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Original Research

Safety and effectiveness of sacituzumab govitecan in patients with metastatic triple-negative breast cancer in real-world settings: first observations from an interdisciplinary breast cancer centre in Germany

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Abstract

Background: Sacituzumab govitecan has been recently approved by the USFDA and EMA for the treatment of patients with metastatic triple-negative breast cancer (mTNBC). We report real-world safety and effectiveness in patients with mTNBC receiving sacituzumab govitecan treatment at a breast cancer centre in Germany.

Methods: Data from patients who had received sacituzumab govitecan as treatment for mTNBC, in both *de novo* and relapsed disease, at the Kliniken Essen-Mitte, Essen, Germany, were collected through institutional records. Data were analysed for safety parameters and survival outcomes and reported using descriptive statistics.

Results: Patients ($N=43$) received a median (range) of 5 (1–28) cycles of sacituzumab govitecan and were followed up for a median of 12.9 months. The most reported adverse events (AEs) of any grade were alopecia ($n=39$; 90.7%), diarrhoea ($n=16$; 37.2%), fatigue ($n=15$, 34.9%), anaemia ($n=15$, 34.9%) and neutropenia ($n=14$, 32.6%). AEs $\geqslant$ Grade 3 with the highest incidence were neutropenia ($n=12$; 27.9%) and diarrhoea ($n=8$; 18.6%). In eight (18.6%) patients, dose of sacituzumab govitecan dose was reduced due to patients' clinical condition prior to commencing treatment; in further 17 (39.5%) patients, sacituzumab govitecan dose had to be reduced or treatment interrupted on account of AEs associated with the drug after treatment had commenced. Median progression-free survival and median overall survival were calculated to be 5.0and 13.1 months, respectively.

Conclusion: The real-world safety and effectiveness profile of sacituzumab govitecan in patients with mTNBC are in line with clinical trial data. Further studies are required to guide optimal use of sacituzumab govitecan against mTNBC, especially in context of management of accompanying AEs.

Keywords: effectiveness, metastatic, real-world evidence, sacituzumab govitecan, safety, triple-negative breast cancer

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Introduction

The recent advances and accompanying improvement in outcomes in the management of metastatic breast cancer (mBC) have not adequately translated to metastatic triple-negative breast cancer (mTNBC). In general, patients with mTNBC have a poorer prognosis in comparison to patients with other breast cancer subtypes due to earlier relapse and shorter survival,[1–3] thereby making therapy improvement an unmet medical

need. At present, the mainstay of mTNBC treatment is chemotherapy – current guidelines recommend single-agent chemotherapy in mTNBC patients with a possibility to escalate to the use of multiple agents when progressive disease resulting in organ failure is suspected.[4–6]

There has been a noticeable shift in the paradigm in the treatment of mTNBC in recent years. The understanding of the interaction between the cancer cell and the host's immune system *via* the expression of programmed cell death protein 1 (PD-1) or programmed death ligand 1 (PD-L1) on tumours, or the role of germline or somatic mutations in the BReast CAncer genes 1 and 2 (*BRCA1*/*BRCA2*), have allowed the use of immune-oncologic agents such as the PD-1 inhibitor pembrolizumab,[7,8] or the PD-L1 inhibitor atezolizumab,[9] and the poly-ADP ribose polymerase inhibitors olaparib[10–12] and talazoparib[13] in a subset of mTNBC patients. A novel strategy in targeted anticancer drug design that is fast gaining attention is the antibody–-drug conjugate (ADC).[14] With this approach, antibodies specific to tumour antigens are linked to potent cytotoxic drugs with the intention of delivering chemotherapeutic agents specifically to the tumour site in anticipation of a better response rate. In addition, it is expected that ADCs will reduce the incidence and severity of systemic side effects, which usually are a limiting factor in the use of cytotoxic chemotherapeutic agents.

Sacituzumab govitecan is an ADC comprising sacituzumab, an antibody against trophoblast cell-surface (Trop-2) antigen, which is expressed in approximately 90% of TNBC tumours,[15] and govitecan, an active metabolite of irinotecan, a topoisomerase 1 inhibitor, which hinders DNA replication and leads to cell death,[16] conjugated through a hydrolysable linker. The phase I/II IMMU-132 trial showed promising results with sacituzumab govitecan treatment in mTNBC patients refractory to at least two previous lines of chemotherapy.[15,17,18] Briefly, the objective response rate (ORR), median progression-free survival (mPFS) and median overall survival (mOS) were calculated to be 33.3%, 5.5 months and 13.0 months, respectively. The phase III ASCENT trial on 529 patients compared sacituzumab govitecan to single-agent chemotherapy with eribulin, capecitabine, vinorelbine or gemcitabine, depending on the investigators' choice.[19] Results from the ASCENT trial demonstrated a substantial improvement with sacituzumab govitecan in comparison with single-agent chemotherapy on ORR (35.0% *versus* 5.0%), mPFS [5.6 months *versus* 1.7 months; hazard ratio (HR): 0.41, 95% confidence interval (CI): 0.32–0.52, $p < 0.001$] and mOS (12.1 months *versus* 6.7 months; HR: 0.48, 95% CI: 0.38–0.59, $p < 0.001$).

At present, sacituzumab govitecan has been approved for the treatment of unresectable locally advanced TNBC and mTNBC by the United States Food & Drugs Administration[20] and the European Medicines Agency.[21] In addition, sacituzumab govitecan is being investigated in other combinations and settings. Data from the ASCENT trial has been subjected to further *post hoc* analysis to identify the role of biomarkers[22] and initial subtype of mTNBC[23] on effectiveness of sacituzumab govitecan; the appropriate line of sacituzumab govitecan treatment[24] in mTNBC; and health-related quality of life parameters following sacituzumab govitecan treatment.[25,26] Sacituzumab govitecan has also demonstrated potential for the treatment of patients with other mBC receptor subtypes – results from a phase I/II trial[27] and the most recent phase III TROPiCS-02 trial[28] showed a substantial improvement in PFS and OS in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative (HR+ HER2−) mBC. The phase III SASCIA trial was designed to compare the invasive disease-free survival in HER2− early breast cancer patients at a high risk of relapse following neoadjuvant therapy, receiving either sacituzumab govitecan or the treatment of physicians' choice in the adjuvant setting.[29]

Although these results are promising, it is equally important to ascertain whether the safety and effectiveness of sacituzumab govitecan is successfully translated in real-world settings where a diverse patient population that is at the least partially outside trial eligibility exists. Here, we present analysis of real-world data collected from mTNBC patients who underwent treatment with sacituzumab govitecan at a large breast cancer centre in Germany.

Methods

Data collection and curation

Data were collected from patients receiving sacituzumab govitecan treatment at the Interdisciplinary Breast Unit of Kliniken Essen-Mitte (KEM; Essen, Germany) in between October 2020 and April 2023. Prior to receiving marketing approval in

Germany, sacituzumab govitecan was available upon request as an investigational medicinal product under compassionate use in mTNBC. Patient eligibility criteria for receiving sacituzumab govitecan under this programme are given in Supplemental Table 1. These criteria were continued for identifying patient eligibility even post-approval. In all matters, patients were treated as per institutional protocols, established guidelines,[30] and standard-of-care in the management of TNBC. A dose reduction strategy for sacituzumab govitecan, when needed, followed the product information sheet available commercially in the European Union[31] and involved a sequential lowering of dose from the recommended 10.0 mg/kg to 7.5 mg/kg first and then to 5.0 mg/kg. Granulocyte colony stimulating factor (GCSF) prophylaxis was not given primarily to all patients receiving sacituzumab govitecan but when indicated according to adverse events (AEs) or pre-existing risk factors for neutropenia or febrile neutropenia.

Data collected were from patients >18 years of age, with a histologically confirmed diagnosis of mTNBC (*de novo* or relapsed disease) that was refractory to at least one previous line of standard-of-care chemotherapy in the metastatic setting. Data from patients receiving sacituzumab govitecan in a clinical trial setting were excluded.

In our analysis, AEs were classified according to NCI-CTCAE v.5 and efficacy through RECIST v.1.1.

Patient consent was obtained prior to sacituzumab govitecan treatment under the compassionate use programme, and as per routine institutional procedure after sacituzumab govitecan had received approval for the treatment of mTNBC in Germany. However, specific consent for retrospective analysis of anonymized patient data was not required according to local institutional ethics committee (Ärztekammer Nordrhein, Düsseldorf, Germany) and national regulations.

Statistical analysis

Descriptive statistics were used to summarize data from patients. This includes frequency and percentages for categorical variables and median and range for continuous variables.

The Kaplan–Meier (KM) survival analysis was conducted to calculate PFS and OS. Given the small cohort, 95% CI were also calculated for the KM estimates. PFS was defined as the length of time from commencing sacituzumab govitecan treatment to first detection of progressive disease or death from any cause. OS was defined as the length of time from commencing sacituzumab govitecan treatment to death from any cause.

Results

Patient characteristics

Data from 43 eligible patients who received sacituzumab govitecan treatment for mTNBC prior to approval and following approval in Germany were included in our analyses. The treatment period with sacituzumab govitecan for the cohort was between October 2020 and April 2023 with a median (range) follow-up of 12.9 (6.6–19.2) months. The median (range) age at diagnosis was 50 (24–65) (Table 1). At presentation, eight (18.6%) patients were diagnosed with *de novo* metastatic disease. The immunohistochemical subtype of primary tumours were confirmed to be triple negative in 23 (53.5%) patients, whereas those in 14 (32.5%) and 6 (13.9%) patients were identified as HR+ HER2− and HER2+, respectively. Subtype conversion to triple negative in the metastatic setting was confirmed immunohistochemically in all patients who received sacituzumab govitecan treatment and had tumour biology other than triple negative in the *de novo* setting.

Treatment regimens employed for the management of patients in the non-metastatic setting ($N=35$) were surgery to the breast including breast conservation surgery and/or lymph node/s excision ($n=34$, 97.1%), radiotherapy ($n=26$, 74.3%), neoadjuvant chemotherapy ($n=23$, 65.7%), endocrine therapy ($n=12$, 34.2%) and adjuvant chemotherapy ($n=9$, 25.7%). In addition, in the primary (*de novo*) metastatic setting ($N=8$) the majority of the patients received chemotherapy ($n=7$, 87.5%).

A total of 36 (83.7%) patients had visceral metastasis with a median (range) of 3 (1–9) sites of metastasis. The most common site of metastasis was lymph node ($n=30$), followed by bone ($n=22$), lung ($n=22$) and liver ($n=22$) (Table 1).

The most administered systemic chemotherapeutic agents in the metastatic setting prior to sacituzumab govitecan treatment were taxanes ($n=38$),

Table 1. Patient characteristics.

Characteristic	*N* = 43
Age in years, median (min, max)	
At diagnosis	50 (24, 65)
At starting SG therapy	57 (32, 76)
TNM classification at diagnosis	
M1	8 (18.6%)
M0N+	21 (48.8%)
M0N0T1	6 (13.9%)
M0N0T2–3	8 (18.6%)
PFS (M0) months, median (min, max)	23.5 (5–340)
Receptor status of primary tumour	
HR-positive	14 (32.5%)
HER2-positive	6* (13.9%)
TNBC	23** (53.5%)
Primary treatment (M0)	35
Breast conservation surgery	24 (68.6%)
Mastectomy	10 (28.4%)
No surgery	1 (2.9%)
Endocrine therapy	12 (34.2%)
Neoadjuvant chemotherapy	23 (65.7%)
Adjuvant chemotherapy	9 (25.7%)
Radiotherapy	26 (74.3%)
Primary treatment (M1)	8
Breast conservation surgery	2 (25%)
Mastectomy	2 (25%)
No surgery	4 (50%)
Endocrine therapy	4 (50%)
Chemotherapy	7 (87.5%)
Patients with visceral metastasis, *n* (%)	36 (83.7%)
Number of sites of metastasis, median (range)	3 (1–9)
Site of metastasis, *n* (%)	
Lymph node	30 (69.8%)
Bone	22 (51.2%)
Lung	22 (51.2%)
Liver	22 (51.2%)
Skin	13 (30.2%)
Brain	10 (23.2%)
Pleura	7 (16.3%)
Peritoneum	4 (9.3%)
Adrenal	2 (4.6%)
Other	4 (9.3%)
Treatment in metastatic setting prior to commencing sacituzumab govitecan, *n* (%)	
Taxane	38
Platinum agents	27
Eribulin	13
Gemcitabine	14
Capecitabine	10
Aromatase inhibitors	7
Other systemic chemotherapy	7
Targeted therapy	
PD-1/PD-L1 inhibitor	18
CDK4/6 inhibitor	8
mTOR inhibitor	3
PARP inhibitor	4
VEGF inhibitor	8
Median (range) lines of treatment in metastatic setting prior to commencing sacituzumab govitecan	2 (1–6)
SG line of treatment, *n* (%)	
1	–
2	17

(Continued)

Table 1. (Continued)

Characteristic	*N* = 43
3	12
4	6
⩾5	8
Number of SG cycles administered, median (range)	5 (1–28)
AEs leading to dose reduction and/or treatment interruption, *n* (%)	17 (39.5)†
AEs leading to treatment discontinuation, *n* (%)	3 (7.0)

*HER2 status in one patient unknown.
**Progesterone receptor status in one patient unknown.
†Not including patients in whom sacituzumab govitecan dose was reduced prior to commencement of sacituzumab govitecan treatment according to clinical judgement.
ADR, adrenal; AE, adverse event; CDK4, cyclin-dependent kinase 4; ER, oestrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; mTOR, mammalian target of rapamycin; PARP, poly-adenosine diphosphate ribose polymerase; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PER, peritoneum; SG, sacituzumab govitecan; TNBC, triple-negative breast cancer; TNM, Tumour-Node-Metastasis; VEGF, vascular endothelial growth factor.

platinum agents ($n = 27$), gemcitabine ($n = 14$) and eribulin ($n = 11$). PD-1/PD-L1 inhibitors ($n = 18$) were the most commonly employed targeted therapy.

Sacituzumab govitecan regimen

Sacituzumab govitecan was administered at the recommended dose of 10 mg/kg on day 1 and day 8 of a 21-day cycle to all except eight (18.6%) patients in whom the initial dose was decreased to 7.5 mg/kg out of clinical judgement. In majority of patients ($n = 17$, 39.5%), sacituzumab govitecan was used in the second line (range: 2–7) with a median (range) duration of exposure of 3.1 (0.03–23.3) months and a median (range) of 5 (1–28) cycles administered (Table 1).

Safety and effectiveness of sacituzumab govitecan regimen

The onset of AEs occurred at any timepoint along the course of the sacituzumab govitecan administration but was more commonly reported during the first couple of cycles. The most frequently reported AE following sacituzumab govitecan treatment was Grade 1/2 alopecia ($n = 39$, 90.7%) (Figure 1). Although patients were offered the choice of using a cold cap for management of alopecia, only five (11.6%) patients opted for it but without any benefit in lessening the severity of alopecia. Neutropenia was reported in 14 (32.6%) patients; this was classified as ⩾Grade 3 in 12 (27.9%) patients. Short-acting prophylaxis with GCSF on days 2, 3 and 4 was used in 11 (25.6%) patients for primary prophylaxis as they were judged to be at a high risk for developing neutropenia due to incidences of prior febrile neutropenia following previous chemotherapeutic regimens. Patients experiencing ⩾Grade 3 neutropenia or febrile neutropenia received secondary short-acting GCSF prophylaxis ($n = 4$, 9.3%) on days 2, 3 and 4 and then days 9, 10 and 11 of the sacituzumab govitecan cycle (q21d). Febrile neutropenia following sacituzumab govitecan treatment was reported in two (4.7%) patients. Other commonly reported AEs include diarrhoea (Grade 1–3; $n = 16$, 37.2%), fatigue (Grade 1–3; $n = 15$, 34.9%) and anaemia ($n = 15$, 34.9%). Diarrhoea was more commonly reported during the first cycle after day 8 and was managed with the anti-diarrhoeal agent loperamide, 4 mg initially followed by 2 mg for every episode of diarrhoea (maximum 16 mg/day). No incidence of diarrhoea was clinically judged to be attributable to cholinergic syndrome.

A total of 18 (41.9%) patients were hospitalized; in 10 (23.3%) of these patients, hospitalization was judged to be due to the AEs resulting from sacituzumab govitecan treatment. Although we could not discern any specific pattern of correlation between incidence and severity of neutropenia, diarrhoea and fatigue by patient age, in general these AEs were more common and severe in older patients (Figure 2).

The recommended dose of sacituzumab govitecan – 10 mg/kg – was reduced as directed in eight (18.6%) patients prior to commencement of treatment out of physicians' clinical judgement and in 13 (30.2%) patients after start of treatment due to AEs associated with sacituzumab govitecan regimen. Dose reduction and/or treatment interruption due to AEs was experienced in a total of 17 (39.5%) patients. The main AE leading to a dose reduction or treatment interruption was diarrhoea (Grade 3; $n = 7$; 16.3%). Furthermore, sacituzumab govitecan treatment was discontinued in three (7.0%) patients due to

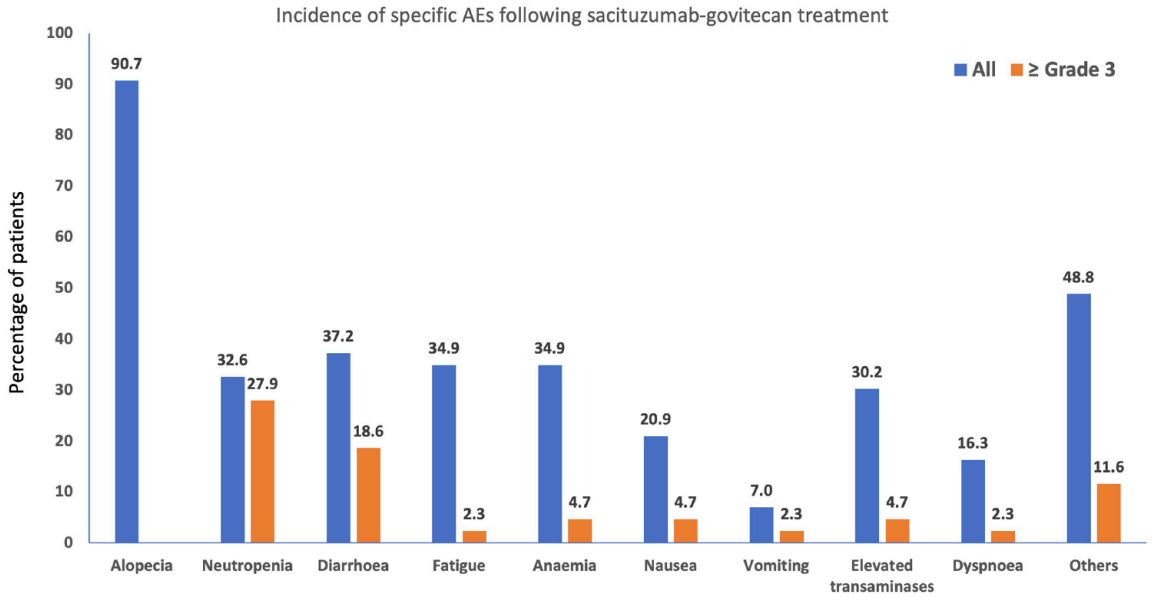

Figure 1. Proportion of patients reporting adverse events.
Adverse events were categorized according to NCI-CTCAE v.5 criteria. For alopecia, all patients had Grade 2 which is the most severe category (⩾50% hair loss).

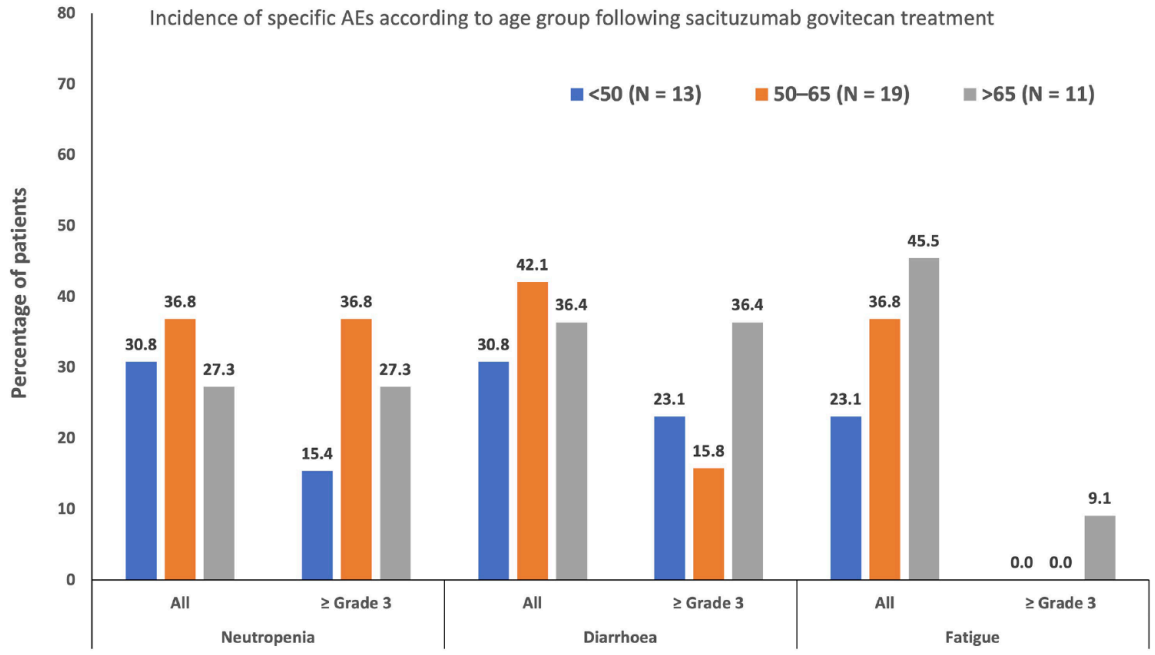

Figure 2. Incidence of adverse events according to age groups.
Adverse events were categorized according to NCI-CTCAE v.5 criteria.

multiple side effects related to sacituzumab govitecan treatment, mainly febrile neutropenia.

Eight (18.6%) deaths were reported in our cohort; however, all of these were judged to be a result of progressive disease and without any perceptible relation to sacituzumab govitecan treatment.

The KM survival analysis showed a mPFS of 5.0 months and a 1-year PFS rate of 18.2%

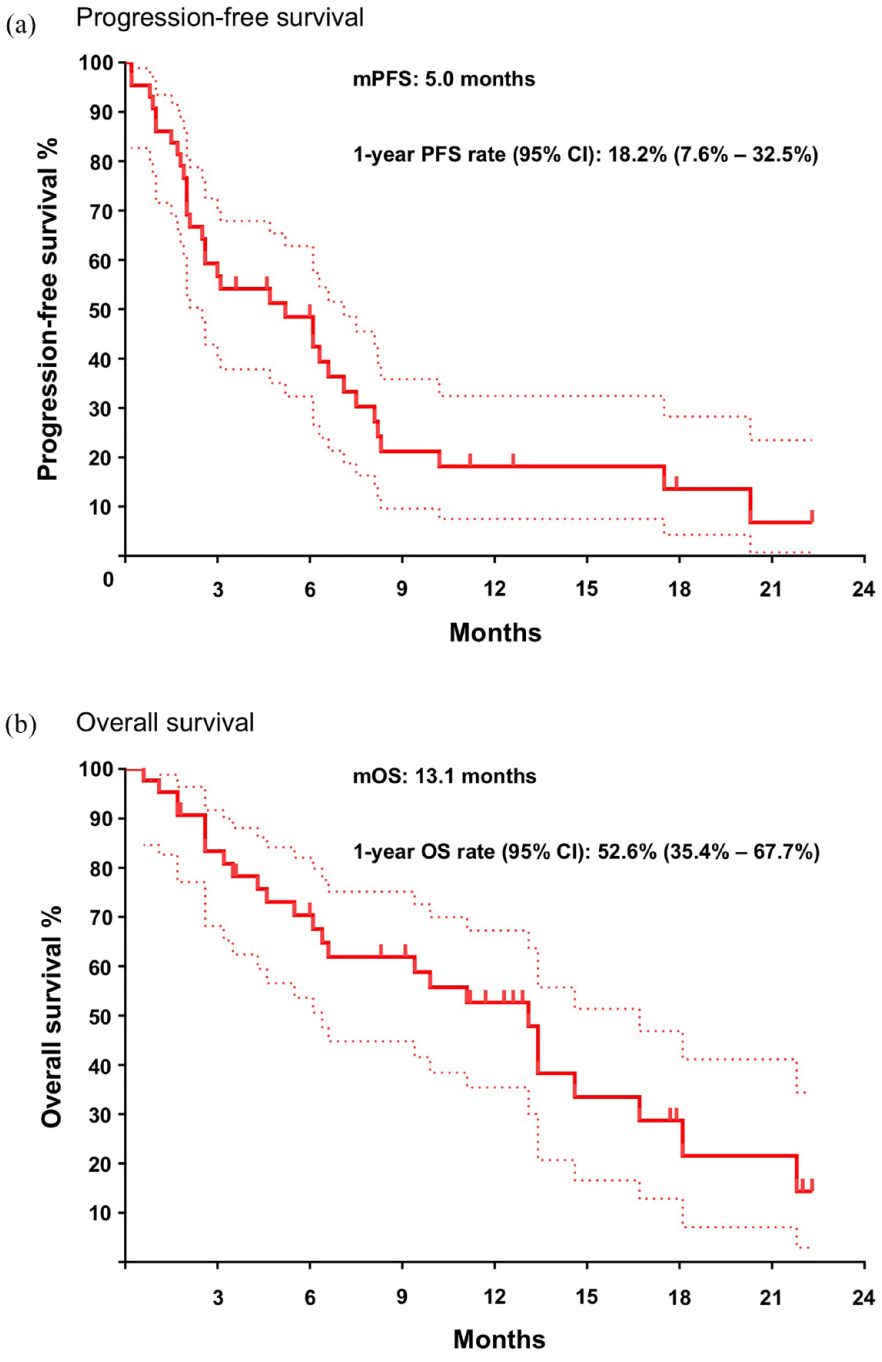

Figure 3. Progression-free survival (a) and overall survival (b) in patients.
Dotted lines represent 95% CI.
CI, confidence interval; OS, overall survival; PFS, progression-free survival.

(95% CI: 7.6–32.5) [Figure 3(a)]. Furthermore, mOS was calculated to be 13.1 months with a 1-year OS rate of 52.6% (95% CI: 35.4–67.7) [Figure 3(b)].

Discussion

Following our recent and growing experience with this new drug, we report that sacituzumab govitecan has a manageable safety profile with

acceptable survival outcomes in mTNBC patients whose metastatic disease is refractory to other lines of single-agent or combination chemotherapy. To the best of our knowledge, this is the first report from real-world settings and reflects the results from clinical trials on sacituzumab govitecan in mTNBC.

The most commonly reported AEs of any grade following sacituzumab treatment in the IMMU-132 trial ($N = 108$) were nausea (88.7%), neutropenia (63.9%), diarrhoea (62.0%), fatigue (54.6%), anaemia (50.0%) and vomiting (49.1%).[17] Similarly, in the sacituzumab govitecan treatment arm of the ASCENT trial ($N = 258$) the most frequently observed AEs of any grade were neutropenia (63.2%), diarrhoea (59.3%), nausea (57.0%), alopecia (46.1%), fatigue (44.6%) and anaemia (34.5%).[19] A similar toxicity profile was also reported for the sacituzumab govitecan arm in a recent interim safety analysis of the SASCIA trial; the commonly reported AEs were neutropenia (87.2%), anaemia (80.0%), alopecia (68.9%), nausea (60.0%) and diarrhoea (46.7%).[32] There was also a substantially large incidence of leucopenia in the sacituzumab govitecan arm of the SASCIA trial – 97.8% – which was not previously observed. Also, the trial population of the adjuvant SASCIA trial was different; in that, they presented with a primary HER2− breast cancer at a high risk of relapse after neoadjuvant chemotherapy. The type and incidence of AEs in our real-world analysis are in line with observations from these clinical trials – diarrhoea (37.2%), fatigue (34.9%), anaemia (34.9%) and neutropenia (32.6%) (Table 2). More importantly, we did not find any new signals of toxicity arising from sacituzumab govitecan treatment. A similar pattern was evident in context of AEs ⩾ Grade 3 when comparing our cohort to that in the clinical trials (Table 2).

Table 2. Comparison of the incidence of adverse events in the KEM cohort with that reported in the IMMU-132 and ASCENT clinical trials.

Adverse event	KEM ($N = 43$)	IMMU-132[17] ($N = 108$)	ASCENT[19] ($N = 258$)
Alopecia			
Any*	39 (90.7)	39 (36.1)	119 (46.1)
Diarrhoea			
Any	16 (37.2)	67 (62.0)	153 (59.3)
⩾Grade 3	8 (18.6)	9 (8.3)	27 (10.5)
Fatigue			
Any	15 (34.9)	59 (54.6)**	115 (44.6)
⩾Grade 3	1 (2.3)	9 (8.3)**	8 (3.1)
Anaemia			
Any	15 (34.9)	54 (50.0)	89 (34.5)
⩾Grade 3	2 (4.6)	12 (11.1)	20 (7.8)
Neutropenia			
Any	14 (32.6)	69 (63.9)	163 (63.2)
⩾Grade 3	12 (27.9)	45 (41.7)	132 (51.2)
Nausea			
Any	9 (20.9)	72 (66.7)	147 (57.0)
⩾Grade 3	2 (4.6)	7 (6.5)	7 (2.7)
Vomiting			
Any	4 (9.3)	53 (49.1)	75 (29.1)
⩾Grade 3	1 (2.3)	7 (6.5)	3 (1.2)

*For alopecia, all patients had Grade 2 which is the most severe category (⩾50% hair loss).
**Includes asthenia cases.
KEM, Kliniken Essen-Mitte.

However, there were a few disparities; the foremost being in the incidence of alopecia. Although the incidence of alopecia in the ASCENT and IMMU-132 trials was 46.1% and 36.1%, respectively,[17,19] we noted an incidence of 90.7%, well over these previously reported values and all cases with the highest level of severity (Grade 2; ⩾50% hair loss) for alopecia. The other AE that followed a pattern discordant to the clinical trials was diarrhoea. Although the incidence of any grade diarrhoea was higher in clinical trials, the relative incidence of ⩾Grade 3 diarrhoea was substantially higher in our cohort. In addition, diarrhoea, when it occurred, happened mostly during the first two cycles of treatment. The incidence of nausea and vomiting was also much lower in our analysis when compared to the clinical trials (Table 2).

In line with findings from the clinical trials, AEs continue to form a substantial concern with the use of sacituzumab govitecan in real-world settings. In the IMMU-132 trial, with a neutropenic incidence of 63.9%, treatment was interrupted in 44.4% of the patients due to AEs, the most

frequent being neutropenia, although no dose reduction or treatment cessation was reported.[17] In the ASCENT trial, the incidence of neutropenia and Grade ⩾3 febrile neutropenia was 63.2% and 6.0%, respectively, and sacituzumab govitecan dose had to lowered or treatment terminated in 22.0% and 4.7% of the patients, respectively, due to AEs.[19] In our analysis, sacituzumab dose had to be reduced or treatment interrupted in 39.5% and treatment discontinued in 7.0% of the patients, respectively, due to AEs; diarrhoea being the major reason. Neutropenic patients in the ASCENT trial were managed by dose reduction and/or treatment delay, and GCSF prophylaxis was administered to 49.0% of the patients when deemed necessary by the investigator. At KEM, GCSF is not given primarily to all patients receiving sacituzumab govitecan but is indicated accordingly for neutropenia or febrile neutropenia or when pre-existing risk factors for these exist. There is a wide debate whether GCSF should be given primarily; however, there is no consensus at present due to lack of robust evidence advocating for it. The primary objective of the phase II PRIMED clinical trial (NCT05520723)[33] is to ascertain whether combining GCSF with other agents such as loperamide during sacituzumab govitecan treatment improves the tolerability of the latter.

The management of alopecia in patients receiving sacituzumab govitecan is still undefined. In our experience, the use of a cold cap does not substantially ameliorate the severity of alopecia, and the majority of our patients prefer to not use it. Although alopecia could be due to altered pharmacokinetics, that is, slower clearance of irinotecan due to polymorphism in the *UGT1A1* gene,[34] which encodes the enzyme involved in metabolism of irinotecan, we tested only a small subset of our patients and hence could not establish an aetiology for the high incidence of any grade or severity of alopecia in our patients. With regard to diarrhoea, patients need to be informed about the likelihood of experiencing any grade of diarrhoea while receiving sacituzumab govitecan treatment. In addition, based on our experience, a standardized therapeutic regimen with loperamide – 4 mg at the first instance of diarrhoea and 2 mg thereafter for every episode of diarrhoea, for a maximum of 16 mg/day – should be advised to all qualifying patients when commencing sacituzumab govitecan treatment. As stated previously, the incidence of nausea was substantially lower in our patients in comparison to that in clinical trials. In the ASCENT trial, nausea and vomiting were managed using a two- to three-drug combination of dexamethasone plus a 5HT3 antagonist, e.g. ondansetron or neurokinin-1 receptor antagonist, e.g. aprepitant. At KEM, all patients received netupitant and palonosetron 1 h after sacituzumab govitecan administration. In addition, patients were also premedicated with cimetidine and clemastine according to institutional protocol. The use of agents as prophylaxis to either curtail or ameliorate the more serious side effects of sacituzumab govitecan is of particular interest.

In clinical trials, sacituzumab govitecan has demonstrated high efficacy. In the IMMU-132 trial, the ORR was found to be 33.3% including complete response in three patients.[17] The clinical benefit rate, including stable disease for >6 months was 45.4%. The mPFS was calculated as 5.5 months with an estimated 1-year PFS rate of 15.1%. Similarly, the mOS was calculated to be 13.0 months with an estimated 1-year OS rate of 51.3%. Efficacy in the ASCENT trial was conducted mainly on study patients without brain metastases but also included overall efficacy evaluation.[19] In patients without brain metastases who were in the sacituzumab govitecan arm ($N = 235$), mPFS was determined to be 5.6 months (95% CI: 4.3–6.3), mOS to be 12.1 months (95% CI: 10.7–14.0) and an ORR of 35.0%. In the entire sacituzumab govitecan arms of the study ($N = 267$), mPFS and mOS were 4.8 months (95% CI: 4.1–5.8) and 11.8 months (95% CI: 10.5–13.8), respectively. We observe a similar trend in our cohort; the mPFS in our patients was 5.0 months with a 1-year PFS rate of 18.2%. Similarly, the mOS in our cohort was 13.1 months with a 1-year OS rate of 52.6%. However, these results need to be interpreted with caution given the differences in the conditions of clinical trials and real-world practice and their impact on the results of survival analysis. For instance, patients in the IMMU-132 and ASCENT trials had received two or more previous lines of chemotherapeutic regimens prior to commencing sacituzumab govitecan treatment; in our analysis, the median line of treatment with sacituzumab govitecan was second. With regard to staging intervals, the institutional practice at KEM is to stage patients every 12 weeks. In comparison, in the IMMU-132 and ASCENT trials, patients were evaluated every 6 weeks at least during the early period of sacituzumab govitecan treatment. We also add here that at the time of survival

analysis a total of nine patients in our cohort had developed brain metastases.

The limitations of our study are the small sample size, owing to collection of data from a single centre, despite summarizing safety information of sacituzumab govitecan treatment even prior to approval in Germany. Potentially interesting subgroup analysis were therefore not deemed appropriate. In addition, our analysis was retrospective by nature. Moreover, our analysis does not compare sacituzumab with standard-of-care chemotherapy thereby preventing us from assessing whether sacituzumab govitecan is better than currently used agents. Despite these, our real-world observations on safety and survival outcomes are reflective of the experience from clinical trials and underline the importance of the medical exchange.

Conclusion

In conclusion, the safety profile and survival outcomes following the real-world use of sacituzumab govitecan appear to mirror the results from the IMMU-132 and ASCENT trials. Further data from clinical trials and post-approval registries are expected to identify appropriate patients who stand to benefit from sacituzumab govitecan therapy. Equally important for the treating physician will be to gain and share centre-specific experience in the optimal management of potential side effects that accompany the use of sacituzumab govitecan, especially since the indication for its use now also includes metastatic HR+HER2– breast cancer.[35] Data from the real-world settings are one major step in decreasing the incidence of potential side effects when offering new drugs to patients.

Declarations

Ethics approval and consent to participate

No specific consent was required since this was a retrospective analysis of anonymized patient data from hospital records.

Consent for publication

No specific consent for publication was required since this was a retrospective analysis of anonymized patient data from hospital records.

Author contributions

Mattea Reinisch: Conceptualization; Data curation; Investigation; Methodology; Project administration; Resources; Supervision; Validation; Visualization; Writing – review & editing.

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Jennifer Spoenlein: Data curation; Investigation; Writing – review & editing.

Satyendra Shenoy: Formal analysis; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Alexander Traut: Data curation; Formal analysis; Software; Validation; Writing – review & editing.

Hakima Harrach: Data curation; Investigation; Writing – review & editing.

Ouafaa Chiari: Data curation; Investigation; Writing – review & editing.

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Competing interests

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Availability of data and materials

Data supporting the findings of this study are available in Tables 1 and 2 and Figures 1 to 3. Drs. Reinisch, Bruzas and Spoenlein had full access to patient data. Dr. Reinisch and Mr. Traut took responsibility for the integrity of the data and data analysis.

Supplemental material

Supplemental material for this article is available online.

References

1. Dent R, Trudeau M, Pritchard KI, *et al*. Triple-negative breast cancer: clinical features and patterns of recurrence. *Clin Cancer Res* 2007; 13: 4429–4434.
2. Kassam F, Enright E, Dent R, *et al*. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. *Clin Breast Cancer* 2009; 9: 29–33.
3. den Brok WD, Speers CH, Gondara L, *et al*. Survival with metastatic breast cancer based on initial presentation, de novo versus relapsed. *Breast Cancer Res Treat* 2017; 161: 549–556.
4. National Comprehensive Cancer Network. NCCN Guidelines® breast cancer, version 4, https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (2022, accessed 01 August 2022).
5. Cardoso F, Paluch-Shimon S, Senkus E, *et al*. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). *Ann Oncol* 2020; 31: 1623–1649.
6. Korde LA, Somerfield MR, Carey LA, *et al*. Neoadjuvant chemotherapy, endocrine therapy, and targeted therapy for breast cancer: ASCO guideline. *J Clin Oncol* 2021; 39: 1485–1505.
7. Cortes J, Cescon DW, Rugo HS, *et al*. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controleed, double-blind, phase 3 clinical trial. *Lancet* 2020; 396: 1817–1828.
8. Cortes J, Rugo HS, Cescon DW, *et al*. Pembrolizumab plus chemotherapy in advanced triple-negative breast cancer. *N Engl J Med* 2022; 387: 217–226.
9. Schmid P, Adams S, Rugo HS, *et al*. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med* 2018; 379: 2108–2121.
10. Robson M, Im SA, Senkus E, *et al*. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017; 377: 523–533.
11. Tutt ANJ, Garber JE, Kaufman B, *et al*. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. *N Engl J Med* 2021; 384: 2394–2405.
12. Eikesdal HP, Yndestad S, Elzawahry A, *et al*. Olaparib monotherapy as primary treatment in unselected triple negative breast cancer. *Ann Oncol* 2021; 32: 240–249.
13. Litton JK, Rugo HS, Ettl J, *et al*. Talazoparib in patients with advanced breast cancer and a germline BRCA mutation. *N Engl J Med* 2018; 379: 753–763.
14. Nagayama A, Vidula N, Ellisen L, *et al*. Novel antibody-drug conjugates for triple negative breast cancer. *Ther Adv Med Oncol* 2020; 12: 1758835920915980.
15. Bardia A, Mayer IA, Diamond JR, *et al*. Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. *J Clin Oncol* 2017; 35: 2141–2148.
16. Pommier Y. DNA topoisomerase I inhibitors: chemistry, biology and interfacial inhibition. *Chem Rev* 2009; 109: 2894–2902
17. Bardia A, Mayer IA, Vahdat LT, *et al*. Sacituzumab govitecan-hziy in refractory

metastatic triple-negative breast cancer. *N Engl J Med* 2019; 380: 741–751.

18. 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: 746–756.
19. Bardia A, Hurvvitz SA, Tolaney SM, *et al.* Sacituzumab govitecan in metastatic triple-negative breast cancer. *N Engl J Med* 2021; 384: 1529–1541.
20. United States Food and Drug Administration. FDA grants regular approval to sacituzumab govitecan for triple-negative breast cancer, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-regular-approval-sacituzumab-govitecan-triple-negative-breast-cancer (2021, accessed 8 July 2022).
21. European Medicines Agency. Trodelvy, https://www.ema.europa.eu/en/medicines/human/EPAR/trodelvy#authorisation-details-section (2021, accessed 8 July 2022).
22. Bardia A, Tolaney SM, Punie K, *et al.* Biomarker analyses in the phase III ASCENT study of Sacituzumab govitecan versus chemotherapy in patients with metastatic triple-negative breast cancer. *Ann Oncol* 2021; 32: 1148–1156.
23. O'Shaughnessy J, Brufsky A, Rugo HS, *et al.* Analysis of patients without and with an initial triple-negative breast cancer diagnosis in thee phase 3 randomized ASCENT study of sacituzumab govitecan in metastatic triple-negative breast cancer. *Breast Cancer Res Treat* 2022; 195: 127–139.
24. Carey LA, Loirat D, Punie K, *et al.* Sacituzumab govitecan as second-line treatment for metastatic triple-negative breast cancer – phase 3 ASCENT study subanalysis. *NPJ Breast Cancer* 2022; 8: 72.
25. Loibl S, Loirat D, Tolaney SM, *et al.* Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. *Eur J Cancer* 2023; 178: 23–33.
26. Bardia A, Tolaney SM, Loirat D, *et al.* Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated, metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study. *J Clin Oncol* 2022; 40(16_Suppl): 1071.
27. Kalinsky K, Diamond JR, Vahdat LT, *et al.* Sacituzumab govitecan in previously treated hormone receptor-positive/HER2-negative metastatic breast cancer: final results from a phase I/II, single-arm, basket trial. *Ann Oncol* 2020; 31: 1709–1718.
28. 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: 3365–3376.
29. Marmé F, Stickeler E, Furlanetto J, *et al.* Phase III postneoadjuvant study evaluating sacituzumab govitecan, an antibody drug conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment: SASCIA. *J Clin Oncol* 2021; 39(15_Suppl): TPS602.
30. Schneeweis A, Fasching PA, Fehm T, *et al.* AGO algorithms fort he treatment of breast cancer: update 2021. *Geburtshilfe Frauenheilkd* 2021; 81: 1101–1111.
31. European Medicines Agency. Trodelvy, summary of product characteristics, https://www.ema.europa.eu/en/documents/product-information/trodelvy-epar-product-information_en.pdf (2022, accessed 1 January 2023).
32. Marmé F, Hanusch C, Furlanetto J, *et al.* Safety interim analysis of the phase III postneoadjuvant SASCIA study evaluating sacituzumab govitecan in patients with primary HER2-negative breast cancer at high relapse risk after neoadjuvant treatment. ESMO Breast Cancer, https://www.gbg.de/wAssets/docs/events-vortraege/2022/2022-ESMO-Breast-SASCIA-Safety-Interim-Analysis.pdf (2022, accessed 31 August 2022).
33. ClinicalTrials.gov. NCT05520723: Multicenter, open-label, single arm, phase II clinical trial to improve sacituzumab govitecan's tolerance inpatients with metastatic triple-negative breast cancer, https://clinicaltrials.gov/study/NCT05520723 (accessed 13 July 2023).
34. 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: 98.
35. U.S. Food & Drug Administration. FDA approves sacituzumab govitecan-hziy for HR-positive breast cancer, https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-sacituzumab-govitecan-hziy-hr-positive-breast-cancer (2023, accessed 13 July 2023).