

Safety in Japanese Advanced Breast Cancer Patients Who Received Abemaciclib in MONARCH 2 and MONARCH 3: Assessment of Treatment-Emergent Neutropenia, Diarrhea, and Increased Alanine Aminotransferase and Aspartate Aminotransferase Levels

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Purpose: Our objective was to gain a better understanding of the safety of abemaciclib in Japanese patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer.

Patients and Methods: Treatment-emergent adverse events (TEAEs) were assessed in pooled Japanese subpopulation data from two phase 3 studies assessing abemaciclib/placebo in combination with fulvestrant (MONARCH 2; M2) or non-steroidal aromatase inhibitors (MONARCH 3; M3). For common, clinically relevant TEAEs, event characteristics and management were summarized by study.

Results: In the Japanese safety subpopulation (abemaciclib: N=101; placebo: N=46), all patients experienced ≥ 1 TEAE (Grade ≥ 3 : abemaciclib, 71.3%; placebo, 23.9%; no Grade 5). Clinically relevant TEAEs that were more frequent in abemaciclib-treated Japanese patients compared to the overall safety populations included diarrhea (any grade, 95.0%; Grade ≥ 3 , 12.9%), neutropenia (any grade, 75.2%; Grade 3–4, 35.6%), increased alanine aminotransferase (ALT; any grade, 39.6%; Grade 3–4, 14.9%), and increased aspartate aminotransferase (AST; any grade, 37.6%; Grade 3–4, 8.9%). Diarrhea was Grade ≤ 3 and successfully managed with medications ($\geq 87\%$) and dose reductions ($\leq 25\%$) and/or omissions ($\leq 23.3\%$). Most Grade ≥ 2 diarrhea occurred in the first treatment cycle, declining thereafter. Neutropenia, the most common Grade ≥ 3 TEAE in abemaciclib-treated Japanese patients, was generally manageable with dose omissions (M2: 42.0%; M3: 23.1%) and/or reductions (M2: 16%; M3: 15.4%). Neutrophil counts plateaued after Cycle 2, recovering to pretreatment levels after discontinuation of abemaciclib. Hepatic events were managed with medication ($\leq 21\%$) and dose adjustments ($\leq 33.3\%$), with most Grade ≥ 2 events occurring in early treatment cycles. Discontinuation of any study treatment in Japanese patients occurred more frequently due to increased ALT/AST (M2: 9.1%/10.5%; M3: 16.7%/10.5%) compared with diarrhea (M2: 0%; M3: 2.8%) or neutropenia (M2: 0%; M3: 3.8%).

Conclusion: Abemaciclib was well tolerated in Japanese patients in MONARCH 2 and MONARCH 3, with common, clinically relevant TEAEs manageable with appropriate interventions.

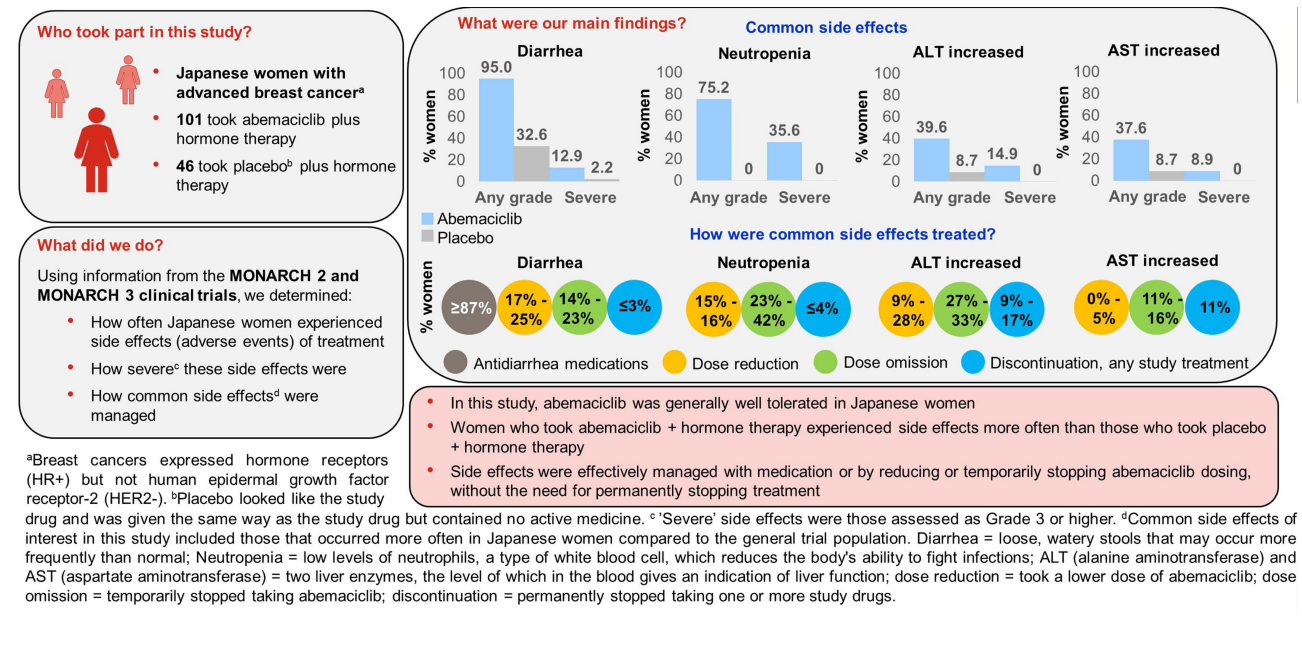
Keywords: abemaciclib, breast cancer, cyclin-dependent kinase 4/6, fulvestrant, nonsteroidal aromatase inhibitor

Plain Language Summary

Why was this study done?

- Breast cancers that express hormone receptors (HR+) but not the human epidermal growth factor receptor 2 (HER2-) are generally initially sensitive to hormone therapies. These therapies become less effective at advanced disease stages.

Graphical Abstract



- Abemaciclib is a new anti-cancer treatment that, when added to hormone therapy, may extend the length of time people with advanced HR+, HER2- breast cancer live without their cancer worsening.
- This study assessed how safe abemaciclib is when used with hormone therapy (either fulvestrant or nonsteroidal aromatase inhibitors) in Japanese women.

What did the researchers do and find?

- This study examined the nature and treatment of three common side effects in Japanese women who enrolled in two global studies that investigated abemaciclib plus hormone therapy in advanced HR+, HER2- breast cancer.
- In these studies, many Japanese women on abemaciclib experienced diarrhea, neutropenia (low blood neutrophil counts), and increased levels of two liver enzymes in the blood, indicators of liver function.
- Although generally not severe, these side effects were experienced more frequently and sometimes at a higher severity by Japanese women compared with the global study population.
- In most cases, these side effects could be effectively managed by reducing or temporarily stopping dosing of abemaciclib or using additional medicines.

What do these results mean?

- These results indicate that abemaciclib plus hormone therapy is generally safe to use in Japanese women with HR+, HER2- advanced breast cancer. The information learned may improve how common side effects of abemaciclib are managed in Japanese women.

Introduction

The incidence of breast cancer in Japan has been continually increasing over recent decades,^{1,2} with breast cancer now representing 21.4% of new cancer diagnoses in Japanese women.³ Over two-thirds of breast cancers are classified as hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) cancers.⁴ For this subtype of cancer, the current frontline therapy in the advanced setting is endocrine therapy (ET) in combination with cyclin-dependent

kinase (CDK) 4/CDK6 inhibitors.^{5,6} Abemaciclib is a selective CDK4/CDK6 inhibitor, dosed twice daily on a continuous schedule.⁷ In two global phase 3 studies, abemaciclib demonstrated efficacy in combination with fulvestrant following progression after initial ET (MONARCH 2) and as initial ET in combination with a nonsteroidal aromatase inhibitor (NSAI) (MONARCH 3).^{8–12} In these studies, abemaciclib had a tolerable safety profile, with most common adverse events effectively managed with supportive medications and/or dose modifications without diminishing progression-free survival.¹³

Based on the global clinical studies, abemaciclib in combination with ET in the first- or second-line setting was approved in Japan for the treatment of HR+, HER2- advanced breast cancer. Recent Japanese subpopulation analyses of the MONARCH 2 and MONARCH 3 studies confirmed that abemaciclib/ET combination therapy is more effective than ET alone in Japanese patients,^{14,15} in accordance with the efficacy data observed in the overall intent-to-treat populations.^{8–12} The subpopulation analyses also indicated that the safety profile of abemaciclib in Japanese patients was broadly consistent with the overall safety profiles of MONARCH 2 and MONARCH 3, with neutropenia and diarrhea the most common treatment-emergent adverse events (TEAEs) in abemaciclib-treated patients.^{8–12,14,15} However, the subpopulation analyses also indicated a higher incidence of specific TEAEs compared with the overall safety populations as well as some potential country-specific clinical management concerns.^{14,15} Given these differences, additional analyses of the Japanese safety profile in MONARCH 2 and MONARCH 3 may further inform treatment decisions and help improve clinical management of abemaciclib-treated patients in Japan. The objective of the current analysis was to gain a better understanding of the safety of abemaciclib in the subpopulation of patients enrolled in Japan in MONARCH 2 and MONARCH 3. We report the frequency of TEAEs in pooled data from the two studies and the characteristics and management of the most common, clinically relevant TEAEs in Japanese patients.

Materials and Methods

Study Design and Patients

MONARCH 2 (NCT02107703) and MONARCH 3 (NCT02246621) were randomized, double-blind, placebo-controlled, global phase 3 studies of abemaciclib in combination with fulvestrant (MONARCH 2) or an NSAI (MONARCH 3) in women with HR+, HER2- locally advanced or metastatic breast cancer. The study design, randomization procedures, treatments, and other methods for the two studies have previously been published in detail.^{8–12}

The current analysis was conducted on patients enrolled in MONARCH 2 and MONARCH 3 study sites in Japan. Both studies included patients who were ≥ 18 years old with a diagnosis of HR+, HER2-, inoperable, locally advanced or metastatic breast cancer, an Eastern Cooperative Oncology Group performance status ≤ 1 , and either non-measurable bone-only disease or measurable disease as defined by the Response Evaluation Criteria In Solid Tumors Version 1.1.¹⁶ In MONARCH 2, patients were postmenopausal or premenopausal with ovarian suppression, chemotherapy-naïve in the metastatic setting, and had disease that progressed on prior ET.^{8,9} In MONARCH 3, patients included postmenopausal women who had not received prior systemic therapy for advanced disease. Prior neoadjuvant/adjuvant ET was permitted in MONARCH 3 if patients had been disease-free for >12 months after completing ET.^{10–12}

All patients provided written, informed consent. MONARCH 2 and MONARCH 3 were conducted in accordance with Good Clinical Practice guidelines, relevant regulations in Japan, and the Declaration of Helsinki (1964) and its amendments. Study protocols were approved by ethical/institutional review boards at each site (lists provided in [Supplementary Tables 5 and 6](#)).

Treatments

Patients were randomized 2:1 to receive abemaciclib (150 mg orally, twice daily) or matching placebo in combination with either fulvestrant (500 mg per label) in MONARCH 2 or NSAI (either 1 mg anastrozole or 2.5 mg letrozole, orally, once daily) in MONARCH 3. In MONARCH 2, the starting dose of abemaciclib was initially 200 mg and was reduced to 150 mg for new patients via a protocol amendment arising from a blinded review of safety data. Patients who were receiving 200 mg had a mandatory dose reduction to 150 mg.

Dose Adjustments

Dose adjustments were allowed in response to toxicity, which was defined as an adverse event possibly related to study treatment in the investigator's judgement. For abemaciclib, dose omissions and/or dose reductions of up to two 50-mg dose levels could be made as necessary in MONARCH 2 and MONARCH 3 (minimum allowed dose: 50 mg twice daily). Discontinuation was required if further dose reduction was needed at 50 mg twice a day. Dose adjustments were permitted for fulvestrant (MONARCH 2) but not for NSAIs (MONARCH 3), as per their labels. MONARCH 2 and MONARCH 3 protocols specified mandatory dose adjustments of abemaciclib for hematologic and non-hematologic toxicities based on the type, severity, persistence, and recurrence of the adverse events. Persistence of toxicity was determined by the investigator. Recurrent toxicity was defined as the same adverse event occurring within 8 weeks from the stop date of the preceding event. Supportive care was permitted for management of toxicities.¹³

For hematologic toxicities, if the patient experienced Grade 3 toxicity, treatment suspension was mandatory until the toxicity resolved to Grade ≤ 2 . The dose of study drug could also be reduced by one dose level, at the discretion of the investigator. For Grade 4 or recurrent Grade 3 hematologic toxicities, treatment suspension until the toxicity resolved to Grade ≤ 2 and dose reduction of one dose level were mandatory.

For most non-hematologic toxicities (except diarrhea), Grade ≥ 3 toxicity resulted in mandatory treatment suspension until the toxicity resolved to Grade ≤ 1 and mandatory dose reduction of one dose level; for persistent or recurrent Grade 2 events that did not resolve to Grade ≤ 1 within 7 days with maximal supportive measures, study treatment suspension and dose reduction were at the discretion of the investigator. At the start of the studies and before the cut-off for this analysis, the MONARCH 2 and MONARCH 3 protocols did not yet have specific guidance for management of events of increased alanine aminotransferase (ALT)/aspartate aminotransferase (AST), which were managed in the same manner as other non-hematologic toxicities. Specific guidance for increased ALT/AST was introduced in later protocol amendments. Per current guidance for Grade 3 or persistent Grade 2 events of increased ALT/AST, dose suspension is required until resolution to baseline or Grade 1; if abemaciclib is resumed, dose reduction is required. For Grade 4 increased ALT/AST or Grade ≥ 2 increased ALT/AST plus increased total bilirubin over two times the upper limit of normal, in the absence of cholestasis, discontinuation of abemaciclib is mandatory. For diarrhea, patients were instructed to take antidiarrheal medication at the first sign of loose stools. Abemaciclib was suspended for Grade 2 diarrhea that did not resolve in ≤ 24 hours. For persistent/recurrent Grade 2 and Grade ≥ 3 diarrhea events, or any grade diarrhea events requiring hospitalization, treatment suspension was required until the toxicity resolved to Grade ≤ 1 , with dose reduction of one dose level at the discretion of the investigator if treatment resumed (updated to mandatory dose reduction of one dose level per later protocol amendment).

Statistical Analyses

Statistical methods for the MONARCH 2 and MONARCH 3 studies have been previously described in detail.⁸⁻¹² Current analyses are based on data cut-off dates used for the Japan New Drug Application (February 14, 2017, for MONARCH 2 and January 31, 2017, for MONARCH 3). Safety was evaluated in all patients who received ≥ 1 dose of study treatment. TEAEs were assessed according to the Medical Dictionary for Regulatory Activities Version 19.1 terminology. Clinically synonymous terms were grouped together under a consolidated preferred term. Severity was graded based on the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0. TEAE incidence and severity were summarized using pooled data from the MONARCH 2 and MONARCH 3 Japanese subpopulations. Data were also assessed separately by study and, for MONARCH 2 and pooled analyses, by starting dose of abemaciclib (150-mg starting dose only or "total", ie, either 150-mg or 200-mg starting dose). For the most common TEAEs, time to onset, time to dose reduction, medications related to the TEAEs, and other data relevant to clinical management were summarized. Clinical laboratory tests were performed at baseline, Day 1 of each cycle (plus Day 15 of Cycle 1 in MONARCH 2), and 30 days following discontinuation of study drug.

Results

Patients

Patient disposition and baseline characteristics for MONARCH 2 and MONARCH 3 Japanese subpopulations have previously been described.^{14,15} In MONARCH 2, the overall safety population included 664 patients (abemaciclib: n=441; placebo: n=223),

of whom 94 patients (14.2%) were enrolled in Japan. Of these, 63 patients were allocated to the abemaciclib arm (20 of whom received a 200-mg dose initially until the mandatory reduction to 150 mg) and 31 patients were allocated to the placebo arm. The MONARCH 3 safety population comprised 488 patients (abemaciclib: n=327; placebo: n=161), including 53 patients (10.9%) enrolled in Japan (abemaciclib: n=38; placebo: n=15). The pooled analyses across the Japanese safety subpopulations of MONARCH 2 and MONARCH 3 included n=81 patients in the “150-mg only” abemaciclib starting dose group, n=101 in the total (150-mg or 200-mg) abemaciclib starting dose group, and n=46 in the combined placebo group.

Safety Overview

In the combined MONARCH 2 and MONARCH 3 analysis, all patients in the Japanese safety subpopulation experienced ≥ 1 TEAE (Table 1), with a higher proportion of patients in the abemaciclib group experiencing Grade ≥ 3 TEAEs (total abemaciclib: 71.3%; 150 mg only: 69.1%) compared with the placebo group (23.9%). No Grade 5 TEAEs were reported in the Japanese subpopulation. Neutropenia was the most common hematological TEAE of any grade and was observed in approximately 75% of the abemaciclib-treated Japanese patients in MONARCH 2 and MONARCH 3 but not in the placebo group (Table 1). Neutropenia was also the most common Grade ≥ 3 TEAE in the abemaciclib group, occurring in approximately a third of Japanese patients (Table 1). The most common non-hematological TEAE in the Japanese subpopulation was diarrhea, which occurred more frequently in the abemaciclib group (total abemaciclib: any grade, 95.0%; Grade ≥ 3 , 12.9%; 150 mg only: any grade, 93.8%; Grade ≥ 3 , 11.1%) than in the placebo group (any grade, 32.6%; Grade ≥ 3 , 2.2%). Other non-hematologic TEAEs of interest included increased ALT and increased AST, which occurred in over a third of patients in the abemaciclib group (total abemaciclib: 39.6% and 37.6% for any grade increased ALT and increased AST, respectively; 150-mg only: 40.7% and 40.7% for any grade increased ALT and increased AST, respectively) but more rarely in the placebo group (increased ALT: any grade, 8.7%; increased AST: any grade, 8.7%). In

Table 1 Pooled Data for the MONARCH 2 and MONARCH 3 Japanese Subpopulations Showing Any Grade and Grade ≥ 3 TEAEs Occurring in $\geq 20\%$ of Abemaciclib-Treated Patients

Preferred Term	Abemaciclib + NSAI or Fulvestrant				Placebo + NSAI or Fulvestrant	
	Total ^a (N=101)		150-mg Dose Only (N=81)		(N=46)	
$\geq 20\%$ in Total Abemaciclib Arm	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
n (%)						
Patients with ≥ 1 TEAE	101 (100)	72 (71.3)	81 (100)	56 (69.1)	46 (100)	11 (23.9)
Hematological events						
Neutropenia	76 (75.2)	36 (35.6)	60 (74.1)	26 (32.1)	0	0
Leukopenia	63 (62.4)	20 (19.8)	49 (60.5)	17 (21.0)	3 (6.5)	1 (2.2)
Anemia	46 (45.5)	9 (8.9)	38 (46.9)	7 (8.6)	2 (4.3)	1 (2.2)
Thrombocytopenia	25 (24.8)	4 (4.0)	17 (21.0)	3 (3.7)	0	0
Non-hematological events						
Diarrhea	96 (95.0)	13 (12.9)	76 (93.8)	9 (11.1)	15 (32.6)	1 (2.2)
ALT increased	40 (39.6)	15 (14.9)	33 (40.7)	15 (18.5)	4 (8.7)	0
AST increased	38 (37.6)	9 (8.9)	33 (40.7)	9 (11.1)	4 (8.7)	0
Nausea	35 (34.7)	3 (3.0)	23 (28.4)	2 (2.5)	11 (23.9)	1 (2.2)
Dysgeusia	29 (28.7)	0	21 (25.9)	0	1 (2.2)	0
Abdominal pain	28 (27.7)	0	20 (24.7)	0	5 (10.9)	0
Vomiting	28 (27.7)	1 (1.0)	21 (25.9)	1 (1.2)	9 (19.6)	0
Stomatitis	25 (24.8)	1 (1.0)	20 (24.7)	1 (1.2)	11 (23.9)	0
Decreased appetite	24 (23.8)	3 (3.0)	16 (19.8)	3 (3.7)	6 (13.0)	1 (2.2)
Rash	24 (23.8)	0	19 (23.5)	0	6 (13.0)	0
Blood creatinine increased	23 (22.8)	0	21 (25.9)	0	0	0
Alopecia	21 (20.8)	0	16 (19.8)	0	3 (6.5)	0

Note: ^aIncludes patients receiving 150-mg and/or 200-mg doses of abemaciclib.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of patients in analysis population; n, number of patients in category; NSAI, nonsteroidal aromatase inhibitor; TEAEs, treatment-emergent adverse events.

addition, increased ALT represented the most common Grade ≥ 3 non-hematologic TEAE (14.9–18.5%) in abemaciclib-treated Japanese patients (0% in placebo group).

[Supplementary Table 1](#) shows a comparison of common TEAEs in abemaciclib-treated patients in the overall population and Japanese subpopulations of MONARCH 2 and MONARCH 3. Abemaciclib-treated patients in the MONARCH 2 and MONARCH 3 overall safety populations had lower rates of Grade ≥ 3 TEAEs (MONARCH 2: 60.5%; MONARCH 3: 57.5%) compared to the Japanese subpopulations (MONARCH 2: 74.6%; MONARCH 3: 65.8%), and this difference in Grade ≥ 3 events was not observed in the placebo arms (Japanese subpopulation: 23.9%; overall MONARCH 2: 23.8%; overall MONARCH 3: 23.0%). The overall safety populations also had lower rates of hematologic toxicities, diarrhea, and increased ALT/AST in abemaciclib-treated patients compared with their Japanese subpopulations ([Supplementary Table 1](#)). Any grade and Grade 3–4 events of increased ALT/AST occurred more frequently in the MONARCH 3 overall safety population (approximately 15–16% any grade; 3–6% Grade 3–4) compared to the MONARCH 2 overall safety population (approximately 12–13% any grade; 2–4% Grade 3–4), and this difference was more pronounced between the Japanese subpopulations (MONARCH 3: approximately 47–50% any grade; 13–24% Grade 3–4; MONARCH 2: approximately 30–35% any grade; 6–10% Grade 3–4; [Supplementary Table 1](#)).

Dose adjustments and discontinuations of study drug in the abemaciclib arms of the Japanese subpopulations of the two studies are summarized in [Supplementary Table 2](#). The majority of patients treated with abemaciclib had at least 1 dose adjustment (MONARCH 2 total: 84.1%; 150-mg only dose: 79.1%; MONARCH 3: 78.9%). Discontinuations of study drug due to TEAEs occurred in Japanese patients in the abemaciclib arm of both studies (discontinuation of any study drug: MONARCH 2 total: 17.5%; 150-mg only dose: 18.6%; MONARCH 3: 28.6%). Dose adjustments and discontinuations due to the most common TEAEs in the Japanese subpopulations are described in more detail below for each of the studies.

Diarrhea

The characteristics of diarrhea events in the Japanese subpopulations of MONARCH 2 and MONARCH 3 are summarized in [Table 2](#). The majority of abemaciclib-treated Japanese patients in MONARCH 2 and MONARCH 3 experienced an event of diarrhea ($\geq 93.0\%$), generally a Grade 1–2 event ($\geq 81.0\%$). There were no Grade ≥ 4 events or serious adverse events (SAEs) of diarrhea in the Japanese subpopulation of either study. The rates of diarrhea events in the Japanese subpopulations were similar across studies and across starting dose groups in MONARCH 2 ([Table 2](#)). The median time to onset of diarrhea following the initiation of abemaciclib treatment was 4 and 6 days in the Japanese subpopulations of MONARCH 2 and MONARCH 3, respectively, with the highest rates of Grade 2 and Grade 3 diarrhea observed in the first treatment cycle and declining thereafter ([Figure 1](#)). The median duration was 9 (MONARCH 2) and 6 days (MONARCH 3) for Grade 2 events and 4 (MONARCH 2) and 10 days (MONARCH 3) for Grade 3 events. Median onset and duration of Grade ≥ 2 diarrhea events in MONARCH 2 were similar for the two starting dose groups ([Table 2](#)).

Diarrhea events were managed with anti-diarrheal medications in $\geq 87\%$ of patients in the abemaciclib arms, most commonly with loperamide ($>76\%$). For Grade ≥ 2 diarrhea not resolving to Grade ≤ 1 within 24 hours, dose adjustments were made as per study protocols. Lower rates of dose adjustments were observed in patients receiving the 150-mg starting dose of abemaciclib (dose reduction: MONARCH 2: 20.0%; MONARCH 3: 16.7%; dose omission: MONARCH 2: 20.0%; MONARCH 3: 13.9%) compared to those in the total abemaciclib group of MONARCH 2 (dose reduction: 25.0%; dose omission: 23.3%; [Table 2](#)). The median time to dose reduction ranged from 29.0 (MONARCH 2) to 39.5 days (MONARCH 3). No patients discontinued study treatment due to diarrhea in the Japanese subpopulation of MONARCH 2; 1 patient discontinued any study treatment due to diarrhea in MONARCH 3 (2.8%).

Neutropenia

The majority of abemaciclib-treated patients experienced neutropenia in the Japanese subpopulations of both MONARCH 2 ($>79\%$) and MONARCH 3 ($>68\%$; [Table 3](#)). Comparatively, MONARCH 3 Japanese patients had more Grade 1–2 neutropenia events (47.4%) than MONARCH 2 Japanese patients (total abemaciclib: 34.9%; 150 mg only: 37.2%) but fewer Grade 3 events (MONARCH 2: total abemaciclib: 42.9%; 150 mg only: 41.9%; MONARCH 3: 21.1%). The rates of neutropenia were not substantially different between the two starting dose groups in MONARCH 2. Notably, there was only one Grade 4 event of neutropenia in MONARCH 2 Japanese patients treated with 200-mg abemaciclib (1.6%), and there were no SAEs of neutropenia

Table 2 Characteristics of Diarrhea Events in the Japanese Subpopulations of MONARCH 2 and MONARCH 3

Characteristics, n (%) ^a	MONARCH 2		MONARCH 3
	Total ^b Abemaciclib + Fulvestrant (N=63)	150-mg Dose Abemaciclib + Fulvestrant (N=43)	Abemaciclib + NSAI (N=38)
Diarrhea^c	60 (95.2)	40 (93.0)	36 (94.7)
Grade 1 or 2	51 (81.0)	35 (81.4)	32 (84.2)
Grade 3	9 (14.3)	5 (11.6)	4 (10.5)
Serious adverse events	0	0	0
Time to onset, median (range), days	4.0 (1.0–59.0)	4.0 (1.0–59.0)	6.0 (2.0–85.0)
Total days of Grade 2, median (range)^d	9.0 (2.0–131.0)	9.0 (2.0–131.0)	6.0 (1.0–36.0)
Total days of Grade 3, median (range)^d	4.0 (1.0–12.0)	4.0 (1.0–9.0)	10.0 (1.0–34.0)
Dose reduction	15 (25.0)	8 (20.0)	6 (16.7)
Time to dose reduction, median (range), days	29.0 (4.0–84.0)	32.0 (15.0–84.0)	39.5 (29.0–372.0)
Dose omission	14 (23.3)	8 (20.0)	5 (13.9)
Discontinuation of any study treatment due to diarrhea	0	0	1 (2.8)
Antidiarrheal medication	59 (93.7)	39 (90.7)	33 (86.8)

Notes: ^aUnless otherwise specified. ^bIncludes patients receiving 150-mg or 200-mg starting doses of abemaciclib. ^cNo Grade 4 or 5 events reported. ^dTotal duration of respective diarrhea for each patient.

Abbreviations: N, number of patients in analysis population; n, number of patients in category; NSAI, nonsteroidal aromatase inhibitor.

in either Japanese subpopulation. The median time to onset of Grade 3–4 neutropenia was 29.0 days in both MONARCH 2 and MONARCH 3 Japanese subpopulations, regardless of starting dose of abemaciclib. The median duration of Grade 3–4 neutropenia was 17 to 23 days in MONARCH 2 and 12 days in MONARCH 3.

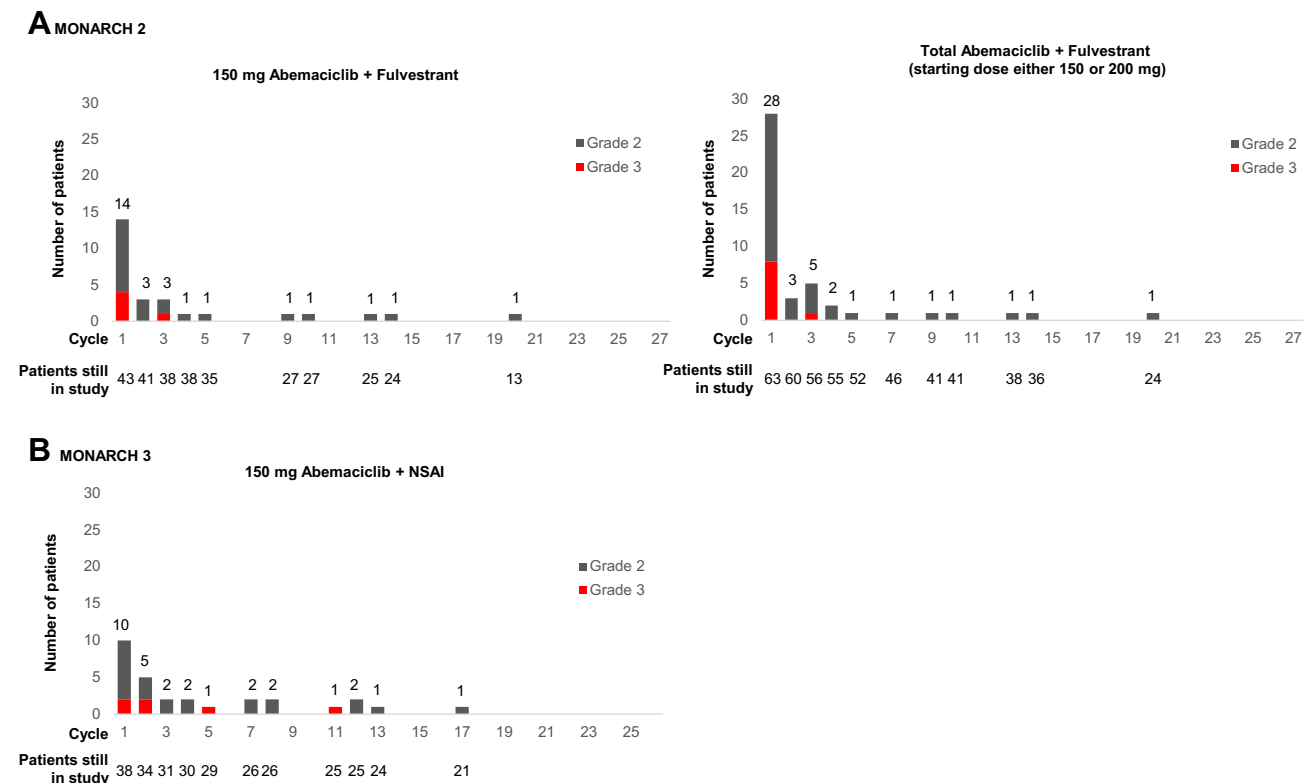


Figure 1 Diarrhea events by treatment cycle in Japanese patients. Summary of Grade ≥2 events of diarrhea per treatment cycle in abemaciclib-treated Japanese patients from (A) MONARCH 2 and (B) MONARCH 3.

Abbreviation: NSAI, nonsteroidal aromatase inhibitor.

Table 3 Characteristics of Neutropenia Events in the Japanese Subpopulations of MONARCH 2 and MONARCH 3

Characteristics, n (%) ^a	MONARCH 2		MONARCH 3
	Total ^b Abemaciclib + Fulvestrant (N=63)	150-mg Dose Abemaciclib + Fulvestrant (N=43)	Abemaciclib + NSAI (N=38)
Neutropenia	50 (79.4)	34 (79.1)	26 (68.4)
Grade 1 or 2	22 (34.9)	16 (37.2)	18 (47.4)
Grade 3	27 (42.9)	18 (41.9)	8 (21.1)
Grade 4	1 (1.6)	0	0
Serious adverse events	0	0	0
Time to onset of Grade 3–4, median (range), days	29.0 (13.0–493.0)	29.0 (15.0–493.0)	29.0 (29.0–162.0)
Total days of Grade 3–4, median (range)^c	23.0 (–12.0–79.0)	17.0 (6.0–77.0)	12.0 (10.0–46.0)
Dose reduction	8 (16.0)	5 (14.7)	4 (15.4)
Time to dose reduction, median (range), days	215.0 (36.0–594.0)	288.0 (43.0–594.0)	44.5 (43.0–65.0)
Dose omission	21 (42.0)	14 (41.2)	6 (23.1)
Discontinuation of any study treatment due to neutropenia	0	0	1 (3.8)
G-CSF/GM-CSF	0	0	0

Notes: ^aUnless otherwise specified. ^bIncludes patients receiving 150-mg or 200-mg starting doses of abemaciclib. ^cTotal duration of respective neutropenia for each patient. **Abbreviations:** G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; N, number of patients in analysis population; n, number of patients in category; NSAI, nonsteroidal aromatase inhibitor.

Neutropenia was managed by dose adjustments, as per protocol guidance. No patient received granulocyte colony-stimulating factor or granulocyte-macrophage colony-stimulating factor. Neutropenia in abemaciclib-treated Japanese patients was more frequently managed with dose omission (MONARCH 2: total abemaciclib: 42.0%; 150 mg only: 41.2%; MONARCH 3: 23.1%) than dose reduction (~15–16%) in both studies (Table 3). Median time to dose reduction due to neutropenia was 215 days in MONARCH 2 and 44.5 days in MONARCH 3. One patient in the abemaciclib arm of MONARCH 3 Japanese subpopulation (3.8%) discontinued any study treatment due to neutropenia. In both MONARCH 2 and MONARCH 3 Japanese subpopulations, neutrophil counts across cycles reached a plateau after Cycle 2, with recovery of neutrophil counts to pretreatment levels during the 30-day post-treatment discontinuation follow-up period (Figure 2). An analysis of the incidence per patient of Grade 3–4 events of neutropenia by baseline neutrophil count revealed that the subgroup of Japanese patients with baseline neutrophil counts $<3.0 \times 10^9/L$ had higher incidence of Grade 3–4 neutropenia (MONARCH 2: total abemaciclib: 63.3%; 150 mg only: 60.0%; MONARCH 3: 41.7%) compared to the subgroup with baseline neutrophil counts $\geq 3.0 \times 10^9/L$ (MONARCH 2: total abemaciclib: 27.3%; 150 mg only: 26.1%; MONARCH 3: 11.5%) in both MONARCH 2 and MONARCH 3 (Supplementary Table 3). A comparison of abemaciclib-treated Japanese and non-Japanese patients revealed that patients in both groups who experienced Grade ≥ 3 neutropenia had lower baseline neutrophil counts (median $<3.0 \times 10^9/L$) than patients who did not experience Grade 3–4 neutropenia (median $>3.3 \times 10^9/L$; Supplementary Table 4).

Increased ALT/AST

The incidence of increased ALT/AST was similar across starting dose groups in MONARCH 2 but higher in MONARCH 3 than in MONARCH 2, with events of any grade increased ALT/AST experienced by approximately a third (30.2–34.9%) of Japanese patients in MONARCH 2 and half the Japanese patients in MONARCH 3 (47.4–50.0%; Table 4). Higher severity (Grade 3–4) events were also more frequent in the MONARCH 3 Japanese subpopulation (increased ALT: 23.7%; increased AST: 13.2%) compared to the MONARCH 2 Japanese subpopulation (increased ALT: total abemaciclib: 9.5%; 150 mg only: 14.0%; increased AST: total abemaciclib: 6.3%; 150 mg only: 9.3%), and a greater proportion of the MONARCH 3 Japanese subpopulation had ≥ 3 incidences of any grade events per patient compared with MONARCH 2 (Table 4). A similar trend was previously observed in the Japanese subpopulation of the placebo groups for the two studies (Grade 1/2 [no Grade 3–4]

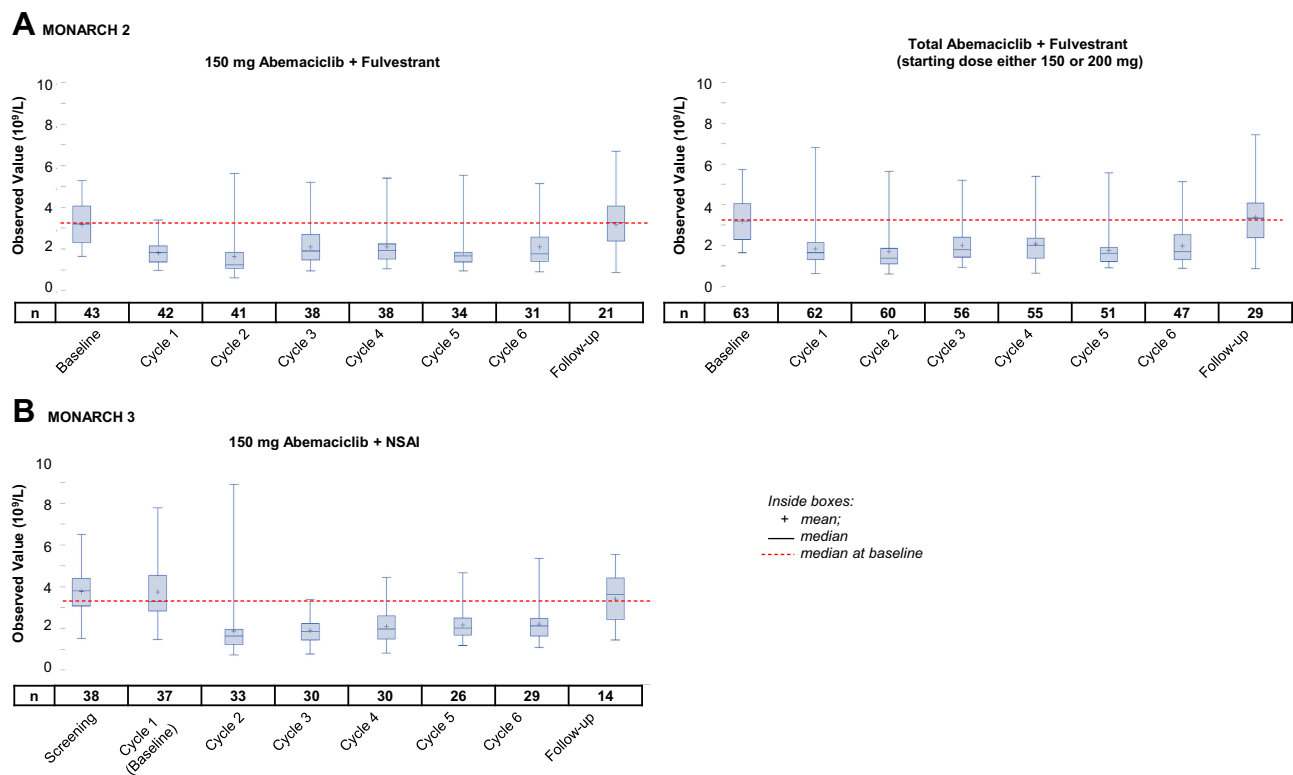


Figure 2 Neutrophil counts by treatment cycle in Japanese patients receiving abemaciclib plus endocrine therapy. Box and whisker plots of neutrophil counts by treatment cycle in the Japanese subpopulations of **(A)** MONARCH 2 and **(B)** MONARCH 3.

Abbreviations: n, number of patients; NSA, nonsteroidal aromatase inhibitor.

increased ALT, MONARCH 2: 3.2%, MONARCH 3: 20.0%; increased AST, MONARCH 2: 6.5%, MONARCH 3: 13.3%).^{14,15} The number and frequency of AST/ALT events did not differ between anastrozole and letrozole groups in MONARCH 3 (data not shown). There were no Grade 4 events of increased AST in the Japanese subpopulations (Table 4), and Grade ≥ 2 events of ALT/AST most frequently occurred during early treatment cycles (Figure 3). TEAEs of increased blood bilirubin were infrequent in the abemaciclib arms of both the Japanese subpopulations (MONARCH 2: any grade, 0%; MONARCH 3: any grade, 2.6%; Grade ≥ 3 , 0%) and the overall populations (MONARCH 2: any grade, 1.6%; Grade ≥ 3 , 0.9%; MONARCH 3: any grade, 1.5%; Grade ≥ 3 , 0.3%) of the two studies.

The median time to onset for Grade 3–4 events of increased ALT in the Japanese subpopulations was 31.5 days in MONARCH 2 and 64.0 days in MONARCH 3. The median times to onset for Grade 3–4 increased AST in the Japanese subpopulations, were 39.5 days and 71 days in MONARCH 2 and MONARCH 3, respectively. Management of hepatic events included medication in 9.5% (MONARCH 2) and 21.1% (MONARCH 3) of patients in the abemaciclib arms, most frequently with glycyrrhizic acid or ursodeoxycholic acid. Dose reductions due to increased ALT occurred in <10% of Japanese patients in MONARCH 2 and 27.8% in MONARCH 3 whereas dose omissions due to increased ALT occurred in roughly a third of Japanese patients in both studies (Table 4). The median time to dose reduction was shorter in MONARCH 2 (74.5–78.0 days) compared with MONARCH 3 (127 days). Dose reductions due to increased AST occurred in 5.3–7.1% of Japanese patients in MONARCH 2, with a median time to dose reduction of 280 days whereas no dose reductions due to increased AST occurred in MONARCH 3. Dose omissions due to increased AST occurred in 10.5% to 14.3% of Japanese patients in MONARCH 2 and 15.8% in MONARCH 3. Increased ALT/AST were the most common TEAEs leading to discontinuation of any study treatment in the Japanese subpopulations (discontinuations due to ALT increased: MONARCH 2: 6.7–9.1%; MONARCH 3: 16.7%; due to AST increased: MONARCH 2: 10.5–14.3%; MONARCH 3: 10.5%).

Table 4 Characteristics of Events of ALT/AST Increased in the Japanese Subpopulations of MONARCH 2 and MONARCH 3

Hepatic Event Characteristics, n (%) ^a	MONARCH 2		MONARCH 3
	Total ^b Abemaciclib + Fulvestrant (N=63)	150-mg Dose Abemaciclib + Fulvestrant (N=43)	Abemaciclib + NSAI (N=38)
ALT increased, any grade	22 (34.9)	15 (34.9)	18 (47.4)
Grade 3–4	6 (9.5)	6 (14.0)	9 (23.7)
>3X ULN ALT and >1.5X ULN TBILI	0	0	0
Incidence per patient, any grade			
1	19 (86.4)	13 (86.7)	12 (66.7)
2	2 (9.1)	1 (6.7)	2 (11.1)
≥3	1 (4.5)	1 (6.7)	4 (22.2)
Incidence per patient, Grade 3–4			
1	6 (100)	6 (100)	9 (100)
2	0	0	0
≥3	0	0	0
Time to onset of any grade, median (range), days	57.0 (15.0–631.0)	36.0 (15.0–393.0)	48.0 (29.0–164.0)
Time to onset of Grade 3–4, median (range), days	31.5 (29.0–59.0)	31.5 (29.0–59.0)	64.0 (29.0–164.0)
Dose reduction	2 (9.1)	1 (6.7)	5 (27.8)
Time to dose reduction, median (range), days	74.5 (71.0–78.0)	78.0 (78.0–78.0)	127 (50.0–179.0)
Dose omission	6 (27.3)	5 (33.3)	6 (33.3)
Discontinuation of any study treatment due to ALT increased	2 (9.1)	1 (6.7)	3 (16.7)
AST increased, any grade	19 (30.2)	14 (32.6)	19 (50.0)
Grade 3–4^c	4 (6.3)	4 (9.3)	5 (13.2)
>3X ULN AST and >1.5X ULN TBILI	0	0	0
Incidence per patient, any grade			
1	15 (78.9)	11 (78.6)	13 (68.4)
2	3 (15.8)	3 (21.4)	4 (21.1)
≥3	1 (5.3)	0	2 (10.5)
Incidence per patient, Grade 3–4			
1	3 (75.0)	3 (75.0)	5 (100)
2	1 (25.0)	1 (25.0)	0
≥3	0	0	0
Time to onset of any grade, median (range), days	59.0 (15.0–501.0)	51.5 (15.0–393.0)	57.0 (29.0–431.0)
Time to onset of Grade 3–4, median (range), days	39.5 (29.0–185.0)	39.5 (29.0–185.0)	71.0 (57.0–164.0)
Dose reduction	1 (5.3)	1 (7.1)	0
Time to dose reduction, median (range), days	280 (280.0–280.0)	280 (280.0–280.0)	NA
Dose omission	2 (10.5)	2 (14.3)	3 (15.8)
Discontinuation of any study treatment due to AST increased	2 (10.5)	2 (14.3)	2 (10.5)
≥1 medications for hepatic events	6 (9.5)	3 (7.0)	8 (21.1)

Notes: ^aUnless otherwise specified. ^bIncludes patients receiving 150-mg or 200-mg starting doses of abemaciclib. ^cNo Grade 4 events.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; N, number of patients in analysis population; n, number of patients in category; NA, not applicable; NSAI, nonsteroidal aromatase inhibitor; TBILI, total bilirubin; ULN, upper limit of normal.

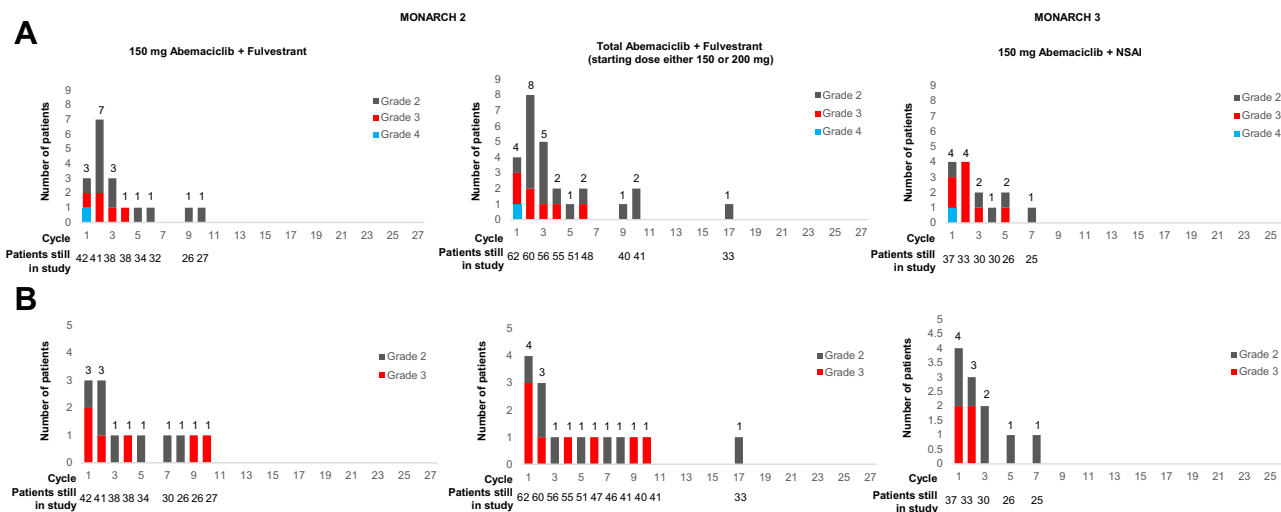


Figure 3 Grades ≥ 2 hepatic events by treatment cycle in Japanese subpopulations. Summary of Grade ≥ 2 events of (A) increased ALT; and (B) increased AST per treatment cycle in abemaciclib-treated Japanese patients from MONARCH 2 and MONARCH 3.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; NSA, nonsteroidal aromatase inhibitor.

Discussion

Abemaciclib/ET combination therapy was more efficacious than ET alone in women with HR+, HER- advanced breast cancer in both the overall study populations and the Japanese subpopulations of MONARCH 2 and MONARCH 3.^{8–12,14,15} The current report summarizes the characteristics and management of the most common and clinically relevant TEAEs associated with abemaciclib/ET combination therapy in Japanese patients from these studies, identifying the main safety concerns in this patient population. Notable differences between the Japanese subpopulations and overall populations included a higher incidence of TEAEs in abemaciclib-treated Japanese patients compared with the overall safety populations. This was driven largely by the higher incidence of any grade diarrhea and neutropenia, the most common TEAEs in the Japanese subpopulations. In addition, the Japanese subpopulations had higher incidences of Grade 3–4 neutropenia and both any grade and Grade 3–4 events of increased ALT/AST. Detailed assessment of the characteristics of diarrhea, neutropenia, and hepatic events, considered further below, indicate that these events were generally manageable with appropriate interventions and dose modifications. It is anticipated that these dose modifications did not substantially affect efficacy in Japanese patients, as prior analyses in the MONARCH 2 and MONARCH 3 overall populations indicated that the progression-free survival benefit derived from abemaciclib was not diminished by dose reductions.¹⁰

Compared to other CDK4/CDK6 inhibitors, abemaciclib is associated with a higher rate of gastrointestinal toxicities.^{17–20} In keeping with this, most abemaciclib-treated Japanese patients in MONARCH 2 and MONARCH 3 experienced ≥ 1 event of diarrhea, generally starting within the first week of treatment. All diarrheal events were Grade ≤ 3 and were effectively managed with antidiarrheal medications and dose adjustments, with most events resolving in ≤ 10 days and only 1 event leading to discontinuation of any study treatment. In addition, the highest rates of Grade 2 and Grade 3 diarrhea were observed in the first treatment cycle, with sharp declines in subsequent cycles, indicating that medication and dose adjustments were generally sufficient to resolve events and prevent recurrence in Japanese patients. Clinicians should be aware of the high probability of diarrhea events shortly after initiation of abemaciclib treatment. For optimal management of this early toxicity, patients should be advised to begin antidiarrheal therapy at the first sign of loose stools. For Grade ≥ 2 diarrhea not resolving with 24 hours, dose suspension should be implemented, with the addition of dose reduction for higher grade and/or persistent or recurrent events.

Due to bone marrow suppression, hematological toxicities are common with CDK4/CDK6 inhibitor treatment.^{17–20} In Japanese patients from MONARCH 2 and MONARCH 3, neutropenia was the most common hematological toxicity and the most common Grade ≥ 3 TEAE, with a median onset of 29.0 days across studies. In this patient population, neutropenia was generally Grade ≤ 3 (1 event of Grade 4), with a median duration of 23.0 days in MONARCH 2 and

12.0 days in MONARCH 3 for Grade 3–4 neutropenia. Neutropenia was managed in Japanese patients more frequently via a period of drug omission than via dose reduction, and this approach was largely successful, with only one event across studies resulting in discontinuation of any study treatment. Importantly, neutrophil counts stabilized within the first two treatment cycles and rapidly recovered to pretreatment levels after the end of the study treatment, indicating that this toxicity was both treatable and reversible.

Exploratory analyses indicated a higher incidence of Grade 3–4 events of neutropenia in the subgroup of Japanese patients with baseline neutrophil counts $<3.0 \times 10^9/L$ compared with those with baseline neutrophil counts $\geq 3.0 \times 10^9/L$. A further analysis revealed that, in MONARCH 2 and MONARCH 3, both Japanese and non-Japanese patients who experienced high-grade neutropenia had lower baseline neutrophil counts compared with those who did not. A similar finding has been reported previously for another CDK4/CDK6 inhibitor, palbociclib, indicating that a low baseline neutrophil count may be a risk factor for subsequent development of high-grade neutropenia following CDK4/CDK6 inhibitor therapy.²¹ Due to the high incidence of neutropenia in abemaciclib-treated patients, regular monitoring of blood counts is recommended (eg, every 2 weeks for the first 2 months of treatment, monthly thereafter for the next 2 months, and as otherwise warranted). Our exploratory analyses suggest that this monitoring should include screening for low neutrophil levels prior to the initiation of abemaciclib treatment, as this may aid in the identification of patients at risk for higher grade toxicities. For Grade ≥ 3 hematological toxicities, dose suspension until the event resolves to Grade ≤ 2 is recommended, with additional dose reduction once resuming treatment in the case of higher grade and recurrent toxicities or as clinically indicated.

Abemaciclib-treated Japanese patients from both MONARCH 2 and MONARCH 3 had high rates of any grade events (up to 50%) and Grade 3–4 events (up to 23.7%) of increased ALT/AST, which were roughly 2 to 4 times higher than the rates observed in abemaciclib arms of the overall safety populations. Increased ALT/AST occurred as isolated events and were not associated with hepatic dysfunction in terms of elevated bilirubin, which occurred infrequently in both studies. In Japanese patients, these hepatic events were generally manageable with medication and dose adjustments, with most Grade ≥ 2 events occurring in early treatment cycles. Events of increased ALT/AST were nonetheless the most common TEAEs leading to discontinuation of any study treatment, occurring in 6.7% to 16.7% of Japanese patients across studies. Interestingly, the incidence of any grade and Grade 3–4 events were higher in patients enrolled in MONARCH 3 compared with those in MONARCH 2, and this difference in incidence was particularly noticeable in the Japanese subpopulations. In addition, the median time to onset for Grade 3–4 events of increased ALT/AST in the Japanese subpopulations was shorter for MONARCH 2 (31.5–39.5 days) than for MONARCH 3 (64.0–71.0 days). Although the mechanisms underlying these differences are not known, as described in the Methods, MONARCH 2 and MONARCH 3 differed in some aspects of their study designs, including different eligibility criteria and treatment regimens, which may influence the rates and characteristics of liver events. Collectively, these data indicate that when Japanese patients are being treated with abemaciclib in combination with either fulvestrant or NSAIs, ALT and AST levels should be regularly assessed, including prior to the start of treatment and every 2 weeks for the first 2 months, every 4 weeks for the next 2 months, and additionally, as warranted. For Grade 3–4 increased ALT/AST, dose suspension until the event resolves to Grade ≤ 1 is recommended. For persistent or recurrent Grade 2 or Grade 3 increased ALT/AST, dose reduction when resuming treatment is recommended. For events of high severity (eg, Grade 4), discontinuation of treatment may be necessary.

The starting dose of abemaciclib had relatively modest effects on the safety profile of Japanese patients in MONARCH 2 and the pooled safety populations. For diarrhea, neutropenia, or increased ALT/AST in Japanese patients, the starting dose of abemaciclib did not appear to substantially affect the rates, onset, or duration of events of any grade although the rates of Grade 3–4 diarrhea and neutropenia were slightly higher in the “total abemaciclib” group of MONARCH 2 (150-mg or 200-mg abemaciclib starting dose) compared with patients who started on 150 mg in MONARCH 2 and MONARCH 3. There were also slightly higher rates of dose adjustments due to these toxicities in the total abemaciclib group in MONARCH 2 compared with 150 mg-treated Japanese patients in MONARCH 2 and MONARCH 3. These findings are in general accord with the safety observations in the overall study populations, in which diarrhea and neutropenia occurred at slightly higher rates in MONARCH 2 compared with MONARCH 3.¹³

It should be noted that while the aim of the current report was to identify and address the most frequent concerns that may arise with abemaciclib treatment in the clinical practice setting in Japan (ie, diarrhea, neutropenia, and ALT/AST increased), less common events, such as venous thromboembolism (VTE) and pneumonitis (interstitial lung disease; ILD) are of special interest for abemaciclib due to their potential seriousness. Although VTE was reported in the overall populations for MONARCH 2 and MONARCH 3 (any grade: 4.8–6.1%; Grade ≥ 3 : 2.0–3.1%),¹⁰ no VTE was reported in the Japanese subpopulations (0% pulmonary embolism; 0% deep vein thrombosis). ILD has previously been reported in abemaciclib-treated patients from both the MONARCH 2 and MONARCH 3 overall safety populations (any grade: 2.0–5.2%; Grade ≥ 3 : 0.7–1.2%)¹³ and Japanese subpopulations (any grade: 4.8–10.5%; Grade ≥ 3 , 0–2.6%),^{14,15} as well as in the real-world setting in Japan.²² Although relatively rare, clinicians should be aware of the risk of ILD in abemaciclib-treated patients in Japan and regularly monitor for symptoms of dyspnea, cough, and fever. In Japan, it is recommended that abemaciclib be discontinued for all grades of ILD except for Grade 1 ILD which is clearly unrelated to abemaciclib, with resumption of treatment if symptoms resolve.

A major limitation of this analysis is the small sample size of the Japanese subpopulations, even when combined, and only descriptive statistics are presented herein. Thus, the findings must be interpreted carefully, as the small sample size limits the conclusions that can be drawn about the data, such as generalizations about real-world TEAE incidence. Similar restrictions are applicable to comparisons between patients started on 150-mg versus 200-mg abemaciclib in the MONARCH 2 Japanese subpopulation. Additionally, the differences between the MONARCH 2 and MONARCH 3 study designs, including treatment, randomization procedures, and patient populations, could potentially influence outcomes and should be considered when interpreting the current findings. Finally, it should be noted that the MONARCH 2 and MONARCH 3 studies were not designed to discern the possible reasons underlying the differences in tolerability to abemaciclib observed between the Japanese subpopulations and global study populations. In the original reports of the Japanese subpopulation analyses for MONARCH 2 and MONARCH 3, study-specific differences between baseline clinical and demographic characteristics were discussed that had the potential to affect response to treatment, highlighting several differences in the patient populations (eg, menopausal status, treatment histories, disease status, post-discontinuation CDK 4/6 inhibitor use, and progesterone receptor status).^{14,15} In addition, it is recognized that a complex interplay of genetic, pharmacogenomic, tumor-biology, and dietary factors can influence differences in the response to CDK4/6 inhibitor/ET combination therapies between Asian and non-Asian populations,^{23–30} which as yet is poorly understood.³¹

Conclusions

Similar to the safety outcomes in the global study populations, abemaciclib was generally well tolerated in Japanese patients in the MONARCH 2 and MONARCH 3 clinical studies. Although higher rates of diarrhea, neutropenia, and increased ALT/AST were observed in the Japanese subpopulation compared to the overall safety population, detailed assessment of event characteristics indicates that these events were generally manageable with appropriate intervention and dose modifications, allowing patients to continue abemaciclib treatment. The current analysis expands our understanding of the abemaciclib safety profile in Japanese patients with HR+, HER2- advanced breast cancer and may be of utility in optimizing treatment outcomes in this patient population.

Abbreviations

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CDK, cyclin-dependent kinase; ET, endocrine therapy; G-CSF, granulocyte colony-stimulating factor; GM-CSF, granulocyte-macrophage colony-stimulating factor; HER2-, human epidermal growth factor receptor 2-negative; HR+, hormone receptor-positive; ILD, interstitial lung disease; N, number of patients in analysis population; n, number of patients in category; NA, not applicable; NSAI, nonsteroidal aromatase inhibitor; SAE, serious adverse events; SD, standard deviation; TBILI, total bilirubin; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Data Sharing Statement

Eli Lilly and Company provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.

Ethics Approval and Informed Consent

All patients included in the studies provided written, informed consent. MONARCH 2 and MONARCH 3 were conducted in accordance with Good Clinical Practice guidelines, relevant regulations in Japan, and the Declaration of Helsinki (1964) and its amendments. Study protocols were approved by ethical review boards at each site (lists supplied in [Supplementary Materials](#)).

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Author Contributions

NM took part in the acquisition and interpretation of the data. TK took part in the conceptualization and design of this study and interpretation of the data. YC and KD took part in the analysis and interpretation of the data. MT took part in the conceptualization and design of this study and the acquisition and interpretation of the data. All authors contributed to drafting and critical revision of the article and have agreed to the journal to which it has been submitted. All authors reviewed and agreed on all versions and revisions of the article before submission and gave final approval of the version to be published. All authors agree to take responsibility for the contents of the article and all aspects of the work.

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