ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

ORIGINAL ARTICLE

Sacituzumab govitecan in patients with metastatic breast cancer: pooled safety analysis of data from patients in North America, Europe, and Asia

H. S. Rugo[1*], S. M. Tolaney[2], J. Cortés[3,4,5,6,7], F. Marmé[8], E. de Azambuja[9], B. Xu[10], J. Sohn[11], Y. Naito[12], T. Valdez[13], D. Gary[13], J. Zhu[14], C. Lai[13] & A. Bardia[15]

[1]City of Hope, Duarte, CA; [2]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [3]Oncology Department, International Breast Cancer Center (IBCC), Pangaea Oncology, Quiron Group, Barcelona; [4]IOB Madrid, Institute of Oncology, Hospital Beata María Ana, Madrid; [5]Oncology Department, Hospital Universitario Torrejón, Ribera Group, Madrid; [6]Department of Medicine, Universidad Europea de Madrid, Faculty of Biomedical and Health Sciences, Madrid; [7]Medica Scientia Innovation Research (MEDSIR), Barcelona, Spain; [8]Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [9]Institut Jules Bordet, Hôpital Universitaire de Bruxelles (H.U.B), l'Université Libre de Bruxelles (ULB), Brussels, Belgium; [10]Cancer Hospital, Chinese Academy of Medical Sciences, Peking Union Medical College, Beijing, China; [11]Yonsei Cancer Center, Seoul, Republic of Korea; [12]National Cancer Center Hospital East, Kashiwa, Japan; [13]Gilead Sciences, Inc., Foster City, CA, USA; [14]Gilead Sciences, Inc., Shanghai, China; [15]David Geffen School of Medicine, University of California, Jonsson Comprehensive Cancer Center, Los Angeles, CA, USA

Available online xxx

Background: Sacituzumab govitecan (SG) is an antibody—drug conjugate that has significantly improved survival outcomes versus standard of care across multiple studies in patients with previously treated metastatic breast cancer (mBC). Cancer treatment is associated with differing rates of treatment-emergent adverse events (TEAEs) based on patient race/location. We evaluated consistency and manageability of SG safety in mBC across multiple clinical studies and regions in this pooled analysis.

Materials and methods: Safety data for patients who received SG treatment (10 mg/kg, days 1 and 8 every 21-day cycle) were pooled from clinical studies in North America/Europe (NA/EU; ASCENT, TROPiCS-02, IMMU-132-01) and Asia (EVER-132-001, EVER-132-002, ASCENT-J02).

Results: The analysis included 969 patients (688 NA/EU, 281 Asia). In NA/EU, 74% of patients experienced grade ≥3 TEAEs. TEAEs leading to treatment discontinuation (5%) or death (1%) were uncommon. The most common TEAEs were neutropenia, nausea, and diarrhea. The safety profile was similar for patients in Asia, with 78% experiencing grade ≥3 TEAEs and low rates of TEAEs leading to treatment discontinuation (4%) or death (3%). Neutropenia, anemia, leukopenia, increased aspartate aminotransferase, increased alanine aminotransferase, and hypoalbuminemia were more frequently reported in Asia versus NA/EU; diarrhea and fatigue were more common in NA/EU.

Conclusions: The safety profile of SG was manageable and consistent with previous studies, with low rates of TEAEs leading to treatment discontinuation or death; some differences in TEAE rates were observed between NA/EU and Asia. This analysis provides further support for SG as a treatment for mBC across multiple patient subgroups.

Key words: sacituzumab govitecan, metastatic triple-negative breast cancer, HR-positive/HER2-negative metastatic breast cancer, safety, pooled analysis

INTRODUCTION

Breast cancer (BC) is the most common malignancy in women worldwide, with an estimated 2.3 million new cases and 666 000 mortalities in 2022.[1] Multiple subtypes of BC have been defined based on the presence or absence of hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2). These include triple-negative BC (TNBC) and HR-positive/HER2-negative BC. HR-positive/HER2-negative status is commonly defined as ≥1% expression of estrogen receptor and/or progesterone receptor in tumor cells (HR-positive) and HER2 0 or 1+ by immunohistochemistry (IHC) or HER2 2+ by IHC and *in situ* hybridization-negative (HER2-negative), per the American Society of Clinical Oncology/College of American Pathologists guidelines.[2,3] TNBC is HR-negative (<1% expression of both estrogen receptor and progesterone receptor)[2] and HER2-negative. TNBC accounts for ∼10%-15% of all BC cases, while HR-positive/HER2-negative is more common and makes up roughly 63%-74% of cases.[4]

Sacituzumab govitecan (SG) is an antibody—drug conjugate (ADC) targeted to Trop-2 and approved for previously

*Correspondence to: Dr Hope S. Rugo, City of Hope, 1500 East Duarte Rd, Duarte, CA 91010, USA. Tel: +1-262-879-4114
E-mail: hrugo@coh.org (H. S. Rugo).

treated metastatic TNBC (mTNBC) and HR-positive/HER2-negative metastatic BC (mBC).[5-9] SG significantly improved progression-free survival and overall survival compared with chemotherapy of physician's choice in patients with previously treated mTNBC and HR-positive/HER2-negative mBC.[10-13] SG has also demonstrated a manageable safety profile, and common treatment-emergent adverse events (TEAEs) associated with SG treatment include neutropenia, diarrhea, and nausea/vomiting.[10,11,13,14]

Previous studies have indicated that specific TEAEs associated with cancer treatment may occur at different rates depending on a patient's race or geographic location. A meta-analysis found that, among patients with cancer who received trastuzumab emtansine, Asian patients were more likely to experience any-grade and grade $\geq$3 thrombocytopenia than patients who were not Asian.[15] Another retrospective study found that Black patients experienced cutaneous events at a higher rate than white patients following enfortumab vedotin treatment.[16]

The uridine diphosphate glucuronosyltransferase (UGT)1A1 enzyme is involved in the metabolism of a variety of drugs. Patients with specific mutations in the *UGT1A1* gene that impact the metabolism of these drugs may experience TEAEs at different rates. An oncology treatment with known differences in TEAEs depending on *UGT1A1* genotype is irinotecan. Irinotecan is converted to an active metabolite, SN-38, which is also the payload molecule attached to SG.[17] SN-38 is subsequently glucuronidated by UGT1A1 as part of the pathway to excretion from the body.[18] The wild-type genotype of *UGT1A1* is referred to as *1/*1. Genetic variants in the *UGT1A1* gene, such as *1/*28 or *28/*28, may reduce the enzymatic activity of the protein, resulting in slower metabolism of SN-38 and subsequently increased risk of TEAEs such as diarrhea or neutropenia.[19-21]

Existing research indicates that patients with *28/*28 genotypes experience higher rates of grade $\geq$3 neutropenia, febrile neutropenia, anemia, and diarrhea than those with *1/*1 (wild-type) or *1/*28 genotypes.[22,23] Following irinotecan treatment, patients with *UGT1A1* *1/*6 or *6/*6 genotypes also experience higher rates of neutropenia and diarrhea compared with those with *1/*1 genotypes.[24] The frequency of specific *UGT1A1* polymorphisms varies among racial and ethnic groups. The *28 allele is more common among people of European ancestry, while the *6 allele is more common among those of East Asian ancestry when the two groups are compared.[25]

We present an analysis of two pools of safety data from clinical studies of SG including patients with mBC from the United States, Canada, and Europe, and patients from China, the Republic of Korea, Japan, and Taiwan, for a global analysis of SG safety in the treatment of mBC. Potential differences in TEAEs based on the patient's geographical location are also examined.

MATERIALS AND METHODS

Clinical studies

Safety data were pooled from multiple clinical studies in North America/Europe (NA/EU) and in Asia. The studies conducted in NA/EU were ASCENT (phase III, NCT02574455), TROPiCS-02 (phase III, NCT03901339), and IMMU-132-01 (phase I/II, NCT01631552), and the studies in Asia were EVER-132-001 (phase IIb, NCT04454437), EVER-132-002 (phase III, NCT04639986), and ASCENT-J02 (phase I/II, NCT05101096). The detailed study designs have been described previously.[10,11,13,14,26,27] Patients included in the analysis were those with HER2-negative mBC, including mTNBC and HR-positive/HER2-negative mBC, who received SG (10 mg/kg intravenously, days 1 and 8 of every 21-day cycle). In all studies, SG treatment continued until loss of clinical benefit, unacceptable toxicity, or death.

Inclusion criteria

ASCENT, EVER-132-001, and the phase II cohort of ASCENT J-02 included patients with locally advanced unresectable mTNBC whose disease had relapsed or was refractory to two or more prior standard chemotherapy regimens (at least one of them for metastatic disease in ASCENT J-02).[10,14,27] In ASCENT and EVER-132-001, previous therapies must have included a taxane.[10,14] Patients in TROPiCS-02 and EVER-132-002 had locally recurrent inoperable or metastatic HR-positive/HER2-negative mBC, with two to four prior systemic chemotherapy regimens for metastatic disease. Patients must have previously received at least one taxane, at least one anticancer endocrine therapy, and, in TROPiCS-02, at least one cyclin-dependent kinase 4/6 inhibitor.[11,13] The IMMU-132-01 study included patients with multiple metastatic epithelial cancers, including non-TNBC and TNBC, whose disease had relapsed or was refractory to one or more prior standard regimen.[28]

UGT1A1 assessment

Whole blood samples were collected at baseline and were used to assess *UGT1A1* genotype using either *UGT1A1* Genotyping Kit (EntroGen, Inc., Woodland Hills, CA) or Sanger sequencing.[12,13,22,28]

Adverse events

In the ASCENT, TROPiCS-02, and IMMU-132-01 studies, TEAEs were defined as any adverse events that started on or after the first dose date until $\leq$30 days after the last dose date. For EVER-132-001, EVER-132-002, and ASCENT-J02, TEAEs were defined as any adverse events that started on or after first dose date until $\leq$30 days after last dose date, or until initiation of subsequent anticancer therapy, whichever occurred first. Safety data were analyzed for manageability and for consistency with prior analyses across pooled mBC studies as well as by NA/EU versus Asia.

TEAEs were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events: version 4.0 for IMMU-132-01; version 4.03 for ASCENT and ASCENT-J02; and version 5.0 for TROPiCS-02, EVER-132-001, and EVER-132-002.

RESULTS

Patient characteristics

This analysis included 969 patients, 688 from NA/EU and 281 from Asia. The NA/EU population consisted of 258 patients enrolled and treated with SG in ASCENT, 268 in TROPiCS-02, and 162 in IMMU-132-01. The median age was 55 years and the majority (75%) of patients were white (Table 1). Most patients (88%) had visceral metastases at baseline, and the most common *UGT1A1* genotypes were *1/*1 (41%) and *1/*28 (40%). Median relative dose intensity was 99% (range 47%-107%) and the median duration of treatment was 4.6 months (range <0.1-62.6 months). The Asia population included 80 patients in EVER-132-001, 165 in EVER-132-002, and 36 in ASCENT-J02, all of whom were of Asian race. Age, sex, and body mass index were comparable between the two groups. However, patients in Asia were more likely to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 1 than those in NA/EU (67% versus 59%); they also had shorter time from metastatic diagnosis to randomization (25.2 months versus 35.7 months). *UGT1A1* genotypes additionally differed between NA/EU and Asia, with *1/*28 and *28/*28 being more common in NA/EU and *1/*1 and *1/*6 being more common in Asia. In Asia, median relative dose intensity was 100% (range 54%-104%) and the median duration of treatment was 5.2 months (range <0.1-24.9 months).

Table 1. Patient demographics and baseline characteristics

	NA/EU (n = 688)	Asia (n = 281)
Median age (range), years	55 (27-86)	51 (23-72)
Sex, *n* (%)		
Female	684 (99)	281 (100)
Male	4 (1)	0
Race, *n* (%)		
White	517 (75)	0
Black	41 (6)	0
Asian	26 (4)	281 (100)
Other/unknown	104 (15)	0
Region, *n* (%)		
North America	442 (64)	0
Europe	246 (36)	0
China	0	198 (70)
South Korea	0	31 (11)
Taiwan	0	16 (6)
Japan	0	36 (13)
Median BMI (range), kg/m^2	25.2 (15.0-61.0)	23.5 (15.8-35.5)
ECOG PS, *n* (%)		
0	281 (41)	92 (33)
1	407 (59)	189 (67)
Visceral metastases at baseline, *n* (%)		
Yes	604 (88)	NR
No	84 (12)	NR
Median time from initial metastatic diagnosis to first dose, (range) months	35.7 (−0.1 to 412.6)	25.2 (1.2-156.2)
Median prior anticancer regimens, *n* (range)	4 (2-9)	NR
UGT1A1 status, *n* (%)		
*1/*1	285 (41)	147 (52)
*1/*28	272 (40)	32 (11)
*28/*28	71 (10)	4 (1)
*1/*6	0	65 (23)
Other/missing	60 (9)	33 (12)

BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; NA/EU, North America/Europe; NR, not reported.

Safety summary

Patients in NA/EU developed grade ≥3 TEAEs at a rate of 74% (Table 2). TEAEs leading to dose reduction, dose interruption, treatment discontinuation, and death occurred in 28%, 61%, 5%, and 1% of patients, respectively. The most common any-grade TEAEs were neutropenia (68%), nausea (63%), and diarrhea (63%) (Figure 1). Neutropenia (51%), leukopenia (10%), and diarrhea (10%) were the most common grade ≥3 TEAEs. The most common TEAEs that led to treatment discontinuation in NA/EU were neutropenia, diarrhea, fatigue, and pneumonia (each <1%). Rates of any-grade and grade ≥3 TEAEs were similar between patients in NA/EU and Asia. Serious adverse events were slightly more common in NA/EU (28%) versus Asia (22%). The rates of TEAEs leading to dose reduction, dose interruption, treatment discontinuation, and death were consistent between the two geographic groups. The most common any-grade and grade ≥3 TEAEs in Asia were neutropenia (87% and 65%, respectively), leukopenia (74% and 46%), and anemia (69% and 17%). Neutropenia, anemia, and leukopenia of any grade or grade ≥3 occurred at higher rates in Asia compared with NA/EU. Reported rates of any-grade increased aspartate aminotransferase, increased alanine aminotransferase, and hypoalbuminemia were also higher in Asia. Diarrhea of any grade or grade ≥3 and fatigue of any grade were more common in NA/EU than in Asia. The most common TEAEs leading to treatment discontinuation in Asia were neutropenia, leukopenia, fatigue, and septic shock (each 1%). Most TEAEs leading to death were not considered treatment-related; the treatment-related adverse events leading to death consisted of one event of septic shock in NA/EU and one each of shock and septic shock in Asia (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2026.106905).

TEAEs by *UGT1A1* genotype

When analyzing TEAEs by *UGT1A1* genotype, patients in NA/EU with *1/*28 and *28/*28 genotypes had higher rates of grade ≥3 TEAEs than those with *1/*1 (wild-type) (75% and 87% versus 68%) (Table 2). Rates of neutropenia, febrile neutropenia, diarrhea, and anemia were all higher in patients with the *28/*28 genotypes than in those with the *1/*1 and *1/*28 genotypes (Supplementary Table S2,

Table 2. Safety summary by *UGT1A1* status

Safety, *n* (%)	NA/EU (*n* = 688)					Asia (*n* = 281)				
UGT1A1 genotype	All patients	*1/*1 (*n* = 285)	*1/*28 (*n* = 272)	*28/*28 (*n* = 71)	*1/*6 (*n* = 0)	All patients	*1/*1 (*n* = 147)	*1/*28 (*n* = 32)	*28/*28 (*n* = 4)	*1/*6 (*n* = 65)
All TEAEs	687 (>99)	285 (100)	271 (>99)	71 (100)	N/A	281 (100)	147 (100)	32 (100)	4 (100)	65 (100)
Grade ≥3	506 (74)	195 (68)	204 (75)	62 (87)		220 (78)	106 (72)	26 (81)	3 (75)	56 (86)
Serious AEs	195 (28)	70 (25)	78 (29)	32 (45)		62 (22)	30 (20)	10 (31)	1 (25)	15 (23)
Led to dose reduction	147/526 (28)[a]	46/216 (21)[a]	68/215 (32)[a]	22/59 (37)[a]		68 (24)	27 (18)	8 (25)	0	22 (34)
Led to dose interruption	417 (61)	176 (62)	161 (59)	46 (65)		177 (63)	86 (59)	24 (75)	3 (75)	40 (62)
Led to discontinuation	36 (5)	13 (5)	14 (5)	5 (7)		11 (4)	7 (5)	1 (3)	0	3 (5)
Led to death	8 (1)	1 (<1)	6 (2)	1 (1)		8 (3)	4 (3)	1 (3)	0	2 (3)

Patients with other *UGT1A1* genotypes: NA/EU, *n* = 10, Asia, *n* = 15; patients with genotype missing: NA/EU, *n* = 50, Asia, *n* = 18.
AE, adverse event; NA, not applicable; NA/EU, North America/Europe; TEAE, treatment-emergent adverse event.
[a]AEs leading to dose reduction were not collected in IMMU-132-01.

available at https://doi.org/10.1016/j.esmoop.2026.106905). Patients with the *1/*28 genotype had a higher rate of grade ≥3 TEAEs than those with *1/*1 and *28/*28 genotypes in Asia (81% versus 72% and 75%), although the number of patients with the *28/*28 genotype in Asia was very low (*n* = 4). Those with the *1/*6 genotype also had higher rates of grade ≥3 TEAEs versus *1/*1 (86% versus 72%). Patients in Asia with *1/*28 and *1/*6 genotypes had higher rates of neutropenia, diarrhea, and anemia than those with *1/*1 genotypes, while the rate of febrile neutropenia was similar (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2026.106905).

Management of TEAEs

Patients in NA/EU were less likely to develop any-grade or grade ≥3 neutropenia if they received primary granulocyte colony-stimulating factor (G-CSF) (Table 3). Loperamide was the most commonly used antidiarrheal, and patients mostly received one prophylactic antinauseant or antiemetic at a time rather than receiving a regimen of two or more agents. Patients in Asia received primary G-CSF prophylaxis at slightly higher rates than in NA/EU (13% versus 9%). Antidiarrheal loperamide and atropine treatment was less common in Asia than in NA/EU, while in Asia other antidiarrheals were more commonly used. Patients in Asia were more likely to receive prophylactic antiemetic/antinauseants (95% versus 75%). It was most common for patients in Asia to receive two concurrent antiemetics/antinauseants (79%), while it was most common for patients in NA/EU to receive one agent (56%).

TEAE onset over time

The rate of neutropenia was highest early during treatment in NA/EU and decreased notably over time (Figure 2). In contrast, the rate of diarrhea remained relatively stable over time. Median time to onset for diarrhea was 13 days, while median time to onset for neutropenia was 16 days (Supplementary Figure S1, available at https://doi.org/10.1016/j.esmoop.2026.106905). A similar trend was noted in patients in Asia. The rate of neutropenia was highest early during treatment and decreased notably over time, while diarrhea occurred at a stable rate over time. The median time to onset of infections (any-grade and grade ≥3) was longer in Asia than in NA/EU. Time to onset of other TEAEs of interest, including neutropenia, febrile neutropenia, diarrhea, and hypersensitivity, was similar between the groups.

DISCUSSION

This analysis is the largest safety analysis of SG in mBC published to date, and included patients in NA/EU and Asia across six clinical studies ranging from phase I/II to phase III. In NA/EU, rates of TEAEs, including TEAEs leading to dose reduction, interruption, and discontinuation and those leading to death, were consistent with previous safety analyses for the individual studies.[10,11,26] Patients with *1/*28 and *28/*28 *UGT1A1* genotypes had higher rates of grade ≥3 TEAEs.

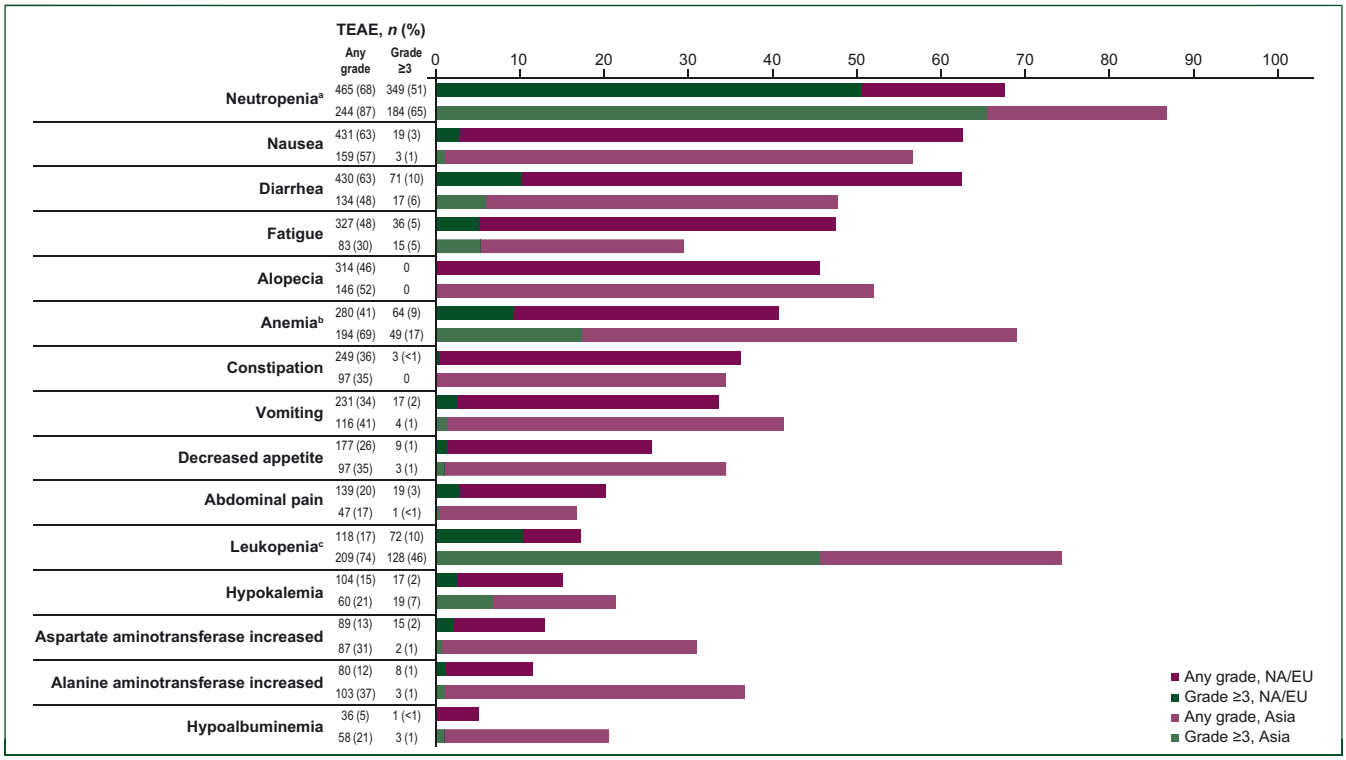

Figure 1. Most common TEAEs. The most common TEAEs that occurred in ≥20% of patients and grade ≥3 TEAEs that occurred in ≥10% of patients in either location were recorded. NA/EU, North America/Europe; TEAE, treatment-emergent adverse event.
[a]Neutropenia includes preferred terms of neutropenia and neutrophil count decreased.
[b]Anemia includes preferred terms of anemia, hemoglobin decreased, and red blood cell count decreased.
[c]Leukopenia includes preferred terms of leukopenia and white blood cell count decreased.

Patients with *28/*28 *UGT1A1* genotypes had higher rates of neutropenia, febrile neutropenia, diarrhea, and anemia than those with *1/*1 (wild-type) genotypes. Although patients with *1/*28 and *28/*28 genotypes had higher rates of TEAEs than those with *1/*1 genotypes, rates of treatment discontinuation or interruption due to TEAEs were similar,

Table 3. Summary of TEAE management

Safety, *n* (%)	**Total patients (*N* = 969)**			
	Primary G-CSF prophylaxis			
	NA/EU (*n* = 688)		Asia (*n* = 281)	
	Received (*n* = 65, 9%)	Did not receive (*n* = 623, 91%)	Received (*n* = 36, 13%)	Did not receive (*n* = 245, 87%)
Any-grade neutropenia	26 (40)	450 (72)	21 (58)	223 (91)
Grade ≥3 neutropenia	19 (29)	347 (56)	17 (47)	170 (69)

	Patients who received an antidiarrheal during SG treatment		**Patients who experienced diarrhea and received an antidiarrheal during SG treatment**	
	NA/EU (*n* = 343, 50%)	Asia (*n* = 120, 43%)	NA/EU (*n* = 298, 43%)	Asia (*n* = 88, 31%)
Any loperamide	304 (89)	59 (49)	271 (91)	56 (64)
Any atropine	67 (20)	6 (5)	58 (19)	5 (6)
Other antidiarrheal	80 (23)	87 (73)	76 (26)	58 (66)

	Nausea and vomiting	
	NA/EU (*n* = 688)	Asia (*n* = 281)
Any nausea	431 (63)	159 (57)
Nausea leading to dose reduction	7/318 (2)[a]	2/159 (1)
Any vomiting	231 (34)	116 (41)
Vomiting leading to dose reduction	5/151 (3)[a]	2/116 (2)
Any antiemetic/antinauseant for prophylaxis of nausea/vomiting	518 (75)	268 (95)
1 agent	289/518 (56)	123/268 (46)
2 concurrently	199/518 (38)	211/268 (79)
3 concurrently	193/518 (37)	104/268 (39)
≥4 concurrently	96/518 (19)	24/268 (9)

AE, adverse event; G-CSF, granulocyte colony-stimulating factor; NA/EU, North America/Europe; SG, sacituzumab govitecan; TEAE, treatment-emergent adverse event.
[a]AEs leading to dose reduction were not collected in IMMU-132-01.

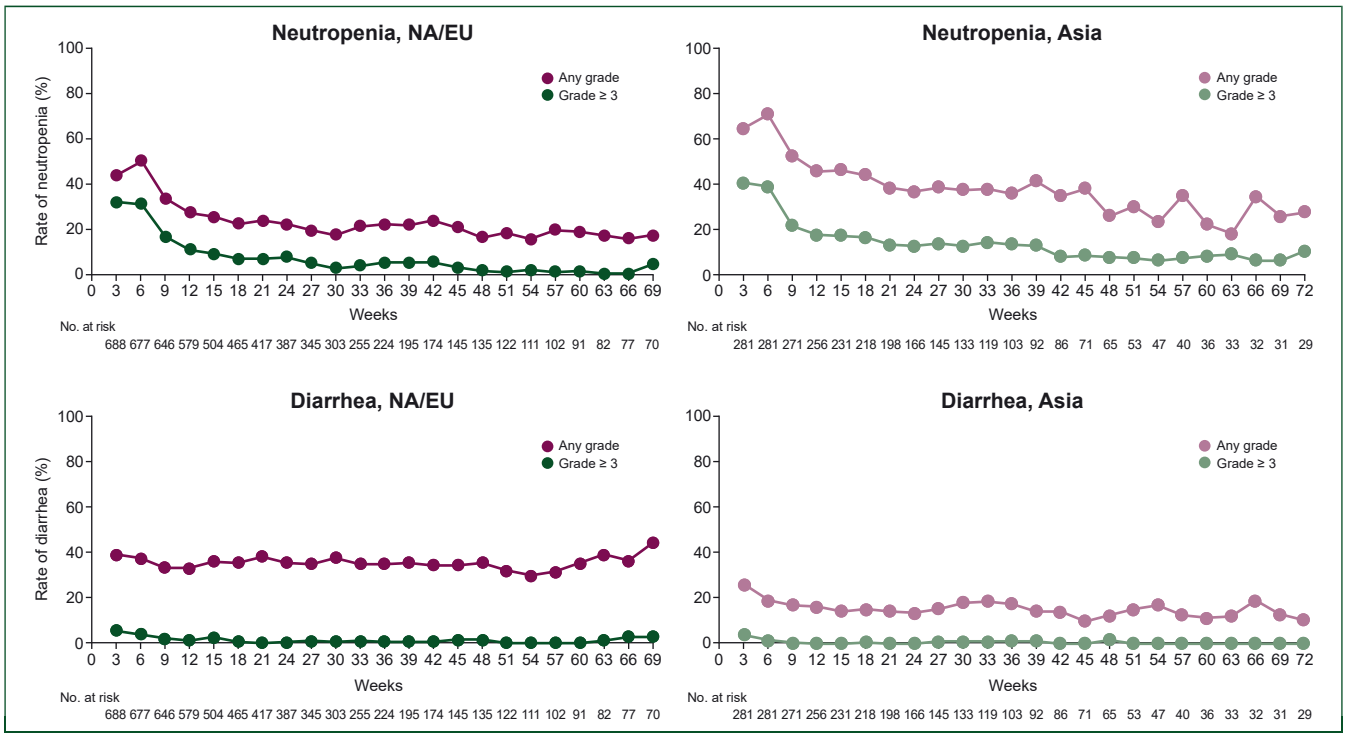

Figure 2. Occurrence of neutropenia and diarrhea over time. The rate at which patients developed neutropenia and diarrhea in North America/Europe and Asia was measured over time.
NA/EU, North America/Europe.

reflecting that management strategies for these TEAEs are effective across *UGT1A1* genotypes. Primary prophylaxis with G-CSF was associated with lower incidence of neutropenia, supporting the recommendation that patients at increased risk of febrile neutropenia should receive primary prophylaxis with G-CSF starting in the first cycle of treatment.[5] Rates of neutropenia were higher at the beginning of treatment and decreased over time, while rates of diarrhea remained relatively stable over the study period. The safety profile of SG in patients in Asia was consistent with the results of the individual clinical studies, and was largely consistent with the safety profile observed in patients in NA/EU.[13,14,27] Hematologic TEAEs such as neutropenia, leukopenia, and anemia were more common in Asia, and diarrhea and fatigue were more common in NA/EU. Patients in Asia with the *1/*6 *UGT1A1* genotype had higher rates of neutropenia, diarrhea, and anemia than those with the *1/*1 genotype, while the rate of febrile neutropenia was similar. Patients in Asia were more likely to receive non-loperamide and non-atropine antidiarrheals, and were more likely to receive two concurrent antinauseant/antiemetics compared with NA/EU, reflecting regional treatment practices. Development of neutropenia and diarrhea over time was similar in Asia and NA/EU. Additionally, the increased rates of neutropenia, anemia, and leukopenia are consistent with existing literature suggesting that Asian patients are more likely to experience hematologic toxicity, such as neutropenia, anemia, leukopenia, and thrombocytopenia, following anticancer treatment, including ADCs, than non-Asian patients.[15,29,30] This suggests a possible shared mechanism may lead to their elevated rates in patients in Asia. Despite this, rates of TEAEs leading to treatment discontinuation or death were low and similar between the groups, suggesting that with appropriate strategies these TEAEs can be adequately managed, allowing participants to remain on treatment. This is further supported by the fact that primary G-CSF prophylaxis was associated with lowered neutropenia rates.

Several factors may contribute to differences in hematologic TEAE rates between NA/EU and Asia. Among these are genetic differences, such as differences in *UGT1A1* alleles. While the most common genotype in both groups was *1/*1, patients in NA/EU were more likely to have the *1/*28 genotype and those in Asia were more likely to have the *1/*6 genotype, consistent with known geographic patterns of allelic distribution in these populations.[25] Differences in *UGT1A1* function could contribute to increased rates of diarrhea and neutropenia in patients with *6 or *28 alleles, as seen in meta-analyses of irinotecan, a prodrug that is metabolized to SN-38, which is the same payload molecule delivered by SG.[21,31-33] The *6 and *28 alleles are associated with reduced enzymatic activity of UGT1A1, which in turn reduces the rate of excretion of SN-38.[34,35] This is supported in our analysis by the increased rate of some TEAEs (neutropenia, febrile neutropenia, diarrhea, anemia) in patients with the *1/*28, *28/*28, and *1/*6 genotypes compared with the *1/*1 genotype across groups. It is unlikely that differences in *UGT1A1* are entirely the cause of the observed regional differences, however, as rates of neutropenia and anemia were still higher in patients in Asia versus those in NA/EU when comparing only patients in the *1/*1 category. Another potential contributing factor to the regional

differences in our analysis is differences in baseline characteristics between the two geographic groups. Patients in Asia were more likely to have an ECOG PS of 1 (67% versus 59%), indicating that these patients may have had more advanced disease or may have had more comorbid conditions. Finally, differences in adverse event management approaches between NA/EU and Asia could alter the likelihood of TEAEs. Patients in Asia were slightly more likely to receive primary G-CSF prophylaxis (13% Asia versus 9% NA/EU) and were more likely to receive non-atropine, non-loperamide antidiarrheals than those in NA/EU, and the number of concurrent antinauseant/antiemetic medications most commonly used differed between Asia and NA/EU. The data reported do not distinguish between prophylactic or 'as-needed' use of antidiarrheals, but not all patients who received antidiarrheals actually had diarrhea, indicating that some of this usage may have been prophylactic. Beyond factors captured by our analysis, it is conceivable that other differences, such as lifestyle factors, diet, and underreporting or overreporting of TEAEs due to cultural perceptions of medical issues, may contribute to reported differences in safety; however, these factors are outside the scope of this analysis.

Our analysis has some limitations, largely due to the type (e.g. differences in data capture across study sponsors) and volume of data (e.g. small sample sizes in individual studies) that can be gathered in clinical studies. While the magnitude of differences in factors such as ECOG PS was relatively small, we cannot exclude the possibility that this is a contributing factor to increased rates of specific TEAEs in each group. Finally, as noted in the preceding text, there are many differences in clinical practice across countries and even individual hospitals within each study region. While factors such as usage of specific medications can be accounted for, in the context of clinical study comparisons it is difficult to quantify less tangible contributors to adverse event management such as the policy and infrastructure surrounding health care, differing cultural expectations, and regional differences such as physical proximity to health care facilities. Because of these factors, it is difficult to determine whether differences in the rates of TEAEs such as neutropenia are caused by biological factors (e.g. *UGT1A1* genotype), environmental factors, reporting factors, or a combination thereof.

To conclude, our analysis represents the largest safety analysis of SG use in patients with mBC to date and incorporates results from Asian clinical study populations. While some small differences in TEAE rates were observed, the safety profile of SG in mBC is consistent across trials and regions. This analysis provides further support for SG as a treatment for patients with mBC with a consistent and manageable safety profile across patient subgroups.

ACKNOWLEDGEMENTS

We extend our thanks to the patients, their families, and all participating investigators. Writing and editorial assistance were provided by Ben Labbe, PhD, of Parexel, and funded by Gilead Sciences, Inc.

FUNDING

This work was supported by Gilead Sciences, Inc (no grant number). The sponsor designed and conducted the study, gathered data, and performed data analysis in collaboration with the study investigator. The first author, with the other authors, members of the steering committee, and sponsor, guided the initial manuscript draft after an agreement to publish, with medical writing assistance funded by the sponsor. All drafts of the manuscript were reviewed and approved by the authors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the study to the protocol.

DISCLOSURE

HSR reports grants and contracts from Ambrx and Stemline Therapeutics; honoraria from AstraZeneca, Chugai, Daiichi Sankyo, F Hoffman-La Roche AG/Genentech, Inc., Gilead Sciences, Inc., Lilly, Merck, Mylan/Viatris, Novartis, OBI Pharma, and Pfizer; and consulting and advisory roles with Bristol Myers Squibb, NAPO, PUMA, and Sanofi. SMT reports grants and contracts from AstraZeneca, Eli Lilly, Exelixis, Genentech/Roche, Gilead Sciences, Inc., Jazz Pharmaceuticals, Merck, Novartis, Pfizer, Sanofi, and Seagen; steering committee participation with AstraZeneca, CytomX, Genentech/Roche, Gilead Sciences, Inc., Lilly, and Jazz Pharmaceuticals; honoraria from Stemline/Menarini; and consulting and advisory roles with Aadi BioPharma, Artios, Arvinas, AstraZeneca, Bayer, BeiGene, BeyondSprings, Bicycle Therapeutics, BioNTech, Blueprint Medicines, Bristol Myers Squibb, Circle Pharma, Cullinan Oncology, Daichii Sankyo, eFFECTOR, Eisai, Eli Lilly, Genentech/Roche, Gilead Sciences, Inc., Incyte Corp, Jazz Pharmaceuticals, Johnson & Johnson/Ambrx, Launch Therapeutics, Menarini/Stemline, Merck, Mersana Therapeutics, Natera, Novartis, Pfizer, Reveal Genomics, Sanofi, Seagen, Sumitovant Biopharmaceuticals, Summit Therapeutics, Systimmune, Tango Therapeutics, Umoja Biopharma, Zentalis, Zuellig Pharma, and Zymeworks. JC reports grants and contracts from Ariad Pharmaceuticals, AstraZeneca, Baxalta GMBH/Servier Affaires, Bayer Healthcare, Daiichi Sankyo, Eisai, Guardant Health, IQVIA, Merck, Pfizer, Piqur Therapeutics, Queen Mary University of London, and Roche; honoraria from AstraZeneca, Daiichi Sankyo, Eisai, Eli Lilly, Gilead Sciences, Inc., Merck, Novartis, Pfizer, Roche, and Stemline Therapeutics; travel expenses from AstraZeneca, Daiichi Sankyo, Eisai, Gilead Sciences, Inc., Merck, Novartis, Pfizer, Roche, and Stemline Therapeutics; consulting and advisory roles with AbbVie, AstraZeneca, Bioasis, Biocon, BioInvent, BioNTech, Boehringer Ingelheim, Bridgebio, Circle Pharma, Clovis Oncology, Daiichi Sankyo, Eli Lilly, Ellipses, Expres2ion Biotechnologies, Gemoab, Gilead Sciences, Inc., Hibercell, Jazz Pharmaceuticals, Leuko, Menarini, Merck, Reveal Genomics, Roche, Scorpion Therapeutics, Seattle Genetics, and Zymeworks; and stock ownership in Leuko and MAJ3 Capital. FM reports grants or contracts from AstraZeneca, Eli Lilly, and Seagen; honoraria from AGO Research GmbH, AstraZeneca, Boehringer

Ingelheim, Daiichi Sankyo, Eisai, Eli Lilly, German Breast Group, Gilead Sciences, Inc., GSK, MSD, Novartis, Pfizer, Roche, Seagen, Stemline/Menarini, and Vaccibody; and consulting or advisory roles with AstraZeneca, BioNTech, Daiichi Sankyo, Eisai, Genomic Health, Gilead Sciences, Inc., Immunicom, Incyte, MSD, Myriad Genetics, Nerviano, Novartis, Novocure, Roche, and Seagen. EdA reports grants and contracts with AstraZeneca, GSK/Novartis, and Roche/GNE; honoraria and/or advisory roles with AstraZeneca, Eli Lilly, Gilead Sciences, Inc., Libbs, MSD, Novartis, Pierre Fabre, Roche/GNE, Seagen, and Zodiac; travel support from AstraZeneca and Gilead Sciences, Inc.; and roles as ESMO Director of Membership (2023-2025) and BSMO President (2023-2026). BX reports consulting and advisory roles with AstraZeneca and Novartis. JS reports grants and contracts from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Celcuity, Daiichi Sankyo, Dragonfly, Eikon, Eli Lilly, Gilead Sciences, Inc., GlaxoSmithKline, Hanmi Pharm, HLB Life Science, Ildong Pharmaceutical, Merck, Novartis, Olema, Pfizer, Qurient, Roche, Samyang Holdings, Sanofi, Seagen, and Sermonix Pharmaceuticals. YN reports grants and contracts from Roche; honoraria from AbbVie, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Chugai, Daiichi Sankyo, Eisai, Eli Lilly, Gilead Sciences, Inc., Guardant Health, MSD, Nihon Kayaku, Novartis, Ono Pharmaceuticals, PDR Pharma, Pfizer, Taiho, and Takeda; and board of directors membership with Japanese Association of Sarcoma Treatment and Organization for the Creation of Cancer Medicine. TV reports employment with Gilead Sciences, Inc. and stock ownership with Gilead Sciences, Inc. and Novovax. DG reports employment and stock ownership with Gilead Sciences, Inc. JZ reports employment and stock ownership with Gilead Sciences, Inc. CL reports employment and stock ownership with Gilead Sciences, Inc. AB reports grants or contracts from AstraZeneca/Daiichi Sankyo, Eli Lilly, Genentech, Gilead Sciences, Inc., Merck, Mersana, Novartis, Pfizer, and Sanofi; honoraria from AstraZeneca/Daiichi Sankyo, Eli Lilly, Genentech, Gilead Sciences, Inc., Menarini, Merck, Novartis, Pfizer, and Sanofi; consulting or advisory roles with AstraZeneca/Daiichi Sankyo, Eisai, Eli Lilly, Genentech, Gilead Sciences, Inc., Menarini, Merck, Mersana, Novartis, Pfizer, and Sanofi; and royalties from UpToDate.

REFRENCES

1. International Agency for Research on Cancer. Global cancer observatory: cancer today. Available at https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf. Accessed May 16, 2025.
2. Allison KH, Hammond MEH, Dowsett M, et al. Estrogen and progesterone receptor testing in breast cancer: ASCO/CAP guideline update. *J Clin Oncol*. 2020;38(12):1346-1366.
3. Wolff AC, Somerfield MR, Dowsett M, et al. Human epidermal growth factor receptor 2 testing in breast cancer. *Arch Pathol Lab Med*. 2023;147(9):993-1000.
4. Vaz-Gonçalves L, Marquart-Wilson L, Protani MM, et al. Capturing breast cancer subtypes in cancer registries: insights into real-world incidence and survival. *J Cancer Policy*. 2025;44:100567.
5. TRODELVY® (sacituzumab govitecan-hziy). Prescribing information. Foster City, CA: Gilead Sciences, Inc. Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/761115s059lbl.pdf. Accessed May 16, 2025.
6. TRODELVY® (sacituzumab govitecan-hziy). Summary of product characteristics. County Cork, Ireland: Gilead Sciences Ireland UC. Available at https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf. Accessed May 16, 2025.
7. Pharmaceuticals and Medical Devices Agency (Japan). List of approved drugs, April 2004 to December 2024. Available at https://www.pmda.go.jp/files/000274881.pdf. Accessed May 20, 2025.
8. Pharmaceutical Technology. Everest's Trodelvy receives approval for breast cancer in China. Available at https://www.pharmaceutical-technology.com/news/everest-trodelvy-breast-cancer/?cf-view. Accessed May 20, 2025.
9. Chang M. Gilead's Trodelvy approved for metastatic triple-negative breast cancer in Korea. Korea Biomedical Review. Available at https://www.koreabiomed.com/news/articleView.html?idxno=21060. Accessed May 20, 2025.
10. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med*. 2021;384(16):1529-1541.
11. Rugo HS, Bardia A, Marmé F, et al. Sacituzumab govitecan in hormone receptor-positive/human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol*. 2022;40(29):3365-3376.
12. Rugo HS, Bardia A, Marmé F, et al. Overall survival with sacituzumab govitecan in hormone receptor-positive and human epidermal growth factor receptor 2-negative metastatic breast cancer (TROPiCS-02): a randomised, open-label, multicentre, phase 3 trial. *Lancet*. 2023;402(10411):1423-1433.
13. Xu B, Wang S, Yan M, et al. Sacituzumab govitecan in HR+HER2- metastatic breast cancer: the randomized phase 3 EVER-132-002 trial. *Nat Med*. 2024;30(12):3709-3716.
14. Xu B, Ma F, Wang T, et al. A phase IIb, single arm, multicenter trial of sacituzumab govitecan in Chinese patients with metastatic triple-negative breast cancer who received at least two prior treatments. *Int J Cancer*. 2023;152(10):2134-2144.
15. Zhang J, Yang Y, Chen R, et al. Assessment of racial differences in the incidence of thrombocytopenia induced by trastuzumab emtansine: a systematic review and meta-analysis. *Ann Transl Med*. 2021;9(14):1139.
16. Vlachou E, Mamtani R, Hahn NM, Iii BJ, Hoffman-Censits J, Nimgaonkar V. Racial differences in cutaneous events among patients receiving enfortumab vedotin. *Clin Genitourin Cancer*. 2024;22(3):102090.
17. Goldenberg DM, Cardillo TM, Govindan SV, Rossi EA, Sharkey RM. Trop-2 is a novel target for solid cancer therapy with sacituzumab govitecan (IMMU-132), an antibody-drug conjugate (ADC). *Oncotarget*. 2015;6(26):22496-22512.
18. Ocean AJ, Starodub AN, Bardia A, et al. Sacituzumab govitecan (IMMU-132), an anti-Trop-2-SN-38 antibody-drug conjugate for the treatment of diverse epithelial cancers: safety and pharmacokinetics. *Cancer*. 2017;123(19):3843-3854.
19. Dean L. Irinotecan therapy and UGT1A1 genotype. In: Pratt VM, Scott SA, Pirmohamed M, Esquivel B, Kattman BL, Malheiro AJ, editors. *Medical Genetics Summaries*. Bethesda (MD): National Center for Biotechnology Information (US); 2012.
20. Takano M, Sugiyama T. UGT1A1 polymorphisms in cancer: impact on irinotecan treatment. *Pharmgenomics Pers Med*. 2017;10:61-68.
21. Liu X, Cheng D, Kuang Q, Liu G, Xu W. Association of UGT1A1*28 polymorphisms with irinotecan-induced toxicities in colorectal cancer: a meta-analysis in Caucasians. *Pharmacogenomics J*. 2014;14(2):120-129.
22. Rugo HS, Tolaney SM, Loirat D, et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. *NPJ Breast Cancer*. 2022;8(1):98.
23. Rugo HS, Tolaney SM, Bardia A, et al. Pooled safety analysis of sacituzumab govitecan (SG) in multiple solid tumor types. *J Clin Oncol*. 2024;42(suppl 16):3029.
24. Atasilp C, Biswas M, Jinda P, et al. Association of UGT1A1*6, UGT1A1*28, or ABCC2 c.3972C>T genetic polymorphisms with

irinotecan-induced toxicity in Asian cancer patients: meta-analysis. *Clin Transl Sci*. 2022;15(7):1613-1633.
25. Nelson RS, Seligson ND, Bottiglieri S, et al. *UGT1A1* guided cancer therapy: review of the evidence and considerations for clinical implementation. *Cancers (Basel)*. 2021;13(7):1566.
26. Bardia A, Mayer IA, Vahdat LT, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. *N Engl J Med*. 2019;380(8):741-751.
27. Naito Y, Nakamura S, Kawaguchi-Sakita N, et al. Preliminary results from ASCENT-J02: a phase 1/2 study of sacituzumab govitecan in Japanese patients with advanced solid tumors. *Int J Clin Oncol*. 2024;29(11):1684-1695.
28. Bardia A, Messersmith WA, Kio EA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. *Ann Oncol*. 2021;32(6):746-756.
29. Komorowski AL, Kruczala M. Does ethnicity matter in chemotherapy for breast cancer? *Gland Surg*. 2020;9(5):1165-1166.
30. Kenmotsu H, Tanigawara Y. Pharmacokinetics, dynamics and toxicity of docetaxel: why the Japanese dose differs from the Western dose. *Cancer Sci*. 2015;106(5):497-504.
31. Hu ZY, Yu Q, Zhao YS. Dose-dependent association between UGT1A1*28 polymorphism and irinotecan-induced diarrhoea: a meta-analysis. *Eur J Cancer*. 2010;46(10):1856-1865.
32. Cheng L, Li M, Hu J, et al. UGT1A1*6 polymorphisms are correlated with irinotecan-induced toxicity: a system review and meta-analysis in Asians. *Cancer Chemother Pharmacol*. 2014;73(3):551-560.
33. Han FF, Guo CL, Yu D, et al. Associations between UGT1A1*6 or UGT1A1*6/*28 polymorphisms and irinotecan-induced neutropenia in Asian cancer patients. *Cancer Chemother Pharmacol*. 2014;73(4):779-788.
34. Gammal RS, Court MH, Haidar CE, et al. Clinical pharmacogenetics implementation consortium (CPIC) guideline for UGT1A1 and atazanavir prescribing. *Clin Pharmacol Ther*. 2016;99(4):363-369.
35. Gupta E, Lestingi TM, Mick R, Ramirez J, Vokes EE, Ratain MJ. Metabolic fate of irinotecan in humans: correlation of glucuronidation with diarrhea. *Cancer Res*. 1994;54(14):3723-3725.