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REVIEW

# The European Medicines Agency review of sacituzumab govitecan for the treatment of triple-negative breast cancer

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Sacituzumab govitecan (SG) is an antineoplastic agent which combines a humanized monoclonal antibody binding to trophoblast cell surface antigen-2 (Trop-2)-expressing cancer cells, linked with cytotoxic moiety SN-38 (govitecan) with topoisomerase I inhibitor action. On 22 November 2021, a marketing authorization valid through the European Union (EU) was issued under the European Medicines Agency (EMA)'s accelerated assessment program for SG as monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease. The assessment was based on results from an open-label, randomized, phase III trial to evaluate the safety, tolerability, pharmacokinetics and efficacy of SG versus treatment of physician's choice (TPC) in patients with mTNBC who received at least two prior treatments including at least one of them for advanced disease. The efficacy results in the overall population, based on mature data, showed a statistically significant improvement of SG over TPC in progression-free survival (PFS) and overall survival (OS). The median PFS was 4.8 months versus 1.7 months [hazard ratio (HR) = 0.43, $n = 529$; 95% CI 0.35-0.54; $P < 0.0001$] and the median OS was 11.8 months versus 6.9 months (HR = 0.51, $n = 529$; 95% CI 0.41-0.62; $P < 0.0001$). The most common (>30%) side effects of SG were diarrhea, neutropenia, nausea, fatigue, alopecia, anemia, constipation and vomiting. The aim of this manuscript is to summarize the scientific review of the application leading to regulatory approval in the EU.

**Key words:** EMA, TNBC, sacituzumab govitecan, ADC, Trop-2

## INTRODUCTION

Triple-negative breast cancer (TNBC), accounts for ~15% of invasive breast cancers.[1-4] TNBC is more common in ages <40 years, non-Hispanic black women and those bearing a breast cancer susceptibility gene (*BRCA*) mutation. Other risk factors for the disease include premenopausal status, obesity and maternal-related factors such as parity and age at first pregnancy.[3,5]

TNBC is defined by a lack of tumor cell expression of the estrogen receptor, progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2).[6] TNBC is associated with aggressive tumor biology, visceral metastases and a poor prognosis. Metastatic TNBC (mTNBC) is considered incurable.[7]

Targeted therapies have benefited patients with other subtypes of breast cancer, and several targeted therapies for hormone receptor positive (HR+) and HER2-positive breast cancer are available; however, sequential single-agent chemotherapy remains the standard of care for patients with mTNBC.[8] There is no preferred or standard regimen used and, in general, patients first receive standard chemotherapy regimens that include either a taxane and/or anthracycline.

However, a majority of patients have disease progression after receiving first-line therapy and standard therapeutic options are limited to chemotherapy (e.g. capecitabine, gemcitabine, vinorelbine or albumin-bound paclitaxel, and combination regimens for patients who present with visceral crisis). Standard chemotherapy is associated with low response rates (10%-15%) and short progression-free survival (PFS) (2-3 months) among patients with pretreated mTNBC.[9-12] Overall survival (OS) among patients with this form of breast cancer has not changed over the past 20 years

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and patients with mTNBC continue to have a considerably worse OS when compared with their metastatic breast cancer counterparts.[13]

For patients whose tumors are programmed death-ligand 1 (PD-L1) positive, both atezolizumab in combination with nab-paclitaxel and pembrolizumab in combination with chemotherapy have been approved for mTNBC in adult patients who have not received prior chemotherapy for metastatic disease. The poly-adenosine diphosphate-ribose polymerase inhibitors (PARPi), olaparib and talazoparib, have been approved for patients with TNBC who harbor a germline *BRCA1* or *BRCA2* mutation and have been previously treated with chemotherapy.[14] Treatment options are limited for patients who have received two or more regimens in the metastatic setting, highlighting the need for advances in therapeutic options for these patients.

On 22 November 2021, sacituzumab govitecan (SG) was approved in the European Union as monotherapy for the treatment of adult patients with unresectable or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, including at least one of them for advanced disease. The Committee for Medicinal Products for Human Use (CHMP) agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. The review was conducted by the CHMP and a positive opinion was issued on 14 October 2021.

## NONCLINICAL ASPECTS AND CLINICAL PHARMACOLOGY

SG is an antibody—drug conjugate (ADC) consisting of a trophoblast cell surface antigen-2 (Trop-2)-directed humanized antibody (hRS7 IgG1κ) and a topoisomerase I inhibitor molecule (SN38) which is a metabolite of irinotecan covalently attached to the antibody by a hydrolysable linker, CL2A. Binding of Trop-2 by the parental RS7 antibody has been shown to result in internalization and processing of the antibody by the targeted cells.[15,16] Because of its hydrolysable linker, SG will release its SN-38 payload both intra- and extracellularly in the tumor microenvironment.[17,18] SG is designed to deliver significantly greater amounts of SN-38 to a Trop-2-expressing tumor than conventional irinotecan chemotherapy.[19] The extracellular release of SN-38 from SG also allows for by-stander killing of Trop-2-negative tumor cells.[20-22] Thus, SG is purposed to deliver cytotoxic chemotherapy to tumors, including adjacent cancer cells, in concentrations that are higher than those with standard chemotherapy and may reduce toxic effects in normal tissues that do not express the target.

SN-38 was clastogenic in an *in vitro* mammalian cell micronucleus test in Chinese hamster ovary cells and was not mutagenic in an *in vitro* bacterial reverse mutation (Ames) assay. In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of SG resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary and atrophy of vaginal epithelial cells at doses $\geq$60 mg/kg (1.9 times the human recommended dose of 10 mg/kg based on body weight allometric scaling). Nonclinical data for the novel excipient MES [2-(N-morpholino) ethanesulfonic acid] reveal no special hazard for humans based on conventional repeated dose toxicity and genotoxicity studies.

The clinical pharmacology package for SG comprises non-compartmental PK analyses for studies IMMU-132-01 and IMMU-132-05, population pharmacokinetic (PK) analyses to examine the effects of intrinsic factors on PK variability and analyses of exposure—efficacy and exposure—safety relationships. The recommended dose and regimen for SG is 10 mg/kg as an intravenous infusion once weekly on days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity. Based on population PK analyses, the central volume distribution of SG was 2.96 l. The mean half-life of SG and free SN-38 was 15.3 and 19.7 h, respectively. Based on population PK analyses, the clearance of SG is 0.14 l/h. No metabolism studies with SG have been conducted. SN-38 (the small molecule moiety of SG) is metabolized via UGT1A1.[23] PK analyses in patients treated with SG ($n = 527$) did not identify an effect of age, race or mild renal impairment on the PK of SG. Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of SG.[24] There are no data on the PK of SG in patients with moderate renal impairment, severe renal impairment or end-stage renal disease. The exposure of SG is similar in patients with mild hepatic impairment [bilirubin $\leq$ upper limit of normal (ULN) and aspartate aminotransferase (AST) $>$ ULN, or bilirubin $>$ 1.0 to $<$ 1.5 ULN and AST of any level; $n = 59$] to patients with normal hepatic function (bilirubin or AST $<$ ULN; $n = 191$). SG exposure is unknown in patients with moderate or severe hepatic impairment. SN-38 exposure may be elevated in such patients due to decreased hepatic UGT1A1 activity.

## CLINICAL EFFICACY

The submission was based on the pivotal phase III study IMMU-132-05 (ASCENT).[25]

Supportive study IMMU-132-01 was an uncontrolled phase I/2II study to determine the maximum acceptable dose and to evaluate the safety and tolerability of SG monotherapy in previously treated metastatic epithelial cancers. The maximum dose administered was 18 mg/kg and in view of common treatment interruptions and dose reductions in phase I, a maximum tolerated dose of SG 12 mg/kg was determined. In phase II, patients were recruited in a sequential manner to 8 mg/kg and subsequently 10 mg/kg both of which met the criteria for a maximum acceptable dose. However, the 10-mg/kg dose compared with the 8-mg/kg dose was associated with a higher objective response rate (22% and 10%, respectively) and clinical benefit rate.[26]

The pivotal study was a controlled open-label phase III study to evaluate the safety, tolerability, PK and efficacy of SG versus treatment of physician's choice (TPC; eribulin, capecitabine, vinorelbine or gemcitabine) in patients with mTNBC.

The study population included patients with either unresectable locally advanced or metastatic (m)TNBC who were refractory or had relapsed after at least two prior standard-of-care chemotherapy regimens, including at least one prior therapy for locally advanced or metastatic disease and including a taxane in any setting. The primary analysis population for efficacy was planned to be the subset of the intention-to-treat (ITT) population without brain metastases at baseline.

The primary endpoint was defined as PFS determined by the independent review committee. OS, defined as the time from date of randomization to the date of death from any cause, was a secondary endpoint.

The pivotal study IMMU-132-05 randomized 529 patients 1 : 1 in both treatment arms (267 in SG and 262 in TPC arm). A total of 61 patients with brain metastases were included in the study: 32 in the SG group and 29 in the TPC group, and these patients were excluded from the primary analysis population for efficacy. The primary efficacy analysis was carried out in the brain metastasis-negative population that consisted of 235 patients in the SG group and 233 patients in the TPC group who had no brain metastases at baseline. The final results were provided with a cut-off date (COD) of 11 March 2020 (median follow-up of 11.2 months for SG and 6.2 months for TPC). A hazard ratio (HR) for PFS of 0.41 ($n = 468$; 95% CI 0.32-0.52; $P < 0.0001$) was observed. The median PFS was 5.6 months versus 1.7 months. For the secondary endpoint OS, a HR of 0.48 ($n = 468$; 95% CI 0.38-0.59; $P < 0.0001$) was observed. The median OS was 12.1 months versus 6.7 months, in patients treated with SG and TPC, respectively.

The efficacy results in the overall population (ITT population) were consistent with the brain metastasis negative population in the pre-specified final analysis as shown in Table 1.

## CLINICAL SAFETY

The clinical safety database consisted of results from 660 patients receiving single-agent SG at the proposed dose of 10 mg/kg IV, derived from the pivotal, randomized, open-label, phase III study IMMU-132-05 and the uncontrolled phase I/II study IMMU-132-01.

The median duration of treatment in study IMMU-132-05 for the SG group compared with the TPC group was 4.4 months versus 1.3 months. A higher percentage of the SG group compared with the TPC group received study treatment $\geq$6 months (36.8% versus 5.8%) and $\geq$12 months (11.2% versus 0.4%). Long-term safety data (i.e. exposure of at least 12 months) were only available for a limited number (11%) of patients exposed to SG.

Most of the adverse events (AEs) reported (Table 2) were treatment-related, the majority being diarrhea (65.1%) and neutropenia (64.0%) followed by nausea (62.4%), fatigue (51.6%), alopecia (46.9%) anemia (39.5%), constipation (37.2%) and vomiting (33.3%). Neutropenia was the most common grade $\geq$3 AE and $\geq$5% of patients experienced other grade $\geq$3 AEs such as decreased neutrophil count, diarrhea, anemia, decreased white blood cell count, febrile neutropenia, fatigue and dyspnea.

## BENEFIT–RISK ASSESSMENT

Based on study IMMU-132-05, SG was associated with a statistically significant and clinically relevant improvement in PFS compared to TPC in patients who received two or more prior systemic therapies including at least one in the advanced setting (Figure 1). A clinically relevant effect was also observed in terms of the secondary endpoint, OS (Figure 2). Although the toxicity was higher compared to standard chemotherapy, toxicities could be regarded as manageable by support with granulocyte colony stimulating-factor and dose modifications. Given the significant improvement in OS, the benefit of treatment with SG outweighed the increased toxicity. Even though the primary analysis was carried out in the brain metastasis negative population, the final approved indication included patients with brain metastases. This was considered justified as results in the overall population (ITT principle) were consistent with the pre-specified final analysis (11 March 2020 COD).

**Table 1. Favorable effects table for Trodelvy (SG) for the treatment of unresectable locally advanced or metastatic TNBC who have received at least two prior therapies**

| Effect | Short description | Unit | SG | TPC | Uncertainties/strength of evidence |
|---|---|---|---|---|---|
| **Favorable effects in ITT population ($N = 529$)** | | | | | |
| **PFS** (median) | Based on IRC per RECIST 1.1 | Months | 4.8 | 1.7 | Clinically meaningful benefit of SG based on mature data; updated results (final database lock Feb 2021) confirm the treatment effect of SG in the ITT population. Benefit in patients with Trop-2 weak expressing tumors appears lower compared to higher expression groups. Benefit for brain metastasis-positive population ($n = 61$) is similar to TPC. - PFS by IRC HR 0.65 (0.35-1.22) - OS HR 0.95 (0.52-1.72) - ORR 3% versus 0% for comparison of SG versus TPC. |
| | | HR (95% CI) | 0.43 (0.35-0.54) | | |
| **OS** (median) | Time from randomization until death | Months | 11.8 | 6.9 | |
| | | HR (95% CI) | 0.51 (0.41-0.62) | | |
| **ORR** | Confirmed CR + PR, by IRC per RECIST 1.1 | % | 31.1 | 4.2 | |
| | | Odds ratio (95% CI) | 10.99 (5.7-21.4) | | |

Data cut-off: 11 March 2020.

CI, confidence interval; CR, complete response; HR, hazard ratio; IRC, independent review committee; ITT, intention to treat; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

**Table 2. Unfavorable effects table for Trodelvy (SG) for the treatment of unresectable locally advanced or metastatic TNBC who have received at least two prior therapies**

| Effect | Short description | Unit | SG | TPC | Uncertainties/strength of evidence |
|---|---|---|---|---|---|
| **Unfavorable effects** | | | | | |
| Tolerability | Drug-related AEs | % | 97.7 | 85.7 | Safety database is limited |
| | G 3-5 AEs | % | 72.1 | 64.7 | No data in patients with moderate hepatic impairment |
| | SAEs | % | 26.7 | 28.1 | have been provided (ongoing Study IMMU-132-15 included |
| | Death due to drug-related AEs | % | 0.4 | 0.9 | as an additional pharmacovigilance activity) |
| | Discontinuation due to drug-related AEs | % | 4.7 | 5.4 | |
| Drug-related AEs | Diarrhea | % | 65.1 | 17.0 | |
| | Neutropenia | % | 64.0 | 43.8 | |
| | Nausea | % | 62.4 | 30.4 | |
| | Fatigue | % | 51.6 | 39.7 | |
| | Alopecia | % | 46.9 | 16.1 | |
| | Anemia | % | 39.5 | 27.7 | |
| | Constipation | % | 37.2 | 23.2 | |
| | Vomiting | % | 33.3 | 16.1 | |

Data cut-off: 11 March 2020.
AEs, adverse events; SAEs, serious adverse events; SG, sacituzumab govitecan; TPC, treatment of physician's choice.

Trop-2 overexpression has been associated with poor survival in human solid tumors.[27] SG specifically binds to Trop-2-expressing cancer cells, releasing SN-38 payload both intra- and extracellularly in the tumor microenvironment.[17,18] Trop-2 expression data were only available for 60% of patients and submission of tumor biopsies for central testing of Trop-2 expression was not mandatory at enrolment. Trop-2 expression was assessed on archival baseline tumor samples. Results showed a treatment benefit of SG in tumors above and below the chosen median cut-off for Trop-2 expression but data suggest a predictive value of Trop-2 expression.[28] The selected method and the single cut-off to determine Trop-2 tumor expression status were not deemed sufficient to determine the benefit in patients with tumors that show only a weak or no Trop-2 expression. This was considered of concern in view of the mechanism of action of SG as targeted therapy and the proportion of ~20% of patients with TNBC without overexpression of Trop-2 according to literature data.[29-31] Further analyses including efficacy by Trop-2 expression quartiles and different low Trop-2 expression cut-offs (determined by different IHC scores) were requested.[28] An association between Trop-2 tumor expression and efficacy outcome could be shown with a smaller treatment effect in

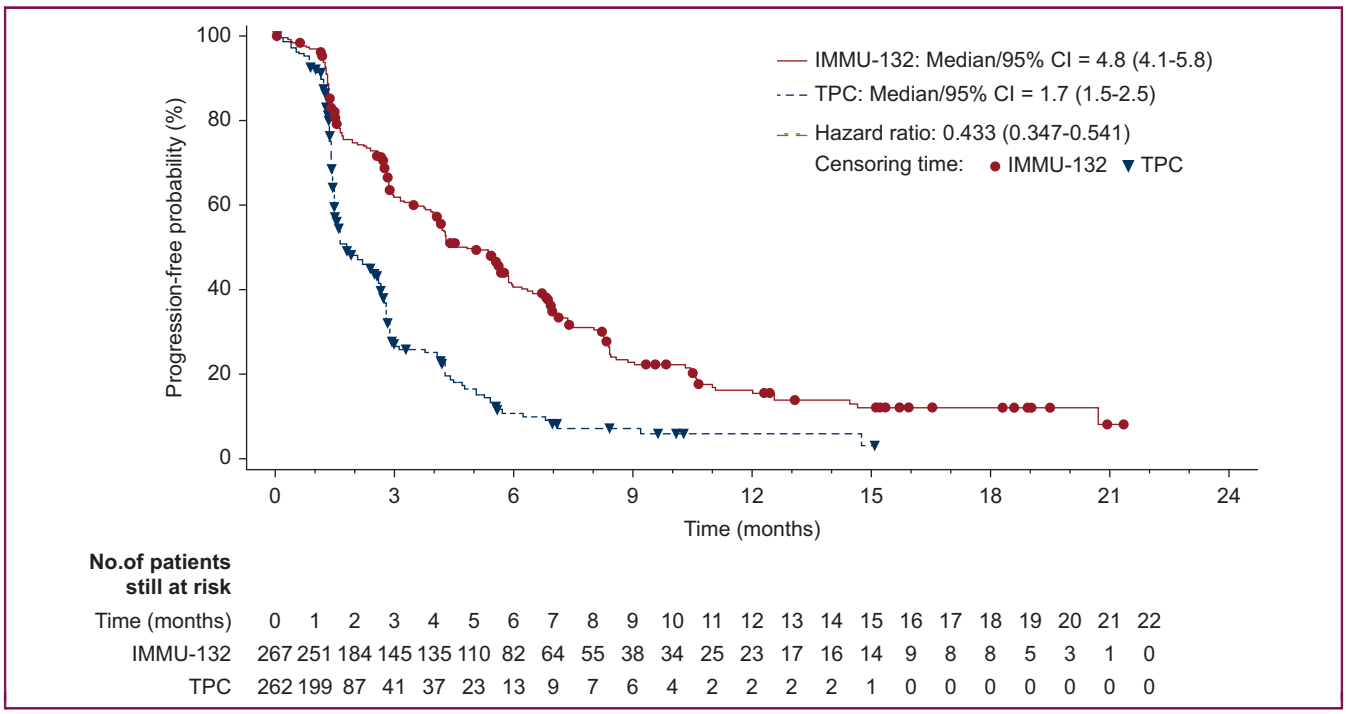


**Figure 1. Kaplan–Meier estimates of PFS by IRC assessment per RECIST v1.1 in the ITT population (study IMMU-132-05).**
PFS is defined as the time from the date of randomization to the date of the first radiological disease progression or death due to any cause, whichever comes first. IRC, independent review committee; ITT, intention to treat; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; TPC, treatment of physician's choice.

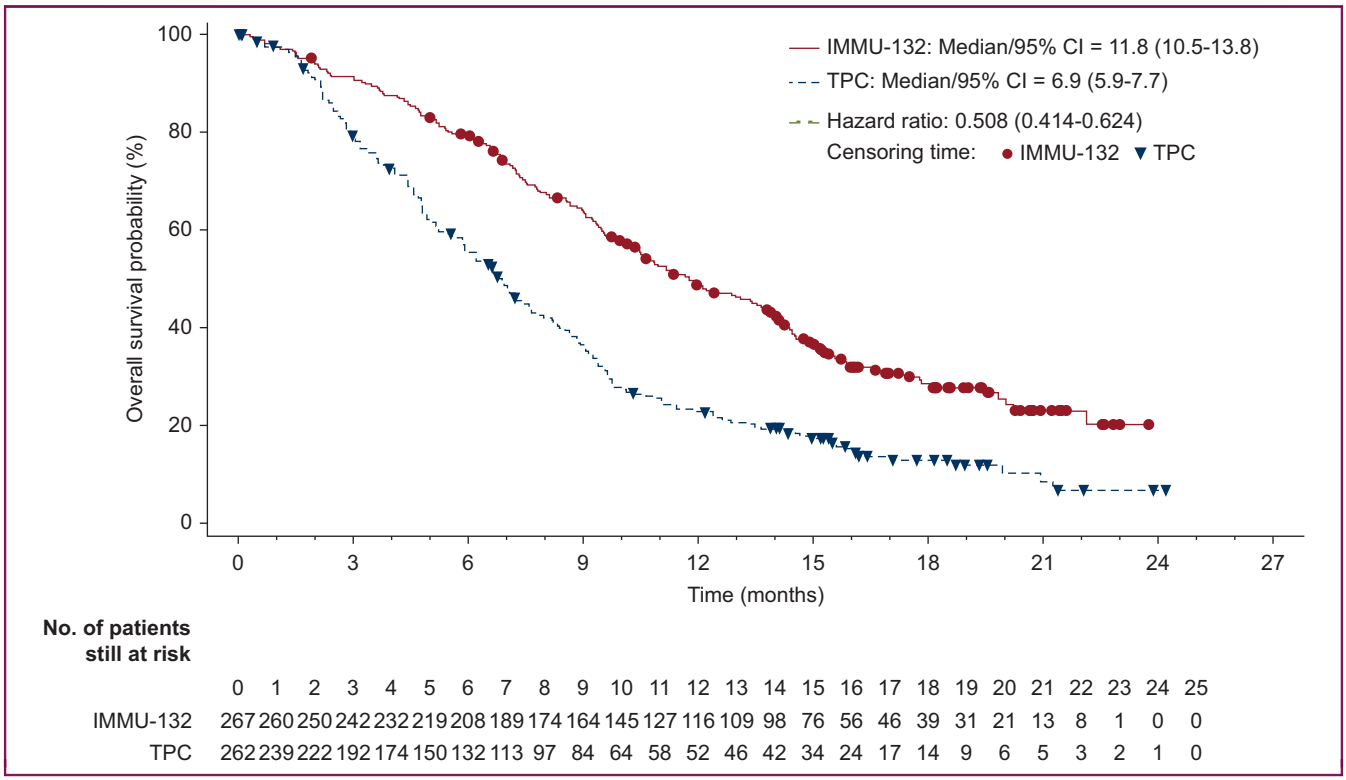


**Figure 2. Kaplan–Meier plot of OS (ITT population).**
OS is defined as the time from date of randomization to the date of death from any cause.
ITT, intention to treat; OS, overall survival; TPC, treatment of physician's choice.

subgroups with low Trop-2 expression relative to participants with high Trop-2 expression. However, conclusions on the clinical relevance of different levels of tumor Trop-2 expression for the treatment with SG are hampered by the retrospective character of the analyses and the limited sample size of the Trop-2-assessable population (with even smaller numbers per quartile). Nevertheless, efficacy of SG appeared superior compared to the control arm also for patients with low Trop-2 expression, even though the treatment effect of SG was smaller in patients with low Trop-2 expression relative to participants with high Trop-2 expression. Therefore, it was assessed that available data do not support a restricted indication.

The indication wording encompasses the treatment of patients with unresectable or mTNBC; yet only a single participant was enrolled with unresectable locally advanced cancer in study IMMU-132-05. In view of the high unmet medical need and expected similar treatment benefits for patients with unresectable disease, the extrapolation of data was considered acceptable in line with other approved breast cancer indications in the EU.

*BRCA* genes are the strongest susceptibility genes identified for breast cancer,[32] and a higher prevalence of *BRCA* mutations has been observed in patients with mTNBC compared to other breast cancer subtypes.[33] Efficacy results appeared to be consistent regardless of the *BRCA* status. However, no firm conclusions could be made, as a small number of participants ($n = 43$; 8.1%) had *BRCA*-positive status and information on *BRCA* mutational status was lacking for 35% of study population.

During the assessment, hypersensitivity, severe diarrhea and serious infection secondary to neutropenia were identified as important risks, whereas embryo-fetal toxicity was classified as a potential risk. There was missing information regarding the use of SG in patients with moderate or severe hepatic impairment and immunogenicity.

Data from the ongoing study IMMU-132-15 will provide information on the use of SG in patients with moderate hepatic impairment. Post-authorization measures regarding immunogenicity have also been imposed and an integrated summary of immunogenicity is expected by September 2022.

Based on the review of the submitted data, CHMP considered by consensus that the benefit–risk balance of SG monotherapy was favorable for the treatment of adult patients with unresectable or metastatic mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease, and hence recommended the granting of the marketing authorization.

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## DISCLOSURE

The authors have declared no conflicts of interest.

## DISCLAIMER

This publication is based on the European Public Assessment Report of Trodelvy, the summary of product characteristics, and other product information as published on the European Medicines Agency (EMA) website (www.ema.europa.eu). For the most current information on this marketing authorization, please refer to the EMA website. The views expressed in this article are the personal views of the author(s) and may not be understood or quoted as being made on behalf of or reflecting the position of the regulatory agency/agencies or organizations with which the author(s) is/are employed/affiliated.

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