.06), which met the prespecified margin for noninferiority. In addition, exploratory analysis showed among patients at low risk tumours (T1, T2, or T3 and N1 cancers), 3 months of therapy with CAPOX was noninferior to 6 months, with a 3-year rate of disease-free survival of 85.0% vs 83.1% (HR 0.85; 95% CI 0.71 to 1.01).¹³ To clarify the potential impact of these results on clinical practice, a special session was implemented at the European Society for Medical Oncology 2017 Annual Meeting,¹⁴ and investigators from Europe, the USA and Asia selected from the IDEA project concluded that the main drivers for the duration of adjuvant treatment were treatment choice and very importantly the patient's attitude to his/her disease. We believe that our safety data with the highest proportion of patients with CAPOX among the six trials will effectively support physician's treatment choice.

In conclusion, the present analysis of safety data from the ACHIEVE study confirmed better compliance and tolerability when oxaliplatin-containing chemotherapy was administered for 3 months as compared with 6 months. Delivering adjuvant therapy for 3 months reduced the incidence of key AEs, including PSN, to the same extent as for 6 months irrespective of 5-FU

backbone (mFOLFOX6 or CAPOX). Another important finding was the significant association between a low CCr and a higher incidence of severe AEs due to CAPOX. When efficacy results from this study are combined with data from all the trials participating in the IDEA project, the balance between changes in survival and toxicity will be assessed in more detail.

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Competing interests MK has received honoraria from Chugai Pharmaceutical, Takeda Pharmaceutical, Yakult Honsha, Taiho Pharmaceutical, Merck Serono. TYa has received honoraria from Chugai Pharmaceutical, Taiho Pharmaceutical, Takeda Pharmaceutical, Boehringer Ingelheim and research funding from Takeda Pharmaceutical. TYo has received honoraria from GlaxoSmithKline, Nippon Boehringer Ingelheim and research funding from Chugai Pharmaceutical, Taiho Pharmaceutical, Eli Lilly. MN has received honoraria from Merck, Takeda Pharmaceutical, Chugai Pharmaceutical, Yakult Honsha, Taiho Pharmaceutical, Eli Lilly and consulting fees from Merck, Bayer. TK has Speakers Bureau from Chugai Pharmaceutical, Takeda Pharmaceutical, Eli Lilly, Taiho Pharmaceutical. MG has received honoraria from Taiho Pharmaceutical, Chugai Pharmaceutical, Yakult Honsha, Ono Pharmaceutical, Takeda Pharmaceutical, Daiichi Sankyo, Nippon Kayaku, Eli Lilly. YM has Speakers Bureau from Chugai Pharmaceutical, Yakult Honsha and research funding from Chugai Pharmaceutical, Yakult Honsha, Kyowa Hakko Kirin. AO has received research funding from Bristol-Myers Squibb.

Patient consent Obtained.

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Data sharing statement Our manuscript does not include additional unpublished

data.

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