トロデルビ®点滴静注 200mg
に関する資料

本資料に記載された情報に係る権利及び内容の責任は、ギリアド・サイエンシズ株式会社に帰属するものであり、当該情報を適正使用以外の営利目的に利用することはできません。

ギリアド・サイエンシズ株式会社

サシツズマブ　ゴビテカン（遺伝子組換え）

第１部 申請書等行政情報及び添付文書に関する情報

1.5 起原又は発見の経緯及び開発の経緯

ギリアド・サイエンシズ株式会社

目次

頁

略号一覧表 5
1　起原又は発見の経緯 6
1.1　転移・再発トリプルネガティブ乳癌 6
1.2　転移・再発トリプルネガティブ乳癌に対する既存の治療選択肢 6
1.2.1　海外の治療法 6
1.2.2　国内の治療法 7
1.3　サシツズマブ　ゴビテカン開発の根拠 8
2　開発の経緯 9
2.1　品質、非臨床及び臨床試験の実施経緯 9
2.2　臨床開発プログラムの概略 11
2.2.1　第 3 相試験の用量選択 11
2.2.2　臨床的有効性及び安全性を評価した試験プログラム 11
2.2.3　臨床データパッケージ 15
2.2.4　国内臨床開発プログラム 15
2.2.5　ベネフィットとリスクに関する評価 15
3　参考文献 17

表目次

頁
表 1　転移・再発トリプルネガティブ乳癌の治療としてのサシツズマブ　ゴビテカンの臨床的有効性及び安全性を裏付ける主な試験 12
表 2　臨床データパッケージ 15

図目次

頁
図 1　品質、非臨床及び臨床試験の実施経緯.....10

略号一覧表

略号	英語	日本語
ADC	antibody drug conjugate	抗体薬物複合体
BRCA	breast cancer susceptibility gene	乳癌感受性遺伝子
CBR	clinical benefit rate	臨床的有用率
ER	estrogen receptor	エストロゲン受容体
ESMO	European Society for Medical Oncology	欧州臨床腫瘍学会
G-CSF	granulocyte colony-stimulating factor	顆粒球コロニー刺激因子
HER2	human epidermal growth factor receptor 2	ヒト上皮増殖因子受容体 2 型
HR	hormone receptor	ホルモン受容体
HRQOL	health-related quality of life	健康関連 QOL
IHC	immunohistochemistry	免疫組織化学染色
ISH	in situ hybridization	in situ ハイブリダイゼーション
MCBS	Magnitude of Clinical Benefit Scale	－
MTD	maximum tolerated dose	最大耐量
NCCN	National Comprehensive Cancer Network	－
ORR	objective response rate	客観的奏効率
OS	overall survival	全生存期間
QOL	quality of life	生活の質
PARP	poly adenosine diphosphate ribose polymerase	ポリアデノシン二リン酸リボースポリメラーゼ
PD-L1	programmed cell death-ligand 1	－
PFS	progression-free survival	無増悪生存期間
PgR	progesterone receptor	プロゲステロン受容体
PK	pharmacokinetic(s)	薬物動態
SG	sacituzumab govitecan; GS-0132; IMMU-132	サシツズマブ　ゴビテカン
TNBC	triple-negative breast cancer	トリプルネガティブ乳癌
TPC	treatment of physician’s choice	医師選択治療
Trop-2	trophoblast cell surface antigen-2	－

1　起原又は発見の経緯

サシツズマブ　ゴビテカン（SG、識別記号:GS-0132 又はIMMU-132）は、抗体薬物複合体（ADC）であり、転移・再発トリプルネガティブ乳癌（転移・再発 TNBC）及びホルモン受容体（HR）陽性ヒト上皮増殖因子受容体 2 型（HER2）陰性転移・再発乳癌を含む様々な上皮性腫瘍を有する患者を対象に評価が進行中である。

1.1　転移・再発トリプルネガティブ乳癌

乳癌は最も多く診断される癌種であり、世界の全ての癌診断例の 11.7%を占める。2020 年の世界の乳癌の新規症例は約 230 万人、死亡数は 68 万 5000 人であった[9]。乳癌は、女性の癌死の約 15%を占めており、肺癌及び気管支癌に次ぐ癌死の主要な原因である[9,25]。2023 年の米国での乳癌の新規症例は 30 万 590 人、死亡数は 4 万 3700 人と推定されている[25]。日本においては、2022 年の乳癌の新規症例は 9 万 5000 人、死亡数は 1 万 5600 人と推定されている[10]。

早期乳癌は、病変の乳房組織に限局した癌又は腋窩リンパ節のみに転移した癌と定義され、治癒可能と考えられる。集学的治療の進歩により、早期乳癌患者における治癒率は約 70%～80%まで上昇した[12]。一方、局所進行又は転移・再発乳癌の予後は不良であり、5 年生存率は約 25%である[7]。進行乳癌に対する根治的治療の選択肢が存在しないことから、治療の本質は緩和療法である。主な治療目標は、生存期間の延長と治療転帰の改善に加え、治療関連毒性を最小限に抑える治療を用いて症状をコントロールすることで、生活の質（QOL）の最大化を図ることである。

TNBC は、腫瘍細胞においてエストロゲン受容体（ER）、プロゲステロン受容体（PgR）の発現がみられず（免疫組織化学染色［IHC］法で ER 及び／又は PgR の発現が 1%未満）、かつ HER2 の発現がみられない（IHC スコア 0 若しくは 1+又は IHC スコア 2+かつ ISH 陰性）ことで定義される[1,3,30]。TNBC は浸潤性乳癌の約 15%を占め[8,15,22]、腫瘍生物学的に悪性度が高く、予後不良である。TNBC は、高齢の女性に比べ若い女性で、人種・民族別では黒人でより多くみられる。他のリスク因子としては、乳癌感受性遺伝子（BRCA）の変異、閉経前、肥満のほか、経産回数や初回妊娠年齢等の母体関連因子なども挙げられる[22,27]。TNBC の多くは内臓転移を来し、転移例は治癒不能とされる[14]。

1.2　転移・再発トリプルネガティブ乳癌に対する既存の治療選択肢

1.2.1　海外の治療法

転移・再発 TNBC 患者に対しては、依然として単剤化学療法による逐次的な治療が標準的に行われている[7]。推奨される又は標準的な治療レジメンは存在せず、一般的に、一次治療ではタキサン系及び／又はアントラサイクリン系薬剤を含む標準的な化学療法レジメンが使用されている。しかしながら、大多数の患者は一次治療後に疾患進行を来し、標準的な治療選択肢は化学療法（カペシタビン、ゲムシタビン、ビノレルビン又は nab-パクリタキセル、急速進行性で生命を脅かす内臓転移を有する場合は併用レジメンなど）に限られている。

治療歴のある転移・再発 TNBC 患者では、標準化学療法による奏効率は低く（10%～15%）、無増悪生存期間（PFS）は短い（2～3 ヵ月）[5,19,20,28]。過去 20 年間、治療歴のある転移・再発 TNBC 患者における全生存期間（OS）に変化はみられておらず、他の転移・再発乳癌と比較しと、転移・再発 TNBC 患者での OS は依然として大幅に劣っている[31]。なお、programmed cell death-ligand 1

（PD-L1）陽性の転移・再発 TNBC 患者に対してはアテゾリズマブと nab-パクリタキセルとの併用療法及びペムブロリズマブと化学療法（nab-パクリタキセル、パクリタキセル、又はゲムシタビン及びカルボプラチン）の併用療法が、生殖細胞系列 BRCA 1 又は BRCA 2 の遺伝子変異を有し化学療法による前治療歴のある TNBC 患者に対してはポリアデノシン二リン酸リボースポリメラーゼ（PARP）阻害剤のオラパリブ及びタラゾパリブが承認されている。全米総合癌情報ネットワーク（National Comprehensive Cancer Network；NCCN）ガイドライン[17]では、SG は転移・再発 TNBC 患者の二次治療として推奨されている（カテゴリー1）。転移・再発 TNBC の二次治療で使用しない場合、以降のラインで SG の使用を検討してもよい。また、近年、生殖細胞系列 BRCA 1 又は BRCA2 の遺伝子変異を有さず、かつ HER2 IHC スコア 1+又は 2+/ISH 陰性の患者に対して、二次治療としてトラスツズマブ　デルクステカンを使用する推奨が NCCN ガイドラインに追加された。欧州臨床腫瘍学会（ESMO）転移・再発乳癌リビングガイドライン 1.1 版（2023 年 5 月）では、SG は、TNBC に対する前治療の化学療法後に推奨される望ましい治療選択肢とされており（ESMO-Magnitude of Clinical Benefit Scale［MCBS］v1.1 スコア：4）、SG 療法が無効であった場合は、トラスツズマブ　デルクステカン（適格な場合）又は化学療法の使用が推奨されている。

1.2.2　国内の治療法

日本では、Hortobagyi が提唱した転移・再発乳癌の治療アルゴリズムや NCCN ガイドライン[17]が一般的に使用されている[13]。

乳癌全身療法に関する日本乳癌学会診療ガイドライン[13]では、PD-L1 陽性の腫瘍又は生殖細胞系列 BRCA 変異を有する患者に対する推奨は、PD-L1 陽性腫瘍を有する患者に対してペムブロリズマブとの併用療法で使用する化学療法の選択肢（nab-パクリタキセル、パクリタキセル、又はゲムシタビン及びカルボプラチン）を含め、NCCN ガイドラインと同様である。PD-L1 陰性の腫瘍を有し生殖細胞系列 BRCA 変異を有する患者には、PARP 阻害剤による治療が推奨される。PD-L1 陰性の腫瘍を有し生殖細胞系列 BRCA 変異のない患者では、単剤化学療法が推奨される。

単剤化学療法の選択肢には、一次又は二次治療としてのアントラサイクリン系薬剤及びタキサン系薬剤がある。加えて、カペシタビン、S-1、ベバシズマブ（パクリタキセルとの併用）、エリブリン（アントラサイクリン系薬剤及びタキサン系薬剤による治療後）が使用可能である。ゲムシタビン単剤療法及びビノレルビン単剤療法は、HER2 陰性転移・再発乳癌に対する治療選択肢として、日本乳癌学会診療ガイドラインに記載されている。

トラスツズマブ　デルクステカンは、化学療法歴を有する HER2 低発現（IHC スコア 1+又は 2+/ISH 陰性）の転移・再発乳癌患者に対する治療薬として、本邦において 2023 年 3 月に承認された。承認は、HR 陰性患者 63 例を含む 557 例の患者を対象とした DESTINY-Breast04 試験に基づいている。2023 年 6 月に、化学療法歴を有する HER2 低発現の転移・再発乳癌患者に対するトラスツズマブ　デルクステカンの使用に関する推奨が日本乳癌学会診療ガイドライン[13]に追加された。これらの治療が無効となった後の治療について、日本乳癌学会診療ガイドラインでは、転移・再発乳癌に対して有効性が示されている化学療法を三次治療以降で用いることが適切であると記載されている。すなわち、残る治療選択肢は、各患者に適用可能な薬剤による逐次化学療法である。

1.3　　サシツズマブ　ゴビテカン開発の根拠

SG は、以下の 3 つの成分より構成される。

1）ヒト化モノクローナル抗体 hRS7 IgG1κ：細胞表面受容体である trophoblast cell surface antigen-2（Trop-2）に結合する
2）カンプトテシン誘導体 SN-38：イリノテカンの活性代謝物であり、トポイソメラーゼ I 阻害作用を有する
3）加水分解性リンカーCL2A：SN-38 と hRS7 IgG1κ を結合させる

親抗体が Trop-2 に結合することにより、抗体が標的細胞内に内在化し、プロセシングを受けることが示されている[24,26]。加水分解性リンカーが切断されると、SG のペイロード（SN-38）が腫瘍微小環境の細胞内外へと放出される[6,11,23]。SG から細胞外へ放出される SN-38 により、複合体が結合しなかった腫瘍細胞に対してもバイスタンダー殺傷効果を示す[16,21,32]。こうした機序により、SG は従来の標準的な化学療法と比較して高濃度の細胞傷害性化学療法薬を隣接する癌細胞を含む腫瘍部位へ送達可能であり、一方で標的非発現の正常組織に対する毒性を低減できる可能性がある。TNBC 及び HR 陽性 HER2 陰性の両サブタイプを含め、乳癌細胞では Trop-2 タンパク質が高発現していることがポリクローナル抗体 IHC 検査で示されている[2]。Trop-2 タンパク質は TNBC で高発現（90%超）していることがモノクローナル抗体のデータから示されており、腫瘍の進行及び予後不良との関連が報告されている[4]。また、近年の研究では、全ての乳癌サブタイプで *TROP2* 遺伝子が高発現しており、発現の様相も類似していることが示された[29]。

2　開発の経緯

2.1　品質、非臨床及び臨床試験の実施経緯

開発の経緯図を図 1 に示す。

図 1　品質、非臨床及び臨床試験の実施経緯

規格	製剤開発	[redacted]
安定性	製剤	
薬理	効力を裏付ける試験	
	副次的薬理試験	
薬物動態	吸収、分布、代謝、排泄	
	その他	
毒性	反復投与	
	遺伝毒性	
	その他	
臨床	海外第1/2相、1試験	
	国内第1/2相、1試験	
	海外第3相、2試験	

2.2　臨床開発プログラムの概略

2.2.1　第 3 相試験の用量選択

転移・再発 TNBC 患者に対する SG の用量は、IMMU-132-01 試験で得られた有効性及び安全性データに基づき選択された。IMMU-132-01 試験の第 1 相パートでは、標準的な 3＋3 デザインに従い、事前に規定した用量レベルの 8、12 及び 18 mg/kg の予定開始用量に基づいて用量漸増を実施した（21 日間を 1 サイクルとし Day 1 及び Day 8 に投与）。その結果、SG 12 mg/kg の用量を最大耐量（MTD）と決定したが、当該用量で数例の被験者が投与延期及び減量に至った。最大許容量を決定するため、IMMU-132-01 試験の第 2 相パートでは、被験者を 8 mg/kg 用量に、次いで 10 mg/kg 用量に逐次的に登録した。これら 2 用量について、癌種を問わずそれぞれ 81 例及び 97 例が投与を受けた時点で中間解析を実施した。いずれの用量も、MTD である 12 mg/kg と比較して初回サイクルでの忍容性が良好であることが示され、より良好な安全性プロファイルで投与サイクルを継続することが可能であった。また、2 用量の投与期間は同程度であり、安全性に重要な差は認められなかった。一方で、様々な癌種を有する患者において、10 mg/kg の用量は 8 mg/kg の用量と比較して有効性が高かった（客観的奏効率［ORR］及び臨床的有用率［CBR］が高かった）[18]。したがって、以上のエビデンス全体から、2 つ以上の全身療法による前治療歴（少なくとも 1 つの進行又は転移・再発乳癌に対する前治療歴を含む）を有する切除不能な局所進行又は転移・再発 TNBC の治療において、SG の用量を 10 mg/kg とすることの妥当性が支持された。

2.2.2　臨床的有効性及び安全性を評価した試験プログラム

SG の有効性及び安全性データ並びに薬物動態（PK）プロファイル及び潜在的な免疫原性の影響に関する情報は、表 1 に概要を示す 4 つの臨床試験から得られた。

日本人被験者における SG の有効性、安全性及び PK は、GS-US-569-6172 試験により評価された。

表 1　転移・再発トリプルネガティブ乳癌の治療としてのサシツズマブ　ゴビテカンの臨床的有効性及び安全性を裏付ける主な試験

Study Region	Description of Study	Data Included in This Submission	Study Population/ Number of Participants	Location of Study Summary and CSR
Metastatic Triple Negative Breast Cancer				
IMMU-132-05 (ASCENT) Overseas For Evaluation	Phase 3, randomized, open-label, controlled, multicenter study to compare the efficacy of SG to TPC as measured by independently reviewed PFS in participants who were BM-negative at baseline.	Efficacy Safety[a] PK Immunogenicity	Participants with locally advanced or metastatic TNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens. Total: 529 randomized (482 treated) SG[b]: 267 randomized (258 treated) TPC[c]: 262 randomized (224 treated)	m2.7.3, Section 2.1, IMMU-132-05 Final, IMMX-PMX-SN38-188 (Report Revision 2), and m2.7.6
GS-US-569-6172 (ASCENT-J02) Japan For Evaluation	A Phase 1/2 open-label study of SG in Japanese participants with advanced solid tumors. Phase 1: to evaluate the safety and tolerability of SG in Japanese participants with advanced solid tumors and to determine the recommended Phase 2 dose of SG in Japanese participants with advanced solid tumors. Phase 2 (metastatic TNBC cohort): To evaluate the efficacy and safety of SG.	Efficacy Safety PK Immunogenicity	Phase 1 part: Participants with advanced solid tumor that was refractory to or intolerant of all standard therapy or for which no standard therapy was available. Phase 2 part (metastatic TNBC cohort): Participants with metastatic TNBC who were refractory to or relapsed after at least 2 prior standard-of-care chemotherapy regimens for unresectable, locally advanced or metastatic BC. Phase 1 part (advanced solid tumor): 16 enrolled (15 treated) Phase 2 part (metastatic TNBC cohort): 36 enrolled and treated	m2.7.3, Section 2.3, GS-US-569-6172 Primary TNBC, and m2.7.6
IMMU-132-01 Overseas For Evaluation	Phase 1/2, open-label, single-arm, basket study. Phase 1: To evaluate the safety and tolerability of SG as a single agent and to determine a maximum acceptable dose[d] and select cancer types for a continued expanded study in Phase 2. Phase 2: To evaluate the safety and efficacy of SG administered at a dose selected in Phase 1.	Efficacy Safety[a] PK Immunogenicity	Participants with metastatic epithelial cancer (except for GBM) that was relapsed or refractory to at least 1 standard therapy for their tumor type. Participants with metastatic TNBC were either refractory to or relapsed after at least 2 prior therapies, including a taxane in any setting. Total: 514 enrolled (402 treated)[e] SG: 144 with mTNBC treated (108 treated)[f]	m2.7.3, Section 2.2, IMMU-132-01 Interim, IMMU-132-01 Final, and m2.7.6

Study Region	Description of Study	Data Included in This Submission	Study Population/ Number of Participants	Location of Study Summary and CSR
HR+/HER2− Metastatic Breast Cancer				
IMMU-132-09 (TROPiCS-02) Overseas For Reference	Phase 3, ongoing, open-label, randomized, multicenter, international study to assess and compare the efficacy of SG to TPC as measured by PFS as determined by BICR using RECIST v1.1.	Safety[a] PK Immunogenicity	Participants with metastatic or locally recurrent inoperable HR+/HER2− BC who have been treated with a CDK 4/6 inhibitor, endocrine therapy, taxane, and at least 2 but no more than 4 prior chemotherapy regimens for metastatic disease (1 of which could be in the neoadjuvant or adjuvant setting if development of unresectable, locally advanced, or metastatic disease occurred within 12 months). Total: 543 randomized (517 treated) SG[b]: 272 randomized (268 treated) TPC[c]: 271 randomized (249 treated)	IMMU-132-09 Primary, IMMU-132-09 Interim 2, and m2.7.6
IMMU-132-01 Overseas For Evaluation	Phase 1/2, open-label, single-arm, basket study. Phase 1: To evaluate the safety and tolerability of SG as a single agent and to determine a maximum acceptable dose[d] and select cancer types for a continued expanded study in Phase 2. Phase 2: To evaluate the safety and efficacy of SG administered at a dose selected in Phase 1.	Safety[a] PK Immunogenicity	Participants with metastatic epithelial cancer (except for GBM) that was relapsed or refractory to at least 1 standard therapy for their tumor type. Participants with HR+/HER2− metastatic BC who had progressed on at least 1 prior hormonal therapy in the metastatic setting. Total: 514 enrolled (402 treated)[e] SG[b]: 54 with confirmed HR+/HER2− (54 treated)[g]	IMMU-132-01 Interim, IMMU-132-01 Final, and m2.7.6

BC= breast cancer; BICR = blinded independent central review; BM = brain metastasis; CDK = cyclin-dependent kinase; CSR = clinical study report; GBM = glioblastoma multiforme; HER2− = human epidermal growth factor receptor 2-negative; HR+ = hormone receptor-positive; mTNBC = metastatic triple-negative breast cancer; IV = intravenous; NSCLC = non–small cell lung cancer; ORR = objective response rate; PFS = progression-free survival; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small cell lung cancer; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; UC = urothelial cancer

a The integrated safety dataset includes all available data up to the data cutoff date from Study IMMU-132-09 (01 July 2022) and final safety data from Studies IMMU-132-01 ([redacted] 20[redacted]) and IMMU-132-05 ([redacted] 20[redacted]).

b Participants received SG 10 mg/kg IV infusion on Days 1 and 8 of a 21-day treatment cycle.

c TPC was eribulin, capecitabine, gemcitabine, or vinorelbine administered per standard of care.

d Starting doses of 8, 10, 12, and 18 mg/kg were evaluated during the dose-escalation phase (Phase 1) of Study IMMU-132-01.

e Of the 514 participants enrolled in Study IMMU-132-01, 495 participants were included in the Overall Safety Population. Of these, 402 participants received SG 10 mg/kg, 81 participants received SG 8 mg/kg, 9 participants received SG 12 mg/kg, and 3 participants received SG 18 mg/kg. The population included the following tumor types: ovarian, endometrial, cervical, TNBC, HR+/HER2− metastatic breast cancer, castration-resistant prostate cancer, colorectal cancer, NSCLC, SCLC, head and neck squamous cell cancer, esophageal, gastric, pancreatic, hepatocellular, renal (clear cell), thyroid (papillary), and metastatic UC. Participants with GBM were also eligible, but were not required to have metastatic disease.

f A total of 144 participants with TNBC were enrolled in the study and received at least 1 dose of SG. Of these 144 participants, 108 participants were treated with SG at a starting dose of 10 mg/kg; these participants were included in the efficacy analyses and are referred to throughout as the TNBC Target Population.

g Overall, 68 participants with non-TNBC were enrolled in Study IMMU-132-01 and received at least 1 dose of SG. Of these 68 participants, 54 were confirmed as HR+/HER2− who had progressed on at least 1 prior hormonal therapy in the metastatic setting, and had received at least 1 dose of SG 10 mg/kg.

Source: m2.7.6, Section 1 and m2.7.3, Sections 2.1, 2.2, and 2.3

2.2.3　臨床データパッケージ

転移・再発 TNBC に対する SG の製造販売承認申請を支持する臨床データパッケージを表 2 に示す。評価資料は海外第 1/2 相試験（IMMU-132-01）、国内第 1/2 相試験（GS-US-569-6172）及び海外第 3 相試験（IMMU-132-05）から構成される。

表 2　臨床データパッケージ

相	評価資料	参考資料
1/2	IMMU-132-01 GS-US-569-6172 (ASCENT-J02)	－
3	IMMU-132-05 (ASCENT)	IMMU-132-09 (TROPiCS-02)

2.2.4　国内臨床開発プログラム

本邦における転移・再発 TNBC の治療薬としての SG の開発に関し、医薬品第 2 相試験終了後相談（受付番号：[redacted]）を 20[redacted] 年 [redacted] 月 [redacted] 日に実施した。対面助言で、医薬品医療機器総合機構（機構）は、相談者側が提案した[redacted]及び[redacted]を全般的に受け入れた。当該相談の結果を踏まえて、[redacted]。[redacted]。

2.2.5　ベネフィットとリスクに関する評価

SG の投与により、アンメットメディカルニーズの高い患者集団である、2 つ以上の前治療歴（少なくとも 1 つの局所進行又は転移・再発乳癌に対する前治療歴を含む）を有する切除不能な局所進行又は転移・再発 TNBC 成人患者において、単剤化学療法との比較で、臨床的に意味のある統計学的に有意な PFS 及び OS の延長がみられた。GS-US-569-6172 試験の転移・再発 TNBC を有する日本人患者において、主要評価項目の ORR 及び PFS を含む全ての副次評価項目の有効性データが IMMU-132-05 試験と同等であったことから、化学療法歴のある HR 陰性かつ HER2 陰性の手術不能又は再発乳癌を有する日本人患者において、IMMU-132-05 試験と同様の SG による OS の延長が期待できると考える。

SG は、生命を脅かす疾患状況下、すなわち、2 つ以上の前治療歴（少なくとも 1 つの局所進行又は転移・再発乳癌に対する前治療歴を含む）を有する切除不能な局所進行又は転移・再発 TNBC での使用及び本患者集団に対する他の既存治療法との比較において、忍容可能な安全性プロファイルを示した。SG の忍容性は、IMMU-132-05 試験での有害事象による投与中止率の低さ（5%未満）から裏付けられている。SG は単剤化学療法よりも長期間にわたって投与可能であり、かつ忍容性を示した（4.4 ヵ月 vs 1.3 ヵ月、範囲：0～30 ヵ月 vs 0～15 ヵ月）。SG の投与で最も臨床的に重要な Grade 3 又は 4 の有害事象は好中球減少症及び下痢であったが、これらは綿密なモニタリングや投与中断／延期、顆粒球コロニー刺激因子（G-CSF）や止瀉剤の投与等の確立された支持療法により適切に管理可能である。また、悪心／嘔吐及び下痢が報告されたものの、5 つの主要な健康関連 QOL（HRQOL）サブスケール（すなわち、全般的健康状態／QOL、身体機能、役

割機能、疼痛及び疲労）において、SG は医師選択治療（TPC）と比較して統計学的に有意及び／又は臨床的に意味のある改善を示した。GS-US-569-6172 試験において新たな安全性シグナルは認められず、転移・再発 TNBC を有する日本人患者における SG の安全性プロファイルは海外集団と同様であることが確認された。

以上より、これらのデータは SG の良好なベネフィット・リスクプロファイルを示しており、化学療法歴のある HR 陰性かつ HER2 陰性の手術不能又は再発乳癌を有する日本人患者の治療薬として SG を使用する妥当性を支持している。

3　参考文献

1 Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, et al. Estrogen and Progesterone Receptor Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Guideline Update. Arch Pathol Lab Med 2020;144 (5):545-63.

2 Ambrogi F, Fornili M, Boracchi P, Trerotola M, Relli V, Simeone P, et al. Trop-2 is a determinant of breast cancer survival. PLoS ONE 2014;9 (5):e96993.

3 Anders CK, Zagar TM, Carey LA. The management of early-stage and metastatic triple-negative breast cancer: a review. Hematol Oncol Clin North Am 2013;27 (4):737-49, viii.

4 Bardia A, Tolaney SM, Punie K, Loirat D, Oliveira M, Kalinsky 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 (9):1148-56.

5 Brufsky A, Valero V, Tiangco B, Dakhil S, Brize A, Rugo HS, et al. Second-line bevacizumab-containing therapy in patients with triple-negative breast cancer: subgroup analysis of the RIBBON-2 trial. Breast Cancer Res Treat 2012;133 (3):1067-75.

6 Cardillo TM, Govindan SV, Sharkey RM, Trisal P, Goldenberg DM. Humanized anti-Trop-2 IgG-SN-38 conjugate for effective treatment of diverse epithelial cancers: preclinical studies in human cancer xenograft models and monkeys. Clin Cancer Res 2011;17 (10):3157-69.

7 Cardoso F, Paluch-Shimon S, Senkus E, Curigliano G, Aapro MS, Andre F, et al. 5th ESO-ESMO international consensus guidelines for advanced breast cancer (ABC 5). Ann Oncol 2020;31 (12):1623-49.

8 DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, et al. Breast cancer statistics, 2019. CA Cancer J Clin 2019;69 (6):438-51.

9 Ferlay J, Ervik M, Colombet M, Mery L, Pineros M, Znaor A, et al. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer. Available at: https://gco.iarc.fr/today/online-analysis-table?v=2020&mode=cancer&mode_population=continents&population=900&populations=900&key=asr&sex=0&cancer=39&type=0&statistic=5&prevalence=0&population_group=0&ages_group%5B%5D=0&ages_group%5B%5D=17&group_cancer=1&include_nmsc=1&include_nmsc_other=1. Accessed: 31 January. 2022:

10 Foundation for Promotion of Cancer Research, CANCER STATISTICS IN JAPAN — 2023. 2023:

11 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):22496-512.

12 Harbeck N, Penault-Llorca F, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers 2019;5 (1):66.

13 Japan Breast Cancer Society. The Japanese Breast Cancer Society Clinical Practice Guidelines for systemic treatment of breast cancer. Available at: https://jbcs.xsrv.jp/guideline/2022/. Accessed: 23 August 2023. Last Updated: June. 2023:

14 Kassam F, Enright K, Dent R, Dranitsaris G, Myers J, Flynn C, et al. Survival outcomes for patients with metastatic triple-negative breast cancer: implications for clinical practice and trial design. Clin Breast Cancer 2009;9 (1):29-33.

15 Kohler BA, Sherman RL, Howlader N, Jemal A, Ryerson AB, Henry KA, et al. Annual Report to the Nation on the Status of Cancer, 1975-2011, Featuring Incidence of Breast Cancer Subtypes by Race/Ethnicity, Poverty, and State. J Natl Cancer Inst 2015;107 (6):djv048.

16 Lopez S, Perrone E, Bellone S, Bonazzoli E, Zeybek B, Han C, et al. Preclinical activity of sacituzumab govitecan (IMMU-132) in uterine and ovarian carcinosarcomas. Oncotarget 2020;11 (5):560-70.

17 National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) Breast Cancer Version 4.2023 - March 23, 2023. 2023:

18 Ocean AJ, Starodub AN, Bardia A, Vahdat LT, Isakoff SJ, Guarino M, 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):3843-54.

19 Park IH, Im SA, Jung KH, Sohn JH, Park YH, Lee KS, et al. Randomized Open Label Phase III Trial of Irinotecan Plus Capecitabine versus Capecitabine Monotherapy in Patients with Metastatic Breast Cancer Previously Treated with Anthracycline and Taxane: PROCEED Trial (KCSG BR 11-01). Cancer Res Treat 2019;51 (1):43-52.

20 Perez EA, Moreno-Aspitia A, Aubrey Thompson E, Andorfer CA. Adjuvant therapy of triple negative breast cancer. Breast Cancer Res Treat 2010;120 (2):285-91.

21 Perrone E, Lopez S, Zeybek B, Bellone S, Bonazzoli E, Pelligra S, et al. Preclinical Activity of Sacituzumab Govitecan, an Antibody-Drug Conjugate Targeting Trophoblast Cell-Surface Antigen 2 (Trop-2) Linked to the Active Metabolite of Irinotecan (SN-38), in Ovarian Cancer. Front Oncol 2020;10:118.

22 Plasilova ML, Hayse B, Killelea BK, Horowitz NR, Chagpar AB, Lannin DR. Features of triple-negative breast cancer: Analysis of 38,813 cases from the national cancer database. Medicine (Baltimore) 2016;95 (35):e4614.

23 Sharkey RM, McBride WJ, Cardillo TM, Govindan SV, Wang Y, Rossi EA, et al. Enhanced Delivery of SN-38 to Human Tumor Xenografts with an Anti-Trop-2-SN-38 Antibody Conjugate (Sacituzumab Govitecan). Clin Cancer Res 2015;21 (22):5131-8.

24 Shih LB, Thorpe SR, Griffiths GL, Diril H, Ong GL, Hansen HJ, et al. The processing and fate of antibodies and their radiolabels bound to the surface of tumor cells in vitro: a comparison of nine radiolabels. J Nucl Med 1994;35 (5):899-908.

25 Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA: Cancer Journal of Clinicians 2023;73 (1):17-48.

26 Stein R, Goldenberg DM, Thorpe SR, Basu A, Mattes MJ. Effects of radiolabeling monoclonal antibodies with a residualizing iodine radiolabel on the accretion of radioisotope in tumors. Cancer Res 1995;55 (14):3132-9.

27 Trivers KF, Lund MJ, Porter PL, Liff JM, Flagg EW, Coates RJ, et al. The epidemiology of triple-negative breast cancer, including race. Cancer Causes Control 2009;20 (7):1071-82.

28 Twelves C, Awada A, Cortes J, Yelle L, Velikova G, Olivo MS, et al. Subgroup Analyses from a Phase

3, Open-Label, Randomized Study of Eribulin Mesylate Versus Capecitabine in Pretreated Patients with Advanced or Metastatic Breast Cancer. Breast Cancer: Basic and Clinical Research 2016;10:77-84.

29 Vidula N, Yau C, Rugo H. Trop2 gene expression (Trop2e) in primary breast cancer (BC): Correlations with clinical and tumor characteristics. Journal of Clinical Oncology ASCO Abstracts 2017.

30 Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/College of American Pathologists Clinical Practice Guideline Focused Update. J Clin Oncol 2018;36 (20):2105-22.

31 Zeichner SB, Terawaki H, Gogineni K. A Review of Systemic Treatment in Metastatic Triple-Negative Breast Cancer. Breast Cancer: Basic and Clinical Research 2016;10:25-36.

32 Zeybek B, Manzano A, Bianchi A, Bonazzoli E, Bellone S, Buza N, et al. Cervical carcinomas that overexpress human trophoblast cell-surface marker (Trop-2) are highly sensitive to the antibody-drug conjugate sacituzumab govitecan. Sci Rep 2020;10 (1):973.

サシツズマブ　ゴビテカン（遺伝子組換え）

第１部 申請書等行政情報及び添付文書に関する情報

1.6 外国における使用状況等に関する資料

ギリアド・サイエンシズ株式会社

目次

頁
略号一覧表 3
1　外国における使用状況 4
2　外国における添付文書 5

略号一覧表

略号	英語	日本語
HER2	human epidermal growth factor receptor 2	ヒト上皮増殖因子受容体 2 型
PD-1	programmed cell death-1	－
PD-L1	programmed cell death-ligand 1	－

1　　外国における使用状況

サシツズマブ　ゴビテカン（遺伝子組換え）（以下、本剤）は、米国で 2020 年 4 月 22 日に 2 つ以上の前治療歴を有する成人の転移・再発トリプルネガティブ乳癌患者の治療薬として迅速承認され、2021 年 4 月 7 日に 2 つ以上の全身療法による前治療歴（少なくとも 1 つの進行乳癌に対する前治療歴を含む）を有する成人の切除不能又は転移・再発トリプルネガティブ乳癌患者の治療薬として正式承認された。また本剤は、欧州経済地域において同適応症の治療薬として 2021 年 11 月 22 日に承認された。当該適応症は 2024 年 5 月末日時点で、米国、欧州経済地域の各国、中国、台湾、韓国、香港、シンガポール、オーストラリア、カナダ、英国、スイス及びブラジルを含む 48 の国又は地域で承認済みである。

さらに本剤は、米国で 2023 年 2 月 3 日に、欧州経済地域では 2023 年 7 月 26 日に、内分泌療法による前治療歴に加え、転移・再発乳癌に対する 2 つ以上の全身療法による前治療歴を有する成人の切除不能な局所進行又は転移・再発ホルモン受容体陽性かつヒト上皮増殖因子受容体 2 型（HER2）陰性乳癌に対する適応症が承認された。当該適応症は 2024 年 5 月末日時点で、米国、欧州経済地域の各国、台湾、香港、シンガポール、オーストラリア、カナダ、スイス及びブラジルを含む 43 の国又は地域で承認済みである。また、米国では、2021 年 4 月 13 日にプラチナ製剤を含む化学療法の治療歴、及び programmed cell death-1（PD-1）阻害剤又は programmed cell death-ligand 1（PD-L1）阻害剤のいずれかの治療歴がある局所進行又は転移性尿路上皮癌の治療薬として迅速承認された。

2　　外国における添付文書

本剤の企業中核データシート（20[redacted]年[redacted]月[redacted]日[redacted]版原文）を以下に添付する。また、米国添付文書（2023 年 2 月改訂）、欧州製品概要（2023 年 7 月改訂）及びそれらの和訳を以下に添付する。

TRODELVY®
(sacituzumab govitecan)

COMPANY CORE DATA SHEET (CCDS)
[redacted]

Gilead Sciences Inc.
333 Lakeside Drive
Foster City, California 94404
USA

[redacted] **20**[redacted]

[redacted]

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use TRODELVY safely and effectively. See full prescribing information for TRODELVY

TRODELVY® (sacituzumab govitecan-hziy) for injection, for intravenous use
Initial U.S. Approval: 2020

WARNING: NEUTROPENIA AND DIARRHEA
See full prescribing information for complete boxed warning.

Severe or life threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis. Initiate anti-infective treatment in patients with febrile neutropenia without delay. (2.3, 5.1)

Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses. (2.3, 5.2)

----------RECENT MAJOR CHANGES----------

Boxed Warning	02/2023
Indications and Usage (1.1)	02/2023
Dosage and Administration (2.3)	02/2023
Dosage and Administration (2.4)	12/2022
Warnings and Precautions (5.1, 5.2, 5.3, 5.4, 5.5)	02/2023

----------INDICATIONS AND USAGE----------
TRODELVY is a Trop-2-directed antibody and topoisomerase inhibitor conjugate indicated for the treatment of adult patients with:

Locally Advanced or Metastatic Breast Cancer
- Unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease. (1.1, 14.1)
- Unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting. (1.1, 14.2)

Locally Advanced or Metastatic Urothelial Cancer
- Locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.[a] (1.2)

[a] This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

----------DOSAGE AND ADMINISTRATION----------
- Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38. (2.1)
- For intravenous infusion only. Do not administer as an intravenous push or bolus.
- The recommended dose is 10 mg/kg once weekly on Days 1 and 8 of continuous 21-day treatment cycles until disease progression or unacceptable toxicity. (2.2)
- Premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting is recommended. (2.2)
- Monitor patients during the infusion and for at least 30 minutes after completion of infusion. Treatment interruption and/or dose reduction may be needed to manage adverse reactions. (2.2)
- See Full Prescribing Information for preparation and administration instructions. (2.4)

----------DOSAGE FORMS AND STRENGTHS----------
For injection: 180 mg lyophilized powder in single-dose vials for reconstitution. (3)

----------CONTRAINDICATIONS----------
Severe hypersensitivity reaction to TRODELVY. (4, 5.3)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity and Infusion-Related Reactions: Hypersensitivity reactions including severe anaphylactic reactions have been observed. Monitor patients for infusion-related reactions. Permanently discontinue TRODELVY if severe or life-threatening reactions occur. (5.3)
- Nausea/Vomiting: Use antiemetic preventive treatment and withhold TRODELVY for patients with Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment. (5.4)
- Patients with Reduced UGT1A1 Activity: Individuals who are homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia following initiation of TRODELVY treatment. (5.5)
- Embryo-Fetal Toxicity: TRODELVY can cause fetal harm. Advise patients of potential risk to a fetus and to use effective contraception. (5.6, 8.1, 8.3)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence ≥ 25%) are (including laboratory abnormalities) were decreased leukocyte count, decreased neutrophil count, decreased hemoglobin, diarrhea, nausea, decreased lymphocyte count, fatigue, alopecia, constipation, increased glucose, decreased albumin, vomiting, decreased appetite, decreased creatinine clearance, increased alkaline phosphatase, decreased magnesium, decreased potassium, and decreased sodium. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-888-983-4668 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- UGT1A1 inhibitors or inducers: Avoid concomitant use. (7)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Advise not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 02/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: NEUTROPENIA AND DIARRHEA
1 INDICATIONS AND USAGE
- 1.1 Locally Advanced or Metastatic Breast Cancer
- 1.2 Locally Advanced or Metastatic Urothelial Cancer

2 DOSAGE AND ADMINISTRATION
- 2.1 Important Use Information
- 2.2 Recommended Dosage
- 2.3 Dose Modifications for Adverse Reactions
- 2.4 Preparation and Administration

3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
- 5.1 Neutropenia
- 5.2 Diarrhea
- 5.3 Hypersensitivity and Infusion Related Reactions
- 5.4 Nausea and Vomiting
- 5.5 Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity
- 5.6 Embryo-Fetal Toxicity

6 ADVERSE REACTIONS
- 6.1 Clinical Trials Experience

7 DRUG INTERACTIONS
- 7.1 Effect of Other Drugs on Trodelvy

8 USE IN SPECIFIC POPULATIONS
- 8.1 Pregnancy
- 8.2 Lactation
- 8.3 Females and Males of Reproductive Potential
- 8.4 Pediatric Use
- 8.5 Geriatric Use
- 8.6 Hepatic Impairment

10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics
- 12.3 Pharmacokinetics
- 12.5 Pharmacogenomics
- 12.6 Immunogenicity

13 NONCLINICAL TOXICOLOGY
- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
- 14.1 Locally Advanced or Metastatic Triple-Negative Breast Cancer
- 14.2 Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer
- 14.3 Locally Advanced or Metastatic Urothelial Cancer

15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: NEUTROPENIA AND DIARRHEA

- **Severe or life threatening neutropenia may occur. Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 or neutropenic fever. Monitor blood cell counts periodically during treatment. Consider G-CSF for secondary prophylaxis *[see Dosage and Administration (2.3)]*. Initiate anti-infective treatment in patient with febrile neutropenia without delay *[see Warnings and Precautions (5.1)]*.**
- **Severe diarrhea may occur. Monitor patients with diarrhea and give fluid and electrolytes as needed. At the onset of diarrhea, evaluate for infectious causes and, if negative, promptly initiate loperamide *[see Warnings and Precautions (5.2)]*. If severe diarrhea occurs, withhold TRODELVY until resolved to ≤ Grade 1 and reduce subsequent doses *[see Dosage and Administration (2.3)]*.**

1 INDICATIONS AND USAGE

1.1 Locally Advanced or Metastatic Breast Cancer

- TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior systemic therapies, at least one of them for metastatic disease.

- TRODELVY is indicated for the treatment of adult patients with unresectable locally advanced or metastatic hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer who have received endocrine-based therapy and at least two additional systemic therapies in the metastatic setting.

1.2 Locally Advanced or Metastatic Urothelial Cancer

- TRODELVY is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC) who have previously received a platinum-containing chemotherapy and either programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor.

  This indication is approved under accelerated approval based on tumor response rate and duration of response *[see Clinical Studies (14.3)]*. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

2 DOSAGE AND ADMINISTRATION

2.1 Important Use Information

Do NOT substitute TRODELVY for or use with other drugs containing irinotecan or its active metabolite SN-38.

2.2 Recommended Dosage

The recommended dosage of TRODELVY is 10 mg/kg administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles. Continue treatment until disease progression or unacceptable toxicity. Do not administer TRODELVY at doses greater than 10 mg/kg.

Administer TRODELVY as an intravenous infusion only. Do not administer as an intravenous push or bolus.

First infusion: Administer infusion over 3 hours. Observe patients during the infusion and for at least 30 minutes following the initial dose, for signs or symptoms of infusion-related reactions *[see Warning and Precautions (5.3)]*.

Subsequent infusions: Administer infusion over 1 to 2 hours if prior infusions were tolerated. Observe patients during the infusion and for at least 30 minutes after infusion.

Premedication

Prior to each dose of TRODELVY, premedication for prevention of infusion reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended.

- Premedicate with antipyretics, H1 and H2 blockers prior to infusion, and corticosteroids may be used for patients who had prior infusion reactions.
- Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist, as well as other drugs as indicated).

2.3 Dose Modifications for Adverse Reactions

Infusion-related Reactions

Slow or interrupt the infusion rate of TRODELVY if the patient develops an infusion-related reaction. Permanently discontinue TRODELVY for life-threatening infusion-related reactions *[see Warnings and Precautions (5.3)]*

Dose Modifications for Adverse Reactions

Withhold or discontinue TRODELVY to manage adverse reactions as described in Table 1. Do not re-escalate the TRODELVY dose after a dose reduction for adverse reactions has been made.

Table 1: Dose Modifications for Adverse Reactions

Adverse Reaction	**Occurrence**	**Dose Modification**
Severe Neutropenia *[see Warnings and Precautions (5.1)]*		
Grade 4 neutropenia ≥ 7 days OR Grade 3-4 febrile neutropenia, OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF).
	Second	50% dose reduction and administer G-CSF.
	Third	Discontinue treatment and administer G-CSF.
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment and administer G-CSF.

Adverse Reaction	Occurrence	Dose Modification
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents *[see Warnings and Precautions (5.2, 5.4)]*, OR Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

2.4 Preparation and Administration

Reconstitution

- TRODELVY is a hazardous drug.
- Follow applicable special handling and disposal procedures[1].
- Calculate the required dose (mg) of TRODELVY based on the patient's body weight at the beginning of each treatment cycle (or more frequently if the patient's body weight changed by more than 10% since the previous administration) *[see Dosage and Administration (2.2)]*.
- Allow the required number of vials to warm to room temperature.
- Using a sterile syringe, slowly inject 20 mL of 0.9% Sodium Chloride Injection, USP, into each 180 mg TRODELVY vial. Each vial contains overfill to compensate for liquid loss during preparation and after reconstitution, the total resulting volume delivers a **concentration of 10 mg/mL**.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discolored.
- Use immediately to prepare a diluted TRODELVY infusion solution.

Dilution

- Calculate the required amount of the reconstituted TRODELVY solution needed to obtain the appropriate dose according to the patient's body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a TRODELVY concentration range of 1.1 mg/mL to 3.4 mg/mL.
- Use 0.9% Sodium Chloride Injection, USP only since the stability of the reconstituted TRODELVY solution has not been determined with other infusion-based solutions. Use a polyvinyl chloride, polypropylene/polyethylene, polyolefin, or ethylene vinyl acetate infusion bag.
- Withdraw and discard the volume of 0.9% Sodium Chloride Injection, USP from the final infusion bag that is necessary to achieve the indicated TRODELVY concentration following the addition of the calculated amount of reconstituted TRODELVY solution.

- Withdraw the calculated amount of the reconstituted TRODELVY solution from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- To minimize foaming, slowly inject the calculated amount of reconstituted TRODELVY solution into the infusion bag. Do not shake the contents.
- If not used immediately, the infusion bag containing TRODELVY solution can be stored refrigerated at 2°C to 8°C (36°F to 46°F) for up to 24 hours protected from light. After refrigeration, administer diluted solution at room temperature up to 25°C (77°F) within 8 hours (including infusion time).

Do Not Freeze or Shake.

Administration

- Administer TRODELVY as an intravenous infusion. Protect infusion bag from light. The infusion bag should be covered during administration to the patient until dosing is complete. It is not necessary to cover the infusion tubing or to use light-protective tubing during the infusion.
- An infusion pump may be used.
- Do not mix TRODELVY, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the intravenous line with 20 mL 0.9% Sodium Chloride Injection, USP.

3 DOSAGE FORMS AND STRENGTHS

For injection: 180 mg off-white to yellowish lyophilized powder in a single-dose vial.

4 CONTRAINDICATIONS

TRODELVY is contraindicated in patients who have experienced a severe hypersensitivity reaction to TRODELVY *[see Warnings and Precautions (5.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Neutropenia

Severe, life-threatening, or fatal neutropenia can occur in patients treated with TRODELVY. Neutropenia occurred in 64% of patients treated with TRODELVY. Grade 3-4 neutropenia occurred in 49% of patients. Febrile neutropenia occurred in 6% of patients. The median time to first onset of neutropenia (including febrile neutropenia) was 16 days and has occurred earlier in some patient populations *[see Warnings and Precautions (5.5)]*. Neutropenic colitis occurred in 1.4% of patients.

Withhold TRODELVY for absolute neutrophil count below 1500/mm^3 on Day 1 of any cycle or neutrophil count below 1000/mm^3 on Day 8 of any cycle. Withhold TRODELVY for neutropenic fever. Dose modifications may be required due to neutropenia. Administer G-CSF as clinically indicated or indicated in Table 1 *[see Dosage and Administration (2.3)]*.

5.2 Diarrhea

TRODELVY can cause severe diarrhea. Diarrhea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 diarrhea occurred in 11% of all patients treated with TRODELVY. One patient had intestinal perforation following diarrhea. Diarrhea that led to dehydration and subsequent acute kidney injury occurred in 0.7% of all patients.

Withhold TRODELVY for Grade 3-4 diarrhea at the time of scheduled treatment administration and resume when resolved to ≤Grade 1 *[see Dosage and Administration (2.3)]*.

At the onset of diarrhea, evaluate for infectious causes and if negative, promptly initiate loperamide, 4 mg initially followed by 2 mg with every episode of diarrhea for a maximum of 16 mg daily. Discontinue loperamide 12 hours after

diarrhea resolves. Additional supportive measures (e.g., fluid and electrolyte substitution) may also be employed as clinically indicated.

Patients who exhibit an excessive cholinergic response to treatment with TRODELVY (e.g., abdominal cramping, diarrhea, salivation, etc.) can receive appropriate premedication (e.g., atropine) for subsequent treatments.

5.3 Hypersensitivity and Infusion-Related Reactions

Serious hypersensitivity reactions including life-threatening anaphylactic reactions have occurred with TRODELVY treatment. Severe signs and symptoms included cardiac arrest, hypotension, wheezing, angioedema, swelling, pneumonitis, and skin reactions *[see Contraindications (4)]*.

Hypersensitivity reactions within 24 hours of dosing occurred in 35% of patients treated with TRODELVY. Grade 3-4 hypersensitivity occurred in 2% of patients treated with TRODELVY. The incidence of hypersensitivity reactions leading to permanent discontinuation of TRODELVY was 0.2%. The incidence of anaphylactic reactions was 0.2%.

Premedication for infusion reactions in patients receiving TRODELVY is recommended. Have medications and emergency equipment to treat infusion-related reactions, including anaphylaxis, available for immediate use when administering TRODELVY *[see Dosage and Administration (2.2)]*.

Closely monitor patients for hypersensitivity and infusion-related reactions during each TRODELVY infusion and for at least 30 minutes after completion of each infusion *[see Dosage and Administration (2.3)]*.

Permanently discontinue TRODELVY for Grade 4 infusion-related reactions *[see Dosage and Administration (2.3)]*.

5.4 Nausea and Vomiting

TRODELVY is emetogenic. Nausea occurred in 64% of all patients treated with TRODELVY. Grade 3-4 nausea occurred in 3% of patients.

Vomiting occurred in 35% of all patients treated with TRODELVY. Grade 3-4 vomiting occurred in 2% of these patients.

Premedicate with a two or three drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or an NK_1 receptor antagonist as well as other drugs as indicated) for prevention of chemotherapy-induced nausea and vomiting (CINV) [*see Dosage and Administration (2.2)*].

Withhold TRODELVY doses for Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and resume with additional supportive measures when resolved to ≤Grade 1 *[see Dosage and Administration (2.3)]*.

Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medications with clear instructions for prevention and treatment of nausea and vomiting.

5.5 Increased Risk of Adverse Reactions in Patients with Reduced UGT1A1 Activity

Patients homozygous for the uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia; and may be at increased risk for other adverse reactions when treated with TRODELVY.

The incidence of neutropenia and anemia was analyzed in 948 patients who received TRODELVY and had UGT1A1 genotype results. In patients homozygous for the UGT1A1 *28 allele (n=112), the incidence of Grade 3-4 neutropenia was 58%. In patients heterozygous for the UGT1A1*28 allele (n=420), the incidence of Grade 3-4 neutropenia was 49%. In patients homozygous for the wild-type allele (n=416), the incidence of Grade 3-4 neutropenia was 43% *[see Clinical*

Pharmacology (12.5)]. In patients homozygous for the UGT1A1 *28 allele, the incidence of Grade 3-4 anemia was 21%. In patients heterozygous for the UGT1A1*28 allele, the incidence of Grade 3-4 anemia was 10%. In patients homozygous for the wild-type allele, the incidence of Grade 3-4 anemia was 9%.

The median time to first neutropenia including febrile neutropenia was 9 days in patients homozygous for the UGT1A1*28 allele, 15 days in patients heterozygous for the UGT1A1*28 allele, and 20 days in patients homozygous for the wild-type allele. The median time to first anemia was 21 days in patients homozygous for the UGT1A1*28 allele, 25 days in patients heterozygous for the UGT1A1*28 allele, and 28 days in patients homozygous for the wild-type allele.

Closely monitor patients with known reduced UGT1A1 activity for adverse reactions. Withhold or permanently discontinue TRODELVY based on clinical assessment of the onset, duration and severity of the observed adverse reactions in patients with evidence of acute early-onset or unusually severe adverse reactions, which may indicate reduced UGT1A1 enzyme activity *[see Dosage and Administration (2.3)]*.

5.6 Embryo-Fetal Toxicity

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. TRODELVY contains a genotoxic component, SN-38, and targets rapidly dividing cells *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Neutropenia *[see Warnings and Precautions (5.1)]*
- Diarrhea *[see Warnings and Precautions (5.2)]*
- Hypersensitivity and Infusion-Related Reactions *[see Warnings and Precautions (5.3)]*
- Nausea and Vomiting *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The pooled safety population described in the Warnings and Precautions section reflect exposure to TRODELVY in 1063 patients from four studies, IMMU-132-01, ASCENT, TROPiCS-02, and TROPHY which included 366 patients with mTNBC, 322 patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer, and 180 patients with mUC. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses of 10 mg/kg until disease progression or unacceptable toxicity. Among the 1063 patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 63 months). In this pooled safety population, the most common (≥ 25%) adverse reactions including laboratory abnormalities were decreased leukocyte count (84%), decreased neutrophil count (75%), decreased hemoglobin (69%), diarrhea (64%), nausea (64%), decreased lymphocyte count (63%), fatigue (51%), alopecia (45%), constipation (37%), increased glucose (37%), decreased albumin (35%), vomiting (35%), decreased appetite (30%), decreased creatinine clearance (28%), increased alkaline phosphatase (28%), decreased magnesium (27%), decreased potassium (26%), and decreased sodium (26%).

Locally Advanced or Metastatic Triple-Negative Breast Cancer

ASCENT Study

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label study (ASCENT) in patients with mTNBC who had previously received a taxane and at least two prior chemotherapies. Patients were randomized (1:1) to receive either TRODELVY (n=258) or single agent chemotherapy (n=224) and were treated until disease progression or unacceptable toxicity *[see Clinical Studies (14.1)]*. For patients treated with TRODELVY, the median duration of treatment was 4.4 months (range: 0 to 23 months).

Serious adverse reactions occurred in 27% of patients receiving TRODELVY. Serious adverse reactions in > 1% of patients receiving TRODELVY included neutropenia (7%), diarrhea (4%), and pneumonia (3%). Fatal adverse reactions occurred in 1.2% of patients who received TRODELVY, including respiratory failure (0.8%) and pneumonia (0.4%). TRODELVY was permanently discontinued for adverse reactions in 5% of patients. Adverse reactions leading to permanent discontinuation in ≥ 1 % of patients who received TRODELVY were pneumonia (1%) and fatigue (1%).

Adverse reactions leading to a treatment interruption of TRODELVY occurred in 63% of patients. The most frequent (≥5%) adverse reactions leading to a treatment interruption were neutropenia (47%), diarrhea (5%), respiratory infection (5%), and leukopenia (5%).

Adverse reactions leading to a dose reduction of TRODELVY occurred in 22% of patients. The most frequent (>4%) adverse reactions leading to a dose reduction were neutropenia (11%) and diarrhea (5%).

Granulocyte-colony stimulating factor (G-CSF) was used in 44% of patients who received TRODELVY.

Tables 2 and 3 summarize adverse reactions and laboratory abnormalities, respectively, in the ASCENT study.

Table 2: Adverse Reactions in ≥ 10% of Patients with mTNBC in ASCENT

	TRODELVY (n=258)		**Single Agent Chemotherapy (n=224)**	
Adverse Reaction	**All Grades %**	**Grade 3 - 4 %**	**All Grades %**	**Grade 3 - 4 %**
Gastrointestinal disorders				
Diarrhea	59	11	17	1
Nausea	57	3	26	0.4
Vomiting	33	2	16	1
Constipation	37	0.4	23	0
Abdominal Pain	30	3	12	1
Stomatitis[i]	17	2	13	1
General disorders and administration site conditions				
Fatigue[ii]	65	6	50	9
Pyrexia	15	0.4	14	2
Infections and infestation				
Urinary tract infection	13	0.4	8	0.4
Upper respiratory tract infection	12	0	3	0
Metabolism and nutrition disorders				

Decreased appetite	28	2	21	1
Musculoskeletal and connective tissue disorders				
Back pain	16	1	14	2
Arthralgia	12	0.4	7	0
Nervous system disorders				
Headache	18	0.8	13	0.4
Dizziness	10	0	7	0
Psychiatric disorders				
Insomnia	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Cough	24	0	18	0.4
Skin and subcutaneous tissue disorders				
Alopecia	47	0	16	0
Rash	12	0.4	5	0.4
Pruritus	10	0	3	0

*Single agent chemotherapy included one of the following single-agents: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (except if patient had ≥ Grade 2 neuropathy, n=52).

Graded per NCI CTCAE v.5.0.

[i.] Including stomatitis, glossitis, mouth ulceration, and mucosal inflammation

[ii.] Including fatigue and asthenia

Table 3: Laboratory Abnormalities in > 10% of Patients with mTNBC in ASCENT

Laboratory Abnormality	**TRODELVY (n=258)**		**Single Agent Chemotherapy (n=224)**	
	All Grades (%)	**Grade 3 - 4 (%)**	**All Grades (%)**	**Grade 3 - 4 (%)**
Hematology				
Decreased hemoglobin	94	9	57	6
Decreased lymphocyte count	88	31	40	24
Decreased leukocyte count	86	41	53	25
Decreased neutrophil count	78	49	48	36
Decreased platelet count	23	1.2	25	2.7
Chemistry				
Increased glucose	49	2.3	43	2.8
Decreased calcium	36	1.6	21	1.4
Decreased magnesium	33	0.4	20	0
Decreased potassium	33	4.3	28	0.9
Increased albumin	32	0.8	25	1.4
Increased aspartate aminotransferase	27	1.2	32	1.4
Increased alanine aminotransferase	26	1.2	26	1.8
Increased alkaline phosphatase	26	0	17	0.5
Decreased phosphate	26	7.8	20	3.3
Decreased sodium	22	0.4	17	0.5
Increased lactate dehydrogenase	18	0	22	0
Decreased glucose	10	0	3.2	0

Study IMMU-132-01

The safety of TRODELVY was evaluated in a single-arm, open-label study (IMMU-132-01) in patients with mTNBC and other malignancies, which included 108 patients with mTNBC who had received at least two prior anticancer therapies for metastatic disease *[see Clinical Studies (14.1)]*. TRODELVY was administered as an intravenous infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses up to 10 mg/kg until disease progression or unacceptable toxicity. The median treatment duration in these 108 patients was 5.1 months (range: 0 to 51 months).

Serious adverse reactions occurred in 31% of the patients. Serious adverse reactions in > 1% of patients receiving TRODELVY included febrile neutropenia (6%) vomiting (5%), nausea (3%), dyspnea (3%), diarrhea (4%), anemia (2%), pleural effusion, neutropenia, pneumonia, dehydration (each 2%).

TRODELVY was permanently discontinued for adverse reactions in 2% of patients. Adverse reactions leading to permanent discontinuation were anaphylaxis, anorexia/fatigue, headache (each 0.9%). Forty- five percent (45%) of patients experienced an adverse reaction leading to treatment interruption. The most common adverse reaction leading to treatment interruption was neutropenia (33%). Adverse reactions leading to dose reduction occurred in 33% of patients treated with TRODELVY, with 24% having one dose reduction, and 9% with two dose reductions. The most common adverse reaction leading to dose reductions was neutropenia/febrile neutropenia.

Tables 4 and 5 summarize adverse reactions and laboratory abnormalities occurring in ≥10% of patients with mTNBC in the IMMU-132-01 study.

Table 4: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any adverse reaction	100	71
Gastrointestinal disorders	95	21
Nausea	69	6
Diarrhea	63	9
Vomiting	49	6
Constipation	34	1
Abdominal pain[i]	26	1
Mucositis[ii]	14	1
General disorders and administration site conditions	77	9
Fatigue[iii]	57	8
Edema[iv]	19	0
Pyrexia	14	0
Metabolism and nutrition disorders	68	22
Decreased appetite	30	1
Dehydration	13	5
Skin and subcutaneous tissue disorders	63	4
Alopecia	38	0
Rash[v]	31	3

Table 4: Adverse Reactions in ≥ 10% of Patients with mTNBC in IMMU-132-01

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Pruritus	17	0
Dry Skin	15	0
Nervous system disorders	56	4
Headache	23	1
Dizziness	22	0
Neuropathy[vi]	24	0
Dysgeusia	11	0
Infections and infestations	55	12
Urinary Tract Infection	21	3
Respiratory Infection[vii]	26	3
Musculoskeletal and connective tissue disorders	54	1
Back pain	23	0
Arthralgia	17	0
Pain in extremity	11	0
Respiratory, thoracic and mediastinal disorders	54	5
Cough[viii]	22	0
Dyspnea[ix]	21	3
Psychiatric disorders	26	1
Insomnia	13	0

Graded per NCI CTCAE v. 4.0

[i.] Including abdominal pain, distention, pain (upper), discomfort, tenderness.

[ii] Including stomatitis, esophagitis, and mucosal inflammation

[iii] Including fatigue and asthenia.

[iv] Including edema; and peripheral, localized, and periorbital edema

[v] Including rash; maculopapular, erythematous, generalized rash; dermatitis acneiform; skin disorder, irritation, and exfoliation

[vi] Including gait disturbance, hypoesthesia, muscular weakness, paresthesia, peripheral and sensory neuropathy

[vii] Including lower and upper respiratory tract infection, pneumonia, influenza, viral upper respiratory infection, bronchitis and respiratory syncytial virus infection

[viii] Includes cough and productive cough

[ix] Includes dyspnea and exertional dyspnea

Table 5: Laboratory Abnormalities observed in ³ 10% of Patients while receiving TRODELVY in IMMU-132-01

Laboratory Abnormality	TRODELVY (n=108)	
	All Grades (%)	Grade 3-4 (%)
Hematology		
Decreased hemoglobin	93	6
Decreased leukocyte count	91	26
Decreased neutrophil count	82	32
Increased activated partial thromboplastin time	60	12
Decreased platelet count	30	3
Chemistry		
Increased alkaline phosphatase	57	2
Decreased magnesium	51	3
Decreased calcium	49	3
Increased aspartate aminotransferase	45	3
Decreased albumin	39	1
Increased alanine aminotransferase	35	2
Increased glucose	31	2.8
Decreased phosphate	29	5
Decrease magnesium	27	1.9
Decreased phosphate	27	6.5
Decreased sodium	25	4.7
Decreased potassium	24	3.7
Decreased glucose	19	2

Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer

TROPiCS-02 Study

The safety of TRODELVY was evaluated in a randomized, active-controlled, open-label, study (TROPiCS-02) in patients with unresectable locally advanced or metastatic HR-positive, HER2-negative breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression occurred within 12 months). Patients were randomized (1:1) to receive either TRODELVY (n=268) or single agent chemotherapy (n=249) and were treated until disease progression or unacceptable toxicity *[see Clinical Studies (14.2)]*.For patients treated with TRODELVY, the median duration of treatment was 4.1 months (range: 0 to 63 months).

Serious adverse reactions occurred in 28% of patients receiving TRODELVY. Serious adverse reactions in >1% of patients receiving TRODELVY included diarrhea (5%), febrile neutropenia (4%), neutropenia (3%), abdominal pain, colitis, neutropenic colitis, pneumonia, and vomiting (each 2%). Fatal adverse reactions occurred in 2% of patients who received TRODELVY including arrhythmia, COVID-19, nervous system disorder, pulmonary embolism, and septic shock (each 0.4%). TRODELVY was permanently discontinued for adverse reactions in 6% of patients. The most frequent (≥0.5%) adverse reactions leading to permanent discontinuation in patients who received TRODELVY were asthenia, general physical health deterioration, and neutropenia (each 0.7%).

Adverse reactions leading to a treatment interruptions of TRODELVY occurred in 66% of patients. The most frequent (≥5%) adverse reaction leading to treatment interruption was neutropenia (50%).

Adverse reaction leading to a dose reduction of TRODELVY occurred in 33% of patients. The most frequent (>5%) adverse reaction leading ot dose reduction were neutropenia (16%) and diarrhea (8%). G-CSF was used in 54% of patients who received TRODELVY.

Tables 6 and 7 summarize adverse reactions and laboratory abnormalities in the TROPiCS-02 study.

Table 6: Adverse Reactions in ≥ 10% of Patients with HR+/HER2- mBC in TROPiCS-02

	TRODELVY (n=268)		**Single Agent Chemotherapy (n=249)**	
Adverse Reaction	**All Grades %**	**Grade 3 - 4 %**	**All Grades %**	**Grade 3 - 4 %**
Gastrointestinal disorders				
Diarrhea	62	10	23	1
Nausea	59	1	35	3
Constipation	34	1	25	0
Vomiting	23	1	16	2
Abdominal Pain	20	0	14	0
Dyspepsia[i]	11	0	6	0
General disorders and administration site conditions				
Fatigue[ii]	60	8	51	4
Metabolism and nutrition disorders				
Decreased appetite	21	2	21	0
Hypokalemia	10	2	4	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	12	0
Nervous system disorders				
Headache	16	1	15	1
Respiratory, thoracic and mediastinal disorders				
Dyspnea [iii]	20	0	17	0
Cough	12	0	7	0
Skin and subcutaneous tissue disorders				
Alopecia	48	0	19	0
Pruritus	12	0	2	0

*Single agent chemotherapy included one of the following single-agents: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22).
Graded per NCI CTCAE v.5.0.
[i.] Including dyspepsia, gastroesophageal reflux disease.
[ii.] Including fatigue, asthenia.
[iii.] Including dyspnea; exertional dyspnea

Other clinically significant adverse reactions in TROPiCS-02 (≤ 10%) include: hypotension (5%), pain (5%), rhinorrhea (5%), hypocalcemia (3%), nasal congestion (3%), skin hyperpigmentation, (3%), colitis or neutropenic colitis (2%), hyponatremia (2%), pneumonia (2%), proteinuria (1%), enteritis (0.4%).

Table 7: Laboratory Abnormalities in > 10% of Patients with HR+/HER2- mBC in TROPiCS-02

Laboratory Abnormality	**TRODELVY (n=268)**		**Single Agent Chemotherapy (n=249)**	
	All Grades (%)	**Grade 3 - 4 (%)**	**All Grades (%)**	**Grade 3 - 4 (%)**
Hematology				
Decreased leukocyte count	88	38	73	26
Decreased neutrophil count	83	53	67	40
Decreased hemoglobin	73	8	59	5
Decreased lymphocyte count	65	21	47	14
Decreased platelet count	21	1	30	4
Eosinophilia	13	0	4	0
Chemistry				
Increased glucose	37	0	31	0
Decreased albumin	32	0	27	0.4
Decreased creatinine clearance	24	2	19	1
Increased alkaline phosphatase	23	0	23	1
Decreased potassium	22	3	12	0.4
Increased alanine aminotransferase	21	1	31	2
Decreased sodium	19	1	17	0.4
Decreased magnesium	18	0	15	0
Decreased phosphate	17	0	10	0
Increased phosphate	16	0	16	0
Increased lactate dehydrogenase	16	0	28	0
Increased aspartate aminotransferase	15	2	25	1
Increased potassium	14	2	9	0

Locally Advanced or Metastatic Urothelial Cancer

TROPHY Study

The safety of TRODELVY was evaluated in a single-arm, open-label study in patients (n=113) with mUC who had received previous platinum-based and anti-PD-1/PD-L1 therapy. TRODELVY was administered as an intravenous

infusion once weekly on Days 1 and 8 of 21-day treatment cycles at doses of 10 mg/kg until disease progression or unacceptable toxicity. (*see Clinical Studies 4.3*)

Serious adverse reactions occurred in 44% of patients. Serious adverse reactions in >1% of patients receiving TRODELVY included infection (18%), neutropenia (12%, including febrile neutropenia in 10%), acute kidney injury (6%), urinary tract infection (6%), sepsis or bacteremia (5%), diarrhea (4%), anemia, venous thromboembolism, and small intestinal obstruction (3% each), pneumonia, abdominal pain, pyrexia, and thrombocytopenia (2% each). Fatal adverse reactions occurred in 3.6% of patients, including sepsis, respiratory failure, epistaxis, and completed suicide.

TRODELVY was permanently discontinued for adverse reactions in 10% of patients. The most frequent adverse reaction leading to permanent discontinuation of study drug was neutropenia (4%, including febrile neutropenia in 2%). Adverse reactions leading to dose interruption occurred in 52% of patients. The most common adverse reactions leading to dose interruption were neutropenia (27%, including febrile neutropenia in 2%), infection (12%), and acute kidney injury (8%). Adverse reactions leading to a dose reduction of TRODELVY occurred in 42% of patients. The most common (> 4%) adverse reactions leading to a dose reduction were neutropenia (13%, including febrile neutropenia in 3%), diarrhea (11%), fatigue (8%), and infection (4%). Granulocyte-colony stimulating factor (G-CSF) was used in 47% of patients who received TRODELVY.

The most common (≥ 25%) adverse reactions including laboratory abnormalities were decreased leukocyte count (78%), diarrhea (72%), decreased hemoglobin (71%), decreased lymphocyte count (71%), decreased neutrophil count (67%), nausea (66%), increased glucose (59%), fatigue (56%), decreased albumin (51%), alopecia (49%), decreased calcium (46%), decreased sodium (43%), decreased appetite (41%), decreased phosphate (41%), increased alkaline phosphatase (36%), constipation (34%), vomiting (34%), increased activated partial thromboplastin time (33%), increased creatinine (32%), decreased magnesium (31%), increased alanine aminotransferase (28%), increased lactate dehydrogenase (28%), abdominal pain (27%), decreased potassium (27%), increased aspartate aminotransferase (26%), and decreased platelet count (25%).

Tables 8 and 9 summarize adverse reactions and laboratory abnormalities occurring in ≥10% of patients with mUC in the TROPHY study.

Table 8: Adverse Reactions Reported in ≥ 15% (Grade 1-4) or ≥ 5% (Grade ≥ 3) of Patients Treated with TRODELVY in TROPHY

	TRODELVY n=113	
Adverse Reaction	**Grade 1-4 %**	**Grade 3-4 %**
Any adverse reaction	94	80
Gastrointestinal disorders		
Diarrhea	72	12
Nausea	66	4
Constipation	34	1
Vomiting	34	1
Abdominal pain[i]	31	2
General disorders and administration site conditions		
Fatigue[ii]	68	5
Pyrexia	19	0
Edema[iii]	17	2

Skin and subcutaneous tissue disorders		
Alopecia	49	0
Rash[iv]	32	2
Metabolism and nutrition disorders		
Decreased appetite	41	3
Weight loss[v]	17	2
Renal and urinary disorders		
Acute kidney injury[vi]	24	7
Hematuria	16	1
Infections and infestations		
Any infection[vii]	50	25
Urinary tract infection	19	12
Respiratory, thoracic and mediastinal disorders		
Cough[viii]	17	0
Dyspnea	16	0
Musculoskeletal disorders		
Back pain	16	0
Vascular disorders		
Venous thromboembolism[ix]	9	6

Graded per NCI CTCAE v.5.0.
[i.] Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
[ii.] Includes fatigue and asthenia
[iii.] Includes edema genital, edema peripheral, peripheral swelling
[iv] Includes dermatitis acneiform, dermatitis bullous, erythema, lichen planus, photosensitivity reaction, pruritus, pruritus generalised, rash, rash macular, rash maculo-papular, rash pruritic, skin papilloma, skin toxicity
[v] Includes failure to thrive and weight decreased
[vi] Includes acute kidney injury, blood creatinine increased, nephropathy toxic, renal failure, renal impairment
[vii] Includes bacteremia, body tinea, bronchitis, candida infection, cellulitis, clostridium difficile infection, corona virus infection, device related infection, diverticulitis, escherichia bacteremia, escherichia pyelonephritis, folliculitis, gastroenteritis, gastroenteritis escherichia coli, herpes zoster, kidney infection, klebsiella sepsis, lung infection, nasopharyngitis, oral candidiasis, oral herpes, pneumonia, pyelonephritis, pyelonephritis acute, respiratory tract infection, rhinitis, sepsis, sinusitis, skin infection, tooth abscess, upper respiratory tract infection, urinary tract infection, urosepsis, vascular device infection, viral infection, viral pharyngitis, vulvovaginal mycotic infection
[viii] Includes cough, productive cough, upper-airway cough syndrome
[ix] Includes deep vein thrombosis, embolism, and pulmonary embolism

Other clinically significant adverse reactions in TROPHY (≤ 15%) include: peripheral neuropathy (12%), sepsis or bacteremia (9%), and pneumonia (4%).

Table 9: Laboratory Abnormalities Reported in ≥ 20% (Any Grade) or ≥ 5% (Grade 3-4) of Patients Treated with TRODELVY in TROPHY

Adverse Reaction	TRODELVY n = 113	
	Any Grade* %	Grade 3-4* %
Hematology		
Decreased leukocyte count	78	38
Decreased lymphocyte count	71	35
Decreased hemoglobin	71	18
Decreased neutrophil count	67	43
Decreased platelet count	25	2
Chemistry		
Increased glucose	59	8
Decreased albumin	51	4
Decreased calcium	46	9
Decreased sodium	43	1
Decreased phosphate	41	15
Increased alkaline phosphatase	36	0
Increased creatinine	32	5
Decreased magnesium	31	2
Increased alanine aminotransferase	28	2
Increased lactate dehydrogenase	28	0
Decreased potassium	27	0
Increased aspartate aminotransferase	26	2
Coagulation		
Increased activated partial thromboplastin time	33	6

*Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available (range: 66 to 111 patients).

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on TRODELVY

UGT1A1 Inhibitors

Concomitant administration of TRODELVY with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38 *[see Warning and Precaution (5.5) and Clinical Pharmacology (12.3, 12.5)]*. Avoid administering UGT1A1 inhibitors with TRODELVY.

UGT1A1 Inducers

Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers *[see Warning and Precaution (5.5) and Clinical Pharmacology (12.3, 12.5)]*. Avoid administering UGT1A1 inducers with TRODELVY.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, TRODELVY can cause teratogenicity and/or embryo-fetal lethality when administered to a pregnant woman. There are no available data in pregnant women to inform the drug-associated risk. TRODELVY contains a genotoxic component, SN-38, and is toxic to rapidly dividing cells *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*. Advise pregnant women and females of reproductive potential of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 – 4% and 15 – 20%, respectively.

Data

Animal data

There were no reproductive and developmental toxicology studies conducted with sacituzumab govitecan-hziy.

8.2 Lactation

Risk Summary

There is no information regarding the presence of sacituzumab govitecan-hziy or SN-38 in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of TRODELVY.

Contraception

Females

TRODELVY can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with TRODELVY and for 6 months after the last dose.

Males

Because of the potential for genotoxicity, advise male patients with female partners of reproductive potential to use effective contraception during treatment with TRODELVY and for 3 months after the last dose.

Infertility

Females

Based on findings in animals, TRODELVY may impair fertility in females of reproductive potential *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of TRODELVY have not been established in pediatric patients.

8.5 Geriatric Use

Of the 366 patients with TNBC who were treated with TRODELVY, 19% of patients were 65 years and 3% were 75 years and older. No overall differences in safety and effectiveness were observed between patients ≥ 65 years of age and younger patients.

Of the 322 patients with HR+/HER2- breast cancer who were treated with TRODELVY, 26% of patients were 65 years and older and 6% were 75 years and older. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%).

Of the 180 patients with UC who were treated with TRODELVY, 59% of patients were 65 years and older and 27% were 75 years and older. No overall differences in effectiveness were observed between patients ≥ 65 years of age and younger patients. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (8%).

8.6 Hepatic Impairment

No adjustment to the starting dosage is required when administering TRODELVY to patients with mild hepatic impairment *[see Clinical Pharmacology (12.3)]*.

The safety of TRODELVY in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN) or severe (total bilirubin > 3.0 × upper limit of normal [ULN]) hepatic impairment has not been established. TRODELVY has not been tested in patients with AST or ALT > 3 ULN without liver metastases, or AST or ALT > 5 ULN with liver metastases. No recommendations can be made for the starting dosage in these patients.

10 OVERDOSAGE

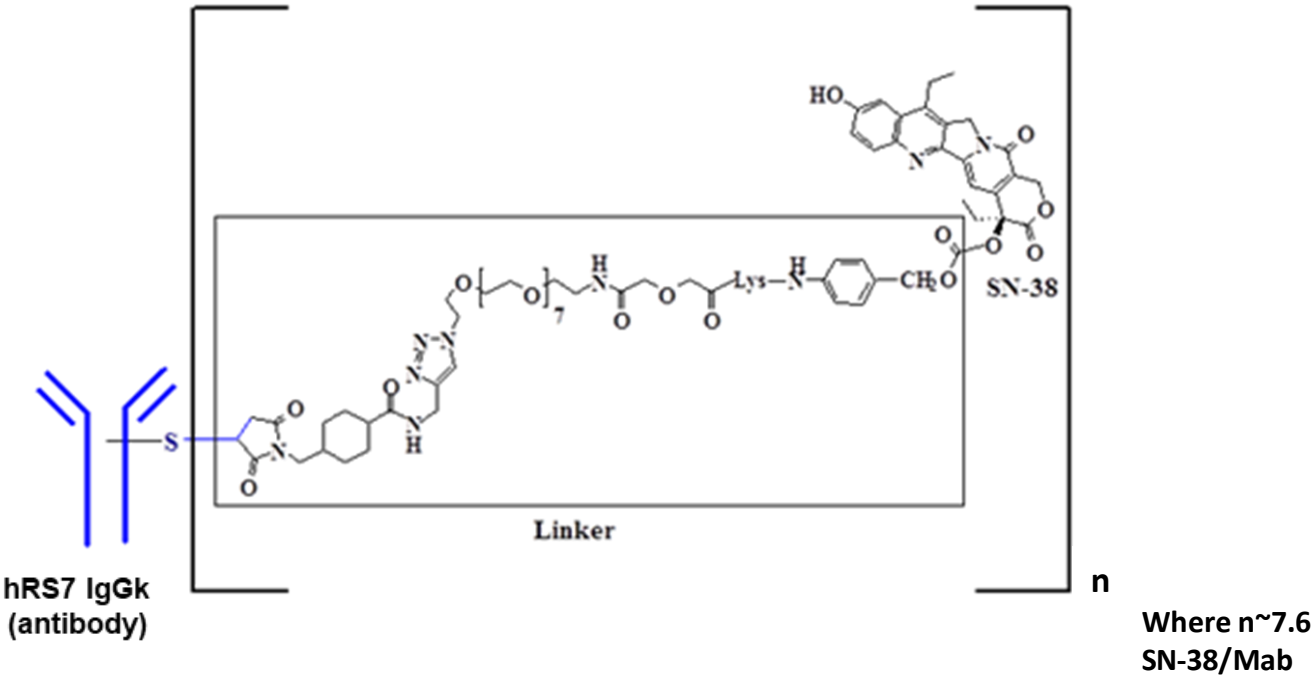
In a clinical trial, planned doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg) of TRODELVY were administered. In these patients, a higher incidence of severe neutropenia was observed.

11 DESCRIPTION

Sacituzumab govitecan-hziy is a Trop-2 directed antibody and topoisomerase inhibitor conjugate, composed of the following three components:

- the humanized monoclonal antibody, hRS7 IgG1κ (also called sacituzumab), which binds to Trop-2 (the trophoblast cell-surface antigen-2);
- the drug SN-38, a topoisomerase inhibitor;
- a hydrolysable linker (called CL2A), which links the humanized monoclonal antibody to SN-38.

The recombinant monoclonal antibody is produced by mammalian (murine myeloma) cells, while the small molecule components SN-38 and CL2A are produced by chemical synthesis. Sacituzumab govitecan-hziy contains on average 7 to 8 molecules of SN-38 per antibody molecule. Sacituzumab govitecan-hziy has a molecular weight of approximately 160 kilodaltons. Sacituzumab govitecan-hziy has the following chemical structure.



TRODELVY (sacituzumab govitecan-hziy) for injection is a sterile, preservative-free, off-white to yellowish lyophilized powder for intravenous use in a 50 mL clear glass single-dose vial, with a rubber stopper and crimp-sealed with an aluminum flip-off cap.

Each single-dose vial of TRODELVY delivers 180 mg sacituzumab govitecan-hziy, 77.3 mg 2-(N-morpholino) ethane sulfonic acid (MES), 1.8 mg polysorbate 80 and 154 mg trehalose dihydrate. Reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP, results in a concentration of 10 mg/mL with a pH of 6.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Sacituzumab govitecan-hziy is a Trop-2-directed antibody-drug conjugate. Sacituzumab is a humanized antibody that recognizes Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker. Pharmacology data suggest that sacituzumab govitecan-hziy binds to Trop-2-expressing cancer cells and is internalized with the subsequent release of SN-38 via hydrolysis of the linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death. Sacituzumab govitecan-hziy decreased tumor growth in mouse xenograft models of triple-negative breast cancer.

12.2 Pharmacodynamics

The TRODELVY exposure-response relationships and pharmacodynamic time course for efficacy have not been fully characterized.

Cardiac electrophysiology

The maximum mean change from baseline was 9.7 msec (the upper bound of the two-sided 90% confidence interval is 16.8 msec) at the recommended dose. A positive exposure-response relationship was observed between QTc increases and SN-38 concentrations.

12.3 Pharmacokinetics

The serum pharmacokinetics of sacituzumab govitecan-hziy and SN-38 were evaluated in patients with mBC who received sacituzumab govitecan-hziy as a single agent at a dose of 10 mg/kg. The pharmacokinetic parameters of sacituzumab govitecan-hziy and free SN-38 are presented in Table 10.

Table 10: Summary of Mean PK Parameters (CV%) of Sacituzumab Govitecan-hziy and Free SN-38*

	Sacituzumab govitecan-hziy (N=693)	**Free SN-38 (N=681)**
C_{max} [ng/mL]	239000 (11%)	98.0 (45%)
AUC_{0-168} [ng*h/mL]	5640000 (22%)	3696 (56%)

*Parameters estimated based on population PK analyses
C_{max}: maximum serum concentration from 0-168 hours after the first dose
AUC_{0-168}: area under serum concentration curve through 168 hours after the first dose

Distribution

Based on population pharmacokinetic analysis, steady state volume of distribution of sacituzumab govetican-hziy is 3.6L.

Elimination

The median elimination half-life ($t_{1/2}$) of sacituzumab govitecan-hziy and free SN-38 in patients with metastatic triple negative breast cancer was 23.4 and 17.6 hours, respectively. Based on population pharmacokinetic analysis, the estimated mean (%CV) clearance of the sacituzumab govitecan-hziy is 0.13 L/h (12%).

Metabolism

No metabolism studies with sacituzumab govitecan-hziy have been conducted. SN-38 (the small molecule moiety of sacituzumab govitecan-hziy) is metabolized via UGT1A1. The glucuronide metabolite of SN-38 (SN-38G) was detectable in the serum of patients.

Specific Populations

Pharmacokinetic analyses in patients treated with TRODELVY did not identify an effect of age (27 to 88 years), race (White, Black, or Asian), or mild renal impairment to moderate renal impairment(CLcr 30 to 89 mL/min) on the pharmacokinetics of sacituzumab govitecan-hziy. Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of sacituzumab govitecan-hziy. There are no data on the pharmacokinetics of sacituzumab govitecan-hziy in patients with severe renal impairment (CLcr 15 to 29 mL/min), or end-stage renal disease (CLcr < 15 mL/min).

Patients with Hepatic Impairment

The exposure of sacituzumab govitecan-hziy is similar in patients with mild hepatic impairment (total bilirubin ≤ ULN with AST > ULN, or bilirubin >1.0 to ≤ 1.5 ULN with any AST; n=257) to patients with normal hepatic function (total bilirubin or AST < ULN; n=526).

Sacituzumab govitecan-hziy and free SN-38 exposures are unknown in patients with moderate (total bilirubin > 1.5 to 3.0 × ULN) or severe (total bilirubin > 3.0 × ULN) hepatic impairment.

Drug Interaction Studies

No drug-drug interaction studies were conducted with sacituzumab govitecan-hziy or its components. Inhibitors or inducers of UGT1A1 may increase or decrease SN-38 exposure, respectively *[see Drug Interactions (7)]*.

12.5 Pharmacogenomics

SN-38 is metabolized via UGT1A1 [*see Clinical Pharmacology (12.3)*]. Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous or heterozygous for the UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anemia from TRODELVY compared to individuals who are wildtype (*1/*1) *[see Warnings and Precautions (5.5)].* Approximately 20% of the Black or African American population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele (*28/*28). Approximately 40% of the Black or African American population, 50% of the White population, and 25% of the East Asian population are heterozygous for the UGT1A1*28 allele (*1/*28). Decreased function alleles other than UGT1A1*28 may be present in certain populations.

12.6 Immunogenicity

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of anti-drug antibodies in the studies described below with the incidence of anti-drug antibodies in other studies, including those of TRODELVY.

During the median 4-month treatment period across clinical studies in patients treated with TRODELVY, 9 (1.1%) of 785 patients developed antibodies to sacituzumab govitecan; 6 of these patients (0.8% of all patients treated with TRODELVY) had neutralizing antibodies against sacituzumab govitecan. Because of the low occurrence of anti-drug antibodies, the effect of these antibodies on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of sacituzumab govitecan is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with sacituzumab govitecan-hziy.

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.

Fertility studies with sacituzumab govitecan-hziy have not been conducted. In a repeat-dose toxicity study in cynomolgus monkeys, intravenous administration of sacituzumab govitecan-hziy on Day 1 and Day 4 resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (≥ 6 times the human recommended dose of 10 mg/kg based on body weight).

14 CLINICAL STUDIES

14.1 Locally Advanced or Metastatic Triple-Negative Breast Cancer

ASCENT

Efficacy was evaluated in a multicenter, open-label, randomized study (ASCENT; NCT02574455) conducted in 529 patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who had relapsed after at least two prior chemotherapies for breast cancer (one of which could be in the neoadjuvant or adjuvant setting provided progression occurred within a 12 month period). All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless there was a contraindication or intolerance to taxanes during or at the end of the first taxane cycle. Magnetic resonance imaging (MRI) to determine brain metastases was required prior to enrollment for patients with known or suspected brain metastases. Patients with brain metastases were allowed to enroll up to a pre-defined maximum of 15% of patients in the ASCENT study. Patients with known Gilbert's disease or bone-only disease were excluded.

Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day (n=267) or physician's choice of single agent chemotherapy (n=262). Single agent chemotherapy was determined by the investigator before randomization from one of the following choices: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (n=52).

Patients were treated until disease progression or unacceptable toxicity. The major efficacy outcome was progression-free survival (PFS) in patients without brain metastases at baseline (i.e., BMNeg) as measured by a blinded, independent, centralized review assessed using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Additional efficacy measures included PFS for the full population (all patients with and without brain metastases) and overall survival (OS).

The median age of patients in the full population (n = 529) was 54 years (range: 27 to 82 years); 99.6% were female; 79% were White, 12% were Black/African American; and 81% of patients were < 65 years of age. All patients had an ECOG performance status of 0 (43%) or 1 (57%). Forty-two percent of patients had hepatic metastases, 9% were BRCA1/BRCA2 mutational status positive, and 70% were TNBC at diagnosis. Twelve percent had baseline brain metastases previously treated and stable (n=61; 32 on TRODELVY arm and 29 on single agent chemotherapy arm). Overall, 29% of patients had received prior PD-1/PD-L1 therapy. Thirteen percent of patients in the TRODELVY group in the full population received only 1 prior line of systemic therapy in the metastatic setting.

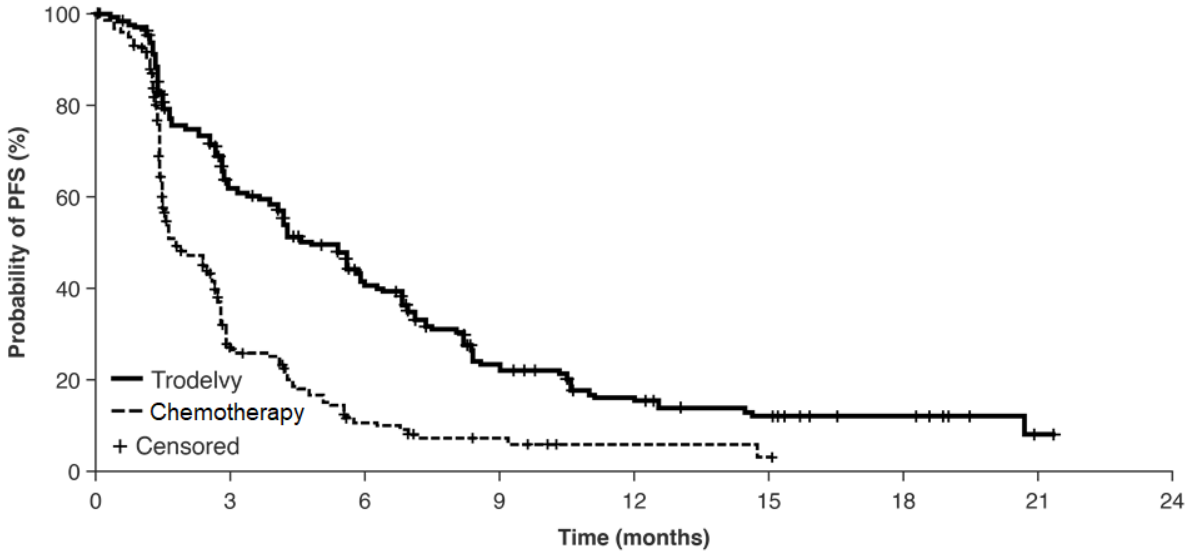
The efficacy results are summarized in Table 11 and are shown in Figure 1 and Figure 2. Efficacy results for the subgroup of patients who had received only 1 prior line of systemic therapy in the metastatic setting (in addition to having disease recurrence or progression within 12 months of neoadjuvant/adjuvant systemic therapy) were consistent with those who had received at least two prior lines in the metastatic setting.

Table 11: Efficacy Results from ASCENT

	All Randomized Patients	
	TRODELVY n=267	**Single Agent Chemotherapy n=262**
Progression-Free Survival[1] per BICR		
Disease Progression or Death (%)	190 (71%)	171 (65%)
Median PFS in months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)
Hazard ratio[2] (95% CI)	0.43 (0.35, 0.54)	
p-value	<0.0001	
Overall Survival		
Deaths (%)	179 (67%)	206 (79%)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.6)
Hazard ratio[2] (95% CI)	0.51 (0.41, 0.62)	
p-value	<0.0001	

[1] 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.
[2] Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
CI = Confidence Interval

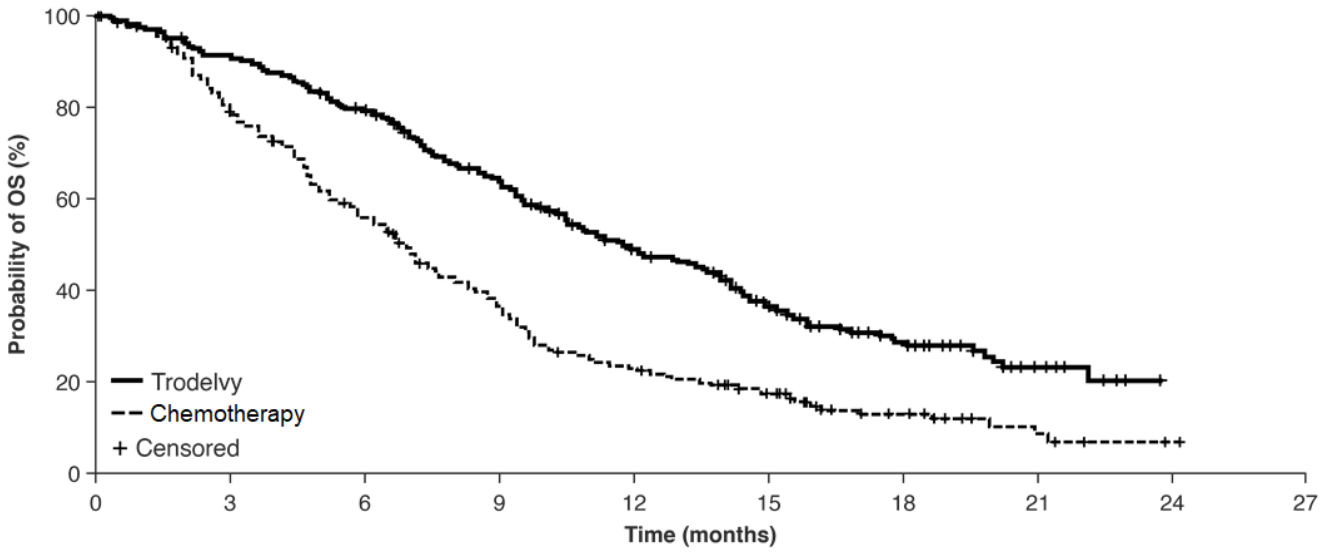
Figure 1: Kaplan-Meier Plot of PFS by BICR (All Randomized Patients) in ASCENT



Number of patients at risk

Trodelvy	267	251	184	145	135	110	82	64	55	38	34	25	23	17	16	14	9	8	8	5	3	1	0
Chemotherapy	262	199	87	41	37	23	13	9	7	6	4	2	2	2	2	1	0	0	0	0	0	0	0

Figure 2: Kaplan-Meier Plot of OS (All Randomized Patients) in ASCENT



Number of patients at risk

Trodelvy	267	260	250	242	232	219	208	189	174	164	145	127	116	109	98	76	56	46	39	31	21	13	8	1	0	0
Chemotherapy	262	239	222	192	174	150	132	113	97	84	64	58	52	46	42	34	24	17	14	9	6	5	3	2	1	0

An exploratory analysis of PFS in patients with previously treated, stable brain metastases showed a stratified HR of 0.65 (95% CI: 0.35, 1.22). The median PFS in the TRODELVY arm was 2.8 months (95% CI: 1.5, 3.9) and the median PFS with single agent chemotherapy was 1.6 months (95% CI: 1.3, 2.9). Exploratory OS analysis in the same population

showed a stratified HR of 0.87 (95% CI: 0.47, 1.63). The median OS in the TRODELVY arm was 6.8 months (95% CI: 4.7, 14.1) and the median OS with single agent chemotherapy was 7.4 months (95% CI: 4.7, 11.1).

IMMU-132-01

The efficacy of TRODELVY was evaluated in a multicenter, single-arm, study (NCT01631552) that enrolled 108 patients with metastatic triple-negative breast cancer (mTNBC) who had received at least two prior anticancer therapies for metastatic disease. Patients with bulky disease, defined as a mass >7 cm, were not eligible. Patients with treated brain metastases not receiving high dose steroids (> 20 mg prednisone or equivalent) for at least four weeks were eligible. Patients with known Gilbert's disease were excluded.

Patients received TRODELVY 10 mg/kg intravenously on Days 1 and 8 of a 21-day treatment cycle. Patients were treated with TRODELVY until disease progression or intolerance to the therapy. Tumor imaging was obtained every 8 weeks, with confirmatory CT/MRI scans obtained 4-6 weeks after an initial partial or complete response, until progression requiring treatment discontinuation. Major efficacy outcome measures were investigator assessed overall response rate (ORR) using RECIST 1.1 and duration of response.

The median age was 55 years (range: 31 to 80 years); 87% of patients were younger than 65 years. The majority of patients were female (99%) and White (76%). At study entry, all patients had an ECOG performance status of 0 (29%) or 1 (71%). Seventy-six percent had visceral disease, 42% had hepatic metastases, 56% had lung/pleura metastases, and 2% had brain metastases. Twelve patients (11%) had Stage IV disease at the time of initial diagnosis.

The median number of prior systemic therapies received in the metastatic setting was 3 (range: 2 to 10). Prior chemotherapies in the metastatic setting included carboplatin or cisplatin (69%), gemcitabine (55%), paclitaxel or docetaxel (53%), capecitabine (51%), eribulin (45%), doxorubicin (24%), vinorelbine (16%), cyclophosphamide (19%), and ixabepilone (8%).

Overall, 98% of patients had received prior taxanes and 86% had received prior anthracyclines either in the (neo)adjuvant or metastatic setting.

Table 12 summarizes the efficacy results.

Table 12: Efficacy results for patients with mTNBC in IMMU-132-01

	TRODELVY (N=108)
Overall Response Rate [i]	
ORR (95% CI)	33.3% (24.6, 43.1)
Complete response	2.8%
Partial response	30.6%
Response duration [i]	
Number of responders	36
Median, Months (95% CI)	7.7 (4.9, 10.8)
Range, Months	1.9+, 30.4+
% with duration ≥6 months	55.6%
% with duration ≥12 months	16.7%

[i] investigator assessment
CI: confidence interval
+: denotes ongoing

14.2 Locally Advanced or Metastatic HR-Positive, HER2-Negative Breast Cancer

TROPiCS-02 Study

The efficacy of TRODELVY was evaluated in a multicenter, open label, randomized study (TROPiCS-02; NCT03901339) conducted in 543 patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+ or IHC 2+/ISH–) breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if recurrence occurred within 12 months).

Patients were randomized (1:1) to receive TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21 day cycle (n=272) or single agent chemotherapy (n=271). Single agent chemotherapy was determined by the investigator before randomization from one of the following choices: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22). Randomization was stratified by the following factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (Yes or No), and endocrine therapy in the metastatic setting for at least 6 months (Yes or No).

Patients were treated until disease progression or unacceptable toxicity. Administration of TRODELVY was permitted beyond RECIST-defined disease progression if the patient was clinically stable and considered by the investigator to be deriving clinical benefit. The primary efficacy outcome measure was PFS as determined by BICR per RECIST v1.1. Additional efficacy measures included OS, ORR by BICR, and DOR by BICR.

The median age of patients in the study population was 56 years (range: 27–86 years), 26% of patients were 65 years or over. The majority of patients were female (99%); 67% were White, 4% were Black and 3% were Asian, and 26% were of unknown race. Patients received a median of 7 (range: 3 to 17) prior systemic regimens in any setting and 3 (range: 0 to 8) prior systemic chemotherapy regimens in the metastatic setting. Approximately 42% of patients had 2 prior chemotherapy regimens for treatment of metastatic disease compared to 58% of patients who had 3 to 4 prior chemotherapy regimens and all patients had an ECOG performance status of 0 (45%) or 1 (55%). Ninety-five percent of patients had visceral metastases. Most patients received endocrine therapy in the metastatic setting for ≥ 6 months (86%).

TRODELVY demonstrated a statistically significant improvement in PFS and OS versus single agent chemotheraphy.

The efficacy results are summarized in Table 13 and Figure 3 and Figure 4.

Table 13: Efficacy Results from TROPiCS-02

	All Randomized Patients	
	TRODELVY n=272	**Single Agent Chemotherapy n=271**
Progression-Free Survival by BICR[1]		
Median PFS in months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Hazard ratio (95% CI)	0.661 (0.529, 0.826)	
p-value[2]	0.0003	

Overall Survival[3]		
Median OS in months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Hazard ratio (95% CI)	0.789 (0.646, 0.964)	
p-value[2]	0.0200	
Objective Response Rate[3] by BICR		
Response Rate, % (95% CI)	21.0 (16.3, 26.3)	14.0 (10.1, 18.7)
Odds ratio (95% CI)	1.625 (1.034, 2.555)	
p-value	0.0348	
Duration of Response[3] (DOR) by BICR		
Median DOR in months (95% CI)	8.1 (6.7, 9.1)	5.6 (3.8, 7.9)

[1] 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.
[2] Stratified log-rank test adjusted for stratification factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (Y/N), and endocrine therapy in the metastatic setting for at least 6 months (Yes or No).
BICR = Blinded Independent Central Review; CI = Confidence Interval
[3] Second interim OS analysis (conducted when 390 OS events were observed)

Figure 3: Kaplan-Meier Plot of PFS by BICR in TROPiCS-02

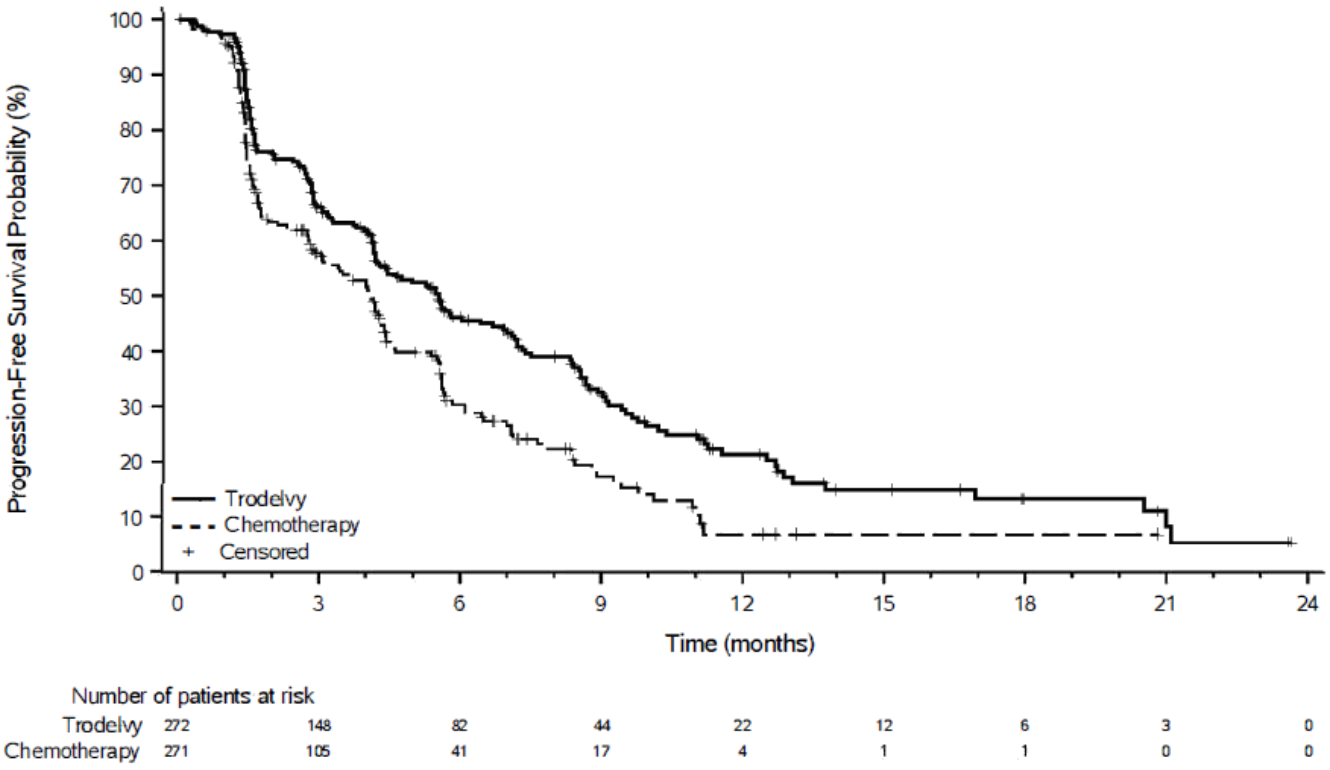
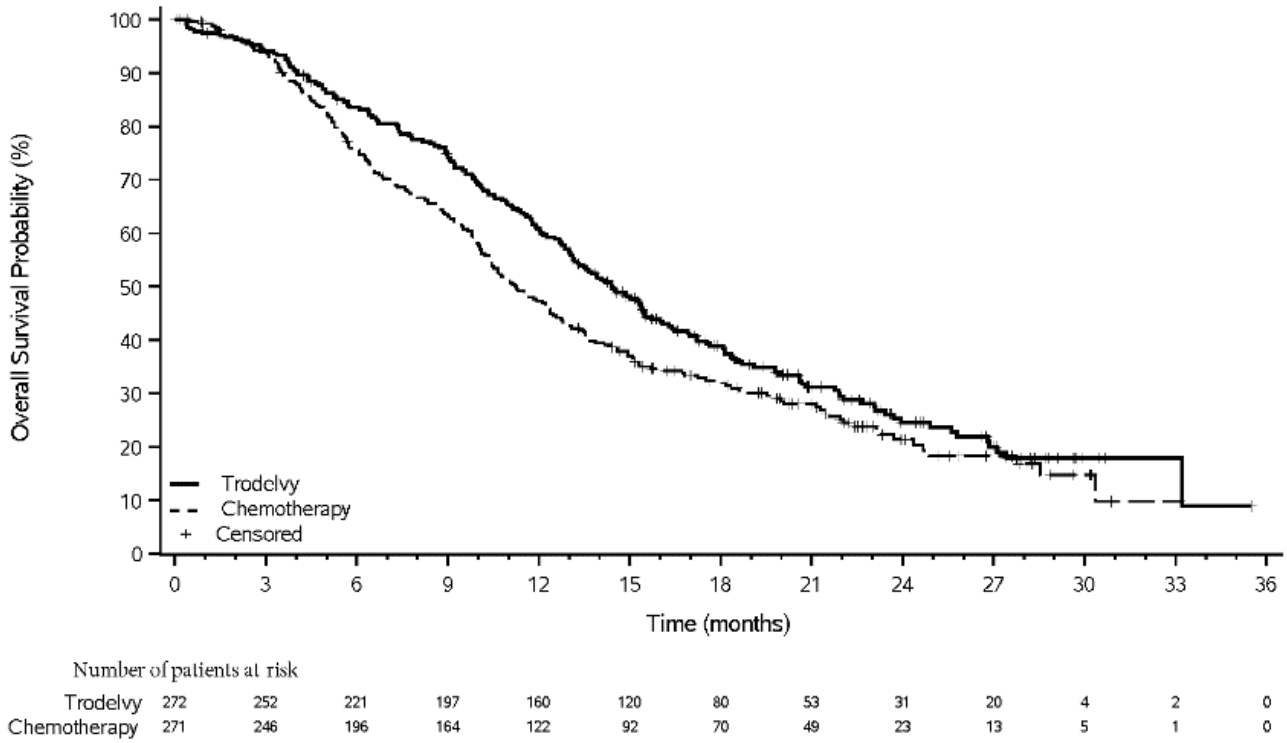


Figure 4: Kaplan-Meier Plot of OS in TROPiCS-02



14.3 Locally Advanced or Metastatic Urothelial Cancer

TROPHY Study

The efficacy of TRODELVY was evaluated in TROPHY (NCT03547973), an single-arm, multicenter study that enrolled 112 patients with locally advanced or mUC who have received prior treatment with a platinum-containing chemotherapy and either PD-1 or PD-L1 inhibitor. Patients were administered TRODELVY 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day treatment cycle. Prior to the administration of TRODELVY, all patients were treated for prevention of chemotherapy induced nausea, vomiting and infusion reactions. Patients were treated until disease progression or unacceptable toxicity.

The median age was 66 years (range: 33 to 90 years), 78% were male, 74% were White, 3% Asian, 3% Black and 20% unknown. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (28%) or 1 (72%). Ninety-six percent of patients had metastatic disease; 67% of patients had visceral metastases, including 34% with liver metastases.

The median number of prior systemic therapies was 3 (range: 1 to 8). Sixty-five percent of patients received prior cisplatin, 21% received prior carboplatin, 13% received both prior cisplatin and carboplatin, and 100% received prior PD-1 or PD-L1 inhibitor. For 34% of patients, the platinum-containing chemotherapy was received in the neoadjuvant/adjuvant setting only. Nine percent of patients received prior enfortumab vedotin.

The major efficacy outcome measures were the ORR and DOR, evaluated by Independent Review Assessment, using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria. Table 14 summarizes the efficacy results.

Table 14: Efficacy results for patients with locally advanced or mUC in TROPHY

	TRODELVY (N=112)
Overall Response Rate [i]	
ORR (95% CI)	27.7% (19.6, 36.9)
Complete response	5.4%
Partial response	22.3%
Response duration[i]	
Number of responders	31
Median, Months (95% CI)	7.2 (4.7, 8.6)
Range, Months	1.4+, 13.7

[i] by independent review assessment
[CI] confidence interval
[+] denotes ongoing

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*.

16 HOW SUPPLIED/STORAGE AND HANDLING

TRODELVY (sacituzumab govitecan-hziy) for injection is a sterile, off-white to yellowish lyophilized powder in a single-dose vial. Each TRODELVY vial is individually boxed in a carton:

- NDC 55135-132-01 contains one 180 mg vial

Store vials in a refrigerator at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light until time of reconstitution. Do not freeze.

TRODELVY is a hazardous drug. Follow applicable special handling and disposal procedures[1].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information)

Neutropenia

Advise patients of the risk of neutropenia. Instruct patients to immediately contact their healthcare provider if they experience fever, chills, or other signs of infection *[see Warnings and Precautions (5.1)]*.

Diarrhea

Advise patients of the risk of diarrhea. Instruct patients to immediately contact their healthcare provider if they experience diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; or inability to get diarrhea under control within 24 hours *[see Warnings and Precautions (5.2)]*.

Hypersensitivity and Infusion-Related Reactions

Inform patients of the risk of serious infusion reactions and anaphylaxis. Instruct patients to immediately contact their healthcare provider if they experience facial, lip, tongue, or throat swelling, urticaria, difficulty breathing, lightheadedness,

dizziness, chills, rigors, wheezing, pruritus, flushing, rash, hypotension, or fever that occur during or within 24 hours following the infusion *[see Warnings and Precautions (5.3)]*.

Nausea/Vomiting

Advise patients of the risk of nausea and vomiting. Premedication according to established guidelines with a two or three drug regimen for prevention of chemotherapy-induced nausea and vomiting (CINV) is also recommended. Additional antiemetics, sedatives, and other supportive measures may also be employed as clinically indicated. All patients should receive take-home medications for preventing and treating delayed nausea and vomiting, with clear instructions. Instruct patients to immediately contact their healthcare provider if they experience uncontrolled nausea or vomiting *[see Warnings and Precautions (5.4)]*.

Embryo-Fetal Toxicity

Advise female patients to contact their healthcare provider if they are pregnant or become pregnant. Inform female patients of the risk to a fetus and potential loss of the pregnancy *[see Use in Specific Populations (8.1)]*.

Contraception

Advise female patients of reproductive potential to use effective contraception during treatment and for 6 months after the last dose of TRODELVY *[see Use in Specific Populations (8.3)]*.

Advise male patients with female partners of reproductive potential to use effective contraception during treatment and for 3 months after the last dose of TRODELVY *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment and for 1 month after the last dose of TRODELVY *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females of reproductive potential that TRODELVY may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured by:

Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404, USA
U.S. License No. 2258

Patient Information

TRODELVY® (troh-DELL-vee)
(sacituzumab govitecan-hziy)
for injection, for intravenous use

What is the most important information I should know about TRODELVY?

TRODELVY can cause serious side effects, including:

- **Low white blood cell count (neutropenia).** Low white blood cell counts are common with TRODELVY and can sometimes be severe and lead to infections that can be life-threatening or cause death. Your healthcare provider should check your blood cell counts during treatment with TRODELVY. If your white blood cell count is too low, your healthcare provider may need to lower your dose of TRODELVY, give you a medicine to help prevent low blood cell count with future doses of TRODELVY, or in some cases may stop TRODELVY. Your healthcare provider may need to give you antibiotic medicines if you develop fever while your white blood cell count is low. **Call your healthcare provider right away if you develop any of the following signs of infection during treatment with TRODELVY**:
  - fever
  - chills
  - cough
  - shortness of breath
  - burning or pain when you urinate
- **Severe diarrhea.** Diarrhea is common with TRODELVY and can also be severe. Severe diarrhea can lead to loss of too much body fluid (dehydration) and kidney problems. Your healthcare provider should monitor you for diarrhea and give you medicine as needed to help control your diarrhea. If you lose too much body fluid, your healthcare provider may need to give you fluids and electrolytes to replace body salts. If you develop diarrhea during treatment with TRODELVY, your healthcare provider should check to see if diarrhea may be caused by an infection. Your healthcare provider may decrease your dose or stop TRODELVY if your diarrhea is severe and cannot be controlled with anti-diarrheal medicines.

  Call your healthcare provider right away:
  - the first time that you get diarrhea during treatment with TRODELVY
  - if you have black or bloody stools
  - if you have symptoms of losing too much body fluid and body salts, such as lightheadedness, dizziness or faintness
  - if you are unable to take fluids by mouth due to nausea or vomiting
  - if you are not able to get your diarrhea under control within 24 hours

What is TRODELVY?

TRODELVY is a prescription medicine used to treat adults with:

- a type of breast cancer called triple-negative breast cancer (TNBC), which is estrogen and progesterone hormone receptor (HR)-negative and human epidermal growth factor receptor 2 (HER2)-negative. TRODELVY may be used:
  - when your breast cancer has spread to other parts of the body (metastatic) or cannot be removed by surgery, **and**
  - if you previously received two or more prior treatments, including at least one treatment for metastatic disease.
- a type of breast cancer that is HR-positive and HER2-negative. TRODELVY may be used:
  - when your breast cancer has spread to other parts of the body or cannot be removed by surgery, **and** if you previously received endocrine therapy and at least two additional treatments for metastatic disease.
- bladder cancer and cancers of the urinary tract that have spread or cannot be removed by surgery. TRODELVY may be used if you have:
  - received a platinum-containing chemotherapy medicine **and**
  - also received an immunotherapy medicine.

It is not known if TRODELVY is safe and effective in people with moderate or severe liver problems.

It is not known if TRODELVY is safe and effective in children.

Do not receive TRODELVY if you have had a severe allergic reaction to TRODELVY. Ask your healthcare provider if you are not sure.

Before receiving TRODELVY, tell your healthcare provider about all of your medical conditions, including if you:

- have been told that you carry a gene for uridine diphosphate-glucuronosyl transferase 1A1 (UGT1A1)*28. People who carry this gene have an increased risk of getting side effects with TRODELVY, especially low white blood cell counts, a fever while your white blood cell count is low, and low red blood cell counts. **See "What is the most important information I should know about TRODELVY?"**
- have liver problems.
- are pregnant or plan to become pregnant. TRODELVY can harm your unborn baby. Your healthcare provider should check to see if you are pregnant before you start receiving TRODELVY.
  - Females who can become pregnant should use effective birth control during treatment and for 6 months after your last dose of TRODELVY. Talk to your healthcare provider about birth control choices that may be right for you during this time. Tell your healthcare provider right away if you become pregnant during treatment with TRODELVY.
  - Males with a female partner who can become pregnant should use effective birth control during treatment and for 3 months after your last dose of TRODELVY.
- are breastfeeding or plan to breastfeed. It is not known if TRODELVY passes into your breastmilk and can harm your baby. Do not breastfeed during treatment and for 1 month after your last dose of TRODELVY.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Certain medicines may affect the way TRODELVY works.

How will I receive TRODELVY?

- Your healthcare provider will give you TRODELVY into your vein through an intravenous (IV) line.
- TRODELVY is given 1 time each week, on Day 1 and on Day 8 of a 21-day treatment cycle.
- You will receive the first dose of TRODELVY over 3 hours. If you tolerate the first dose well, future doses may be given over 1 to 2 hours.
- Before each dose of TRODELVY, you will receive medicines to help prevent infusion-related reactions, and nausea and vomiting.
- You will be monitored for side effects during and for at least 30 minutes after you receive each infusion of TRODELVY.
- Your healthcare provider may slow down or temporarily stop your infusion of TRODELVY if you have an infusion-related reaction, or permanently stop TRODELVY if you have a life-threatening infusion-related reaction.
- Your healthcare provider will decide how long you will continue to receive TRODELVY.

What are the possible side effects of TRODELVY?

TRODELVY can cause serious side effects, including:

- **See "What is the most important information I should know about TRODELVY?"**
- **Allergic and infusion-related reactions**. Serious allergic reactions can happen during treatment with TRODELVY, including life-threatening allergic reactions, and infusion-related reactions. Tell your healthcare provider or nurse right away if you get any of the following symptoms of an allergic or infusion-related reaction during your infusion of TRODELVY or within 24 hours after you receive a dose of TRODELVY:
  - swelling of your face, lips, tongue, or throat
  - hives
  - skin rash, itching, or flushing of your skin
  - fever
  - difficulty breathing or wheezing
  - lightheadedness, dizziness, feeling faint or pass out
  - chills or shaking chills (rigors)
- **Nausea and vomiting**. Nausea and vomiting are common with TRODELVY and can sometimes be severe. Before each dose of TRODELVY, you will receive medicines to help prevent nausea and vomiting. You should be given medicines to take home with you, along with instructions about how to take them to help prevent and treat any nausea and vomiting after you receive TRODELVY. Call your healthcare provider right away if you have nausea or vomiting that is not controlled with the medicines prescribed for you. Your healthcare provider may decide to decrease your dose or stop TRODELVY if your nausea and vomiting is severe and cannot be controlled with anti-nausea medicines.

The most common side effects of TRODELVY include:

- decreased white blood cell (leukocyte and lymphocyte) and red blood cell counts
- feeling tired or weak
- hair loss
- constipation
- increased sugar levels in the blood
- decreased protein levels (albumin) in the blood
- decreased appetite
- changes in kidney function test
- increased levels of enzyme called alkaline phosphatase in the blood (test for liver or bone problems)
- decreased levels of magnesium, potassium, and sodium in the blood

TRODELVY may cause fertility problems in females, which could affect your ability to have a baby. Talk to your healthcare provider if fertility is a concern for you.

These are not all of the possible side effects of TRODELVY.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of TRODELVY.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about TRODELVY that is written for health professionals.

What are the ingredients in TRODELVY?

Active ingredient: sacituzumab govitecan-hziy

Inactive ingredients: 2-(N-morpholino) ethane sulfonic acid (MES), polysorbate 80 and trehalose dihydrate

Manufactured by: Gilead Sciences, Inc., 333 Lakeside Dr., Foster City, CA 94404, USA
U.S. License No. 2258
761115-GS-007

For more information about TRODELVY, go to www.TRODELVY.com or call 1-888-983-4668.

The Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 02/2023

添付文書のハイライト
このハイライトには、本剤を安全かつ効果的に使用するために必要な全ての情報が含まれているわけではない。本剤の添付文書全文を参照のこと。

TRODELVY® (sacituzumab govitecan-hziy) 点滴静注用
米国における初回承認：2020 年

警告：好中球減少症及び下痢
枠内の警告全文については，全処方情報を参照すること。

重度又は生命を脅かす好中球減少症が発現する可能性がある。好中球絶対数が 1500/mm³未満又は発熱性好中球減少症の場合は本剤を休薬すること。本剤投与中は定期的に血球数を観察すること。二次予防として顆粒球コロニー刺激因子（G-CSF）の投与を考慮すること。発熱性好中球減少症が認められた患者には、抗感染症治療を速やかに開始すること。(2.3, 5.1)
重度の下痢が発現する場合がある。下痢がみられる患者の状態を観察し、必要に応じて水分及び電解質の補充を行うこと。下痢の発現時に感染性・非感染性の鑑別を行い、非感染性の場合は直ちにロペラミドの投与を開始すること。重度の下痢が発現した場合、Grade 1 以下に回復するまで本剤を休薬し、以降の投与は用量を減量すること。(2.3, 5.2)

----------最近の主な変更点----------

枠内の警告	2023/02
効能・効果（1.1）	2023/02
用法・用量（2.3）	2023/02
用法・用量（2.4）	2022/12
警告及び使用上の注意（5.1、5.2、5.3、5.4、5.5）	2023/02

----------効能・効果----------

本剤は、以下の成人患者の治療を適応とする trophoblast cell-surface antigen 2（Trop-2）標的抗体及びトポイソメラーゼ阻害剤複合体である。

局所進行又は転移・再発乳癌

- 2 つ以上の全身療法による前治療歴（少なくとも 1 つの転移・再発乳癌に対する前治療歴を含む）を有する手術不能な局所進行又は転移・再発トリプルネガティブ乳癌（TNBC）患者。(1.1, 14.1)
- 内分泌療法による前治療歴に加え、転移・再発乳癌に対する 2 つ以上の全身療法による前治療歴を有する手術不能な局所進行又は転移・再発ホルモン受容体（HR）陽性かつヒト上皮増殖因子受容体 2 型（HER2）陰性（IHC 法 0、IHC 法 1+又は IHC 法 2+かつ ISH 法陰性）乳癌患者。(1.1, 14.2)

局所進行又は転移性尿路上皮癌

- プラチナ製剤を含む化学療法による前治療歴に加え、抗 programmed cell death-1（PD-1）抗体又は抗 programmed cell death-ligand 1（PD-L1）抗体による前治療歴を有する局所進行又は転移性尿路上皮癌（UC）患者。[a]（1.2）

[a] この適応症は、客観的奏効率（ORR）及び奏効期間（DOR）に基づき迅速承認のもとで承認されている*［臨床試験（14.3）参照］*。この適応症に対する継続的な承認は、検証的試験における臨床的有用性の検証及び記述を条件とする場合がある。

----------用法・用量----------

- 本剤をイリノテカン又はその活性代謝物 SN-38 を含有する薬剤の代替として使用しないこと。また、イリノテカン又はその活性代謝物 SN-38 を含有する薬剤と併用投与しないこと。(2.1)
- 本剤は点滴静注し、静脈内プッシュ投与又はボーラス投与は行わないこと。
- 通常、1 回 10 mg/kg（体重）を、21 日間を 1 サイクルとし、各サイクルの 1 日目及び 8 日目に点滴静注する。本剤の投与は疾患進行又は許容できない毒性の発現まで継続すること。(2.2)
- Infusion reaction 及びがん薬物療法に伴う悪心・嘔吐を予防するために、前投与を行うことが望ましい。(2.2)
- 点滴静注中及び点滴静注後少なくとも 30 分間は、患者の状態を観察すること。副作用を管理するために本剤の休薬及び／又は減量が必要となる場合がある。(2.2)

調製及び投与に関する指示については、添付文書全文を参照のこと。(2.4)

----------剤形・含量----------

点滴静注用：溶解用の 1 バイアル中に凍結乾燥粉末 180 mg。(3)

----------禁忌----------

本剤に対する重度の過敏症。(4, 5.3)

----------警告及び使用上の注意----------

- 過敏症及び Infusion reaction：重度のアナフィラキシー反応を含む過敏症が認められている。Infusion reaction がないか患者の状態を観察すること。重度又は生命を脅かす反応が発現した場合は、本剤の投与を中止すること。(5.3)
- 悪心／嘔吐：制吐薬による予防的治療を行うこと。投与予定日に Grade 3 の悪心又は Grade 3-4 の嘔吐が発現した場合は、本剤を休薬すること。(5.4)
- UGT1A1 活性が低下している患者：ウリジン二リン酸グルクロン酸転移酵素 1A1（UGT1A1）*28 アレルをホモ接合体としてもつ患者では、本剤の投与開始後に好中球減少症、発熱性好中球減少症及び貧血のリスクが上昇する。(5.5)
- 胚・胎児毒性：本剤は胎児に悪影響を及ぼす可能性がある。胎児への潜在的リスクについて患者に説明するとともに、適切な避妊を行うよう指導すること。(5.6, 8.1, 8.3)

----------副作用----------

主な副作用（臨床検査値異常を含む）（発現頻度 25%以上）は、白血球数減少、好中球数減少、ヘモグロビン減少、下痢、悪心、リンパ球数減少、疲労、脱毛症、便秘、ブドウ糖増加、アルブミン減少、嘔吐、食欲減退、クレアチニン・クリアランス減少、アルカリホスファターゼ増加、マグネシウム減少、カリウム減少及びナトリウム減少であった。(6.1)

副作用が疑われる場合は、Gilead Sciences, Inc.（1-888-983-4668）又は FDA（1-800-FDA-1088 又は www.fda.gov/medwatch）に連絡すること。

----------薬物相互作用----------

- UGT1A1 阻害剤又は誘導剤：併用を避けること。(7)

----------特別な集団への投与----------

- 授乳：授乳しないよう指導すること。(8.2)

患者カウンセリング情報及び FDA 承認済み患者向け添付文書については 17 項を参照のこと。

2023 年 2 月改訂

添付文書全文：目次*

警告：好中球減少症及び下痢
1 効能・効果
1.1 局所進行又は転移・再発乳癌
1.2 局所進行又は転移性尿路上皮癌
2 用法・用量
2.1 重要な基本的情報
2.2 推奨用量
2.3 副作用に対する用量調節
2.4 調製及び投与
3 剤形・含量
4 禁忌
5 警告及び使用上の注意
5.1 好中球減少症
5.2 下痢
5.3 過敏症及び Infusion reaction
5.4 悪心及び嘔吐
5.5 UGT1A1 の活性が低下している患者における副作用のリスク上昇
5.6 胚・胎児毒性
6 副作用
6.1 臨床試験での使用経験
7 薬物相互作用
7.1 他の薬剤が本剤に及ぼす影響
8 特別な集団への投与
8.1 妊娠
8.2 授乳
8.3 生殖能を有する者
8.4 小児等への投与
8.5 高齢者への投与
8.6 肝機能障害
10 過量投与
11 性状
12 臨床薬理
12.1 作用機序
12.2 薬力学
12.3 薬物動態
12.5 ゲノム薬理学
12.6 免疫原性
13 非臨床毒性
13.1 がん原性、変異原性、受胎能障害
14 臨床試験
14.1 局所進行又は転移・再発トリプルネガティブ乳癌
14.2 局所進行又は転移・再発HR陽性かつHER2陰性乳癌
14.3 局所進行又は転移性尿路上皮癌
15 参考文献
16 包装・保存及び取扱い上の注意
17 患者カウンセリング情報

* 添付文書全文から削除された項目又は小項目は記載していない。

添付文書全文

警告：好中球減少症及び下痢

- **重度又は生命を脅かす好中球減少症が発現する可能性がある。好中球絶対数が 1500/mm³ 未満又は発熱性好中球減少症の場合は本剤を休薬すること。本剤投与中は定期的に血球数を観察すること。二次予防として顆粒球コロニー刺激因子（G-CSF）の投与を考慮すること *［用法・用量（2.3）参照］*。発熱性好中球減少症が認められた患者には、抗感染症治療を速やかに開始すること *［警告及び使用上の注意（5.1）参照］*。**
- **重度の下痢が発現する場合がある。下痢がみられる患者の状態を観察し、必要に応じて水分及び電解質の補充を行うこと。下痢の発現時に感染性・非感染性の鑑別を行い、非感染症の場合は直ちにロペラミドの投与を開始すること *［警告及び使用上の注意（5.2）参照］*。重度の下痢が発現した場合、Grade 1 以下に回復するまで本剤を休薬し、以降の投与量を減量すること *［用法・用量（2.3）参照］*。**

1 効能・効果

1.1 局所進行又は転移・再発乳癌

- 本剤は、2 つ以上の全身療法による前治療歴（少なくとも 1 つの転移・再発乳癌に対する前治療歴を含む）を有する手術不能な局所進行又は転移・再発トリプルネガティブ乳癌（TNBC）の成人患者に対する治療を適応とする。

- 本剤は、内分泌療法による前治療歴に加え、転移・再発乳癌に対する 2 つ以上の全身療法による前治療歴を有する手術不能な局所進行又は転移・再発ホルモン受容体（HR）陽性かつヒト上皮増殖因子受容体 2 型（HER2）陰性（IHC 法 0、IHC 法 1+又は IHC 法 2+かつ ISH 法陰性）乳癌患者に対する治療を適応とする。

1.2 局所進行又は転移性尿路上皮癌

- 本剤は、プラチナ製剤を含む化学療法による前治療歴に加え、抗 programmed cell death-1（PD-1）抗体又は抗 programmed cell death-ligand 1（PD-L1）抗体による前治療歴を有する局所進行又は転移性尿路上皮癌（UC）患者に対する治療を適応とする。

  この適応症は、客観的奏功率（ORR）及び奏効期間（DOR）に基づき迅速承認のもとで承認されている *［臨床試験（14.3）参照］*。この適応症に対する継続的な承認は、検証的試験における臨床的有用性の検証及び記述を条件とする場合がある。

2 用法・用量

2.1 重要な基本的情報

本剤をイリノテカン又はその活性代謝物 SN-38 を含有する薬剤の代替として使用しないこと。また、イリノテカン又はその活性代謝物 SN-38 を含有する薬剤と併用投与しないこと。

2.2 推奨用量

通常、1 回 10 mg/kg（体重）を、21 日間を 1 サイクルとし、各サイクルの 1 日目及び 8 日目に点滴静注する。本剤の投与は疾患進行又は許容できない毒性の発現まで継続すること。本剤を 10 mg/kg を超える用量で投与しないこと。

本剤は点滴静注し、静脈内プッシュ投与又はボーラス投与は行わないこと。

初回投与：本剤の初回投与は 3 時間かけて行うこと。点滴静注中及び点滴静注後少なくとも 30 分間は、Infusion reaction の徴候又は症状がないか患者の状態を観察すること*［警告及び使用上の注意（5.3）参照］*。

2 回目以降の投与：前回の投与で忍容性が良好であれば、それ以降の投与は 1～2 時間かけて行うこと。点滴静注中及び点滴静注後少なくとも 30 分間は、患者の状態を観察すること。

前投与

Infusion reaction 及びがん薬物療法に伴う悪心・嘔吐（CINV）を予防するために、前投与を行うことが望ましい。

- 本剤の投与前に解熱薬、H1 及び H2 拮抗薬の前投与を行うことが望ましい。過去に Infusion reaction が認められた患者にはコルチコステロイドを使用してもよい。
- 2 剤又は 3 剤併用療法（デキサメタゾンと 5-HT3 受容体拮抗薬又は NK_1 受容体拮抗薬のいずれかと併用、及び必要に応じて他の薬剤など）による前投与を行うことが望ましい。

2.3 副作用に対する用量調節

Infusion reaction

Infusion reaction が認められた場合、本剤の注入速度を遅くするか投与を中断すること。生命を脅かす Infusion reaction が認められた場合は、本剤の投与を中止すること*［警告及び使用上の注意（5.3）参照］*。

副作用に対する用量調節

表 1 の記載に従い、副作用を管理するために本剤を休薬又は中止すること。副作用により本剤を減量した場合には、再増量しないこと。

表 1：副作用に対する用量調節

Adverse Reaction	**Occurrence**	**Dose Modification**
Severe Neutropenia *[see Warnings and Precautions (5.1)]*		
Grade 4 neutropenia ≥ 7 days OR Grade 3-4 febrile neutropenia, OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction and administer granulocyte-colony stimulating factor (G-CSF).
	Second	50% dose reduction and administer G-CSF.
	Third	Discontinue treatment and administer G-CSF.
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment and administer G-CSF.
Severe Non-Neutropenic Toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any Grade 3-4 nausea, vomiting or diarrhea due to treatment that is not controlled with antiemetics and anti-diarrheal agents *[see*	First	25% dose reduction
	Second	50% dose reduction

Adverse Reaction	Occurrence	Dose Modification
Warnings and Precautions (5.2, 5.4)], OR Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

2.4　調製及び投与

溶解方法

- 本剤は有害な薬剤である。
- 適用される特別な取扱い及び廃棄手順に従うこと[1]。
- 各投与サイクル開始時の患者の体重に基づき、本剤の必要投与量（mg）を算出する（前回の投与から体重が10%超変動した場合は、より頻回に算出する）*［用法・用量（2.2）参照］*。
- 必要数のバイアルを室温に戻す。
- 滅菌シリンジを用いて、0.9%塩化ナトリウム注射液（米国薬局方）20 mL を本剤 180 mg の各バイアルにゆっくり注入する。各バイアルには、調製中及び溶解後の損失を考慮して過量充填されており、結果として生じる総量は **10 mg/mL の濃度**である。
- バイアルをゆっくりと回して混和し、最長 15 分間かけて溶解する。振とうはしないこと。非経口製剤は、溶液及び容器の状態から可能な限り、投与前に粒子状物質及び変色の有無について目視で確認すること。溶液は目視できる微粒子がなく、澄明かつ黄色でなければならない。溶解後の液に濁り又は変色が認められる場合は使用しないこと。
- 速やかに使用し、本剤の点滴静注用希釈溶液を調製する。

希釈方法

- 患者の体重に応じた投与量を得るために必要な溶解液量を算出する。
- 本剤の濃度範囲 1.1～3.4 mg/mL で適切な用量を送達するための輸液の最終容量を決定する。
- 溶解液は 0.9%塩化ナトリウム注射液（米国薬局方）のみを使用すること。他の輸液を使用した場合の希釈後の安定性は確認できていない。ポリ塩化ビニル、ポリプロピレン／ポリエチレン、ポリオレフィン又はエチレン酢酸ビニル製の輸液バッグを使用すること。
- 最終輸液バッグから、算出した量の本剤溶解液を添加した後に、指示された本剤濃度を達成するために、必要な量の 0.9%塩化ナトリウム注射液（米国薬局方）を抜き取り、廃棄する。
- シリンジを用いて、必要量の本剤溶解液をバイアルから抜き取る。バイアルに残った溶解液は廃棄すること。
- 必要量の本剤溶解液を輸液バッグに、泡立ちを最小限に抑えるためゆっくり注入する。内容物を振とうしないこと。
- 直ちに使用しない場合、本剤の入った輸液バッグは遮光して 2～8°C（36～46°F）で最長 24 時間の冷蔵保存が可能である。冷蔵保存後、希釈溶液は、25°C（77°F）以下の室温で 8 時間以内（点滴時間を含む）に投与すること。

凍結させたり、振とうしないこと。

投与方法

- 本剤は点滴静注すること。輸液バッグは遮光すること。本剤投与中は、投与が完了するまで輸液バッグを覆うこと。点滴中に点滴チューブを覆ったり、遮光チューブを使用する必要はない。
- 輸液ポンプを使用してもよい。
- 他剤と混注したり、他剤とともに点滴静注したりしないこと。
- 点滴静注終了後、静脈ラインを 20 mL の 0.9%塩化ナトリウム注射液（米国薬局方）で洗い流すこと。

3 剤形・含量

点滴静注用：1 バイアル中に微黄白色～帯黄色の凍結乾燥粉末 180 mg。

4 禁忌

本剤に対する重度の過敏症の既往を有する患者への本剤の投与は禁忌である*［警告及び使用上の注意（5.3）参照］*。

5 警告及び使用上の注意

5.1 好中球減少症

本剤を投与した患者に、重度、生命を脅かす又は致死的な好中球減少症があらわれることがある。本剤を投与した患者の 64%に好中球減少症が発現した。患者の 49%に Grade 3-4 の好中球減少症が発現した。患者の 6%に発熱性好中球減少症が発現した。好中球減少症（発熱性好中球減少症を含む）の初回発現までの期間は 16 日（中央値）であり、一部の患者ではより早期に発現した*［警告及び使用上の注意（5.5）参照］*。好中球減少性大腸炎の発現頻度は 1.4%であった。

投与サイクルの 1 日目に好中球絶対数が 1500/mm^3 未満の場合、又は投与サイクルの 8 日目に好中球絶対数が 1000/mm^3 未満の場合は、本剤を休薬する。発熱性好中球減少症が認められた場合は、本剤を休薬する。好中球減少症が発現した場合には、用量調節が必要となる場合がある。臨床的に必要な場合又は表 1 に示すように、G-CSF を投与すること*［用法・用量（2.3）参照］*。

5.2 下痢

重度の下痢があらわれることがある。本剤の投与を受けた全ての患者における下痢及び Garde 3-4 の下痢の発現頻度は、それぞれ 64%及び 11%であった。1 例の患者で、下痢に続いて腸穿孔が認められた。全ての患者の 0.7%は、下痢により脱水を起こし、その後急性腎障害に至った。

投与予定日に Grade 3-4 の下痢があらわれた場合は本剤を休薬し、Grade 1 以下に回復した時点で投与を再開すること*［用法・用量（2.3）参照］*。

下痢の発現時に感染性・非感染性の鑑別を行い、非感染性の場合は直ちにロペラミドの投与を開始すること。最初に 4 mg を投与し、その後、下痢の発現ごとに 2 mg を投与する。最大 16 mg/日とする。下痢が消失してから 12 時間後にロペラミドの投与を中止する。臨床的に必要な場合、追加の支持療法（水分及び電解質の補充など）の実施を考慮すること。

本剤の投与により過度のコリン作動性反応（腹部痙攣、下痢、流涎など）が認められた場合には、それ以降の本剤投与前に、適切な治療（アトロピンなどの投与）の実施を考慮すること。

5.3 過敏症及び Infusion reaction

本剤の投与により、生命を脅かすアナフィラキシー反応などの重篤な過敏症があらわれることがある。重度の徴候及び症状として、心停止、低血圧、喘鳴、血管浮腫、腫脹、肺臓炎及び皮膚反応が認められた*［禁忌（4）参照］*。

本剤投与後 24 時間以内に発現した過敏症の発現頻度は 35%であった。Grade 3-4 の過敏症の発現頻度は 2%であった。本剤の投与中止に至った過敏症の発現頻度は 0.2%であった。アナフィラキシー反応の発現頻度は 0.2%であった。

本剤の投与を受ける患者には、Infusion reaction に対する前投与を行うことが望ましい。本剤の投与時には、アナフィラキシーを含む Infusion reaction を治療するための薬剤や緊急用の装置をすぐに使用できるようにしておくこと*［用法・用量（2.2）参照］*。

本剤の点滴静注中及び点滴静注後少なくとも 30 分間は、過敏症及び Infusion reaction について患者を注意深く観察すること*［用法・用量（2.3）参照］*。

Grade 4 の Infusion reaction が認められた場合は、本剤の投与を中止すること*［用法・用量（2.3）参照］*。

5.4 悪心及び嘔吐

本剤は催吐性を有する薬剤である。本剤の投与を受けた全ての患者における悪心及び嘔吐の発現頻度は、それぞれ 64%及び 35%であった。

本剤の投与を受けた全ての患者における Garde 3-4 の悪心及び嘔吐の発現頻度は、それぞれ 3%及び 2%であった。

がん薬物療法に伴う悪心・嘔吐（CINV）を予防するために、2 剤又は 3 剤併用療法（デキサメタゾンと 5-HT3 受容体拮抗薬又は NK_1 受容体拮抗薬のいずれかと併用、及び必要に応じて他の薬剤など）による前投与を行うこと*［用法・用量（2.2）参照］*。

予定投与日に Grade 3 の悪心又は Grade 3-4 の嘔吐が発現した場合は、本剤を休薬し、Grade 1 以下に回復した時点で、追加の支持療法を行った上で本剤の投与を再開すること*［用法・用量（2.3）参照］*。

臨床的に必要であれば、追加の制吐薬の投与及びその他の支持療法の実施を考慮すること。また、全ての患者に、悪心及び嘔吐の予防及び治療のため、自宅で服用できる薬剤を処方し、十分説明すること。

5.5 UGT1A1 の活性が低下している患者における副作用のリスク上昇

ウリジン二リン酸グルクロン酸転移酵素 1A1（UGT1A1）*28 アレルをホモ接合体としてもつ患者では、好中球減少症、発熱性好中球減少症、貧血及びその他の副作用のリスクが上昇する。

好中球減少症と貧血の発現率については、本剤の投与を受け、UGT1A1 遺伝子型の結果がある患者 948 例を対象に評価した。UGT1A1*28 アレルをホモ接合体としてもつ患者（112 例）では、Grade 3-4 の好中球減少症の発現率は 58%であった。UGT1A1*28 アレルをヘテロ接合体としてもつ患者（420 例）では、Grade 3-4 の好中球減少症の発現率は 49%であった。野生型アレルをホモ接合体としてもつ患者（416 例）では、Grade 3-4 の好中球減少症の発現率は 43%であった*［臨床薬理（12.5）参照］*。UGT1A1*28 アレルをホモ接合体としてもつ患者では、Grade 3-4 の貧血の発現率は 21%であった。UGT1A1*28 アレルをヘテロ接合体としてもつ患者では、Grade 3-4 の貧血の発現率は 10%であった。野生型アレルをホモ接合体としてもつ患者では、Grade 3-4 の貧血の発現率は 9%であった。

好中球減少症（発熱性好中球減少症を含む）の初回発現までの期間の中央値は、UGT1A1*28 アレルをホモ接合体としてもつ患者では 9 日、UGT1A1*28 アレルをヘテロ接合体としてもつ患者では 15 日、野生型アレルをホモ接合体としてもつ患者では 20 日であった。貧血の初回発現までの期間の中央値は、UGT1A1*28 アレルをホモ接合体としてもつ患者では 21 日、UGT1A1*28 アレルをヘテロ接合体としてもつ患者では 25 日、野生型アレルをホモ接合体としてもつ患者では 28 日であった。

UGT1A1 活性の低下が判明している場合は、副作用について患者を注意深く観察すること。UGT1A1 酵素活性の低下を示唆すると考えられる急性で早期発症型又は極めて重度の副作用が認められた患者では、認められた副作用の発現、持続期間及び重症度の臨床評価に基づき、本剤を休薬又は中止すること*［用法・用量（2.3）参照］*。

5.6 胚・胎児毒性

本剤の作用機序から、本剤を妊婦に投与すると催奇形性及び／又は胚・胎児死亡を引き起こす可能性がある。本剤は遺伝毒性を有する SN-38 を含有し、分裂が活発な細胞を標的とする*［臨床薬理（12.1）及び非臨床毒性（13.1）参照］*。妊婦及び妊娠可能な女性には胎児への潜在的リスクについて説明すること。妊娠可能な女性には、本剤投与中及び本剤投与終了後 6 ヵ月間は適切な避妊を行うよう指導すること。パートナーが妊娠する可能性のある男性患者に対して、本剤投与中及び本剤投与終了後 3 ヵ月間は適切な避妊を行うよう指導すること*［特別な集団への投与（8.1、8.3）参照］*。

6 副作用

以下の副作用については、添付文書の他の項で詳細に考察されている。

- 好中球減少症*［警告及び使用上の注意（5.1）参照］*
- 下痢*［警告及び使用上の注意（5.2）参照］*
- 過敏症及び Infusion reaction*［警告及び使用上の注意（5.3）参照］*
- 悪心及び嘔吐*［警告及び使用上の注意（5.4）参照］*

6.1 臨床試験での使用経験

臨床試験は多種多様な条件下で実施されるため、ある薬剤の臨床試験で認められた副作用発現率を他の薬剤の臨床試験で認められた発現率と直接比較することはできず、臨床現場で認められる発現率を反映していない可能性がある。

「警告及び使用上の注意」の項に記載されている併合安全性解析対象集団は、IMMU-132-01 試験、ASCENT 試験、TROPiCS-02 試験及び TROPHY 試験の 4 試験のいずれかに参加した 1063 例の患者における本剤への曝露を反映しており、転移・再発 TNBC 患者 366 例、ホルモン受容体（HR）陽性かつヒト上皮増殖因子受容体 2 型（HER2）陰性乳癌患者 322 例及び転移性 UC 患者 180 例が含まれていた。本剤は、21 日間を 1 サイクルとして、10 mg/kg の用量で各サイクルの 1 日目及び 8 日目に点滴静注した。疾患進行又は許容できない毒性が認められるまで投与を継続した。本剤の投与を受けた 1063 例における投与期間の中央値は 4.1 ヵ月（範囲：0～63 ヵ月）であった。この併合安全性解析対象集団では、臨床検査値異常を含む主な副作用（25%以上）は、白血球数減少（84%）、好中球数減少（75%）、ヘモグロビン減少（69%）、下痢（64%）、悪心（64%）、リンパ球数減少（63%）、疲労（51%）、脱毛症（45%）、便秘（37%）、ブドウ糖増加（37%）、アルブミン減少（35%）、嘔吐（35%）、食欲減退（30%）、クレアチニン・クリアランス減少（28%）、アルカリホスファターゼ増加（28%）、マグネシウム減少（27%）、カリウム減少（26%）及びナトリウム減少（26%）であった。

<u>局所進行又は転移・再発トリプルネガティブ乳癌</u>

ASCENT 試験

本剤の安全性は、タキサン系抗悪性腫瘍剤及び 2 つ以上の化学療法レジメンによる前治療歴を有する転移・再発 TNBC 患者を対象とした無作為化、実薬対照、非盲検試験（ASCENT 試験）において評価された。患者を本剤群

（258 例）又は単剤化学療法群（224 例）に 1：1 の比率で無作為に割り付け、疾患進行又は許容できない毒性が認められるまで投与した*［臨床試験（14.1）参照］*。本剤の投与を受けた患者における投与期間の中央値は 4.4 ヵ月（範囲：0～23 ヵ月）であった。

重篤な副作用は本剤の投与を受けた患者の 27%に発現した。本剤の投与を受けた患者の 1%超に認められた重篤な副作用は、好中球減少症（7%）、下痢（4%）及び肺炎（3%）であった。本剤の投与を受けた患者の 1.2%に致死的な副作用が発現し、その内訳は呼吸不全（0.8%）及び肺炎（0.4%）であった。患者の 5%では副作用のために本剤の投与が中止された。本剤の投与を受けた患者で投与中止に至った副作用（1%以上）は、肺炎（1%）及び疲労（1%）であった。

本剤の休薬に至った副作用は患者の 63%に発現した。休薬に至った主な副作用（5%以上）は、好中球減少症（47%）、下痢（5%）、呼吸器感染（5%）及び白血球減少症（5%）であった。

本剤の減量に至った副作用は患者の 22%に発現した。減量に至った主な副作用（4%超）は、好中球減少症（11%）及び下痢（5%）であった。

G-CSF は本剤を投与した患者の 44%で使用されていた。

ASCENT 試験における副作用及び臨床検査値異常の要約をそれぞれ表 2 及び表 3 に示す。

表 2：ASCENT 試験で転移・再発 TNBC 患者の 10%以上に認められた副作用

	TRODELVY (n=258)		**Single Agent Chemotherapy (n=224)**	
Adverse Reaction	**All Grades %**	**Grade 3 - 4 %**	**All Grades %**	**Grade 3 - 4 %**
Gastrointestinal disorders				
Diarrhea	59	11	17	1
Nausea	57	3	26	0.4
Vomiting	33	2	16	1
Constipation	37	0.4	23	0
Abdominal Pain	30	3	12	1
Stomatitis[i]	17	2	13	1
General disorders and administration site conditions				
Fatigue[ii]	65	6	50	9
Pyrexia	15	0.4	14	2
Infections and infestation				
Urinary tract infection	13	0.4	8	0.4
Upper respiratory tract infection	12	0	3	0
Metabolism and nutrition disorders				
Decreased appetite	28	2	21	1
Musculoskeletal and connective tissue disorders				
Back pain	16	1	14	2
Arthralgia	12	0.4	7	0

Nervous system disorders				
Headache	18	0.8	13	0.4
Dizziness	10	0	7	0
Psychiatric disorders				
Insomnia	11	0	5	0
Respiratory, thoracic and mediastinal disorders				
Cough	24	0	18	0.4
Skin and subcutaneous tissue disorders				
Alopecia	47	0	16	0
Rash	12	0.4	5	0.4
Pruritus	10	0	3	0

*Single agent chemotherapy included one of the following single-agents: eribulin (n=139), capecitabine (n=33), gemcitabine (n=38), or vinorelbine (except if patient had ≥ Grade 2 neuropathy, n=52).

Graded per NCI CTCAE v.5.0.

[i.] Including stomatitis, glossitis, mouth ulceration, and mucosal inflammation

[ii.] Including fatigue and asthenia

表 3：ASCENT 試験で転移・再発 TNBC 患者の 10%超に認められた臨床検査値異常

Laboratory Abnormality	**TRODELVY (n=258)**		**Single Agent Chemotherapy (n=224)**	
	All Grades (%)	**Grade 3 - 4 (%)**	**All Grades (%)**	**Grade 3 - 4 (%)**
Hematology				
Decreased hemoglobin	94	9	57	6
Decreased lymphocyte count	88	31	40	24
Decreased leukocyte count	86	41	53	25
Decreased neutrophil count	78	49	48	36
Decreased platelet count	23	1.2	25	2.7
Chemistry				
Increased glucose	49	2.3	43	2.8
Decreased calcium	36	1.6	21	1.4
Decreased magnesium	33	0.4	20	0
Decreased potassium	33	4.3	28	0.9
Increased albumin	32	0.8	25	1.4
Increased aspartate aminotransferase	27	1.2	32	1.4
Increased alanine aminotransferase	26	1.2	26	1.8
Increased alkaline phosphatase	26	0	17	0.5
Decreased phosphate	26	7.8	20	3.3
Decreased sodium	22	0.4	17	0.5
Increased lactate dehydrogenase	18	0	22	0
Decreased glucose	10	0	3.2	0

IMMU-132-01 試験

本剤の安全性は、転移・再発乳癌に対する 2 つ以上の抗癌療法による前治療歴を有する転移・再発 TNBC 患者 108 例を含む転移・再発 TNBC 患者及びその他の悪性腫瘍患者を対象としたシングルアーム、非盲検試験（IMMU-132-01 試験）で評価された*［臨床試験（14.1）参照］*。本剤は、21 日間を 1 サイクルとして、最大 10 mg/kg の用量で各サイクルの 1 日目及び 8 日目に点滴静注した。疾患進行又は許容できない毒性の発現まで投与を継続した。この 108 例の投与期間の中央値は 5.1 ヵ月（範囲：0〜51 ヵ月）であった。

重篤な副作用は患者の 31%に発現した。本剤を投与した患者の 1%超で認められた重篤な副作用は、発熱性好中球減少症（6%）、嘔吐（5%）、悪心（3%）、呼吸困難（3%）、下痢（4%）、貧血（2%）、胸水、好中球減少症、肺炎及び脱水（各 2%）であった。

患者の 2%では副作用のために本剤の投与が中止された。投与中止に至った副作用は、アナフィラキシー、食欲不振／疲労、頭痛（各 0.9%）であった。患者の 45%が休薬に至った副作用を発現した。休薬に至った主な副作用は、好中球減少症（33%）であった。減量に至った副作用は本剤を投与された患者の 33%に発現し、24%が 1 回、9%が 2 回減量した。減量に至った主な副作用は、好中球減少症／発熱性好中球減少症であった。

IMMU-132-01 試験で転移・再発 TNBC 患者の 10%以上に発現した副作用及び臨床検査値異常を表 4 及び表 5 に要約する。

表 4：IMMU-132-01 試験で転移・再発 TNBC 患者の 10%以上に認められた副作用

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Any adverse reaction	100	71
Gastrointestinal disorders	95	21
Nausea	69	6
Diarrhea	63	9
Vomiting	49	6
Constipation	34	1
Abdominal pain[i]	26	1
Mucositis[ii]	14	1
General disorders and administration site conditions	77	9
Fatigue[iii]	57	8
Edema[iv]	19	0
Pyrexia	14	0
Metabolism and nutrition disorders	68	22
Decreased appetite	30	1
Dehydration	13	5
Skin and subcutaneous tissue disorders	63	4
Alopecia	38	0
Rash[v]	31	3
Pruritus	17	0
Dry Skin	15	0

Adverse Reaction	TRODELVY (n=108)	
	Grade 1-4 (%)	Grade 3-4 (%)
Nervous system disorders	56	4
Headache	23	1
Dizziness	22	0
Neuropathy[vi]	24	0
Dysgeusia	11	0
Infections and infestations	55	12
Urinary Tract Infection	21	3
Respiratory Infection[vii]	26	3
Musculoskeletal and connective tissue disorders	54	1
Back pain	23	0
Arthralgia	17	0
Pain in extremity	11	0
Respiratory, thoracic and mediastinal disorders	54	5
Cough[viii]	22	0
Dyspnea[ix]	21	3
Psychiatric disorders	26	1
Insomnia	13	0

Graded per NCI CTCAE v. 4.0

[i.] Including abdominal pain, distention, pain (upper), discomfort, tenderness.

[ii] Including stomatitis, esophagitis, and mucosal inflammation

[iii] Including fatigue and asthenia.

[iv] Including edema; and peripheral, localized, and periorbital edema

[v] Including rash; maculopapular, erythematous, generalized rash; dermatitis acneiform; skin disorder, irritation, and exfoliation

[vi] Including gait disturbance, hypoesthesia, muscular weakness, paresthesia, peripheral and sensory neuropathy

[vii] Including lower and upper respiratory tract infection, pneumonia, influenza, viral upper respiratory infection, bronchitis and respiratory syncytial virus infection

[viii] Includes cough and productive cough

[ix] Includes dyspnea and exertional dyspnea

表 5：IMMU-132-01 試験で本剤投与を受けた患者の 10%以上に認められた臨床検査値異常

Laboratory Abnormality	TRODELVY (n=108)	
	All Grades (%)	Grade 3-4 (%)
Hematology		
Decreased hemoglobin	93	6
Decreased leukocyte count	91	26
Decreased neutrophil count	82	32
Increased activated partial thromboplastin time	60	12
Decreased platelet count	30	3
Chemistry		
Increased alkaline phosphatase	57	2
Decreased magnesium	51	3
Decreased calcium	49	3
Increased aspartate aminotransferase	45	3
Decreased albumin	39	1
Increased alanine aminotransferase	35	2
Increased glucose	31	2.8
Decreased phosphate	29	5
Decrease magnesium	27	1.9
Decreased phosphate	27	6.5
Decreased sodium	25	4.7
Decreased potassium	24	3.7
Decreased glucose	19	2

局所進行又は転移・再発 HR 陽性かつ HER2 陰性乳癌

TROPiCS-02 試験

本剤の安全性は、CDK 4/6 阻害剤、内分泌療法及びタキサン系薬剤による治療を受け、かつ、転移・再発乳癌に対する 2 つ以上の化学療法レジメン（このうち 1 つは術前又は術後薬物療法も可とした。ただし、当該療法から 12 ヵ月以内に進行を認めた場合）による治療後に進行を認めた切除不能な局所進行又は転移・再発 HR 陽性かつ HER2 陰性（IHC 法 0、IHC 法 1+又は IHC 法 2+かつ ISH 法陰性）乳癌患者を対象とした無作為化、実薬対照、非盲検試験（TROPiCS-02 試験）において評価された。患者を本剤群（268 例）又は単剤化学療法群（249 例）に 1：1 の比率で無作為に割り付け、疾患進行又は許容できない毒性が認められるまで投与した*［臨床試験（14.2）参照］*。本剤の投与を受けた患者における投与期間の中央値は 4.1 ヵ月（範囲：0～63 ヵ月）であった。

重篤な副作用は本剤の投与を受けた患者の 28%に発現した。本剤を投与した患者の 1%超に認められた重篤な副作用は、下痢（5%）、発熱性好中球減少症（4%）、好中球減少症（3%）、腹痛、大腸炎、好中球減少性大腸炎、肺

炎及び嘔吐（各 2%）であった。本剤を投与した患者の 2%に致死的な副作用が発現し、その内訳は不整脈、COVID-19、神経系障害、肺塞栓症及び敗血症性ショック（各 0.4%）であった。患者の 6%では副作用のために本剤の投与が中止された。本剤の投与を受けた患者に発現した投与中止に至った主な副作用（0.5%以上）は、無力症、全身健康状態悪化及び好中球減少症（各 0.7%）であった。

本剤の休薬に至った副作用は患者の 66%に発現した。休薬に至った主な副作用（5%以上）は、好中球減少症（50%）であった。

本剤の減量に至った副作用は患者の 33%に発現した。減量に至った主な副作用（5%超）は、好中球減少症（16%）及び下痢（8%）であった。G-CSF は本剤の投与を受けた患者の 54%で使用されていた。

TROPiCS-02 試験における副作用及び臨床検査値異常を表 6 及び表 7 に要約する。

表 6：TROPiCS-02 試験で HR 陽性 HER2 陰性転移・再発乳癌患者の 10%以上に認められた副作用

	TRODELVY (n=268)		**Single Agent Chemotherapy (n=249)**	
Adverse Reaction	**All Grades %**	**Grade 3 - 4 %**	**All Grades %**	**Grade 3 - 4 %**
Gastrointestinal disorders				
Diarrhea	62	10	23	1
Nausea	59	1	35	3
Constipation	34	1	25	0
Vomiting	23	1	16	2
Abdominal Pain	20	0	14	0
Dyspepsia[i]	11	0	6	0
General disorders and administration site conditions				
Fatigue[ii]	60	8	51	4
Metabolism and nutrition disorders				
Decreased appetite	21	2	21	0
Hypokalemia	10	2	4	0
Musculoskeletal and connective tissue disorders				
Arthralgia	15	0	12	0
Nervous system disorders				
Headache	16	1	15	1
Respiratory, thoracic and mediastinal disorders				
Dyspnea [iii]	20	0	17	0
Cough	12	0	7	0
Skin and subcutaneous tissue disorders				
Alopecia	48	0	19	0
Pruritus	12	0	2	0

*Single agent chemotherapy included one of the following single-agents: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22).
Graded per NCI CTCAE v.5.0.
[i.] Including dyspepsia, gastroesophageal reflux disease.
[ii.] Including fatigue, asthenia.
[iii.] Including dyspnea; exertional dyspnea

TROPiCS-02 試験で認められたその他の臨床的に重要な副作用（10%以下）は、低血圧（5%）、疼痛（5%）、鼻漏（5%）、低カルシウム血症（3%）、鼻閉（3%）、皮膚色素過剰（3%）、大腸炎又は好中球減少性大腸炎（2%）、低ナトリウム血症（2%）、肺炎（2%）、蛋白尿（1%）及び小腸炎（0.4%）であった。

表 7：TROPiCS-02 試験で HR 陽性 HER2 陰性転移・再発乳癌患者の 10%超に認められた臨床検査値異常

Laboratory Abnormality	**TRODELVY (n=268)**		**Single Agent Chemotherapy (n=249)**	
	All Grades (%)	**Grade 3 - 4 (%)**	**All Grades (%)**	**Grade 3 - 4 (%)**
Hematology				
Decreased leukocyte count	88	38	73	26
Decreased neutrophil count	83	53	67	40
Decreased hemoglobin	73	8	59	5
Decreased lymphocyte count	65	21	47	14
Decreased platelet count	21	1	30	4
Eosinophilia	13	0	4	0
Chemistry				
Increased glucose	37	0	31	0
Decreased albumin	32	0	27	0.4
Decreased creatinine clearance	24	2	19	1
Increased alkaline phosphatase	23	0	23	1
Decreased potassium	22	3	12	0.4
Increased alanine aminotransferase	21	1	31	2
Decreased sodium	19	1	17	0.4
Decreased magnesium	18	0	15	0
Decreased phosphate	17	0	10	0
Increased phosphate	16	0	16	0
Increased lactate dehydrogenase	16	0	28	0
Increased aspartate aminotransferase	15	2	25	1
Increased potassium	14	2	9	0

局所進行又は転移性尿路上皮癌

TROPHY 試験

本剤の安全性は、プラチナベースの抗 PD-1/PD-L1 療法による前治療歴を有する転移性 UC 患者（113 例）を対象としたシングルアーム、非盲検試験で評価された。本剤は、21 日間を 1 サイクルとして、10 mg/kg の用量で各サイクルの 1 日目及び 8 日目に点滴静注した。疾患進行又は許容できない毒性の発現まで投与を継続した*［臨床試験（14.3）参照］*。

重篤な副作用は患者の 44%に発現した。本剤を投与した患者の 1%超に認められた重篤な副作用は、感染（18%）、好中球減少症（12%、発熱性好中球減少症［10%］を含む）、急性腎障害（6%）、尿路感染（6%）、敗血症又は菌血症（5%）、下痢（4%）、貧血、静脈血栓塞栓症及び小腸閉塞（各 3%）、肺炎、腹痛、発熱及び血小板減少症（各 2%）であった。致死的な副作用は患者の 3.6%に発現し、その内訳は敗血症、呼吸不全、鼻出血及び自殺既遂であった。

患者の 10%では副作用のために本剤の投与が中止された。治験薬の投与中止に至った主な副作用は好中球減少症（4%、発熱性好中球減少症［2%］を含む）であった。休薬に至った副作用は患者の 52%に認められた。休薬に至った主な副作用は、好中球減少症（27%、発熱性好中球減少症［2%］を含む）、感染（12%）及び急性腎障害（8%）であった。本剤の減量に至った副作用は患者の 42%に発現した。減量に至った主な副作用（4%超）は、好中球減少症（13%、発熱性好中球減少症［3%］を含む）、下痢（11%）、疲労（8%）及び感染（4%）であった。G-CSF は本剤を投与した患者の 47%で使用されていた。

臨床検査値異常を含む主な副作用（25%以上）は、白血球数減少（78%）、下痢（72%）、ヘモグロビン減少（71%）、リンパ球数減少（71%）、好中球数減少（67%）、悪心（66%）、ブドウ糖増加（59%）、疲労（56%）、アルブミン減少（51%）、脱毛症（49%）、カルシウム減少（46%）、ナトリウム減少（43%）、食欲減退（41%）、リン酸塩減少（41%）、アルカリホスファターゼ増加（36%）、便秘（34%）、嘔吐（34%）、活性化部分トロンボプラスチン時間増加（33%）、クレアチニン増加（32%）、マグネシウム減少（31%）、アラニンアミノトランスフェラーゼ増加（28%）、乳酸脱水素酵素増加（28%）、腹痛（27%）、カリウム減少（27%）、アスパラギン酸アミノトランスフェラーゼ増加（26%）及び血小板数減少（25%）であった。

TROPHY 試験における転移性 UC 患者の 10%以上に発現した副作用及び臨床検査値異常を表 8 及び表 9 に要約する。

表 8：TROPHY 試験で本剤の投与を受けた患者の 15%以上（Grade 1-4）又は 5%以上（Grade 3 以上）に認められた副作用

	TRODELVY n=113	
Adverse Reaction	**Grade 1-4 %**	**Grade 3-4 %**
Any adverse reaction	94	80
Gastrointestinal disorders		
Diarrhea	72	12
Nausea	66	4
Constipation	34	1
Vomiting	34	1
Abdominal pain[i]	31	2

General disorders and administration site conditions		
Fatigue[ii]	68	5
Pyrexia	19	0
Edema[iii]	17	2
Skin and subcutaneous tissue disorders		
Alopecia	49	0
Rash[iv]	32	2
Metabolism and nutrition disorders		
Decreased appetite	41	3
Weight loss[v]	17	2
Renal and urinary disorders		
Acute kidney injury[vi]	24	7
Hematuria	16	1
Infections and infestations		
Any infection[vii]	50	25
Urinary tract infection	19	12
Respiratory, thoracic and mediastinal disorders		
Cough[viii]	17	0
Dyspnea	16	0
Musculoskeletal disorders		
Back pain	16	0
Vascular disorders		
Venous thromboembolism[ix]	9	6

Graded per NCI CTCAE v.5.0.
[i]Includes abdominal discomfort, abdominal pain, abdominal pain lower, abdominal pain upper, gastrointestinal pain
[ii] Includes fatigue and asthenia
[iii]Includes edema genital, edema peripheral, peripheral swelling
[iv]Includes dermatitis acneiform, dermatitis bullous, erythema, lichen planus, photosensitivity reaction, pruritus, pruritus generalised, rash, rash macular, rash maculo-papular, rash pruritic, skin papilloma, skin toxicity
[v]Includes failure to thrive and weight decreased
[vi]Includes acute kidney injury, blood creatinine increased, nephropathy toxic, renal failure, renal impairment
[vii]Includes bacteremia, body tinea, bronchitis, candida infection, cellulitis, clostridium difficile infection, corona virus infection, device related infection, diverticulitis, escherichia bacteremia, escherichia pyelonephritis, folliculitis, gastroenteritis, gastroenteritis escherichia coli, herpes zoster, kidney infection, klebsiella sepsis, lung infection, nasopharyngitis, oral candidiasis, oral herpes, pneumonia, pyelonephritis, pyelonephritis acute, respiratory tract infection, rhinitis, sepsis, sinusitis, skin infection, tooth abscess, upper respiratory tract infection, urinary tract infection, urosepsis, vascular device infection, viral infection, viral pharyngitis, vulvovaginal mycotic infection
[viii]Includes cough, productive cough, upper-airway cough syndrome
[ix]Includes deep vein thrombosis, embolism, and pulmonary embolism

TROPHY 試験におけるその他の臨床的に重要な副作用（15%以下）は、末梢性ニューロパチー（12%）、敗血症又は菌血症（9%）及び肺炎（4%）であった。

表 9：TROPHY 試験で本剤の投与を受けた患者の 20%以上（全 Grade）又は 5%以上（Garde 3-4）に認められた臨床検査値異常

Adverse Reaction	TRODELVY n = 113	
	Any Grade* %	Grade 3-4* %
Hematology		
Decreased leukocyte count	78	38
Decreased lymphocyte count	71	35
Decreased hemoglobin	71	18
Decreased neutrophil count	67	43
Decreased platelet count	25	2
Chemistry		
Increased glucose	59	8
Decreased albumin	51	4
Decreased calcium	46	9
Decreased sodium	43	1
Decreased phosphate	41	15
Increased alkaline phosphatase	36	0
Increased creatinine	32	5
Decreased magnesium	31	2
Increased alanine aminotransferase	28	2
Increased lactate dehydrogenase	28	0
Decreased potassium	27	0
Increased aspartate aminotransferase	26	2
Coagulation		
Increased activated partial thromboplastin time	33	6

*Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available (range: 66 to 111 patients).

7 薬物相互作用

7.1 他の薬剤が本剤に及ぼす影響

UGT1A1 阻害剤

本剤と UGT1A1 阻害剤の併用により SN-38 の全身曝露量が増加し、副作用の発現率が高くなる可能性がある*［警告及び使用上の注意（5.5）及び臨床薬理（12.3、12.5）参照］*。本剤と UGT1A1 阻害剤の併用は避けること。

UGT1A1 誘導剤

UGT1A1 誘導剤を併用中の患者では、SN-38 の曝露量が低下する可能性がある*［警告及び使用上の注意（5.5）及び臨床薬理（12.3、12.5）参照］*。本剤と UGT1A1 誘導剤の併用は避けること。

8 特別な集団への投与

8.1 妊娠

リスクの要約

本剤の作用機序から、本剤を妊婦に投与すると催奇形性及び／又は胚・胎児死亡を引き起こす可能性がある。妊婦における薬物関連リスクに関する情報は得られていない。本剤は遺伝毒性を有するSN-38を含有し、分裂が活発な細胞に対して毒性を示す*［臨床薬理（12.1）及び非臨床毒性（13.1）参照］*。妊婦及び妊娠可能な女性には胎児への潜在的リスクについて説明すること。

適応集団における重大な先天異常及び自然流産の推定背景リスクは不明である。米国の一般集団では、臨床的に確認された妊娠における重大な先天異常及び自然流産の推定背景リスクは、それぞれ 2～4%及び 15～20%である。

データ

動物データ

sacituzumab govitecan-hziy を用いた生殖発生毒性試験は実施していない。

8.2 授乳

リスクの要約

ヒトでの sacituzumab govitecan-hziy 及び SN-38 の乳汁移行、授乳児への影響、及び乳汁産生への影響に関する情報はない。授乳児に重篤な副作用が発現する可能性があるため、本剤投与中及び本剤投与終了後 1 ヵ月間は授乳を行わないよう指導すること。

8.3 生殖能を有する者

妊娠検査

本剤投与開始前に妊娠可能な女性の妊娠の有無を確認すること。

避妊

女性

本剤を妊婦に投与すると胎児に悪影響を及ぼすおそれがある*［特別な集団への投与（8.1）参照］*。妊娠可能な女性には、本剤投与中及び本剤投与終了後 6 ヵ月間は適切な避妊を行うよう指導すること。

男性

遺伝毒性のおそれがあることから、パートナーが妊娠する可能性のある男性患者に対して、本剤投与中及び本剤投与終了後 3 ヵ月間は適切な避妊を行うよう指導すること。

不妊症

女性

動物試験での所見に基づくと、本剤は妊娠可能な女性の受胎能を低下させる可能性がある*［非臨床毒性（13.1）参照］*。

8.4 小児等への投与

小児患者における本剤の安全性及び有効性は確立されていない。

8.5 高齢者への投与

本剤の投与を受けた TNBC 患者 366 例のうち、19%が 65 歳以上、3%が 75 歳以上であった。全体として、65 歳以上の患者と 65 歳未満の患者との間で安全性及び有効性に差は認められなかった。

本剤の投与を受けた HR 陽性かつ HER2 陰性乳癌患者 322 例のうち、26%が 65 歳以上、6%が 75 歳以上であった。全体として、65 歳以上の患者と 65 歳未満の患者との間で有効性に差は認められなかった。副作用による中止率は、65 歳以上の患者（14%）の方が 65 歳未満の患者（3%）よりも高かった。

本剤の投与を受けた UC 患者 180 例のうち、59%が 65 歳以上、27%が 75 歳以上であった。全体として、65 歳以上の患者と 65 歳未満の患者との間で有効性に差は認められなかった。副作用による中止率は、65 歳以上の患者（14%）の方が 65 歳未満の患者（8%）よりも高かった。

8.6 肝機能障害

軽度の肝機能障害を有する患者に本剤を投与する際、開始用量の調節は不要である*［臨床薬理（12.3）参照］*。

中等度（総ビリルビンが基準値上限［ULN］の 1.5 倍超～3 倍）又は重度（総ビリルビンが ULN の 3 倍超）の肝機能障害を有する患者における安全性は確立されていない。AST 若しくは ALT が ULN の 3 倍超で肝転移のない患者又は AST 若しくは ALT が ULN の 5 倍超で肝転移のある患者に対して、本剤は検討されていない。したがって、これらの患者に対して推奨可能な開始用量はない。

10過量投与

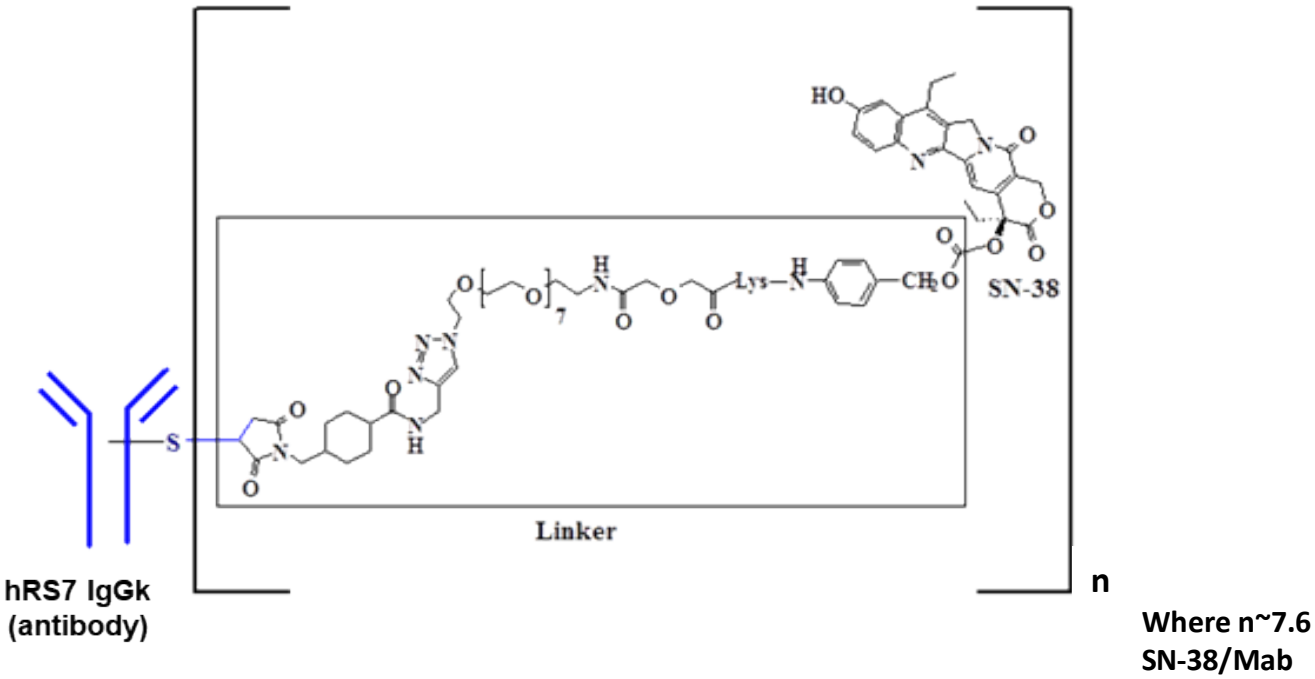
臨床試験では、本剤は 18 mg/kg（最大推奨用量 10 mg/kg の約 1.8 倍）まで投与されており、18 mg/kg 投与の患者では、重度の好中球減少症の発現頻度が高かった。

11性状

Sacituzumab govitecan-hziy は、Trop-2 標的抗体及びトポイソメラーゼ阻害剤複合体であり、以下の 3 つの成分で構成される。

- Trop-2（trophoblast cell-surface antigen-2）に結合するヒト化モノクローナル抗体 hRS7 IgG1κ（サシツズマブとも呼ばれる）、
- トポイソメラーゼ阻害剤の SN-38、
- ヒト化モノクローナル抗体と SN-38 を結合させる加水分解性リンカー（CL2A と呼ばれる）。

遺伝子組換えモノクローナル抗体は哺乳類（マウス骨髄腫）細胞により産生されるが、低分子成分 SN-38 及び CL2A は化学合成により産生される。Sacituzumab govitecan-hziy は、抗体 1 分子あたり平均 7～8 分子の SN-38 を含有する。Sacituzumab govitecan-hziy の分子量は約 160 キロダルトンである。Sacituzumab govitecan-hziy の化学構造は以下のとおりである。



TRODELVY（sacituzumab govitecan-hziy）点滴静注用は、50 mL の透明ガラス製バイアルに充填された、静脈内投与用の微黄白色～帯黄色の無菌防腐剤無添加凍結乾燥粉末であり、ゴム栓及びアルミニウム製フリップオフキャップで圧着密封されている。

本剤の各バイアルには、sacituzumab govitecan-hziy 180 mg、2-（*N*-モルホリノ）エタンスルホン酸（MES）77.3 mg、ポリソルベート 80 1.8 mg 及びトレハロース二水和物 154 mg が含まれる。0.9%塩化ナトリウム注射液（米国薬局方）20 mL で溶解したとき、濃度は 10 mg/mL、pH は 6.5 である。

12　臨床薬理

12.1 作用機序

sacituzumab govitecan-hziy は Trop-2 を標的とする抗体薬物複合体（ADC）であり、ヒト化抗体であるサシツズマブとトポイソメラーゼI阻害剤を有する低分子部分の SN-38 が、リンカーを介して共有結合している。薬理学的データから、sacituzumab govitecan-hziy は Trop-2 発現癌細胞に結合し、細胞内に取り込まれた後にリンカーが加水分解され、SN-38 が放出されると考えられる。SN-38 はトポイソメラーゼIに作用し、トポイソメラーゼ I によるデオキシリボ核酸（DNA）一本鎖切断の再ライゲーションを阻害することにより DNA を傷害し、アポトーシス及び細胞死を誘導する。Sacituzumab govitecan-hziy は、ヒトトリプルネガティブ乳癌（TNBC）を異種移植した担癌マウスにおいて腫瘍増殖を抑制した。

12.2 薬力学

本剤の曝露-反応関係及び有効性の薬力学的経時変化は十分に明らかにされていない。

心臓電気生理学

推奨用量におけるベースラインからの最大平均変化量は 9.7 msec（両側 90%信頼区間［CI］の上限は 16.8 msec）であった。QTc 延長と SN-38 濃度との間に正の曝露-反応関係が認められた。

12.3 薬物動態

Sacituzumab govitecan-hziy 10 mg/kg の用量で単剤投与を受けた転移・再発乳癌患者を対象として、sacituzumab govitecan-hziy 及び SN-38 の血清中薬物動態を評価した。Sacituzumab govitecan-hziy 及び遊離 SN-38 の薬物動態パラメータを表 10 に示す。

表 10：Sacituzumab govitecan-hziy 及び遊離 SN-38 の平均薬物動態パラメータ（CV%）の要約*

	Sacituzumab govitecan-hziy (N=693)	**Free SN-38 (N=681)**
C_{max} [ng/mL]	239000 (11%)	98.0 (45%)
AUC_{0-168} [ng*h/mL]	5640000 (22%)	3696 (56%)

*Parameters estimated based on population PK analyses
C_{max}: maximum serum concentration from 0-168 hours after the first dose
AUC_{0-168}: area under serum concentration curve through 168 hours after the first dose

分布

母集団薬物動態解析に基づくと、sacituzumab govitecan-hziy の定常状態における分布容積は 3.6 L である。

排泄

転移・再発 TNBC 患者における sacituzumab govitecan-hziy 及び遊離 SN-38 の消失半減期（$t_{1/2}$）の中央値は、それぞれ 23.4 時間及び 17.6 時間であった。母集団薬物動態解析により推定された、sacituzumab govitecan-hziy のクリアランスの平均値（%CV）は 0.13 L/h（12%）である。

代謝

Sacituzumab govitecan-hziy の代謝に関する試験は実施していない。SN-38（sacituzumab govitecan-hziy の低分子部分）は UGT1A1 を介して代謝される。SN-38 のグルクロン酸抱合体（SN-38G）は患者の血清中で検出された。

特別な集団

本剤の投与を受けた患者の薬物動態解析の結果、年齢（27～88 歳）、人種（白人、黒人、アジア系）、軽度～中等度の腎機能障害（CLcr が 30～89 mL/min）は sacituzumab govitecan-hziy の薬物動態に影響を及ぼさなかった。Sacituzumab govitecan-hziy の低分子部分である SN-38 の消失において、腎排泄の寄与はわずかであることが知られている。重度の腎機能障害患者（CLcr が 15～29 mL/min）及び末期腎不全患者（CLcr が 15 mL/min 未満）における sacituzumab govitecan-hziy の薬物動態は検討されていない。

肝機能障害患者

軽度の肝機能障害（総ビリルビンが ULN 以下かつ AST が ULN 超、又はビリルビンが ULN 超～ULN の 1.5 倍以下かつ AST 値は問わない）を有する患者（257 例）における sacituzumab govitecan-hziy の曝露量は、正常な肝機能（総ビリルビン及び AST が ULN 未満）を有する患者（526 例）と同程度である。

中等度（総ビリルビンが ULN の 1.5 倍超～3 倍）又は重度（総ビリルビンが ULN の 3 倍超）の肝機能障害を有する患者における sacituzumab govitecan-hziy 及び遊離 SN-38 の曝露量は不明である。

薬物相互作用試験

Sacituzumab govitecan-hziy 及びその成分の薬物相互作用試験は実施しなかった。UGT1A1 阻害剤又は UGT1A1 誘導剤は SN-38 の曝露量をそれぞれ増加又は減少させる可能性がある*［薬物相互作用（7）参照］*。

12.5 ゲノム薬理学

SN-38 は UGT1A1 を介して代謝される*［臨床薬理（12.3）参照］*。UGT1A1*28 アレルなどの UGT1A1 遺伝子の遺伝的変異体は UGT1A1 酵素活性の低下をもたらす。UGT1A1*28 アレルがホモ接合体又はヘテロ接合体の患者は、野生型（*1/*1）の患者と比較して、本剤による好中球減少症、発熱性好中球減少症及び貧血のリスクが高い*［警告及び使用上の注意（5.5）参照］*。黒人／アフリカ系アメリカ人集団の約 20%、白人集団の約 10%、東アジア人集団の約 2%は、UGT1A1*28 アレル（*28/*28）がホモ接合体である。黒人／アフリカ系アメリカ人集団の約 40%、白人集団の約 50%、東アジア人集団の約 25%は、UGT1A1*28 アレル（*1/*28）がヘテロ接合体である。特定の集団では、UGT1A1*28 以外の機能低下アレルが存在することがある。

12.6 免疫原性

抗体産生の検出は、測定法の感度及び特異性に大きく依存する。測定方法が異なるため、以下に記載した試験における抗薬物抗体の発現率と本剤を含む他の試験における抗薬物抗体の発現率との意味のある比較はできない。

投与期間 4 ヵ月（中央値）の間に、本剤の投与を受けた患者を対象とした臨床試験全体で、785 例中 9 例（1.1%）に sacituzumab govitecan-hziy に対する抗体が発現した。これらの患者のうち 6 例（本剤の投与を受けた全患者の 0.8%）に sacituzumab govitecan-hziy に対する中和抗体が認められた。抗薬物抗体の発現率は低いため、これらの抗体が sacituzumab govitecan-hziy の薬物動態、薬力学、安全性及び／又は有効性に及ぼす影響は不明である。

13 非臨床毒性

13.1 がん原性、変異原性、受胎能障害

Sacituzumab govitecan-hziy のがん原性試験は実施していない。

SN-38 は、チャイニーズハムスター卵巣細胞を用いた *in vitro* 哺乳類細胞小核試験で染色体異常誘発性を示し、細菌を用いた *in vitro* 復帰突然変異（Ames）試験で変異原性を示さなかった。

Sacituzumab govitecan-hziy の受胎能試験は実施していない。カニクイザルを用いた反復投与毒性試験において、sacituzumab govitecan-hziy を 1 日目及び 4 日目に静脈内投与したところ、60 mg/kg 以上（体重に基づくヒト推奨用量 10 mg/kg の 6 倍以上）の用量で子宮内膜萎縮、子宮出血、卵巣の卵胞閉鎖の増加及び膣上皮細胞の萎縮が認められた。

14 臨床試験

14.1 局所進行又は転移・再発トリプルネガティブ乳癌

ASCENT 試験

有効性は、乳癌に対する 2 つ以上の化学療法（このうち 1 つは術後又は術前薬物療法も可とした。ただし、当該療法から 12 ヵ月以内に進行を認めた場合に限る）による前治療後に再発した切除不能な局所進行又は転移・再発トリプルネガティブ乳癌（TNBC）患者 529 例を対象とした多施設共同、非盲検、無作為化試験（ASCENT 試験、NCT02574455）で評価された。タキサン系薬剤に対して禁忌又は不耐容がタキサン系薬剤の初回サイクル中若しくは初回サイクル終了時に認められた場合を除き、全ての患者が術後薬物療法、術前薬物療法又は進行癌に対する治療のいずれかでタキサン系薬剤による前治療を受けていた。脳転移が確認されている又は疑われる患者については、脳転移を判定する磁気共鳴画像法（MRI）を登録前に実施することを必須とした。脳転移を有する患者は、事前に規定した患者数の最大 15%まで ASCENT 試験に登録可能とした。ジルベール病が確認されている患者又は骨病変のみを有する患者は除外した。

患者は、21 日間を 1 サイクルとして、各サイクルの 1 日目及び 8 日目に本剤 10 mg/kg を点滴静注する群（267 例）又は医師が選択した単剤化学療法を行う群（262 例）のいずれかに 1：1 の比率で無作為に割り付けられた。単剤化学療法は、無作為化前に治験責任医師がエリブリン（139 例）、カペシタビン（33 例）、ゲムシタビン（38 例）又はビノレルビン（52 例）の選択肢から 1 つ決定した。

疾患進行又は許容できない毒性が認められるまで投与を継続した。有効性の主要評価項目は、ベースライン評価時に脳転移が認められなかった患者（BM Neg）を対象とした無増悪生存期間（PFS）とし、固形がんの治療効果判定のための新ガイドライン（RECIST）第 1.1 版の基準に基づき盲検下独立中央判定により評価した。追加の有効性評価項目は、全体集団（脳転移の有無を問わない全患者）を対象とした PFS 及び全生存期間（OS）とした。

全体集団（529 例）における患者の年齢の中央値は 54 歳（範囲：27 歳～82 歳）であった。99.6%が女性、79%が白人、12%が黒人／アフリカ系アメリカ人であった。患者の 81%が 65 歳未満であった。全患者の米国東海岸がん臨床試験グループ（ECOG）パフォーマンスステータス（PS）は 0（43%）又は 1（57%）であった。患者の 42%は肝転移を有し、9%は BRCA1/BRCA2 変異は陽性であり、70%は診断時に TNBC であった。12%はベースライン時に脳転移の治療歴があり、安定していた（61 例、32 例が本剤群、29 例が単剤化学療法群）。

全体として、患者の 29%が抗 PD-1/PD-L1 抗体による前治療を受けていた。全体集団の本剤群の 13%は、転移・再発乳癌に対する全身療法を 1 つのみ受けていた。

有効性の結果を表 11 に要約し、図 1 及び図 2 に示す。（術前又は術後薬物全身療法から 12 ヵ月以内の再発又は進行に加えて）転移・再発乳癌に対する 1 つのみの全身療法の前治療歴を有する患者のサブグループの有効性の結果は、転移・再発乳癌に対する 2 つ以上の前治療歴を有する患者の結果と一致していた。

表 11：ASCENT 試験の有効性の結果

	All Randomized Patients	
	TRODELVY n=267	**Single Agent Chemotherapy n=262**
Progression-Free Survival[1] per BICR		
Disease Progression or Death (%)	190 (71%)	171 (65%)
Median PFS in months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)
Hazard ratio[2] (95% CI)	0.43 (0.35, 0.54)	
p-value	<0.0001	
Overall Survival		
Deaths (%)	179 (67%)	206 (79%)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.6)
Hazard ratio[2] (95% CI)	0.51 (0.41, 0.62)	
p-value	<0.0001	

[1] 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.
[2] Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
CI= Confidence Interval

図 1：ASCENT 試験における盲検下独立判定委員会判定（BICR）による PFS の Kaplan-Meier 曲線（無作為化された全患者）

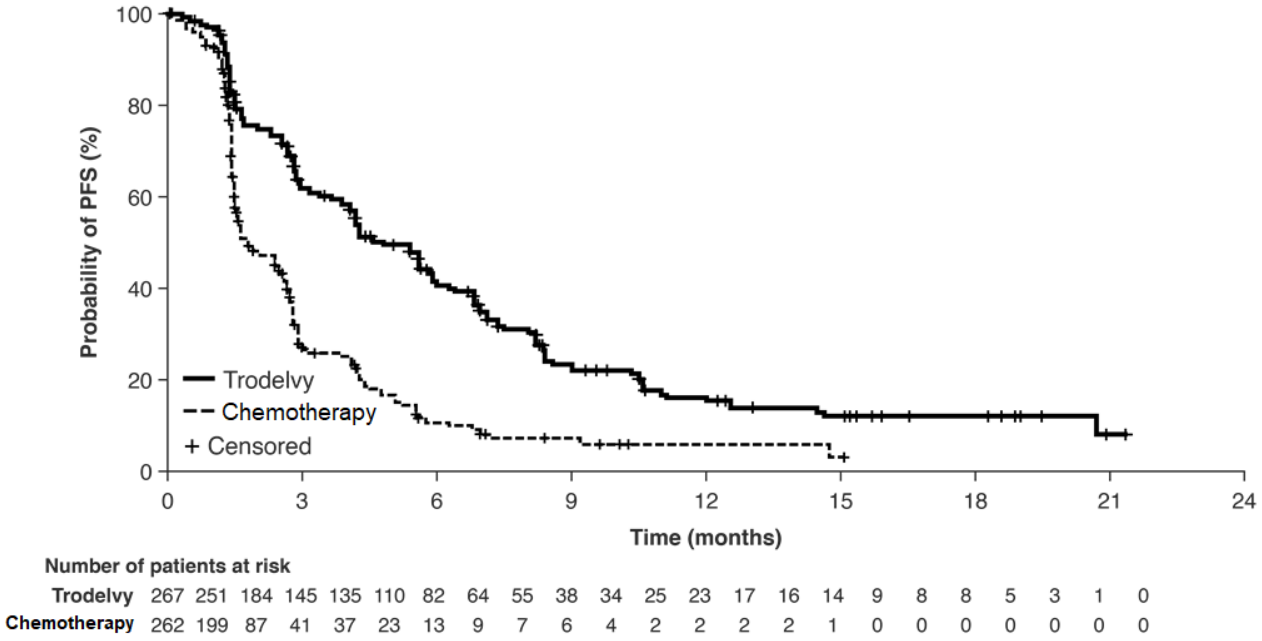
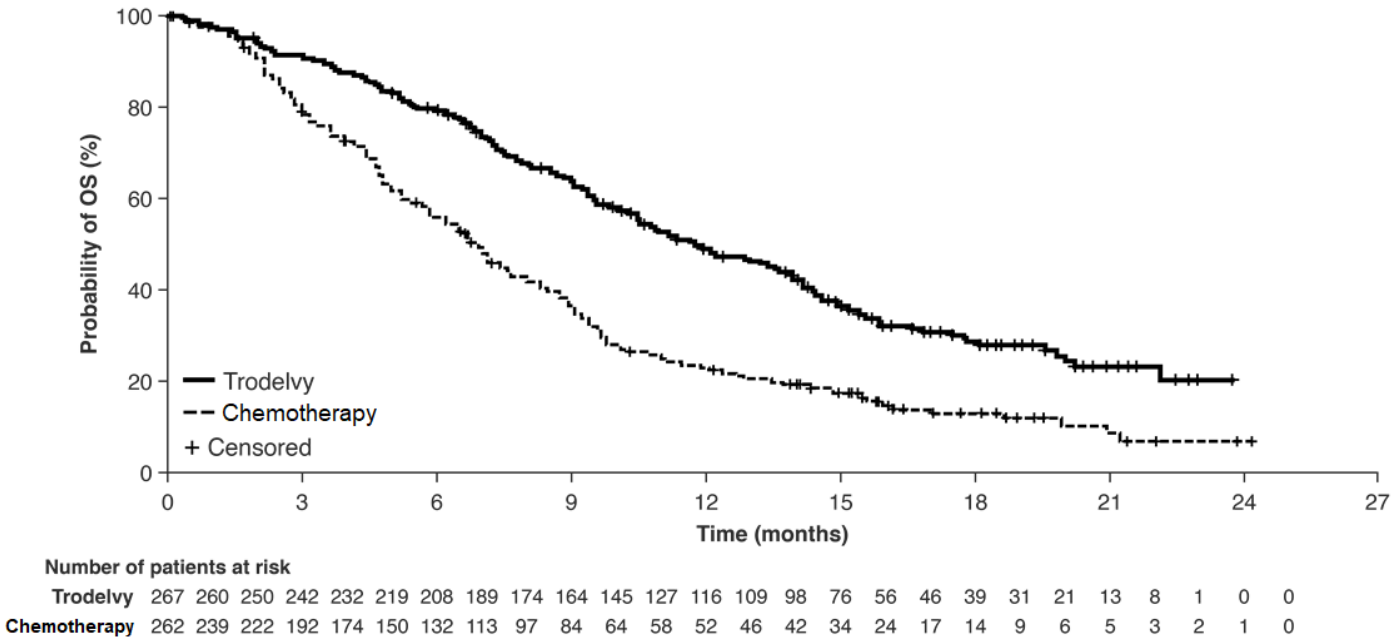


図 2：ASCENT 試験における OS の Kaplan-Meier 曲線（無作為化された全患者）



脳転移の治療歴があり、安定していた患者を対象とした PFS の探索的解析の結果、層別ハザード比は 0.65（95% CI：0.35、1.22）であった。本剤群の PFS 中央値は 2.8 ヵ月（95% CI：1.5、3.9）であり、単剤化学療法群の PFS 中

央値は 1.6 ヵ月（95% CI：1.3、2.9）であった。同集団を対象とした OS の探索的解析では、層別ハザード比は 0.87（95% CI：0.47、1.63）であった。本剤群の OS 中央値は 6.8 ヵ月（95% CI：4.7、14.1）であり、単剤化学療法群の OS 中央値は 7.4 ヵ月（95% CI：4.7、11.1）であった。

IMMU-132-01 試験

本剤の有効性は、転移・再発乳癌に対する 2 つ以上の抗癌剤による前治療歴を有する転移・再発 TNBC 患者 108 例を登録した多施設共同、シングルアーム試験において評価された（NCT01631552）。7 cm を超える腫瘤として定義される巨大病変を有する患者は不適格とした。脳転移の治療を受け、高用量ステロイド（20 mg 超のプレドニゾン又は相当量）の投与を 4 週間以上受けていない患者を適格とした。ジルベール病であることが確認されている患者は除外した。

21 日間を 1 サイクルとして、各サイクルの 1 日目及び 8 日目に本剤 10 mg/kg を点滴静注した。疾患進行又は治療に不耐容となるまで本剤を投与した。腫瘍の画像検査は投与中止を要する進行が認められるまで 8 週間ごとに実施し、最初に部分奏効又は完全奏効が認められてから 4～6 週間後に確定のための CT/MRI スキャンを実施した。主な有効性評価項目は、RECIST 第 1.1 版に基づく治験責任医師判定による ORR 及び DOR とした。

年齢の中央値は 55 歳（範囲：31～80 歳）であった。患者の 87%は 65 歳未満であった。患者の大半は女性（99%）及び白人（76%）であった。試験登録時、全ての患者の ECOG PS は 0（29%）又は 1（71%）であった。76%が内臓疾患、42%が肝転移、56%が肺／胸膜転移、2%が脳転移を有していた。12 例（11%）は初回診断時にステージ IV であった。

転移・再発乳癌に対する全身療法による前治療数の中央値は 3（範囲：2～10）であった。転移・再発乳癌に対する化学療法による前治療歴には、カルボプラチン又はシスプラチン（69%）、ゲムシタビン（55%）、パクリタキセル又はドセタキセル（53%）、カペシタビン（51%）、エリブリン（45%）、ドキソルビシン（24%）、ビノレルビン（16%）、シクロホスファミド（19%）及びイキサベピロン（8%）があった。

全体として、患者の 98%がタキサン系薬剤による前治療を受けており、86%がアントラサイクリン系薬剤による前治療を（術前）薬物療法として、あるいは転移・再発乳癌に対して受けていた。

有効性の結果を表 12 に要約する。

表 12：IMMU-132-01 試験における転移・再発 TNBC 患者の有効性の結果

	TRODELVY (N=108)
Overall Response Rate [i]	
ORR (95% CI)	33.3% (24.6, 43.1)
Complete response	2.8%
Partial response	30.6%
Response duration [i]	
Number of responders	36
Median, Months (95% CI)	7.7 (4.9, 10.8)
Range, Months	1.9+, 30.4+
% with duration ≥6 months	55.6%
% with duration ≥12 months	16.7%

[i] investigator assessment
CI: confidence interval
+: denotes ongoing

14.2 局所進行又は転移・再発 HR 陽性かつ HER2 陰性乳癌

TROPiCS-02 試験

本剤の有効性は、CDK 4/6 阻害剤、内分泌療法及びタキサン系薬剤による治療を受け、かつ、転移・再発乳癌に対する 2 つ以上の化学療法（このうち 1 つは術前又は術後薬物療法も可とした。ただし、当該療法から 12 ヵ月以内に再発が認めた場合に限る）による治療後に進行を認めた切除不能な局所進行又は転移・再発 HR 陽性かつ HER2 陰性（IHC 法 0、IHC 法 1+又は IHC 法 2+かつ ISH 法陰性）乳癌患者 543 例を対象とした多施設共同、非盲検、無作為化試験（TROPiCS-02 試験、NCT03901339）において評価された。

患者は、21 日間を 1 サイクルとして、各サイクルの 1 日目及び 8 日目に本剤 10 mg/kg を点滴静注する群（272 例）又は単剤化学療法群（271 例）のいずれかに 1：1 の比率で無作為に割り付けられた。単剤化学療法は、治験責任医師が無作為化前にエリブリン（130 例）、ビノレルビン（63 例）、ゲムシタビン（56 例）又はカペシタビン（22 例）のうち、いずれか 1 つを決定した。無作為化に際し、転移・再発乳癌に対する化学療法レジメンによる前治療数（2 つ又は 3～4 つ）、内臓転移（あり又はなし）及び転移・再発乳癌に対する少なくとも 6 ヵ月間の内分泌療法による前治療歴（あり又はなし）を層別因子とした。

疾患進行又は許容できない毒性が認められるまで投与を継続した。患者が臨床的に安定しており、臨床的有用性が得られていると治験責任医師が判断した場合、RECIST の定義による疾患進行後も本剤の投与を可能とした。有効性の主要評価項目は、RECIST 第 1.1 版に基づき BICR が判定した PFS とした。その他の有効性評価項目は、OS、BICR による ORR 及び BICR による DOR とした。

試験対象集団の年齢の中央値は 56 歳（範囲：27～86 歳）であり、患者の 26%が 65 歳以上であった。患者のほぼ全例が女性（99%）であり、67%が白人、4%が黒人、3%がアジア系、26%が人種不明であった。患者が過去に受けた全身療法レジメン（設定を問わず）による前治療数の中央値は 7（範囲：3～17）であり、転移・再発乳癌に対する全身化学療法レジメンによる前治療数の中央値は 3（範囲：0～8）であった。転移・再発乳癌に対する化学療法レジメンによる前治療数が 2 つであった患者の割合は約 42%であったのに対し、3～4 つであった患者の割合は 58%であった。全患者の ECOG PS は 0（45%）又は 1（55%）であった。患者の 95%には内臓転移があった。ほとんどの患者（86%）は転移・再発乳癌に対する少なくとも 6 ヵ月間の内分泌療法による前治療歴を有していた。

本剤は、単剤化学療法と比較して、PFS 及び OS において統計学的に有意な改善を示した。

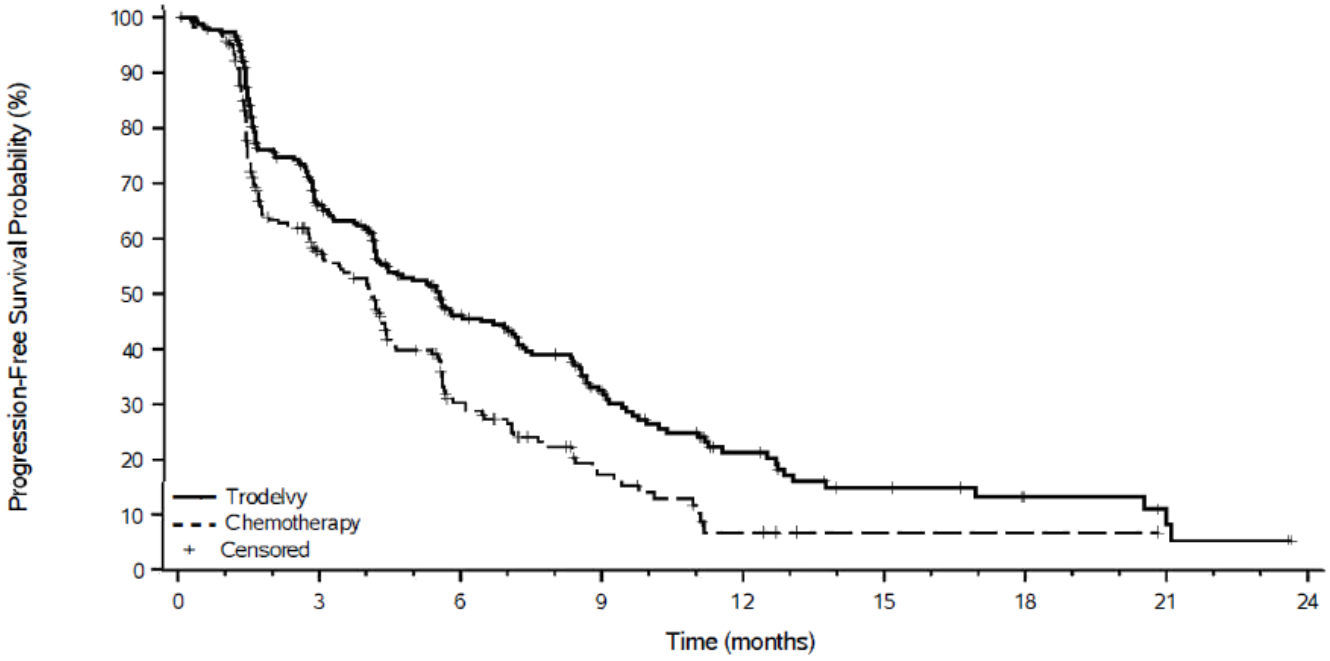
有効性の結果を表 13 に要約し、図 3 及び図 4 に示す。

表 13：TROPiCS-02 試験の有効性の結果

	All Randomized Patients	
	TRODELVY n=272	**Single Agent Chemotherapy n=271**
Progression-Free Survival by BICR[1]		
Median PFS in months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Hazard ratio (95% CI)	0.661 (0.529, 0.826)	
p-value[2]	0.0003	
Overall Survival[3]		
Median OS in months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Hazard ratio (95% CI)	0.789 (0.646, 0.964)	
p-value[2]	0.0200	
Objective Response Rate[3] by BICR		
Response Rate, % (95% CI)	21.0 (16.3, 26.3)	14.0 (10.1, 18.7)
Odds ratio (95% CI)	1.625 (1.034, 2.555)	
p-value	0.0348	
Duration of Response[3] (DOR) by BICR		
Median DOR in months (95% CI)	8.1 (6.7, 9.1)	5.6 (3.8, 7.9)

[1] 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.
[2] Stratified log-rank test adjusted for stratification factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (Y/N), and endocrine therapy in the metastatic setting for at least 6 months (Yes or No).
BICR = Blinded Independent Central Review; CI = Confidence Interval
[3] Second interim OS analysis (conducted when 390 OS events were observed)

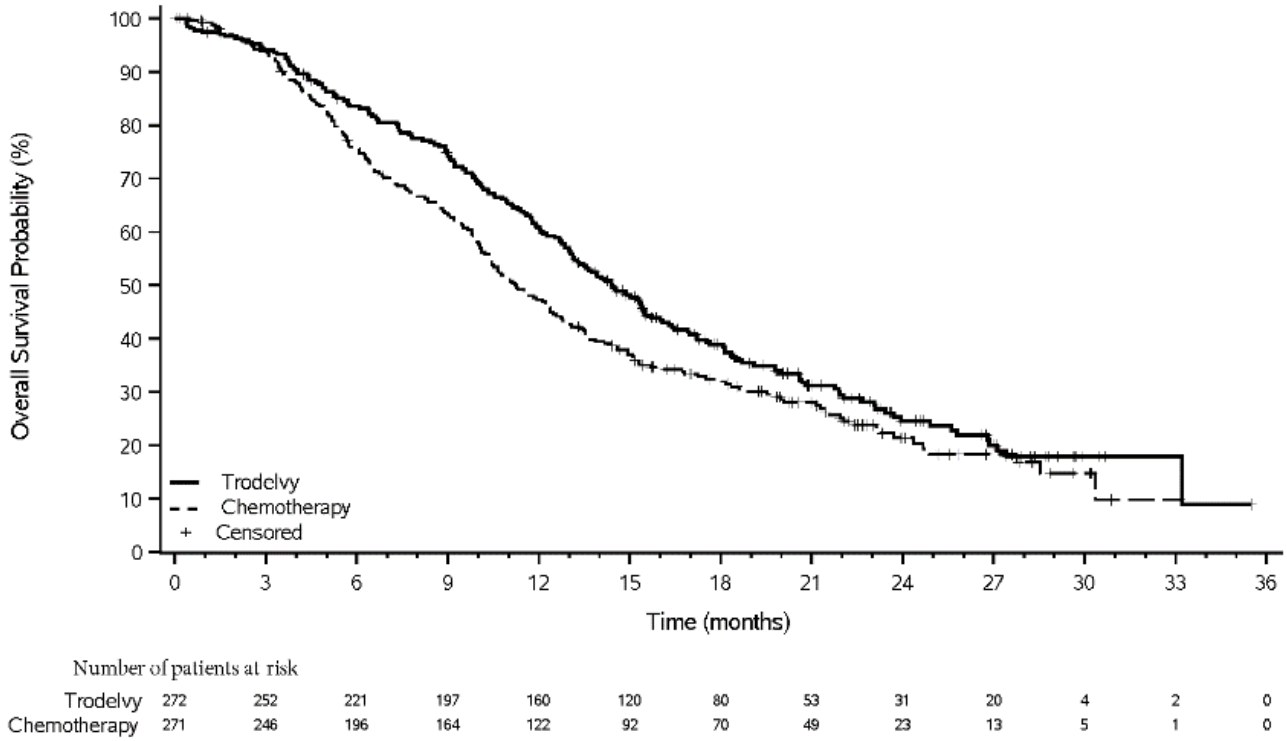
図 3：TROPiCS-02 試験における BICR による PFS の Kaplan-Meier 曲線



Number of patients at risk

Trodelvy	272	148	82	44	22	12	6	3	0
Chemotherapy	271	105	41	17	4	1	1	0	0

図 4：TROPiCS-02 試験における OS の Kaplan-Meier 曲線



14.3 局所進行又は転移性尿路上皮癌

TROPHY 試験

本剤の有効性は、プラチナ製剤を含む化学療法の前治療歴及び抗 PD-1 又は PD-L1 抗体による前治療歴を有する局所進行又は転移性 UC 患者 112 例を登録したシングルアーム、多施設共同試験（TROPHY 試験、NCT03547973）において評価された。21 日間を 1 サイクルとして、各サイクルの 1 日目及び 8 日目に、本剤 10 mg/kg を点滴静注した。本剤投与前に、全ての患者はがん薬物療法によって発現する悪心、嘔吐及び Infusion reaction の予防的治療を行った。疾患進行又は許容できない毒性が認められるまで投与を継続した。

年齢の中央値は 66 歳（範囲：33～90 歳）であり、78%が男性、74%が白人、3%がアジア系、3%が黒人、20%が人種不明であった。全患者のベースライン時の ECOG PS は、0（28%）又は 1（72%）であった。患者の 96%には転移病変があり、67%には内臓転移、34%には肝転移があった。

全身療法による前治療数の中央値は 3（範囲：1～8）であった。患者の 65%にシスプラチン、21%にカルボプラチン、13%にシスプラチンとカルボプラチンの両方、100%に抗 PD-1 又は PD-L1 抗体の前治療歴があった。患者の 34%は、術前／術後薬物療法のみにおいて、プラチナ製剤を含む化学療法の前治療歴を有し、患者の 9%がエンホルツマブ　ベドチンの前治療歴を有していた。

主な有効性評価項目は、固形がんの治療効果判定のための新ガイドライン（RECIST）第 1.1 版に基づき独立判定により評価した ORR 及び DOR とした。有効性の結果を表 14 に要約する。

表 14：TROPHY 試験における局所進行又は転移性 UC 患者の有効性の結果

	TRODELVY (N=112)
Overall Response Rate [i]	
ORR (95% CI)	27.7% (19.6, 36.9)
Complete response	5.4%
Partial response	22.3%
Response duration[i]	
Number of responders	31
Median, Months (95% CI)	7.2 (4.7, 8.6)
Range, Months	1.4+, 13.7

[i] by independent review assessment
CI confidence interval
+ denotes ongoing

15参考文献

1. “OSHA Hazardous Drugs.” OSHA. *http://www.osha.gov/SLTC/hazardousdrugs/index.html*.

16包装・保存及び取扱い上の注意

TRODELVY（sacituzumab govitecan-hziy）点滴静注用は、バイアルに充填された無菌、微黄白色～帯黄色の凍結乾燥粉末である。本剤の各バイアルは個別に箱に入っている。

- NDC 55135-132-01 の内容は 1 バイアル（180 mg）である。

バイアルは溶解時まで、遮光のために元の箱に入れたまま、2～8°C（36～46°F）で冷蔵庫に保存すること。凍結させないこと。

本剤は有害な薬剤である。適用される特別な取扱い及び廃棄手順に従うこと [1]。

17患者カウンセリング情報

FDA 承認済みの患者向け添付文書（患者向け情報）を読むよう患者に指導すること。

好中球減少症

好中球減少症のリスクについて患者に説明すること。発熱、悪寒又はその他の感染の徴候が認められた場合は、直ちに医療提供者に連絡するよう患者に指示すること *［警告及び使用上の注意（5.1）参照］*。

下痢

下痢のリスクについて患者に説明すること。投与中に初めて下痢が発現した場合（黒色便又は血便、頭部ふらふら感、浮動性めまい、浮動性めまい感などの脱水症状、悪心や嘔吐のため水分を経口摂取出来ない場合、又は 24 時間以内に下痢がコントロールできない場合）は、直ちに医療提供者に連絡するよう患者に指示すること。*［警告及び使用上の注意（5.2）参照］*。

過敏症及び Infusion reaction

重篤な Infusion reaction及びアナフィラキシーのリスクについて患者に説明すること。投与中又は投与後 24 時間以内に、顔面、口唇、舌又は咽頭の腫脹、蕁麻疹、呼吸困難、頭部ふらふら感、浮動性めまい、悪寒、悪寒戦慄、喘鳴、そう痒症、潮紅、発疹、低血圧又は発熱が発現した場合は、直ちに医療提供者に連絡するよう患者に指示すること *［警告及び使用上の注意（5.3）参照］*。

悪心/嘔吐

悪心及び嘔吐のリスクについて患者に説明すること。がん薬物療法によって発現する悪心・嘔吐（CINV）を予防するための 2 剤又は 3 剤レジメンによる確立されたガイドラインに従った前投与を行うことも望ましい。臨床的に必要であれば、追加の制吐薬、鎮静薬及びその他の支持療法を用いてもよい。全ての患者に、遅発性悪心及び嘔吐の予防及び治療のため、明確な指示とともに自宅で服薬できる薬剤を処方すべきである。コントロールできない悪心又は嘔吐が発現した場合は直ちに医療提供者に連絡するよう患者に指示すること*［警告及び使用上の注意（5.4）参照］*。

胚・胎児毒性

女性患者には、妊娠している場合又は妊娠した場合、医療提供者に連絡するよう指示すること。女性患者に、胎児への危険性及び妊娠喪失の可能性について説明すること*［特別な集団への投与（8.1 項）参照］*。

避妊

妊娠可能な女性患者に対して、本剤投与中及び本剤投与終了後 6 ヵ月間は適切な避妊を行うよう指導すること*［特別な集団への投与（8.3）を参照］*。

パートナーが妊娠する可能性のある男性患者に対して、本剤投与中及び本剤投与終了後 3 ヵ月間は適切な避妊を行うよう指導すること*［特別な集団への投与（8.3）を参照］*。

授乳

本剤投与中及び本剤投与終了後 1 ヵ月間は授乳を行わないよう患者に指導すること*［特別な集団への投与（8.2）参照］*。

不妊症

妊娠可能な女性には、本剤は受胎能を低下させる可能性があることを説明すること*［特別な集団への投与（8.3）参照］*。

製造元：

Gilead Sciences, Inc.
333 Lakeside Dr.
Foster City, CA 94404, USA
U.S. License No. 2258

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Trodelvy 200 mg powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 200 mg sacituzumab govitecan.
After reconstitution, one mL of solution contains 10 mg sacituzumab govitecan.

Sacituzumab govitecan is a Trop-2-directed antibody-drug conjugate (ADC). Sacituzumab is a humanised monoclonal antibody (hRS7 IgG1κ) that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a hydrolysable linker. Approximately 7-8 molecules of SN-38 are attached to each antibody molecule.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion
Off-white to yellowish powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Trodelvy as monotherapy is indicated 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 (see section 5.1).

Trodelvy as monotherapy is indicated for the treatment of adult patients with unresectable or metastatic hormone receptor (HR)-positive, HER2-negative breast cancer who have received endocrine-based therapy, and at least two additional systemic therapies in the advanced setting (see section 5.1).

4.2 Posology and method of administration

Trodelvy must only be prescribed and administered to patients by healthcare professionals experienced in the use of anti-cancer therapies and administered in an environment where full resuscitation facilities are available.

Posology

The recommended dose of sacituzumab govitecan is 10 mg/kg body weight administered as an intravenous infusion once weekly on Day 1 and Day 8 of 21-day treatment cycles. Treatment should be continued until disease progression or unacceptable toxicity.

Prevention treatment

Prior to each dose of sacituzumab govitecan, treatment for prevention of infusion-related reactions and prevention of chemotherapy-induced nausea and vomiting (CINV) is recommended (see section 4.4).

Dose modifications for infusion-related reactions

The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur (see section 4.4).

Dose modifications for adverse reactions

Dose modifications to manage adverse reactions of sacituzumab govitecan are described in Table 1. The sacituzumab govitecan dose should not be re-escalated after a dose reduction for adverse reactions has been made.

Table 1: Recommended dose modifications for adverse reactions

Adverse reaction	**Occurrence**	**Dose modification**
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days or less if clinically indicated, OR Grade 3-4 febrile neutropenia , OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	Administer granulocyte-colony stimulating factor (GCSF) as soon as clinically indicated
	Second	25% dose reduction; administer G-CSF as soon as clinically indicated
	Third	50% dose reduction; administer G-CSF as soon as clinically indicated
	Fourth	Discontinue treatment; administer G-CSF as soon as clinically indicated
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment; administer G-CSF as soon as clinically indicated
Severe non-neutropenic toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any Grade 3-4 nausea, vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrhoeal agents, OR Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, Grade 3 nausea or Grade 3-4 vomiting, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

Special populations

Elderly
No dose adjustment is required in patients ≥ 65 years old. Data from sacituzumab govitecan in patients ≥ 75 years are limited.

Hepatic impairment
No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild hepatic impairment (bilirubin ≤ 1.5 upper limit of normal [ULN] and aspartate aminotransferase [AST]/alanine aminotransferase [ALT] < 3 ULN).

The safety of sacituzumab govitecan in patients with moderate or severe hepatic impairment has not been established. Sacituzumab govitecan has not been studied in patients with any of the following: serum bilirubin > 1.5 ULN, or AST or ALT > 3 ULN in patients without liver metastases, or AST or ALT > 5 ULN in patients with liver metastases. The use of sacituzumab govitecan should be avoided in these patients.

Renal impairment
No adjustment to the starting dose is required when administering sacituzumab govitecan to patients with mild or moderate renal impairment.

Sacituzumab govitecan has not been studied in patients with severe renal impairment or end-stage renal disease (Creatinine Clearance [CrCl] < 15 mL/min).

Paediatric population
The safety and efficacy of sacituzumab govitecan in children aged 0 to 18 years have not been established. No data are available.

Method of administration

Sacituzumab govitecan is for intravenous use only. It must be reconstituted and diluted by a healthcare professional experienced in the handling of anti-cancer therapies. It must be administered as an intravenous infusion, not as an intravenous push or bolus.

First infusion: the infusion should be administered over a period of 3 hours.

Subsequent infusions: the infusion should be administered over a period of 1 to 2 hours if prior infusions were tolerated.

Patients have to be observed during each infusion and for at least 30 minutes after each infusion for signs or symptoms of infusion-related reactions (see section 4.4).

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Neutropenia

Sacituzumab govitecan can cause severe or life-threatening neutropenia (see section 4.8). Fatal infections in the setting of neutropenia have been observed in clinical studies with sacituzumab govitecan. Sacituzumab govitecan should not be administered if the absolute neutrophil count is below 1500/mm^3 on Day 1 of any cycle or if the neutrophil count is below 1000/mm^3 on Day 8 of any cycle. Therefore, it is recommended that patients' blood counts are monitored as clinically indicated during treatment. Sacituzumab govitecan should not be administered in case of neutropenic fever. Treatment with granulocyte-colony stimulating factor and dose modifications may be required due to severe neutropenia (see sections 4.2 and 4.8).

Diarrhoea

Sacituzumab govitecan can cause severe diarrhoea (see section 4.8). Diarrhoea in some cases was observed to have led to dehydration and subsequent acute kidney injury. Sacituzumab govitecan should not be administered in case of Grade 3-4 diarrhoea at the time of scheduled treatment and treatment should only be continued when resolved to ≤ Grade 1 (see section 4.2 and 4.8). At the onset of diarrhoea, and if no infectious cause can be identified, treatment with loperamide should be initiated. Additional supportive measures (e.g. fluid and electrolyte substitution) may also be employed as clinically indicated.

Patients who exhibit an excessive cholinergic response to treatment with sacituzumab govitecan (e.g. abdominal cramping, diarrhoea, salivation, etc.) can receive appropriate treatment (e.g. atropine) for subsequent treatments with sacituzumab govitecan.

Hypersensitivity

Sacituzumab govitecan can cause severe and life-threatening hypersensitivity (see section 4.8). Anaphylactic reactions have been observed in clinical studies with sacituzumab govitecan and the use of sacituzumab govitecan is contraindicated in patients with a known hypersensitivity to sacituzumab govitecan (see section 4.3).

Pre-infusion treatment, including antipyretics, H1 and H2 blockers, or corticosteroids (e.g. 50 mg hydrocortisone or equivalent, orally or intravenously), for patients receiving sacituzumab govitecan is recommended. Patients should be closely observed for infusion-related reactions during each sacituzumab govitecan infusion and for at least 30 minutes after completion of each infusion. The infusion rate of sacituzumab govitecan should be slowed down or infusion interrupted if the patient develops an infusion-related reaction. Sacituzumab govitecan should be permanently discontinued if life-threatening infusion-related reactions occur (see section 4.2).

Nausea and vomiting

Sacituzumab govitecan is emetogenic (see section 4.8). Antiemetic preventive treatment with two or three medicinal products (e.g. dexamethasone with either a 5-hydroxytryptamine 3 [5-HT3] receptor antagonist or a Neurokinin-1 [NK-1] receptor antagonist as well as other medicinal products as indicated) is recommended for prevention of chemotherapy-induced nausea and vomiting (CINV).

Sacituzumab govitecan should not be administered in case of Grade 3 nausea or Grade 3-4 vomiting at the time of scheduled treatment administration and treatment should only be continued with additional supportive measures when resolved to ≤ Grade 1 (see section 4.2). Additional antiemetics and other supportive measures may also be employed as clinically indicated. All patients should be given take-home medicinal products with clear instructions for prevention and treatment of nausea and vomiting.

Use in patients with reduced UGT1A1 activity

SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via uridine diphosphate-glucuronosyl transferase (UGT1A1). Genetic variants of the UGT1A1 gene such as the UGT1A1*28 allele lead to reduced UGT1A1 enzyme activity. Individuals who are homozygous for

UGT1A1*28 allele are at increased risk for neutropenia, febrile neutropenia, and anaemia and are at increased risk for other adverse reactions following initiation of sacituzumab govitecan treatment (see section 4.8). Approximately 20% of the Black population, 10% of the White population, and 2% of the East Asian population are homozygous for the UGT1A1*28 allele. Decreased function alleles other than UGT1A1*28 may be present in certain populations. Patients with known reduced UGT1A1 activity should be closely monitored for adverse reactions. When unknown, no testing of UGT1A1 status is required as the management of adverse reactions including the recommended dose modifications will be the same for all patients.

Embryo-foetal toxicity

Based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered to a pregnant woman. Sacituzumab govitecan contains a genotoxic component, SN-38, and targets rapidly dividing cells. Pregnant women and women of childbearing potential should be informed of the potential risk to the foetus. The pregnancy status of females of reproductive potential should be verified prior to the initiation of sacituzumab govitecan (see section 4.6).

Sodium

This medicinal product will be further prepared for administration with sodium-containing solution (see section 6.6) and this should be considered in relation to the total sodium intake to the patient from all sources per day.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

UGT1A1 inhibitors

Concomitant administration of sacituzumab govitecan with inhibitors of UGT1A1 may increase the incidence of adverse reactions due to potential increase in systemic exposure to SN-38. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inhibitors (e.g. propofol, ketoconazole, EGFR tyrosine kinase inhibitors).

UGT1A1 inducers

Exposure to SN-38 may be reduced in patients concomitantly receiving UGT1A1 enzyme inducers. Sacituzumab govitecan should be used with caution in patients receiving UGT1A1 inducers (e.g. carbamazepine, phenytoin, rifampicin, ritonavir, tipranavir).

Based on the limited data available from patients who received UGT1A1 inhibitors (n=16) or inducers (n=5) while being treated with sacituzumab govitecan, free SN-38 exposures in these patients were comparable to those in patients who did not receive UGT1A1 inhibitor or inducer.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential have to use effective contraception during treatment and for 6 months after the last dose.
Male patients with female partners of childbearing potential have to use effective contraception during treatment with sacituzumab govitecan and for 3 months after the last dose.

Pregnancy

There are no available data on the use of sacituzumab govitecan in pregnant women. However, based on its mechanism of action, sacituzumab govitecan can cause teratogenicity and/or embryo-foetal lethality when administered during pregnancy. Sacituzumab govitecan contains a genotoxic component, SN-38, and targets rapidly dividing cells.
Sacituzumab govitecan should not be used during pregnancy unless the clinical condition of the woman requires treatment with sacituzumab govitecan.
The pregnancy status of women of childbearing potential should be verified prior to the initiation of sacituzumab govitecan.
Women who become pregnant must immediately contact their doctor.

Breast-feeding

It is unknown whether sacituzumab govitecan or its metabolites are excreted in human milk. A risk to breastfed newborns/infants cannot be excluded. Breast-feeding should be discontinued during treatment with sacituzumab govitecan and for 1 month after the last dose.

Fertility

Based on findings in animals, sacituzumab govitecan may impair fertility in females of reproductive potential (see section 5.3). No human data on the effect of sacituzumab govitecan on fertility are available.

4.7 Effects on ability to drive and use machines

Sacituzumab govitecan has minor influence on the ability to drive and use machines, e.g. dizziness, fatigue (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most common adverse reactions reported in patients treated with sacituzumab govitecan were: neutropenia (67.6%), nausea (62.6%), diarrhoea (62.5%), fatigue (61.5%), alopecia (45.6%), anaemia (40.7%), constipation (36.2%), vomiting (33.6%), decreased appetite (25.7%), dyspnoea (22.1%) and abdominal pain (20.2%).

The most common grade 3 or higher adverse reactions were neutropenia (50.7%), leukopenia (10.5%), diarrhoea (10.3%), anaemia (9.3%), fatigue (6.8%), febrile neutropenia (6.1%), hypophosphataemia (4.2%), dyspnoea (3.1%), lymphopenia (2.9%), abdominal pain (2.8%), nausea (2.8%), vomiting (2.5%), hypokalaemia (2.5%), pneumonia (2.3%) and aspartate aminotransferase increased (2.2%).

The most frequently reported serious adverse reactions in patients treated with sacituzumab govitecan were febrile neutropenia (4.8%), diarrhoea (3.9%), neutropenia (2.6%) and pneumonia (2%).

Tabulated list of adverse reactions

The frequencies of adverse reactions are based on pooled data from three clinical studies involving 688 patients who received sacituzumab govitecan 10 mg/kg body weight for the treatment of metastatic TNBC and HR+/HER2- breast cancer. The median exposure to sacituzumab govitecan in this data set was 4.63 months.

The adverse reaction frequencies are based on all-cause adverse event frequencies, where a proportion of the events for an adverse reaction may have other causes than sacituzumab govitecan, such as the disease, other medicinal products or unrelated causes. The severity of adverse drug reactions was

assessed based on the Common Terminology Criteria for Adverse Events (CTCAE), defining grade 1 = mild, grade 2 = moderate, grade 3 = severe, grade 4 = life threatening, and 5 = death.

Adverse reactions are listed by System Organ Class and frequency category. Frequency categories are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); and not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: List of adverse reactions

System organ class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Urinary tract infection Upper respiratory tract infection
	Common	Sepsis Pneumonia Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes
Blood and lymphatic system disorders		
	Very common	Neutropenia[1] Anaemia[2] Leukopenia[3] Lymphopenia[4]
	Common	Febrile neutropenia Thrombocytopenia[5]
Immune system disorders		
	Very common	Hypersensitivity[6]
Metabolism and nutrition disorders		
	Very common	Decreased appetite Hypokalaemia Hypomagnesaemia
	Common	Dehydration Hyperglycaemia Hypophosphataemia Hypocalcaemia Hyponatraemia
Psychiatric disorders		
	Very common	Insomnia
	Common	Anxiety
Nervous system disorders		
	Very common	Headache Dizziness
	Common	Dysgeusia
Vascular disorders		
	Common	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Very common	Dyspnoea[7] Cough
	Common	Epistaxis Productive cough Rhinorrhoea Nasal congestion Upper airway cough syndrome
Gastrointestinal disorders		
	Very common	Diarrhoea Vomiting

		Nausea Constipation Abdominal Pain
	Common	Neutropenic colitis[8] Colitis Stomatitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension
	Uncommon	Enteritis
Skin and subcutaneous tissue disorders		
	Very common	Alopecia Rash Pruritus
	Common	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin
Musculoskeletal and connective tissue disorders		
	Very common	Back pain Arthralgia
	Common	Musculoskeletal chest pain Muscle spasms
Renal and urinary disorders		
	Common	Haematuria Proteinuria Dysuria
General disorders and administration site conditions		
	Very common	Fatigue[9]
	Common	Pain Chills
Investigations		
	Common	Weight decreased Blood alkaline phosphatase increased Activated partial thromboplastin time prolonged Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications		
	Uncommon	Infusion related reaction

1: Includes the following preferred terms: neutropenia; neutrophil count decreased.
2: Includes the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.
3: Includes the following preferred terms: leukopenia; white blood cell count decreased.
4: Includes the following preferred terms: lymphopenia; lymphocyte count decreased.
5: Includes the following preferred terms: thrombocytopenia; platelet count decreased.
6: Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: dyspnoea; hypotension; flushing; erythema; chest discomfort; rhinitis allergic; wheezing; oedema; urticaria; anaphylactic reaction; mouth ulceration**;** skin exfoliation; swollen tongue; throat tightness
7: Includes the following preferred terms: dyspnoea; dyspnoea exertional
8: Includes the preferred term of neutropenic colitis and events reported as typhlitis
9: Includes the following preferred terms: fatigue, asthenia

Description of selected adverse reactions

Neutropenia
The median time to onset of neutropenia (including febrile neutropenia) following the start of the first treatment cycle was 16 days. The median duration of neutropenia was 8 days.

Neutropenia occurred in 67.6% (465/688) of patients treated with sacituzumab govitecan, including Grade 3-4 neutropenia in 50.7% of patients. Neutropenia was the reason for dose reduction in 12.4% of patients. Neutropenic colitis was observed in 1% (7/688) of patients.

Febrile neutropenia occurred in 6.1% (42/688) of patients treated with sacituzumab govitecan. Febrile neutropenia was the reason for dose reduction in 2.9% of patients.

Use in patients with reduced UGT1A1 activity
The incidence of Grade 3-4 neutropenia was 60.6% (43/71) in patients homozygous for the UGT1A1*28 allele, 52.9% (144/272) in patients heterozygous for the UGT1A1*28 allele, and 49.1% (140/285) in patients homozygous for the wild-type allele. The incidence of Grade 3-4 febrile neutropenia was 14.1% (10/71) in patients homozygous for the UGT1A1*28 allele, 5.9% (16/272) in patients heterozygous for the UGT1A1*28 allele, and 4.6% (13/285) in patients homozygous for the wild-type allele. The incidence of Grade 3-4 anaemia was 15.5% (11/71) in patients homozygous for the UGT1A1*28 allele, 7.4% (20/272) in patients heterozygous for the UGT1A1*28 allele, and 8.1% (23/285) in patients homozygous for the wild-type allele.

Compared to patients homozygous for the wild-type allele, earlier median onset of neutropenia and anaemia was observed in patients homozygous for the UGT1A1*28 allele and in patients heterozygous for the UGT1A1*28 allele.

Diarrhoea
The median time to onset of diarrhoea following the start of the first treatment cycle was 13 days. The median duration of diarrhoea was 8 days.

Diarrhoea occurred in 62.5% (430/688) of patients treated with sacituzumab govitecan. Grade 3 events occurred in 10.3% (71/688) of patients. Three of 688 patients (< 1%) discontinued treatment because of diarrhoea.

Hypersensitivity
Hypersensitivity reactions reported up to the end of the day following dosing occurred in 33.0% (227/688) of patients treated with sacituzumab govitecan. Grade 3 and above hypersensitivity occurred in 1.7% (12/688) of patients treated with sacituzumab govitecan. The incidence of hypersensitivity reactions leading to permanent discontinuation of sacituzumab govitecan was 0.1% (1/688).

Immunogenicity
Across clinical studies in patients treated with sacituzumab govitecan, 9 (1.1%) of 785 patients developed antibodies to sacituzumab govitecan; 6 of these patients (0.8% of all patients treated with sacituzumab govitecan) had neutralizing antibodies against sacituzumab govitecan.

Special Populations
There was no difference in discontinuation rate due to adverse events in patients aged 65 years or older compared with younger patients with mTNBC. There was a higher discontinuation rate due to adverse reactions in patients aged 65 years or older (14%) compared with younger patients (3%) with HR+/HER2- metastatic breast cancer. There was a higher incidence rate of serious adverse events in patients aged 75 years or older (67%) compared to patients aged 65 years or older (43%) and patients younger than 65 years (24%) with HR+/HER2- metastatic breast cancer.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In clinical studies, doses of up to 18 mg/kg (approximately 1.8 times the maximum recommended dose of 10 mg/kg body weight) led to a higher incidence of severe neutropenia.

In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, in particular severe neutropenia, and appropriate treatment instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies, ATC code: L01FX17.

Mechanism of action

Sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalised with the subsequent release of SN-38 from a hydrolysable linker. SN-38 interacts with topoisomerase I and prevents re-ligation of topoisomerase I-induced single strand breaks. The resulting DNA damage leads to apoptosis and cell death.

Clinical efficacy and safety

Unresectable or metastatic Triple Negative Breast Cancer (ASCENT)

The efficacy and safety of sacituzumab govitecan was assessed in ASCENT (IMMU-132-05), an international Phase 3, multicentre, open-label, randomised study conducted in 529 patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who had relapsed after at least two prior chemotherapies (no upper limit) for breast cancer. Earlier adjuvant or neoadjuvant therapy for more limited disease qualified as one of the required prior regimens if the development of unresectable, locally advanced or metastatic disease occurred within a 12-month period of time after completion of chemotherapy. All patients received previous taxane treatment in either the adjuvant, neoadjuvant, or advanced stage unless they had a contraindication or were intolerant to taxanes. Poly-ADP ribose polymerase (PARP) inhibitors were allowed as one of the two prior chemotherapies for patients with a documented germline BRCA1/BRCA2 mutation.

Patients were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Day 1 and Day 8 of a 21-day treatment cycle or Treatment of Physician's Choice (TPC) which was dosed based on body surface area and per the approved product information. TPC was determined by the investigator before randomisation from one of the following single-agent regimens: eribulin (n = 139), capecitabine (n = 33), gemcitabine (n = 38), or vinorelbine (except if patient had ≥ Grade 2 neuropathy, n = 52). Patients with stable brain metastases (pre-treated, non-progressive, without anti-seizure medicinal products and on stable corticosteroid dose for at least 2 weeks) were eligible. Magnetic resonance imaging (MRI) to determine brain metastases was required only for patients with known or suspected brain metastases. Patients with known Gilbert's disease, bone-only disease, known history of unstable angina, myocardial infarction, or congestive heart failure, active chronic inflammatory bowel disease or gastrointestinal (GI) perforation, human immunodeficiency virus (HIV), active hepatitis B or C infection, live vaccine within 30 days, or who have previously received irinotecan were excluded.

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy endpoint was progression-free survival (PFS) in patients without brain metastases at baseline (i.e. BMNeg) as measured by a blinded, independent, centralised review (BICR) group of radiology experts using Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 criteria. Secondary efficacy endpoints included PFS by BICR for the overall population, including all patients with and without brain metastases, overall survival (OS), objective response rate (ORR) and duration of response (DOR).

The primary analysis included 235 BMNeg patients in the sacituzumab govitecan group and 233 BMNeg patients in the TPC group. The analysis of the overall population included 267 patients in the sacituzumab govitecan group and 262 patients in the TPC group.

The demographics and baseline characteristics of the overall population (n = 529) were: median age of 54 years (range: 27–82 years) and 81% < 65 years; 99.6% female; 79% White; 12% Black; median number of prior systemic therapies was 4; 69% had previously received 2 to 3 prior chemotherapies; 31% had previously received > 3 prior chemotherapies; 42% had hepatic metastases; 12% had present or a history of brain metastases. 8% were BRCA1/BRCA2 mutational status positive; BRCA status was available for 339 patients. At study entry, all patients had an ECOG performance status of 0 (43%) or 1 (57%). The median time from diagnosis of Stage 4 to study entry was 16.2 months (range: -0.4 to 202.9 months). The most frequent prior chemotherapies were cyclophosphamide (83%), anthracycline (83%) including doxorubicin (53%), paclitaxel (78%), carboplatin (65%), capecitabine (67%), gemcitabine (36%), docetaxel (35%), and eribulin (33%). Overall, 29% of patients had received prior PD-1/PD-L1 therapy. Thirteen percent of patients in the sacituzumab govitecan group in the overall population received only 1 prior line of systemic therapy in the metastatic setting.

The efficacy results in the BMNeg population showed a statistical significant improvement of sacituzumab govitecan over TPC in PFS and OS with hazard ratios (HR) of 0.41 (n=468; 95% CI: 0.32, 0.52; p-value: <0.0001) and 0.48 (n=468; 95% CI: 0.38, 0.59; p-value: <0.0001), respectively. The median PFS was 5.6 months *vs* 1.7 months; the median OS was 12.1 months *vs* 6.7 months, in patients treated with sacituzumab govitecan and TPC, respectively.

The efficacy results in the overall population were consistent with the BMNeg population in the pre-specified final analysis (11 March 2020 cut-off date) and are summarised in Table 3.

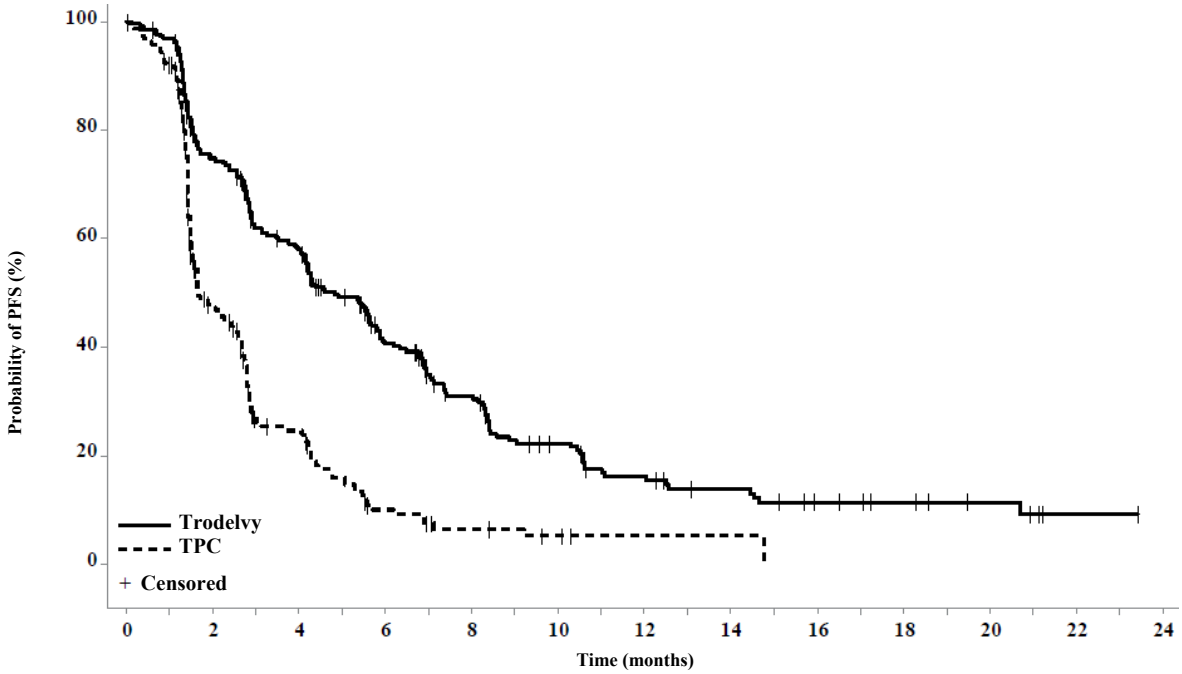
Table 3: Efficacy endpoints (overall population) - Pre-specified Final Analysis

	Pre-specified Final Analysis (11 March 2020 cut-off date)	
	Sacituzumab govitecan n=267	**Treatment of physician's choice (TPC) n=262**
Progression-free survival[1]		
Number of events (%)	190 (71.2)	171 (65.3)
Median PFS in months (95% CI)	4.8 (4.1,5.8)	1.7 (1.5, 2.5)
Hazard ratio (95% CI)	0.43 (0.35, 0.54)	
p-value[2]	<0.0001	
Overall Survival		
Number of deaths (%)	179 (67.0)	206 (78.6)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)
Hazard ratio (95% CI)	0.51 (0.41, 0.62)	
p-value[2]	<0.0001	
Overall response rate (ORR)		
Number of responders (%)	83 (31)	11 (4)
Odds ratio (95% CI)	10.99 (5.66, 21.36)	
p-value[3]	<0.0001	
Complete response, n (%)	10 (4)	2 (1)
Partial response, n (%)	73 (27)	9 (3)
Duration of response (DOR)		
Median DOR in months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, NE)

1 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.
2 Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
3 Based on Cochran-Mantel-Haenszel test.
CI = Confidence Interval

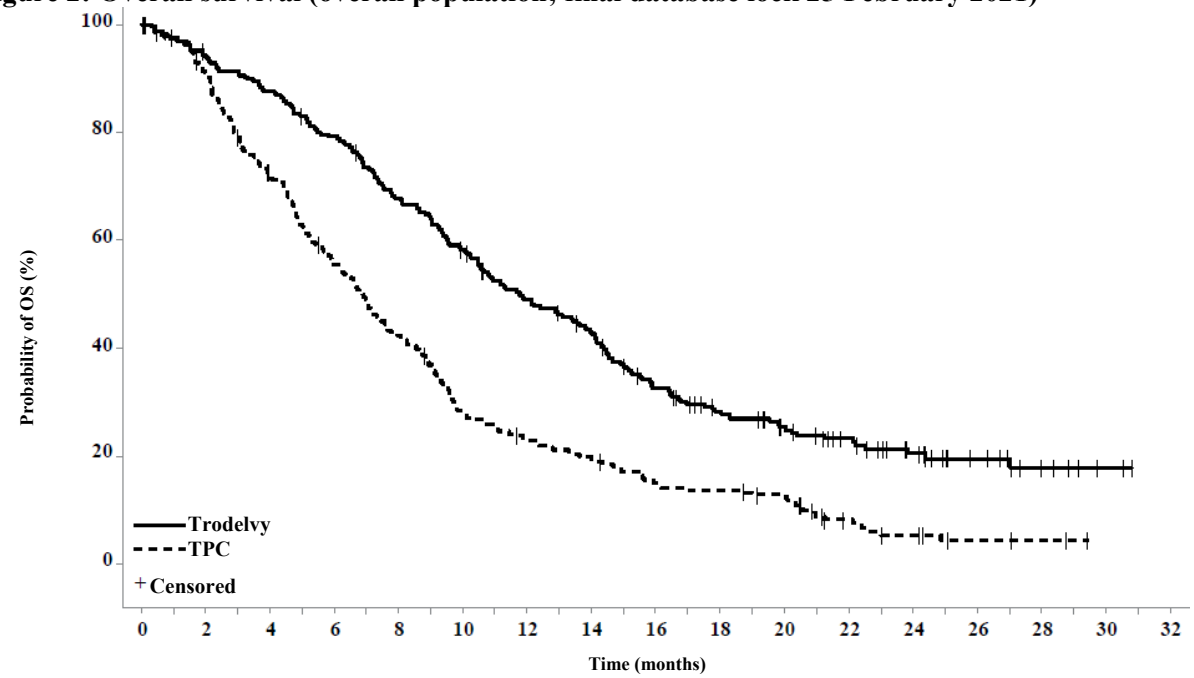
In an updated efficacy analysis (final database lock 25 February 2021), results were consistent with the pre-specified final analysis. The median PFS by BICR was 4.8 months vs 1.7 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.41; 95% CI: 0.33, 0.52). The median OS was 11.8 months vs 6.9 months, respectively (HR of 0.51; 95% CI: 0.42, 0.63). Kaplan-Meier curves for updated PFS by BICR and OS are presented in Figures 1 and 2.

Figure 1: Progression free survival (overall population; final database lock 25 February 2021) by BICR



Number of Patients at Risk													
Trodelvy	267	184	135	82	55	34	23	17	11	8	5	1	0
TPC	262	86	36	12	6	3	1	1	0	0	0	0	0

Figure 2: Overall survival (overall population; final database lock 25 February 2021)



Number of Patients at Risk																
Trodelvy	267	250	232	209	178	152	125	108	79	62	49	37	25	14	7	2	0
TPC	262	222	174	132	101	66	54	45	34	31	26	12	7	3	2	0	0

Sub-group analysis

In subgroup analyses, improvements in PFS and OS in patients treated with sacituzumab govitecan compared to TPC were consistent across patient subgroups irrespective of age, race, BRCA status, prior number of systemic therapies overall (2 and >2, 2-3 and >3) and in the metastatic setting (1 and >1), prior therapy with anthracycline or PDL1, and liver metastases.

Brain metastases
An exploratory analysis of PFS and OS in patients with previously treated, stable brain metastases showed a stratified HR of 0.65 (n=61; 95% CI: 0.35, 1.22) and 0.87 (n=61; 95% CI: 0.47, 1.63), respectively. The median PFS was 2.8 months *vs* 1.6 months; the median OS was 6.8 months *vs* 7.5 months, in patients treated with sacituzumab govitecan and TPC, respectively.

Trop-2 expression
Additional subgroup analyses were conducted to evaluate the efficacy by tumour Trop-2 expression levels and the results were consistent across the different scoring methods used. In patients with low Trop-2 levels using membrane H-score by quartiles, benefit of sacituzumab govitecan over TPC was shown for both PFS (HR 0.64; 95% CI: 0.37, 1.11) and OS (HR of 0.71; 95% CI: 0.42, 1.21).

Unresectable or metastatic hormone receptor (HR)-positive/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (TROPiCS-02)

The efficacy of sacituzumab govitecan was evaluated in a multicentre, open-label, randomised study TROPiCS-02 (IMMU-132-09) conducted in 543 patients with unresectable locally advanced or metastatic HR-positive, HER2-negative (IHC 0, IHC 1+, or IHC 2+/ISH-) breast cancer whose disease has progressed after the following in any setting: a CDK 4/6 inhibitor, endocrine therapy, and a taxane; patients received at least two prior chemotherapies in the metastatic setting (one of which could be in the neoadjuvant or adjuvant setting if progression or recurrence occurred within 12 months of completion of the chemotherapy). Patients with bone-only disease, active chronic inflammatory bowel disease and known history of bowel obstruction, known history of unstable angina or myocardial infarction or congestive heart failure or active hepatitis B or C infection were excluded from the study.

Patients were randomised (1:1) to receive sacituzumab govitecan 10 mg/kg as an intravenous infusion on Days 1 and 8 of a 21-day cycle (n=272) or TPC (n=271). TPC was determined by the investigator before randomisation from one of the following single-agent regimens: eribulin (n=130), vinorelbine (n=63), gemcitabine (n=56), or capecitabine (n=22). Randomisation was stratified based on prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).

Patients were treated until disease progression or unacceptable toxicity. The primary efficacy outcome measure was PFS as determined by BICR per RECIST v1.1. Additional efficacy outcome measures were OS, ORR by BICR, and DOR by BICR.

The median age of the study population was 56 years (range: 27-86 years), and 26% of patients were 65 years or over. Almost all patients were female (99%). The majority of patients were White (67%); 4% were Black, 3% were Asian, and 26% were of unknown race. Patients received a median of 7 (range: 3 to 17) prior systemic regimens in any setting and 3 (range: 0 to 8) prior systemic chemotherapy regimens in the metastatic setting. Approximately 42% of patients had 2 prior chemotherapy regimens for metastatic disease compared to 58% of patients who had 3 to 4 prior chemotherapy regimens. Most patients received endocrine therapy in the metastatic setting for ≥ 6 months (86%). Patients had an ECOG performance status of 0 (44%) or 1 (56%). Ninety-five percent of patients had visceral metastases; 4.6% of patients had stable, pre-treated brain metastases.

Sacituzumab govitecan demonstrated a statistically significant improvement in PFS by BICR and OS versus TPC. The improvement in PFS by BICR and OS was generally consistent across pre-specified subgroups. Efficacy results are summarized in Table 4.

Table 4. Efficacy endpoints – Pre-specified Final Analysis

	Sacituzumab govitecan n=272	TPC n=271
Progression-Free Survival by BICR[1]		
Number of events (%)	170 (62.5%)	159 (58.7%)
Median PFS in months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Hazard ratio (95% CI)	0.661 (0.529, 0.826)	
p-value[2]	0.0003	
PFS rate at 12 months, % (95% CI)	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)
Overall Survival[3]		
Number of events (%)	191 (70.2%)	199 (73.4%)
Median OS in months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Hazard ratio (95% CI)	0.789 (0.646, 0.964)	
p-value[2]	0.0200	
Objective Response Rate by BICR[3]		
Number of responders (%)	57 (21.0%)	38 (14.0%)
Odds ratio (95% CI)	1.625 (1.034, 2.555)	
p-value	0.0348	

[1] PFS is defined as the time from the date of randomisation to the date of the first radiological disease progression or death due to any cause, whichever comes first (data cut-off 3 January 2022).
[2] Stratified log-rank test adjusted for stratification factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).
[3] Based on second interim OS analysis (data cut-off 1 July 2022).
BICR = Blinded Independent Central Review; CI = Confidence Interval

In an updated efficacy analysis with a median duration of follow-up of 12.8 months (data cut-off 1 December 2022), results were consistent with the pre-specified final analysis. The median PFS by BICR was 5.5 months vs 4.0 months, in patients treated with sacituzumab govitecan and TPC, respectively (HR of 0.65; 95% CI: 0.53, 0.81). The median OS was 14.5 months vs 11.2 months, respectively (HR of 0.79; 95% CI: 0.65, 0.95). Kaplan-Meier curves for updated PFS by BICR and OS are presented in Figures 3 and 4.

Figure 3: Progression free survival by BICR (data cut-off 1 December 2022)

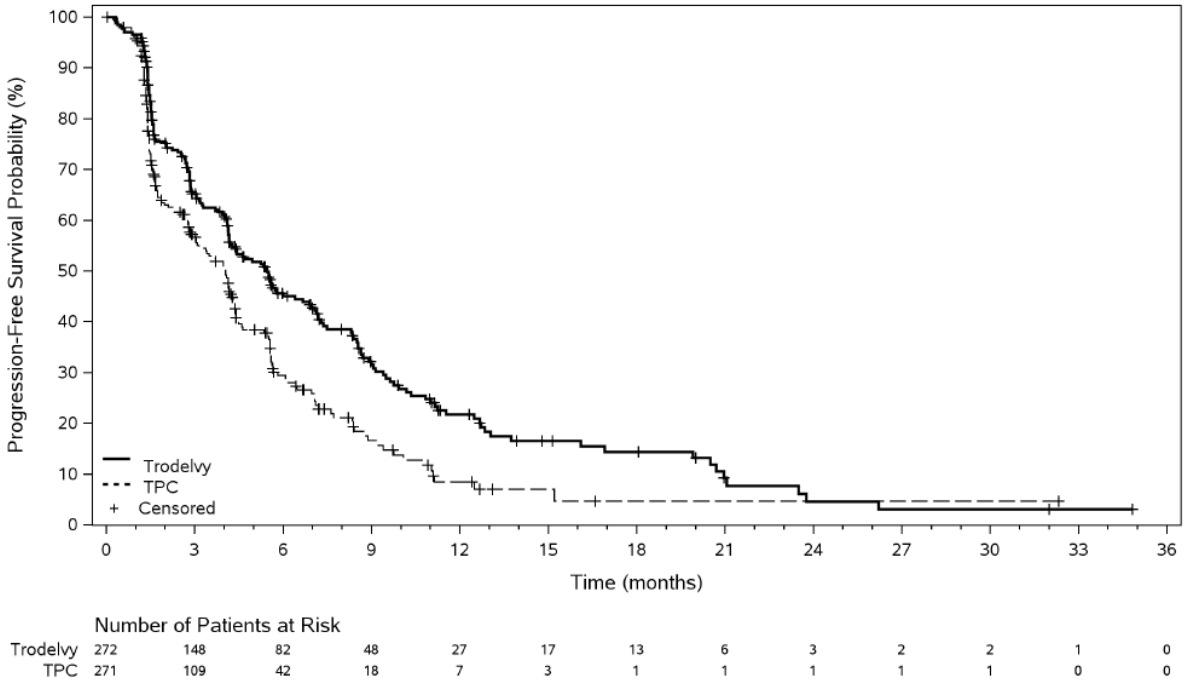
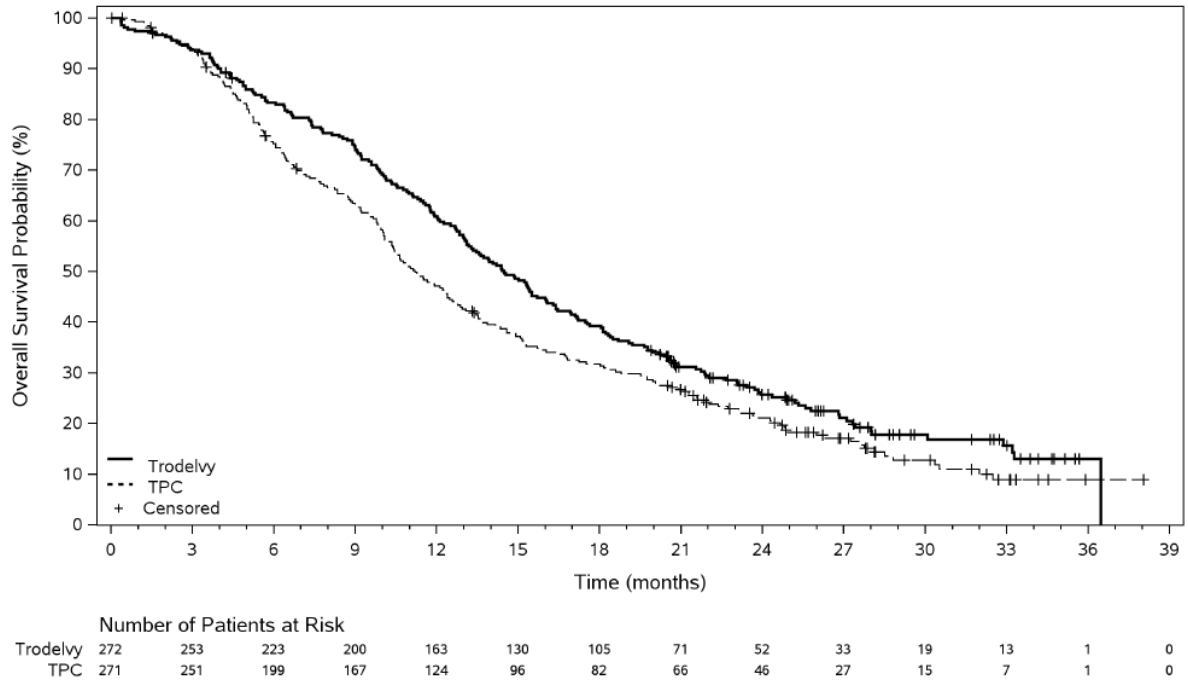


Figure 4: Overall Survival (data cut-off 1 December 2022)



Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with sacituzumab govitecan in all subsets of the paediatric population for the treatment of breast cancer (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

The serum pharmacokinetics of sacituzumab govitecan and SN-38 were evaluated in the ASCENT study in a population of mTNBC patients who received sacituzumab govitecan as a single agent at a

dose of 10 mg/kg body weight. The pharmacokinetic parameters of sacituzumab govitecan and free SN-38 are presented in Table 5.

Table 5: Summary of mean PK parameters (CV%) of sacituzumab govitecan and free SN-38

	Sacituzumab govitecan	**Free SN-38**
C_{max} [ng/mL]	242 000 (22%)	91 (65%)
AUC_{0-168} [ng*h/mL]	5 560 000 (24%)	2 730 (41%)

C_{max}: maximum serum concentration
AUC_{0-168}: area under serum concentration curve through 168 hours

Distribution

Based on population pharmacokinetic analyses, the steady state volume of distribution of sacituzumab govitecan was 3.58 L.

Elimination

The median elimination half-life ($t_{1/2}$) of sacituzumab govitecan and free SN-38 in patients with metastatic triple negative breast cancer was 23.4 and 17.6 hours, respectively. Based on population pharmacokinetic analyses, the clearance of sacituzumab govitecan is 0.128 L/h.

Metabolism

No metabolism studies with sacituzumab govitecan have been conducted.
SN-38 (the small molecule moiety of sacituzumab govitecan) is metabolised via UGT1A1.

Special populations

Pharmacokinetic analyses in patients treated with sacituzumab govitecan (n = 789) did not identify an effect of age, race, and mild or moderate renal impairment on the pharmacokinetics of sacituzumab govitecan.

Renal impairment
Renal elimination is known to contribute minimally to the excretion of SN-38, the small molecule moiety of sacituzumab govitecan. There are no data on the pharmacokinetics of sacituzumab govitecan in patients with severe renal impairment or end-stage renal disease (CrCl < 15 mL/min).

Hepatic Impairment
The exposure of sacituzumab govitecan is similar in patients with mild hepatic impairment (bilirubin ≤ ULN and AST > ULN, or bilirubin > 1.0 to ≤ 1.5 ULN and AST of any level; n = 257) to patients with normal hepatic function (bilirubin and AST ≤ ULN; n = 526).
Sacituzumab govitecan and free SN-38 exposures are unknown in patients with moderate or severe hepatic impairment.

5.3 Preclinical safety data

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 sacituzumab govitecan resulted in endometrial atrophy, uterine hemorrhage, increased follicular atresia of the ovary, and atrophy of vaginal epithelial cells at doses ≥ 60 mg/kg (1.9 times the human recommended dose of 10 mg/kg based on body weight allometric scaling).

Non-clinical data for the novel excipient MES reveal no special hazard for humans based on conventional repeated dose toxicity and genotoxicity studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

2-(*N*-morpholino)ethane sulfonic acid (MES)
Polysorbate 80 (E433)
Trehalose dihydrate

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

3 years.

After reconstitution

The reconstituted solution should be used immediately to prepare the diluted solution for infusion. If not used immediately, the infusion bag containing diluted solution can be stored in a refrigerator (2°C to 8°C) for up to 24 hours protected from light.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I colourless, clear glass 50 mL vial, with an elastomeric butyl stopper and sealed with an aluminum flip-off overseal containing 200 mg of sacituzumab govitecan.

Each pack contains one vial.

6.6 Special precautions for disposal and other handling

Trodelvy is a cytotoxic medicinal product. Applicable special handling and disposal procedures have to be followed.

Reconstitution

- Calculate the required dose (mg) of Trodelvy based on the patient's body weight at the beginning of each treatment cycle (or more frequently if the patient's body weight changed by more than 10% since the previous administration).
- Allow the required number of vials to warm to room temperature (20°C to 25°C).
- Using a sterile syringe, slowly inject 20 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into each vial. The resulting concentration will be 10 mg/mL.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. The product should be inspected visually for particulate matter and discoloration prior to administration. The

solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discoloured.
- Use immediately to prepare a diluted solution for infusion.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to the patient's body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a sacituzumab govitecan concentration range of 1.1 mg/mL to 3.4 mg/mL.
- Withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the final infusion bag that is equivalent to the required volume of the reconstituted solution.
- Withdraw the calculated amount of the reconstituted solution from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- To minimize foaming, slowly inject the required volume of reconstituted solution into a polyvinyl chloride, polyolefin (polypropylene and/or polyethylene) or ethylene vinyl acetate infusion bag. Do not shake the contents.
- If necessary, adjust the volume in the infusion bag as needed with sodium chloride 9 mg/mL (0.9%) solution for injection, to obtain a concentration of 1.1 mg/mL to 3.4 mg/mL. Only sodium chloride 9 mg/mL (0.9%) solution for injection should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.
- If not used immediately, the infusion bag containing diluted solution can be stored refrigerated 2°C to 8°C for up to 24 hours protected from light. Do not freeze. After refrigeration, administer the diluted solution at room temperature up to 25°C within 8 hours (including infusion time).

Administration

- Administer Trodelvy as an intravenous infusion. Protect the infusion bag from light. The infusion bag should be covered during administration to the subject until dosing is complete. It is not necessary to cover the infusion tubing or to use light-protective tubing during the infusion.
- An infusion pump may be used.
- Do not mix Trodelvy, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the intravenous line with 20 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1592/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 November 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

BSP Pharmaceuticals S.p.A.
Via Appia km 65,561
04013 Latina Scalo (LT)
Italy

Name and address of the manufacturer responsible for batch release

Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
Co. Cork, T45 DP77
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Trodelvy 200 mg powder for concentrate for solution for infusion
sacituzumab govitecan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial of powder contains 200 mg sacituzumab govitecan. After reconstitution, one mL of solution contains 10 mg sacituzumab govitecan.

3. LIST OF EXCIPIENTS

Excipients: 2-(*N*-morpholino)ethane sulfonic acid (MES), polysorbate 80, trehalose dihydrate.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use after reconstitution and dilution.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1592/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Trodelvy 200 mg powder for concentrate
sacituzumab govitecan
For IV use after reconstitution and dilution

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

200 mg
10 mg/mL after reconstitution

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Trodelvy 200 mg powder for concentrate for solution for infusion
sacituzumab govitecan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side affects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Trodelvy is and what it is used for
2. What you need to know before you are given Trodelvy
3. How you will be given Trodelvy
4. Possible side effects
5. How to store Trodelvy
6. Contents of the pack and other information

1. What Trodelvy is and what it is used for

Trodelvy is a cancer medicine that contains the active substance sacituzumab govitecan. One part of the medicine is a monoclonal antibody that attaches specifically to a protein on the surface of breast cancer cells called Trop-2. The other active part of Trodelvy is SN-38, a substance that can kill cancer cells. Once the medicine has attached to cancer cells, the SN-38 enters the cancer cells and kills them, thereby helping to fight your cancer.

Trodelvy is used to treat a type of breast cancer in adults called triple-negative breast cancer (TNBC). Trodelvy should only be used after patients have tried at least two other treatments for their cancer, including at least one of them for a locally advanced cancer or metastasised cancer.

Trodelvy is used to treat a type of breast cancer in adults called hormone receptor -positive (HR+), human epidermal growth factor receptor 2 -negative (HER2-) breast cancer. Trodelvy should only be used after patients have tried a treatment including a hormonal anticancer treatment and at least two additional other treatments for a locally advanced cancer or metastasised cancer.

The medicine is used when it is not possible to remove the cancer with surgery, because the cancer has spread to areas outside the breast (locally advanced) or has spread to other sites in the body (metastasised).

Talk to your doctor or nurse if you have any questions about how Trodelvy works or why this medicine has been prescribed for you.

2. What you need to know before you are given Trodelvy

You <u>must not be given</u> Trodelvy if you are **allergic** to **sacituzumab govitecan** or any of the other **ingredients** of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

Warnings and precautions

Infusion-related reactions

Trodelvy is given by drip into a vein. Some people may develop infusion-related reactions which can be severe or life-threatening. **Seek urgent medical attention** if you have any of the following signs and symptoms of **infusion-related reactions:**

- itching
- sudden outbreak of swollen, pale red bumps or plaques (wheals) on the skin
- fever
- sudden severe shivering accompanied by a feeling of coldness
- excessive sweating
- breathing difficulties and wheezing
- chest pain, heart palpitations

Your doctor may give you medicines before Trodelvy to help relieve the symptoms. During each infusion and for 30 minutes after, you will be closely monitored for these signs and symptoms of infusion-related reactions. Your doctor will slow down the infusion rate or stop it if you develop a serious infusion-related reaction.

Neutropenia

This medicine can cause neutropenia, a condition where there are too few neutrophils in your blood, which increases the risk of infections. These infections can be severe, life-threatening and may lead to death. **Seek urgent medical attention** if you have the following signs and symptoms of **neutropenia or infections:**

- a fever (a temperature of 38.5°C or higher)
- chills or sweating
- sore throat, sores in the mouth, or a toothache
- stomach pain
- pain near the anus
- pain or burning when urinating, or urinating more often
- diarrhoea or sores around the anus
- a cough or shortness of breath

Your doctor will take blood samples to monitor the levels of neutrophils in your blood. You will not be given Trodelvy if the neutrophils are below a certain level on Day 1 or Day 8 of any treatment cycle.
Your doctor will adjust the amount of medicine you are given if you have severe neutropenia.

Diarrhoea

Seek urgent medical attention if you suffer from **severe diarrhoea** whilst receiving Trodelvy.
Your Trodelvy treatment will be postponed until your diarrhoea has improved. You will be given loperamide to treat your diarrhoea, as long as you do not have an infection. If appropriate, you will also be given fluids.
Your doctor may also give you medicine, such as atropine, to help with stomach cramps, diarrhoea, and excessive saliva in mouth before your next treatment infusion.
Your diarrhoea can lead to dehydration and sudden kidney damage. Talk to your doctor if you experience dark-coloured urine or decreased urine volume.

Nausea and vomiting

This medicine can cause nausea and vomiting. **Seek urgent medical attention** if you suffer from severe **nausea and vomiting** whilst receiving Trodelvy.

Your doctor will give you some medicines before your cancer therapy, and in between infusion sessions to help relieve nausea and vomiting. You will **not be given** Trodelvy if you **have severe nausea and vomiting,** and will only be given Trodelvy when the symptoms have been controlled.

Patients who have the UGT1A1*28 gene

Some patients are more likely to have certain side effects from the medicine due to their genetic make-up. If you have the UGT1A1*28 gene, your body breaks the medicine down more slowly. This means you are more likely to develop certain side effects (such as neutropenia with or without fever and low level of red blood cells (anaemia)), than those who do not have the gene. These patients will be closely followed-up by their doctor.

Talk to your doctor, or nurse before you are given Trodelvy if you:
- have liver problems
- have kidney problems
- are a female of child-bearing age (see 'Pregnancy', 'Male and female Contraception' and 'Breast-feeding')
- are taking medicines to treat other conditions (see 'Other medicines and Trodelvy')
- have experienced any problems after receiving any infusions in the past.

While you are being given Trodelvy, your doctor will monitor you closely for side effects. If you get any serious side effects, your doctor may give you other medicines to treat these side effects, they may change how much Trodelvy you receive or may stop giving you Trodelvy altogether.

See section 4. for a list of all the possible side effects related to Trodelvy.

Children and adolescents

Trodelvy should not be given to children and adolescents under 18 years old because there is no information on how it works in this age group.

Other medicines and Trodelvy

Tell your doctor if you are taking, have recently taken or might take **any other medicines**.
Some medicines may affect the way Trodelvy works and may raise the level of Trodelvy's active substance in your blood, increasing the risk of side effects. They are:
- **propofol**, given as an anesthetic in surgery.
- **ketoconazole**, used to treat fungal infections.
- **tyrosine kinase inhibitors**, used to treat cancer (medicines ending in -nib).

Some medicines may lower the level of Trodelvy's active substance in your blood, decreasing its effects:
- **carbamazepine** or **phenytoin**, used to treat epilepsy.
- **rifampicin**, used to treat tuberculosis.
- **ritonavir or tipranavir**, used to treat HIV.

Pregnancy

Trodelvy **should not be used** during pregnancy because it may harm the baby. Tell your doctor immediately if you are pregnant, think you may be pregnant, or are planning to have a baby.

Male and female contraception

Women who might get pregnant must use effective contraception during treatment with Trodelvy, and for 6 months after the last dose of Trodelvy.
Men with female partners who could become pregnant must use effective contraception during treatment and for 3 months after the last dose of Trodelvy.

Breast-feeding

Do not breast-feed during treatment with Trodelvy and for 1 month after the last dose. It is unknown whether this medicine passes into breast milk and could affect the baby.

Driving and using machines

Trodelvy may affect your ability to drive and use machines e.g. feeling dizzy, fatigue. You should therefore be cautious when driving, using tools or operating machines after being given Trodelvy.

3. How you will be given Trodelvy

Trodelvy will only be given to you by your doctor or a nurse experienced in using anti-cancer therapies.

It is important that your doctor or nurse specialising in your care has confirmed you can take this medicine by carrying out a blood test prior to treatment.

Medicines given before Trodelvy treatment
You will be given some medicines before receiving Trodelvy to help stop infusion-related reactions and any nausea and vomiting. Your doctor will decide what medicines you may need and how much to take.

How much Trodelvy you will be given
Treatment for your cancer is repeated in 21-day (3-week) cycles. The recommended dose of Trodelvy is **10 mg for each kg of your body weight** at the start of each cycle (Day 1 of each cycle) and again one week later (Day 8 of each cycle).

How you will be given your medicine
A doctor or nurse will give the medicine via an intravenous infusion (a drip into your vein).
First infusion: you will be given your first infusion of medicine over 3 hours.
Second and subsequent infusions: you will be given the other infusions over 1 to 2 hours if your first infusion was uneventful.
Your doctor or nurse will monitor you during and for 30 minutes after each infusion for signs and symptoms of infusion-related reactions.

Infusion-related reactions
Your doctor will slow down the infusion rate of your medicine if you develop an infusion-related reaction. The medicine will be stopped if the infusion-related reaction is life-threatening. See section 2.

Dose of medicine when experiencing some side-effects
Your doctor may change or stop your dose if you experience certain side effects. See section 4.

If you are given more Trodelvy than you should

Since the infusion is given to you by your doctor or other appropriately trained staff, an overdose is unlikely. If you inadvertently receive too much medicine, your doctor will monitor you and give you additional treatment as required.

If a dose of Trodelvy is missed

If you forget or miss your appointment, call your doctor or your treatment centre to make another appointment as soon as possible. Do not wait until your next planned visit. For the treatment to be fully effective, it is very important not to miss a dose.

If you stop treatment with Trodelvy

You should not stop the therapy early without talking with your doctor first.

The therapy for breast cancer with Trodelvy usually requires a number of treatments. The number of infusions that you receive will depend on how you are responding to treatment. Therefore, you should continue receiving Trodelvy even if you see your symptoms improve and until your doctor decides that Trodelvy should be stopped. If the treatment is stopped too early, your symptoms may return.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects

Seek urgent medical attention if you get any of the following very common serious side effects *(may affect more than 1 in 10 people):*

- **Low white blood cell count (neutropenia)** which may cause the following signs and symptoms:
  - a fever, which is a body temperature of 38.5°C or higher: this is called febrile neutropenia
  - chills or sweating
  - sore throat, sores in the mouth, or a toothache
  - stomach pain
  - pain near the anus or sores around the anus
  - pain or burning when urinating, or urinating often
  - diarrhoea
  - a cough or shortness of breath

- **Diarrhoea** (even without other signs)

- **Hypersensitivity reactions (including infusion-related reactions)** which may cause the following signs and symptoms:
  - swollen lips, tongue, eyes, throat or face
  - swelling or a raised, itchy, red skin rash
  - outbreak of swollen, pale red bumps or plaques (wheals) on the skin that appear suddenly
  - fever
  - a sudden attack of severe shivering accompanied by a feeling of coldness
  - excessive sweating
  - wheezing, chest or throat tightness, shortness of breath, dizziness, feeling of fainting, breathlessness
  - chest pain, heart palpitations

- **Feeling sick (nausea), being sick (vomiting)**

Other possible side effects

Other side effects are listed below. If any of these become severe or serious, tell your doctor immediately.

Very common *(may affect more than 1 in 10 people)*
- burning sensation during urination and frequent, and urgent need to urinate
- cough, sore throat, runny nose, headache, and sneezing
- lack of enough red blood cells (anaemia)
- low level of white blood cells (lymphocytes or leukocytes)
- loss of appetite
- low blood level of potassium or magnesium
- trouble sleeping
- feeling dizzy
- shortness of breath
- constipation; stomach pain
- hair loss; rash; general itching
- back pain; joint pain
- tiredness

Common *(may affect up to 1 in 10 people)*
- shiver, fever, general discomfort, pale or discoloured skin, shortness of breath due to overwhelmed bloodstream by bacteria (sepsis)
- infection of the lungs (pneumonia)
- blocked nose, pain in your face, wheezing
- hacking cough which may bring up clear, yellow-grey or greenish phlegm
- flu like symptoms; herpes infection in the mouth
- low number of platelets, which may lead to bleeding and bruising (thrombocytopenia)
- high blood level of glucose
- decreased water in the body
- low blood level of phosphate, calcium or sodium
- anxiety
- change in your sense of taste
- low blood pressure
- nose bleeding; a cough reflex triggered by the drip down of mucus in the back of your throat
- inflammation of the small and large bowel (colitis)
- inflamed and sore mouth; pain in upper stomach area; reflux; bloated stomach
- darkening of the skin; acne-like skin problem; dry skin
- muscle pain in the chest; muscle spasms
- blood in urine; excess protein in urine
- chills
- weight loss
- increase in enzymes called alkaline phosphatase or lactate dehydrogenase, abnormal blood tests related to coagulation

Uncommon *(may affect up to 1 in 100 people)*
- inflammation of the small intestine (enteritis)

Reporting of side effects

If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system

listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Trodelvy

Trodelvy will be stored by healthcare professionals at the hospital or clinic where you receive treatment. The storage details are as follows:

- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date which is stated on the vial label and carton after EXP. The expiry date refers to the last day of that month.
- Store in a refrigerator (2°C - 8°C). Do not freeze.
- Keep the vial in the outer carton in order to protect from light.
- After reconstitution and dilution, if not used immediately, the infusion bag containing diluted solution can be stored in a refrigerator (2°C - 8°C) for up to 24 hours protected from light.
- Do not use this medicine if you notice the reconstituted solution is cloudy or discoloured.

Trodelvy is a cytotoxic medicine. Applicable special handling and disposal procedures must be followed.

6. Contents of the pack and other information

What Trodelvy contains:

- The active substance is sacituzumab govitecan. One vial of powder contains 200 mg sacituzumab govitecan. After reconstitution, one mL of solution contains 10 mg of sacituzumab govitecan
- The other ingredients are 2-(N-morpholino)ethane sulfonic acid (MES), polysorbate 80 and trehalose dihydrate.

What Trodelvy looks like and contents of the pack

The medicine is an off-white to yellowish powder for concentrate for solution for infusion supplied in a glass vial. Each pack contains 1 vial.

Marketing Authorisation Holder
Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

Manufacturer
Gilead Sciences Ireland UC
IDA Business and Technology Park
Carrigtohill
County Cork, T45 DP77
Ireland

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Gilead Sciences Belgium SRL-BV
Tél/Tel: + 32 (0) 24 01 35 50

Lietuva
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

България
Gilead Sciences Ireland UC
Тел.: + 353 (0) 1 686 1888

Česká republika
Gilead Sciences s.r.o.
Tel: + 420 910 871 986

Danmark
Gilead Sciences Sweden AB
Tlf: + 46 (0) 8 5057 1849

Deutschland
Gilead Sciences GmbH
Tel: + 49 (0) 89 899890-0

Eesti
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Ελλάδα
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: + 30 210 8930 100

España
Gilead Sciences, S.L.
Tel: + 34 91 378 98 30

France
Gilead Sciences
Tél: + 33 (0) 1 46 09 41 00

Hrvatska
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Ireland
Gilead Sciences Ireland UC
Tel: + 353 (0) 214 825 999

Ísland
Gilead Sciences Sweden AB
Sími: + 46 (0) 8 5057 1849

Italia
Gilead Sciences S.r.l.
Tel: + 39 02 439201

Κύπρος
Gilead Sciences Ελλάς Μ.ΕΠΕ.
Τηλ: + 30 210 8930 100

Latvija
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Luxembourg/Luxemburg
Gilead Sciences Belgium SRL-BV
Tél/Tel: + 32 (0) 24 01 35 50

Magyarország
Gilead Sciences Ireland UC
Tel.: + 353 (0) 1 686 1888

Malta
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Nederland
Gilead Sciences Netherlands B.V.
Tel: + 31 (0) 20 718 36 98

Norge
Gilead Sciences Sweden AB
Tlf: + 46 (0) 8 5057 1849

Österreich
Gilead Sciences GesmbH
Tel: + 43 1 260 830

Polska
Gilead Sciences Poland Sp. z o.o.
Tel.: + 48 22 262 8702

Portugal
Gilead Sciences, Lda.
Tel: + 351 21 7928790

România
Gilead Sciences (GSR) S.R.L.
Tel: + 40 31 631 18 00

Slovenija
Gilead Sciences Ireland UC
Tel: + 353 (0) 1 686 1888

Slovenská republika
Gilead Sciences Slovakia s.r.o.
Tel: + 421 232 121 210

Suomi/Finland
Gilead Sciences Sweden AB
Puh/Tel: + 46 (0) 8 5057 1849

Sverige
Gilead Sciences Sweden AB
Tel: + 46 (0) 8 5057 1849

United Kingdom (Northern Ireland)
Gilead Sciences Ireland UC
Tel: + 44 (0) 8000 113 700

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

The following information is intended for healthcare professionals only:

Trodelvy is a cytotoxic medicine. Applicable special handling and disposal procedures have to be followed.

This medicinal product must not be mixed with other medicinal products except those mentioned below.

Reconstitution

- Calculate the required dose (mg) of Trodelvy based on the patient's body weight at the beginning of each treatment cycle (or more frequently if the patient's body weight changed by more than 10% since the previous administration).
- Allow the required number of vials to warm to room temperature (20°C to 25°C).
- Using a sterile syringe, slowly inject 20 mL of sodium chloride 9 mg/mL (0.9%) solution for injection into each vial. The resulting concentration will be 10 mg/mL.
- Gently swirl vials and allow to dissolve for up to 15 minutes. Do not shake. The product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be free of visible particulates, clear and yellow. Do not use the reconstituted solution if it is cloudy or discoloured.
- Use immediately to prepare a diluted solution for infusion.

Dilution

- Calculate the required volume of the reconstituted solution needed to obtain the appropriate dose according to the patient's body weight.
- Determine the final volume of the infusion solution to deliver the appropriate dose at a sacituzumab govitecan concentration range of 1.1 mg/mL to 3.4 mg/mL.
- Withdraw and discard a volume of sodium chloride 9 mg/mL (0.9%) solution for injection from the final infusion bag that is equivalent to the required volume of the reconstituted solution.
- Withdraw the calculated amount of the reconstituted solution from the vial(s) using a syringe. Discard any unused portion remaining in the vial(s).
- To minimize foaming, slowly inject the required volume of reconstituted solution into a polyvinyl chloride, polyolefin (polypropylene and/or polyethylene) or ethylene vinyl acetate infusion bag. Do not shake the contents.
- If necessary, adjust the volume in the infusion bag as needed with sodium chloride 9 mg/mL (0.9%) solution for injection, to obtain a concentration of 1.1 mg/mL to 3.4 mg/mL. Only sodium chloride 9 mg/mL (0.9%) solution for injection should be used since the stability of the reconstituted product has not been determined with other infusion-based solutions.
- If not used immediately, the infusion bag containing diluted solution can be stored refrigerated 2°C to 8°C for up to 24 hours protected from light. Do not freeze. After refrigeration, administer the diluted solution at room temperature up to 25°C within 8 hours (including infusion time).

Administration

- Administer Trodelvy as an intravenous infusion. Protect the infusion bag from light.
- The infusion bag should be covered during administration to the subject until dosing is complete. It is not necessary to cover the infusion tubing or to use light-protective tubing during the infusion.

- An infusion pump may be used.
- Do not mix Trodelvy, or administer as an infusion, with other medicinal products.
- Upon completion of the infusion, flush the intravenous line with 20 mL sodium chloride 9 mg/mL (0.9%) solution for injection.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

ANNEX IV

CONCLUSIONS ON THE REQUEST FOR ONE-YEAR MARKETING PROTECTION PRESENTED BY THE EUROPEAN MEDICINES AGENCY

Conclusions presented by the European Medicines Agency on:

- **one-year marketing protection**

The CHMP reviewed the data submitted by the marketing authorisation holder, taking into account the provisions of Article 14(11) of Regulation (EC) No 726/2004, and considers that the new therapeutic indication brings significant clinical benefit in comparison with existing therapies as further explained in the European Public Assessment Report.

別添 I

製品概要

▼本剤は追加モニタリングの対象である。これにより、新たな安全性情報を速やかに特定することができる。医療従事者は副作用の疑いを報告することが求められる。副作用の報告方法については 4.8 項を参照のこと。

1. 販売名

Trodelvy 200 mg 点滴静注用

2. 組成・性状

1 バイアル中に凍結乾燥粉末のサシツズマブ　ゴビテカン 200 mg を含有する。
溶解後、溶液 1 mL 中にサシツズマブ　ゴビテカン 10 mg を含有する。

サシツズマブ　ゴビテカンは trophoblast cell surface antigen-2（Trop-2）を標的とする抗体薬物複合体（ADC）であり、ヒト化抗 Trop-2 抗体（hRS7 IgG1κ）であるサシツズマブとトポイソメラーゼ I 阻害作用を有する低分子部分の SN-38 が、加水分解性リンカーを介して共有結合している。各抗体分子には約 7～8 分子の SN-38 が結合している。

添加剤の一覧については 6.1 項を参照のこと。

3. 剤形

点滴静注用の凍結乾燥製剤。
微黄白色～帯黄色の粉末である。

4. 臨床的特性

4.1 効能・効果

単剤療法としての本剤は、2 つ以上の全身療法による前治療歴（少なくとも 1 つの転移・再発乳癌に対する前治療歴を含む）を有する手術不能又は転移・再発トリプルネガティブ乳癌（TNBC）の成人患者の治療を適応とする（5.1 項参照）。

単剤療法としての本剤は、内分泌療法による前治療歴に加え、転移・再発乳癌に対する 2 つ以上の全身療法による前治療歴を有する手術不能又は転移・再発ホルモン受容体（HR）陽性かつヒト上皮増殖因子受容体 2 型（HER2）陰性乳癌の成人患者の治療を適応とする（5.1 項参照）。

4.2 用量及び用法

本剤は、緊急時に十分対応できる医療施設において、抗癌療法の使用経験のある医療従事者によってのみ処方及び投与されなければならない。

用量
本剤の推奨用量は 10 mg/kg（体重）とし、21 日間を 1 サイクルとし、各サイクルの 1 日目及び 8 日目に点滴静注する。本剤の投与は、疾患進行又は許容できない毒性の発現まで継続すること。

予防投与
本剤の投与前に、Infusion reaction の予防及びがん薬物療法に伴う悪心・嘔吐（CINV）の予防のための投与を行うことが望ましい（4.4 項参照）。

Infusion reaction に対する用量調節
Infusion reaction が認められた場合、本剤の注入速度を遅くするか投与を中断すること。生命を脅かす Infusion reaction が認められた場合は、本剤の投与を中止すること（4.4 項参照）。

副作用に対する用量調節
本剤の副作用を管理するための用量調節を表 1 に示す。副作用により本剤を減量した場合は、再増量しないこと。

表 1:副作用発現時に推奨される用量調節

Adverse reaction	**Occurrence**	**Dose modification**
Severe neutropenia		
Grade 4 neutropenia ≥ 7 days or less if clinically indicated, OR Grade 3-4 febrile neutropenia , OR At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing by 2 or 3 weeks for recovery to ≤ Grade 1	First	Administer granulocyte-colony stimulating factor (G-CSF) as soon as clinically indicated
	Second	25% dose reduction; administer G-CSF as soon as clinically indicated
	Third	50% dose reduction; administer G-CSF as soon as clinically indicated
	Fourth	Discontinue treatment; administer G-CSF as soon as clinically indicated
At time of scheduled treatment, Grade 3-4 neutropenia which delays dosing beyond 3 weeks for recovery to ≤ Grade 1	First	Discontinue treatment; administer G-CSF as soon as clinically indicated
Severe non-neutropenic toxicity		
Grade 4 non-hematologic toxicity of any duration, OR Any Grade 3-4 nausea, vomiting or diarrhoea due to treatment that is not controlled with antiemetics and anti-diarrhoeal agents, OR Other Grade 3-4 non-hematologic toxicity persisting > 48 hours despite optimal medical management, OR At time of scheduled treatment, Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, which delays dose by 2 or 3 weeks for recovery to ≤ Grade 1	First	25% dose reduction
	Second	50% dose reduction
	Third	Discontinue treatment
In the event of Grade 3-4 non-neutropenic hematologic or non-hematologic toxicity, Grade 3 nausea or Grade 3-4 vomiting, which does not recover to ≤ Grade 1 within 3 weeks	First	Discontinue treatment

<u>特別な集団</u>

高齢者

65歳以上の患者に対する用量調節は不要である。75歳以上の患者における本剤のデータは限られている。

肝機能障害

軽度の肝機能障害（ビリルビンが基準値上限［ULN］の 1.5 倍以下かつアスパラギン酸アミノトランスフェラーゼ［AST］／アラニンアミノトランスフェラーゼ［ALT］が ULN の 3 倍未満）を有する患者に本剤を投与する場合、開始用量の調節は不要である。

中等度又は重度の肝機能障害を有する患者における本剤の安全性は確立されていない。血清ビリルビンが ULN の 1.5 倍超、AST 又は ALT が ULN の 3 倍超の肝転移のない患者、AST 又は ALT が ULN の 5 倍超の肝転移のある患者を対象とした本剤の試験は実施していない。これらの患者への本剤の投与は避けること。

腎機能障害

軽度又は中等度の腎機能障害を有する患者に本剤を投与する場合、開始用量の調節は不要である。

重度の腎機能障害又は末期腎不全（クレアチニンクリアランス［CLcr］が 15 mL/min 未満）を有する患者を対象とした本剤の試験は実施していない。

小児集団
0 歳から 18 歳の小児における本剤の安全性及び有効性は確立されていない。データは得られていない。

投与方法
本剤は点滴静注でのみ投与すること。抗癌療法の取扱いに精通した医療従事者が溶解・希釈すること。静脈内プッシュ投与又はボーラス投与は行わないこと。

本剤の初回投与は 3 時間かけて行うこと。

前回の投与で忍容性が良好であれば、それ以降の投与は 1～2 時間かけて行うこと。

点滴静注中及び点滴静注後少なくとも 30分間は、Infusion reactionの徴候又は症状がないか患者の状態を観察すること（4.4 項参照）。

投与前の本剤の溶解及び希釈に関する指示については、6.6項を参照のこと。

4.3 禁忌

本剤の有効成分又は 6.1 項に示す添加剤のいずれかに対する過敏症の既往歴のある患者への本剤の投与は禁忌である。

4.4 特別な警告及び使用上の注意

トレーサビリティ
生物学的製剤のトレーサビリティ向上のため、投与した製品の名称及びバッチ番号を明確に記録すること。

好中球減少症
本剤の投与により、重度又は生命を脅かす好中球減少症があらわれることがある（4.8 項参照）。本剤の臨床試験では、好中球減少症に伴う致死的な感染症が認められている。投与サイクルの 1 日目に好中球絶対数が 1500/mm^3 未満の場合、又は投与サイクルの 8 日目に好中球絶対数が 1000/mm^{3}未満の場合は、本剤を投与しないこと。そのため、本剤投与中は臨床的に必要な場合に患者の血球数を観察することが推奨される。発熱性好中球減少症が認められた場合、本剤を投与しないこと。重度の好中球減少症により、顆粒球コロニー刺激因子（G-CSF）の投与及び用量調節が必要となることがある（4.2 項及び 4.8 項参照）。

下痢
本剤の投与により、重度の下痢があらわれることがある（4.8 項参照）。一部の症例では下痢により脱水を来し、その後急性腎障害に至った。投与予定日に Grade 3-4 の下痢が発現した場合、本剤を投与してはならず、Grade 1 以下に回復した場合にのみ投与を継続すること（4.2 項及び 4.8 項参照）。下痢が発現し、感染性の原因が特定できない場合は、ロペラミドによる治療を開始すること。臨床的に必要な場合、追加の支持療法（水分及び電解質の補充など）の実施を考慮すること。

本剤の投与により過度のコリン作動性反応（腹部痙攣、下痢、流涎など）が認められた場合には、それ以降の本剤投与前に、適切な治療（アトロピンなどの投与）の実施を考慮すること。

過敏症
本剤投与により、重度かつ生命を脅かす過敏症があらわれることがある（4.8 項参照）。本剤の臨床試験においてアナフィラキシー反応が認められており、本剤に対する過敏症が確認されている患者に本剤の投与は禁忌である（4.3 項参照）。

本剤の投与を受ける患者には、解熱薬、H1 及び H2 拮抗薬又はコルチコステロイド（ヒドロコルチゾン 50 mg 又は相当量の経口投与又は静脈内投与など）を含めた前投与を行うことが望ましい。本剤の点滴静注中及び点滴静注後少なくとも 30分間は、Infusion reactionについて患者を注意深く観察すること。Infusion reaction が認められた場合は、本剤の注入速度を遅くするか、投与を中断すること。生命を脅かす Infusion reaction が認められた場合は、本剤の投与を中止すること（4.2 項参照）。

悪心及び嘔吐
本剤は催吐性を有する薬剤である（4.8 項参照）。がん薬物療法に伴う悪心・嘔吐（CINV）の予防のため、2 剤又は 3 剤の医薬品（デキサメタゾンと 5-ヒドロキシトリプタミン 3［5-HT3］受容体拮抗薬又はニューロキニン 1［NK-1］受容体拮抗薬のいずれかと併用、及び必要に応じて他の薬剤など）による制吐療法を行うことが望ましい。

投与予定日に Grade 3 の悪心又は Grade 3-4 の嘔吐が発現した場合は、本剤を投与してはならず、Grade 1 以下に回復した時点で、追加の支持療法を行い、本剤の投与を継続すること（4.2 項参照）。臨床的に必要であれば、追加の制吐薬の投与及びその他の支持療法の実施を考慮すること。全ての患者に、悪心及び嘔吐の予防及び治療に関する明確な指示を行うとともに、自宅で服薬できる薬剤を処方すること。

UGT1A1 活性が低下している患者への投与
SN-38（本剤の低分子部分）は UDP グルクロン酸転移酵素 1A1（UGT1A1）を介して代謝される。UGT1A1*28 アレルなどの UGT1A1 遺伝子の遺伝的変異体は UGT1A1 酵素活性の低下をもたらす。UGT1A1*28 アレルホモ接合体を有する場合、好中球減少症、発熱性好中球減少症及び貧血のリスクが増加し、本剤の投与開始後にその他の副作用のリスクが増加する（4.8 項参照）。黒人集団の約 20%、白人集団の約 10%、東アジア人集団の約 2%は、UGT1A1*28 アレルホモ接合体を有する。特定の集団では、UGT1A1*28 以外の機能低下アレルが存在することがある。UGT1A1 活性の低下が確認されている場合は、副作用について患者を注意深く観察すること。UGT1A1 活性の低下が不明の場合、用量調節を含めて副作用の管理が全ての患者で同じであるため、UGT1A1 遺伝子検査の実施は不要である。

胚・胎児毒性
本剤の作用機序から、本剤を妊婦に投与すると催奇形性及び／又は胚・胎児死亡を引き起こす可能性がある。本剤は遺伝毒性を有する SN-38 を含有し、分裂が活発な細胞を標的とする。妊婦及び妊娠可能な女性には、胎児への潜在的リスクについて説明すること。本剤投与開始前に、妊娠可能な女性の妊娠の有無を確認すること（4.6 項参照）。

ナトリウム
本剤はさらにナトリウム含有溶液を用いて調製して投与するため（6.6項参照）、患者が 1 日に摂取する全てのナトリウム源から得られる総ナトリウム量を考慮すること。

4.5　他の医薬品との相互作用及びその他の相互作用

相互作用試験は実施していない。

UGT1A1 阻害剤
本剤と UGT1A1 阻害剤を併用投与すると、SN-38 の全身曝露量が増加し、副作用の発現率が上昇する可能性がある。UGT1A1 阻害剤（プロポフォール、ケトコナゾール、上皮成長因子受容体［EGFR］チロシンキナーゼ阻害剤など）の投与を受けている患者には、本剤を慎重に投与すること。

UGT1A1 誘導剤
UGT1A1 酵素誘導剤を併用している患者では、SN-38 の曝露量が減少する可能性がある。UGT1A1 誘導剤（カルバマゼピン、フェニトイン、リファンピシン、リトナビル、チプラナビルなど）の投与を受けている患者には、本剤を慎重に投与すること。

本剤の投与期間中に UGT1A1 阻害剤（16 例）又は UGT1A1 誘導剤（5 例）の投与を受けた患者から得られた限られたデータに基づくと、これらの患者における遊離 SN-38 の曝露量は、UGT1A1 阻害剤又は UGT1A1 誘導剤の投与を受けなかった患者と同程度であった。

4.6　受胎能、妊娠及び授乳

妊娠可能な女性／男女における避妊
妊娠する可能性のある女性は、本剤投与中及び本剤投与終了後 6 ヵ月間は適切な避妊を行うこと。
パートナーが妊娠する可能性のある男性は、本剤投与中及び本剤投与終了後 3 ヵ月間は適切な避妊を行うこと。

妊娠
妊婦への本剤の投与に関するデータは得られていない。しかし、本剤の作用機序から、本剤を妊娠中に投与すると催奇形性及び／又は胚・胎児死亡を引き起こす可能性がある。本剤は遺伝毒性を有する SN-38 を含有し、分裂が活発な細胞を標的とする。
本剤は、妊婦の臨床状態により本剤の投与が必要な場合を除き、妊娠中に使用しないこと。
本剤投与開始前に、妊娠可能な女性の妊娠の有無を確認すること。
妊娠した女性は直ちに医師に連絡すること。

授乳
サシツズマブ　ゴビテカン又はその代謝物がヒト乳汁中に移行するかどうかは不明である。授乳中の新生児／乳児に対するリスクは除外できない。本剤投与中及び本剤投与終了後 1 ヵ月間は授乳を中止すること。

受胎能
動物試験での所見に基づくと、本剤は妊娠可能な女性の受胎能を低下させる可能性がある（5.3 項参照）。ヒトの受胎能に対する本剤の影響に関するデータは得られていない。

4.7　運転及び機械操作能力に対する影響

本剤は、浮動性めまい、疲労など、運転及び機械操作能力に軽微の影響を及ぼす（4.8 項参照）。

4.8　副作用

安全性プロファイルの要約
本剤の投与を受けた患者に報告された主な副作用は、好中球減少症（67.6%）、悪心（62.6%）、下痢（62.5%）、疲労（61.5%）、脱毛症（45.6%）、貧血（40.7%）、便秘（36.2%）、嘔吐（33.6%）、食欲減退（25.7%）、呼吸困難（22.1%）及び腹痛（20.2%）であった。

Grade 3 以上の主な副作用は、好中球減少症（50.7%）、白血球減少症（10.5%）、下痢（10.3%）、貧血（9.3%）、疲労（6.8%）、発熱性好中球減少症（6.1%）、低リン血症（4.2%）、呼吸困難（3.1%）、リンパ球減少症（2.9%）、腹痛（2.8%）、悪心（2.8%）、嘔吐（2.5%）、低カリウム血症（2.5%）、肺炎（2.3%）及びアスパラギン酸アミノトランスフェラーゼ増加（2.2%）であった。

本剤の投与を受けた患者でよくみられた主な重篤な副作用は、発熱性好中球減少症（4.8%）、下痢（3.9%）、好中球減少症（2.6%）及び肺炎（2%）であった。

副作用一覧表
副作用の発現頻度は、転移・再発 TNBC 及び転移・再発 HR 陽性かつ HER2 陰性乳癌の治療として本剤 10 mg/kg（体重）の投与を受けた患者 688 例を対象とした 3 つの臨床試験の併合データに基づいている。このデータセットにおける本剤の曝露期間の中央値は 4.63 ヵ月であった。

副作用の発現頻度は、理由を問わず全ての有害事象の発現頻度に基づいており、副作用の事象の一部は、疾患、他の医薬品、又は関連のない原因など、本剤以外の原因によるものである可能性

がある。副作用の重症度は、有害事象共通用語規準（CTCAE）に基づいて評価し、Grade 1 = 軽度、Grade 2 = 中等度、Grade 3 = 重度、Grade 4 = 生命を脅かす、及び Grade 5 = 死亡と定義した。

副作用は器官別大分類及び発現頻度の分類別に示す。発現頻度の分類は、非常に高頻度（very common; 1/10 以上）、高頻度（common; 1/100 以上 1/10 未満）、低頻度（uncommon; 1/1,000 以上 1/100 未満）、まれ（rare; 1/10,000 以上 1/1,000 未満）、非常にまれ（very rare; 1/10,000 未満）、不明（not known; 入手可能なデータから推定不能）と定義されている。各発現頻度グループ内では、重篤度の高い順に副作用を示す。

表2：副作用一覧

System organ class (SOC)	Frequency	Adverse reactions
Infections and infestations		
	Very common	Urinary tract infection Upper respiratory tract infection
	Common	Sepsis Pneumonia Influenza Bronchitis Nasopharyngitis Sinusitis Oral herpes
Blood and lymphatic system disorders		
	Very common	Neutropenia[1] Anaemia[2] Leukopenia[3] Lymphopenia[4]
	Common	Febrile neutropenia Thrombocytopenia[5]
Immune system disorders		
	Very common	Hypersensitivity[6]
Metabolism and nutrition disorders		
	Very common	Decreased appetite Hypokalaemia Hypomagnesaemia
	Common	Dehydration Hyperglycaemia Hypophosphataemia Hypocalcaemia Hyponatraemia
Psychiatric disorders		
	Very common	Insomnia
	Common	Anxiety
Nervous system disorders		
	Very common	Headache Dizziness
	Common	Dysgeusia
Vascular disorders		
	Common	Hypotension
Respiratory, thoracic and mediastinal disorders		
	Very common	Dyspnoea[7] Cough
	Common	Epistaxis Productive cough Rhinorrhoea Nasal congestion Upper airway cough syndrome

Gastrointestinal disorders		
	Very common	Diarrhoea Vomiting Nausea Constipation Abdominal Pain
	Common	Neutropenic colitis[8] Colitis Stomatitis Abdominal pain upper Dyspepsia Gastrooesophageal reflux disease Abdominal distension
	Uncommon	Enteritis
Skin and subcutaneous tissue disorders		
	Very common	Alopecia Rash Pruritus
	Common	Rash maculopapular Skin hyperpigmentation Dermatitis acneiform Dry skin
Musculoskeletal and connective tissue disorders		
	Very common	Back pain Arthralgia
	Common	Musculoskeletal chest pain Muscle spasms
Renal and urinary disorders		
	Common	Haematuria Proteinuria Dysuria
General disorders and administration site conditions		
	Very common	Fatigue[9]
	Common	Pain Chills
Investigations		
	Common	Weight decreased Blood alkaline phosphatase increased Activated partial thromboplastin time prolonged Blood lactate dehydrogenase increased
Injury, poisoning and procedural complications		
	Uncommon	Infusion related reaction

1: Includes the following preferred terms: neutropenia; neutrophil count decreased.
2: Includes the following preferred terms: anaemia; haemoglobin decreased; red blood cell count decreased.
3: Includes the following preferred terms: leukopenia; white blood cell count decreased.
4: Includes the following preferred terms: lymphopenia; lymphocyte count decreased.
5: Includes the following preferred terms: thrombocytopenia; platelet count decreased.
6: Hypersensitivity events reported up to the end of the day after treatment was administered. Includes events coded to the following preferred terms: dyspnoea; hypotension; flushing; erythema; chest discomfort; rhinitis allergic; wheezing; oedema; urticaria; anaphylactic reaction; mouth ulceration**;** skin exfoliation; swollen tongue; throat tightness
7: Includes the following preferred terms: dyspnoea; dyspnoea exertional
8: Includes the preferred term of neutropenic colitis and events reported as typhlitis
9: Includes the following preferred terms: fatigue, asthenia

特定の副作用の説明

好中球減少症

初回投与サイクル開始後の好中球減少症（発熱性好中球減少症を含む）の発現までの期間の中央値は 16 日であった。好中球減少症の持続期間の中央値は 8 日であった。

好中球減少症は本剤の投与を受けた患者の 67.6%（465/688 例）に発現し、Grade 3-4 の好中球減少症は患者の 50.7%に発現した。患者の 12.4%では好中球減少症が減量の理由であった。好中球減少性大腸炎は患者の 1%（7/688 例）に認められた。

発熱性好中球減少症は本剤の投与を受けた患者の 6.1%（42/688 例）に発現した。患者の 2.9%では発熱性好中球減少症が減量の理由であった。

UGT1A1 活性が低下している患者への投与

Grade 3-4の好中球減少症の発現率は、UGT1A1*28アレルをホモ接合体としてもつ患者では 60.6%（43/71 例）、UGT1A1*28 アレルをヘテロ接合体としてもつ患者では 52.9%（144/272 例）、野生型アレルをホモ接合体としてもつ患者では 49.1%（140/285 例）であった。Grade 3-4 の発熱性好中球減少症の発現率は、UGT1A1*28 アレルをホモ接合体としてもつ患者では 14.1%（10/71 例）、UGT1A1*28 アレルをヘテロ接合体としてもつ患者では 5.9%（16/272 例）、野生型アレルをホモ接合体としてもつ患者では 4.6%（13/285 例）であった。Grade 3-4 の貧血の発現率は、UGT1A1*28 アレルをホモ接合体としてもつ患者では 15.5%（11/71 例）、UGT1A1*28 アレルをヘテロ接合体としてもつ患者では 7.4%（20/272 例）、野生型アレルをホモ接合体としてもつ患者では 8.1%（23/285 例）であった。

好中球減少症及び貧血が初回発現するまでの期間（中央値）は、野生型アレルをホモ接合体としてもつ患者と比較して、UGT1A1*28 アレルをホモ接合体としてもつ患者及び UGT1A1*28 アレルをヘテロ接合体としてもつ患者で短かった。

下痢

初回投与サイクル開始後の下痢の発現までの期間の中央値は 13 日であった。下痢の持続期間の中央値は 8 日であった。

下痢は本剤の投与を受けた患者の 62.5%（430/688 例）に発現した。Grade 3 の事象は患者の 10.3%（71/688 例）に認められた。688 例中 3 例（1%未満）が下痢により投与を中止した。

過敏症

投与後 1 日以内に報告された過敏症は、本剤の投与を受けた患者の 33.0%（227/688 例）に発現した。Grade 3 以上の過敏症は、本剤の投与を受けた患者の 1.7%（12/688 例）に発現した。本剤の投与中止に至った過敏症の発現頻度は 0.1%（1/688 例）であった。

免疫原性

本剤の投与を受けた患者を対象とした臨床試験全体で、785 例中 9 例（1.1%）にサシツズマブ ゴビテカンに対する抗体が発現した。これらの患者のうち 6 例（本剤の投与を受けた全患者の 0.8%）にサシツズマブ　ゴビテカンに対する中和抗体が認められた。

特別な集団

転移・再発 TNBC 患者における有害事象による中止率は、65 歳以上の患者と 65 歳未満の患者で差は認められなかった。転移・再発 HR 陽性かつ HER2 陰性乳癌患者における副作用による中止率は、65歳以上の患者（14%）の方が 65歳未満の患者（3%）よりも高かった。転移・再発HR陽性かつ HER2 陰性乳癌患者における重篤な有害事象の発現頻度は、75 歳以上の患者（67%）の方が 65 歳以上の患者（43%）及び 65 歳未満の患者（24%）よりも高かった。

副作用の疑いの報告

医薬品承認後の副作用の疑いの報告は重要である。これにより、医薬品のベネフィット・リスクバランスの継続的なモニタリングが可能となる。医療従事者は、付録 V に記載されている国内報告システムを介して副作用の疑いを報告することが求められる。

4.9　過量投与

臨床試験では、18 mg/kg（最大推奨用量10 mg/kg［体重］の約1.8倍）までの用量で重度の好中球減少症の発現頻度が上昇した。

過量投与の場合、副作用、特に重度の好中球減少症の徴候又は症状がないか患者の状態を注意深く観察し、適切な治療を開始すること。

5.　薬理学的特性

5.1　薬力学的特性

薬効分類：抗悪性腫瘍薬、モノクローナル抗体及びADC、その他のモノクローナル抗体、ATCコード：L01FX17。

作用機序

サシツズマブ　ゴビテカンはTrop-2発現癌細胞に結合し、細胞内に取り込まれた後にリンカーが加水分解され、SN-38が放出されると考えられる。SN-38はトポイソメラーゼIに作用し、トポイソメラーゼIによるデオキシリボ核酸（DNA）一本鎖切断の再ライゲーションを阻害することによりDNAを傷害し、アポトーシス及び細胞死を誘導する。

臨床的有効性及び安全性

切除不能又は転移・再発TNBC（ASCENT試験）

本剤の有効性及び安全性は、乳癌に対する2つ以上（上限なし）の化学療法による前治療後に再発した切除不能な局所進行又は転移・再発トリプルネガティブ乳癌（TNBC）患者529例を対象とした、国際共同、多施設共同、非盲検、無作為化、第3相試験（ASCENT試験［IMMU-132-05試験］）で評価した。限局性病変に対するより早期の術後又は術前薬物療法については、切除不能な局所進行又は転移・再発が化学療法終了から12ヵ月以内に認められた場合には、化学療法による前治療の1つとみなした。タキサン系薬剤に対して禁忌又は不耐容が認められた場合を除き、全ての患者が術後薬物療法、術前薬物療法又は進行癌に対する治療のいずれかでタキサン系薬剤による前治療を受けていた。生殖細胞系列乳癌感受性遺伝子（BRCA）1/2変異陽性の患者におけるポリアデノシン二リン酸リボースポリメラーゼ（PARP）阻害剤については、2つの化学療法歴の1つとして許容された。

患者は、21日間を1サイクルとして、本剤10 mg/kgを各サイクルの1日目及び8日目に点滴静注する群（本剤群）、又は体表面積に基づき承認された製品情報に従って投与する医師選択治療（TPC）群（TPC群）に1：1の比率で無作為に割り付けられた。TPCは無作為化前に治験責任医師が決定し、エリブリン（139例）、カペシタビン（33例）、ゲムシタビン（38例）又はビノレルビン（Grade 2以上のニューロパチーを有する患者を除く、52例）のいずれかによる単剤療法とした。安定した脳転移（治療歴があり、進行性ではなく、抗痙攣薬を使用せず、コルチコステロイドを2週間以上安定して投与されている）を有する患者を適格とした。脳転移を判定する磁気共鳴画像法（MRI）は、脳転移が確認されている又は疑われる患者についてのみ必須とした。ジルベール病が確認されている患者、骨病変のみを有する患者、不安定狭心症、心筋梗塞又はうっ血性心不全の既往、活動性の慢性炎症性腸疾患又は消化管（GI）穿孔の既往、ヒト免疫不全ウイルス（HIV）、活動性のB型又はC型肝炎感染、30日以内の生ワクチン接種歴を有する患者、又はイリノテカンの投与歴を有する患者は除外した。

疾患進行又は許容できない毒性が認められるまで投与を継続した。有効性の主要評価項目は、ベースライン評価時に脳転移が認められなかった（BMNeg）患者における無増悪生存期間（PFS）とし、固形がんの治療効果判定のための新ガイドライン（RECIST）第1.1版に基づき盲検下独立中央判定（BICR）の放射線学専門家グループが評価した。有効性の副次評価項目は、脳転移の有無を問わない全患者を含む全体集団のBICR判定によるPFS、全生存期間（OS）、客観的奏効率（ORR）及び奏効期間（DOR）とした。

主要解析は、本剤群のBMNeg患者235例及びTPC群のBMNeg患者233例を対象とした。全体集団の解析は、本剤群の267例及びTPC群の262例を対象とした。

全体集団（529 例）の人口統計学的特性及びベースライン特性は、年齢の中央値が 54 歳（範囲：27～82 歳）、患者の 81%が 65 歳未満、99.6%が女性、79%が白人、12%が黒人であった。全身療法による前治療数の中央値は 4 であり、患者の 69%に 2～3 つの化学療法歴、31%に 4 つ以上の化学療法歴があった。患者の 42%に肝転移が認められ、12%に脳転移があるか脳転移の既往があった。患者の 8%は BRCA1/BRCA2 変異陽性であり、BRCA 変異状況は患者 339 例から得られた。試験登録時、全ての患者で米国東海岸がん臨床試験グループ（ECOG）パフォーマンスステータス（PS）は 0（43%）又は 1（57%）であった。ステージ 4 の診断から試験登録までの期間の中央値は 16.2 ヵ月（範囲：−0.4～202.9 ヵ月）であった。主な化学療法歴は、シクロホスファミド（83%）、ドキソルビシン（53%）を含むアントラサイクリン系薬剤（83%）、パクリタキセル（78%）、カルボプラチン（65%）、カペシタビン（67%）、ゲムシタビン（36%）、ドセタキセル（35%）及びエリブリン（33%）であった。全体として、患者の 29%が PD-1/PD-L1 による前治療を受けていた。全体集団の本剤群の 13%は、転移・再発乳癌に対する全身療法を 1 つのみ受けていた。

BMNeg 集団における有効性の結果では、PFS 及び OS において本剤群は TPC 群と比較して統計学的に有意な改善を示し、ハザード比はそれぞれ 0.41（468 例、95% CI：0.32、0.52、p 値：<0.0001）及び 0.48（468 例、95% CI：0.38、0.59、p 値：<0.0001）であった。PFS の中央値は本剤群で 5.6 ヵ月、TPC 群で 1.7 ヵ月であり、OS の中央値は本剤群で 12.1 ヵ月、TPC 群で 6.7 ヵ月であった。

全体集団における有効性の結果は、事前に規定した最終解析（2020 年 3 月 11 日のカットオフ日）における BMNeg 集団の結果と一致しており、表 3 に要約する。

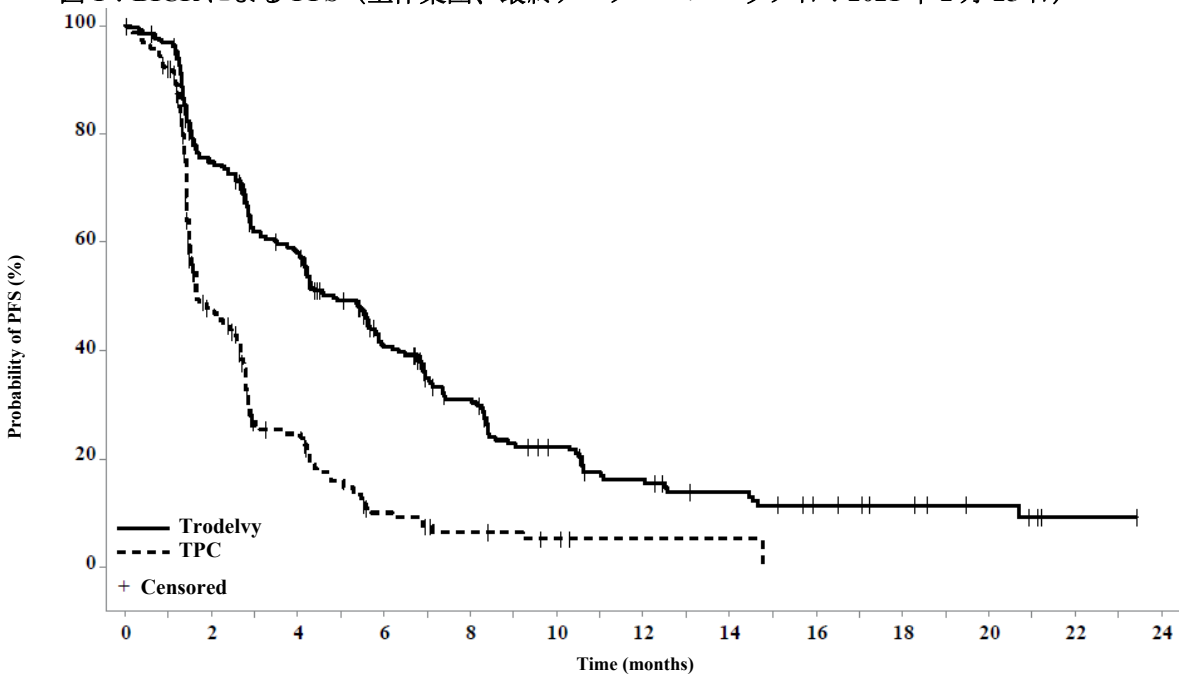
表 3：有効性評価項目（全体集団）―事前に規定した最終解析

	Pre-specified Final Analysis (11 March 2020 cut-off date)	
	Sacituzumab govitecan n=267	**Treatment of physician's choice (TPC) n=262**
Progression-free survival[1]		
Number of events (%)	190 (71.2)	171 (65.3)
Median PFS in months (95% CI)	4.8 (4.1,5.8)	1.7 (1.5, 2.5)
Hazard ratio (95% CI)	0.43 (0.35, 0.54)	
p-value[2]	<0.0001	
Overall Survival		
Number of deaths (%)	179 (67.0)	206 (78.6)
Median OS in months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)
Hazard ratio (95% CI)	0.51 (0.41, 0.62)	
p-value[2]	<0.0001	
Overall response rate (ORR)		
Number of responders (%)	83 (31)	11 (4)
Odds ratio (95% CI)	10.99 (5.66, 21.36)	
p-value[3]	<0.0001	
Complete response, n (%)	10 (4)	2 (1)
Partial response, n (%)	73 (27)	9 (3)
Duration of response (DOR)		
Median DOR in months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, NE)

1 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.
2 Stratified log-rank test adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.
3 Based on Cochran-Mantel-Haenszel test.
CI = Confidence Interval

最新の有効性解析（最終データベースロック日：2021年2月25日）の結果は、事前に規定した最終解析の結果と一致していた。BICRによるPFSの中央値は、本剤群で4.8ヵ月、TPC群で1.7ヵ月であった（ハザード比：0.41、95% CI：0.33、0.52）。OSの中央値はそれぞれ11.8ヵ月及び6.9ヵ月であった（ハザード比：0.51、95% CI：0.42、0.63）。BICRによる最新のPFS及びOSのKaplan-Meier曲線を図1及び図2に示す。

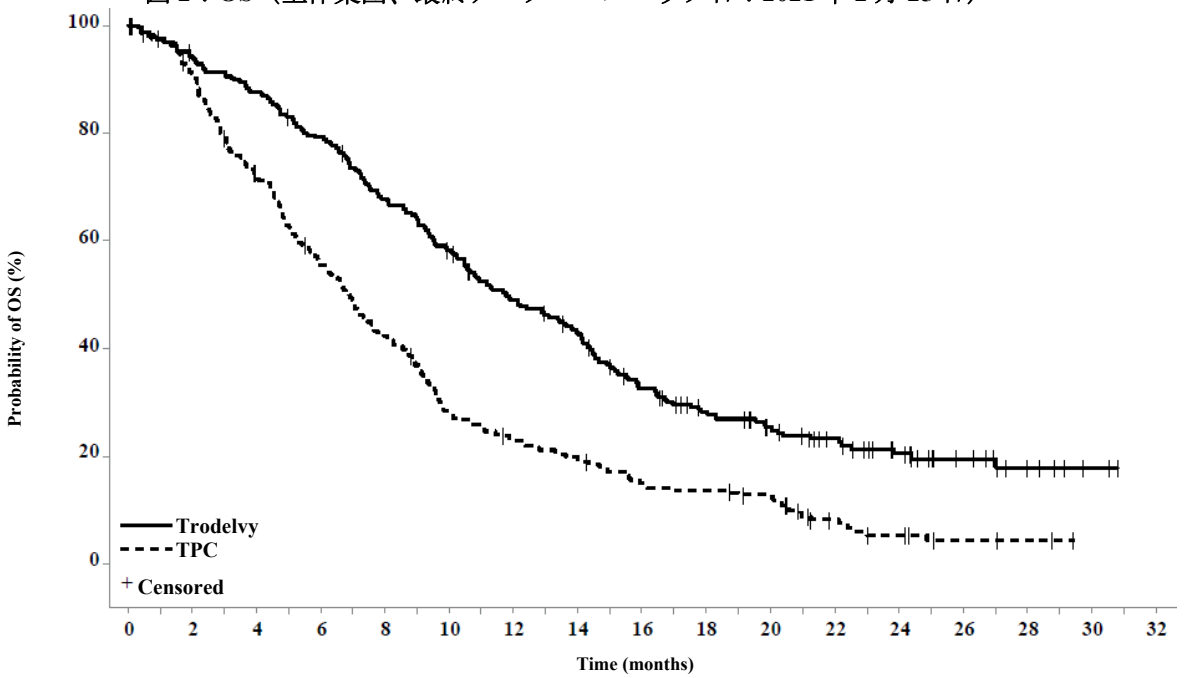
図 1：BICR による PFS（全体集団、最終データベースロック日：2021 年 2 月 25 日）



Number of Patients at Risk

Trodelvy	267	184	135	82	55	34	23	17	11	8	5	1	0
TPC	262	86	36	12	6	3	1	1	0	0	0	0	0

図 2：OS（全体集団、最終データベースロック日：2021 年 2 月 25 日）



Number of Patients at Risk

Trodelvy	267	250	232	209	178	152	125	108	79	62	49	37	25	14	7	2	0
TPC	262	222	174	132	101	66	54	45	34	31	26	12	7	3	2	0	0

サブグループ解析

サブグループ解析において、本剤群では TPC 群と比較して PFS 及び OS の改善が、年齢、人種、BRCA 変異状況、全身療法による前治療数（2 つ及び 3 つ以上、2～3 つ及び 4 つ以上）及び転移・再発乳癌に対する全身療法による前治療数（1 つ及び 2 つ以上）、アントラサイクリン系薬剤又は PD-L1 による治療歴、並びに肝転移の有無にかかわらず、患者サブグループ全体で一貫して認められた。

脳転移
前治療歴があり、安定した脳転移を有する患者における PFS 及び OS の探索的解析の結果、それぞれの層別ハザード比は 0.65（61 例、95% CI：0.35、1.22）及び 0.87（61 例、95% CI：0.47、1.63）であった。PFS の中央値は本剤群で 2.8 ヵ月、TPC 群で 1.6 ヵ月であり、OS の中央値は本剤群で 6.8 ヵ月、TPC 群で 7.5 ヵ月であった。

Trop-2 の発現
腫瘍 Trop-2 発現レベル別に有効性を評価するために追加のサブグループ解析を実施したところ、使用した様々なスコアリング方法を通じて結果は一致していた。細胞膜の H スコアに基づく Trop-2 の発現レベルが四分位別で低い患者においても、PFS（ハザード比：0.64、95% CI：0.37、1.11）及び OS（ハザード比：0.71、95% CI：0.42、1.21）のいずれについても、TPC に対する本剤のベネフィットが示された。

切除不能又は転移・再発 HR 陽性かつ HER2 陰性乳癌（TROPiCS-02 試験）
本剤の有効性は、CDK 4/6 阻害剤、内分泌療法及びタキサン系薬剤による治療を受け、かつ、転移・再発乳癌に対する 2 つ以上の化学療法レジメン（このうち 1 つは術前又は術後薬物療法も可とした。ただし、当該療法完了から 12 ヵ月以内に進行又は再発を認めた場合に限る）による前治療後に進行を認めた切除不能な局所進行又は転移・再発 HR 陽性かつ HER2 陰性（IHC 法 0、IHC 法 1+又は IHC 法 2+かつ ISH 法陰性）乳癌患者 543 例を対象とした多施設共同、非盲検、無作為化試験（TROPiCS-02［IMMU-132-09］試験）において評価された。骨病変のみを有する患者、活動性の慢性炎症性腸疾患及び腸閉塞の既往を有する患者、不安定狭心症又は心筋梗塞の既往を有する患者、うっ血性心不全の既往を有する患者、活動性の B 型又は C 型肝炎感染を有する患者は本試験から除外した。

患者は、本剤群（21 日間を 1 サイクルとして、本剤 10 mg/kg を 1 日目及び 8 日目に点滴静注）（272 例）又は TPC 群（271 例）に 1：1 の比率で無作為に割り付けられた。TPC は無作為化前に治験責任医師が決定し、エリブリン（130 例）、ビノレルビン（63 例）、ゲムシタビン（56 例）又はカペシタビン（22 例）のいずれかによる単剤療法とした。無作為化に際し、転移・再発乳癌に対する化学療法レジメンによる前治療数（2 つ又は 3～4 つ）、内臓転移（あり又はなし）及び転移・再発乳癌に対する少なくとも 6 ヵ月間の内分泌療法による前治療歴（あり又はなし）を層別因子とした。

疾患進行又は許容できない毒性が認められるまで投与を継続した。有効性の主要評価項目は、RECIST 第 1.1 版に基づき BICR が判定した PFS とした。その他の有効性評価項目は、OS、BICR による ORR 及び BICR による DOR であった。

試験対象集団の年齢の中央値は 56 歳（範囲： 27～86 歳）であり、患者の 26%が 65 歳以上であった。患者のほぼ全例（99%）が女性であった。患者の大多数（67%）は白人であり、4%が黒人、3%がアジア系、26%が人種不明であった。患者が過去に受けた全身療法レジメン（設定を問わず）による前治療数の中央値は 7（範囲：3～17）であり、転移・再発乳癌に対する全身化学療法レジメンによる前治療数は 3（範囲：0～8）であった。転移・再発乳癌に対する化学療法レジメンによる前治療数が 2 つであった患者の割合は約 42%であったのに対し、3～4 つであった患者の割合は 58%であった。大部分の患者（86%）は転移・再発乳癌に対する少なくとも 6 ヵ月間の内分泌療法による前治療歴を有していた。患者の ECOG PS は 0（44%）又は 1（56%）であった。患者の 95%には内臓転移があり、患者の 4.6%には安定している脳転移（治療歴あり）があった。

本剤は、TPC と比較して、BICR による PFS 及び OS において統計学的に有意な改善を示した。BICR による PFS 及び OS に認められた改善は、事前に規定したサブグループ間で概ね一致していた。有効性の結果を表 4 に要約する。

表 4. 有効性評価項目－事前に規定した最終解析

	Sacituzumab govitecan n=272	TPC n=271
Progression-Free Survival by BICR[1]		
Number of events (%)	170 (62.5%)	159 (58.7%)
Median PFS in months (95% CI)	5.5 (4.2, 7.0)	4.0 (3.1, 4.4)
Hazard ratio (95% CI)	0.661 (0.529, 0.826)	
p-value[2]	0.0003	
PFS rate at 12 months, % (95% CI)	21.3 (15.2, 28.1)	7.1 (2.8, 13.9)
Overall Survival[3]		
Number of events (%)	191 (70.2%)	199 (73.4%)
Median OS in months (95% CI)	14.4 (13.0, 15.7)	11.2 (10.1, 12.7)
Hazard ratio (95% CI)	0.789 (0.646, 0.964)	
p-value[2]	0.0200	
Objective Response Rate by BICR[3]		
Number of responders (%)	57 (21.0%)	38 (14.0%)
Odds ratio (95% CI)	1.625 (1.034, 2.555)	
p-value	0.0348	

[1] PFS is defined as the time from the date of randomisation to the date of the first radiological disease progression or death due to any cause, whichever comes first (data cut-off 3 January 2022).
[2] Stratified log-rank test adjusted for stratification factors: prior chemotherapy regimens for metastatic disease (2 vs. 3-4), visceral metastasis (yes vs. no), and endocrine therapy in the metastatic setting for at least 6 months (yes vs. no).
[3] Based on second interim OS analysis (data cut-off 1 July 2022).
BICR = Blinded Independent Central Review; CI = Confidence Interval

最新の有効性解析（追跡期間の中央値：12.8ヵ月、データカットオフ日：2022年12月1日）の結果は、事前に規定した最終解析の結果と一致していた。BICRによるPFSの中央値は、本剤群で5.5ヵ月、TPC群で4.0ヵ月であった（ハザード比：0.65、95% CI：0.53、0.81）。OSの中央値はそれぞれ14.5ヵ月及び11.2ヵ月であった（ハザード比：0.79、95% CI：0.65、0.95）。BICRによる最新のPFS及びOSのKaplan-Meier曲線を図3及び図4に示す。

図3：BICRによるPFS（データカットオフ日：2022年12月1日）

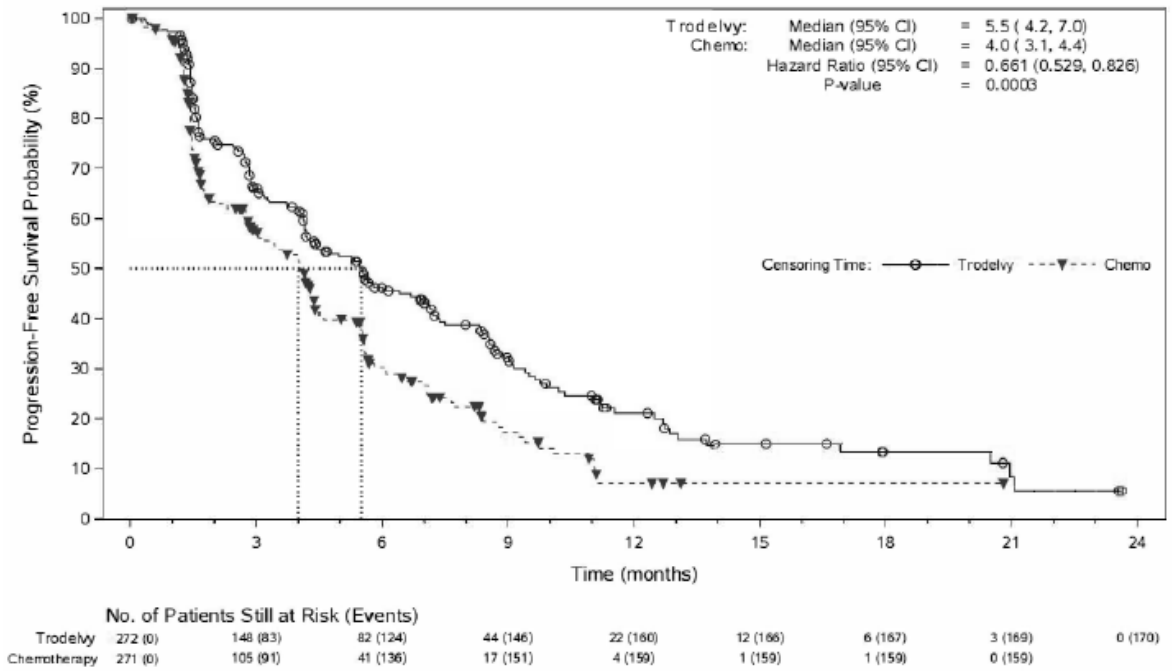
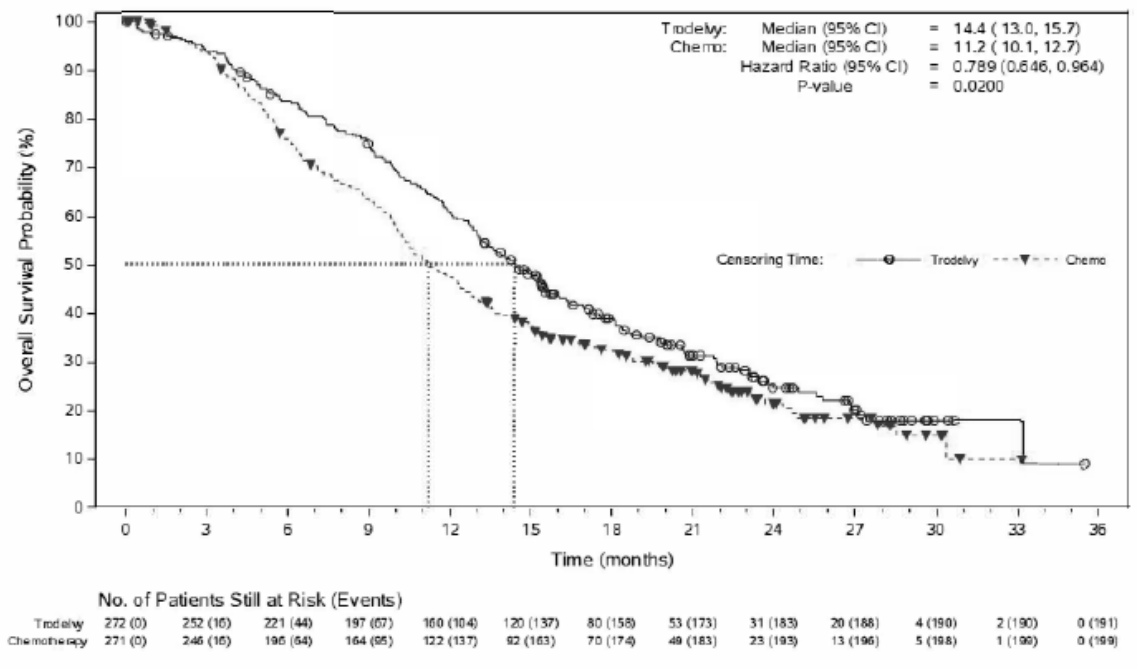


図 4：OS（データカットオフ日：2022 年 12 月 1 日）



小児集団
欧州医薬品庁（EMA）は、小児集団の全ての部分集団を対象とした乳癌の治療に関する本剤の試験結果の提出義務を免除している（小児への投与に関する情報については 4.2 項を参照）。

5.2 薬物動態学的特性

ASCENT 試験では、本剤 10 mg/kg（体重）の用量で単剤投与を受けた転移・再発 TNBC 患者集団を対象として、サシツズマブ　ゴビテカン及び SN-38 の血清中薬物動態を評価した。サシツズマブ　ゴビテカン及び遊離 SN-38 の薬物動態パラメータを表 5 に示す。

表 5：サシツズマブ　ゴビテカン及び遊離 SN-38 の薬物動態パラメータの平均値（CV%）の要約

	Sacituzumab govitecan	**Free SN-38**
C_{max} [ng/mL]	242 000 (22%)	91 (65%)
$AUC_{0\text{-}168}$ [ng*h/mL]	5 560 000 (24%)	2 730 (41%)

C_{max}: maximum serum concentration
$AUC_{0\text{-}168}$: area under serum concentration curve through 168 hours

分布
母集団薬物動態解析に基づくと、サシツズマブ　ゴビテカンの定常状態における分布容積は 3.58 L であった。

排泄
転移・再発 TNBC 患者におけるサシツズマブ　ゴビテカン及び遊離 SN-38 の消失半減期（$t_{1/2}$）の中央値は、それぞれ 23.4 時間及び 17.6 時間であった。母集団薬物動態解析に基づくと、サシツズマブ　ゴビテカンのクリアランスは 0.128 L/h である。

代謝
本剤の代謝に関する試験は実施していない。
本剤の低分子部分である SN-38 は UGT1A1 を介して代謝される。

特別な集団
本剤の投与を受けた患者（789 例）の薬物動態解析の結果、年齢、人種、及び軽度又は中等度の腎機能障害は、サシツズマブ　ゴビテカンの薬物動態に影響を及ぼさなかった。

腎機能障害
本剤の低分子部分である SN-38 の消失において、腎排泄の寄与はわずかであることが知られている。重度の腎機能障害患者及び末期腎不全患者（CLcr：15 mL/min 未満）における本剤の薬物動態は検討されていない。

肝機能障害
軽度の肝機能障害（ビリルビンが ULN 以下かつ AST が ULN 超、又はビリルビンが ULN 超～ULN の 1.5 倍以下かつ AST 値は問わない、257 例）を有する患者におけるサシツズマブ　ゴビテカンの曝露量は、肝機能が正常な患者（ビリルビン及び AST が ULN以下、526例）と同程度であった。
中等度又は重度の肝機能障害を有する患者におけるサシツズマブ　ゴビテカン及び遊離 SN-38 の薬物動態は検討されていない。

5.3　非臨床安全性データ

SN-38 は、チャイニーズハムスター卵巣細胞を用いた *in vitro* 哺乳類細胞小核試験で染色体異常誘発性を示し、細菌を用いた *in vitro* 復帰突然変異（Ames）試験で変異原性を示さなかった。
カニクイザルを用いた反復投与毒性試験において、本剤の静脈内投与により、60 mg/kg（体重アロメトリックスケーリングに基づくヒト推奨用量 10 mg/kg の 1.9 倍）以上の用量で子宮内膜萎縮、子宮出血、卵巣の卵胞閉鎖の増加及び膣上皮細胞の萎縮が認められた。

新規添加剤 MES の非臨床データでは、通常の反復投与毒性試験及び遺伝毒性試験に基づく、ヒトに対する特別な危険性は示されていない。

6.　製剤学的特性

6.1　添加剤一覧

2-（*N*-モルホリノ）エタンスルホン酸（MES）
ポリソルベート 80（E433）
トレハロース二水和物

6.2　配合禁忌

本剤は、6.6 項に記載のない他の医薬品と混合してはならない。

6.3　有効期間

未開封バイアル
3 年間。

溶解後
溶解後の溶液は速やかに使用し、点滴静注用希釈液を調製する。直ちに使用しない場合、希釈溶液が入った輸液バッグは冷蔵庫（2～8℃）で遮光して最長 24 時間保存することができる。

6.4　保存に関する特別な注意

冷蔵庫（2～8℃）で保存すること。
凍結させないこと。
遮光のため、バイアルは外箱に入れて保存すること。

本剤の溶解及び希釈後の保存条件については、6.3 項を参照のこと。

6.5　容器の性状及び内容

サシツズマブ　ゴビテカン 200 mg を含有する無色透明ガラス製 Type I バイアル（50 mL バイアル）、エラストマー製ブチルストッパー付き、アルミニウム製フリップオフオーバーシール付き。

1 箱に 1 バイアルが入っている。

6.6 廃棄及びその他の取扱いに関する特別な注意

本剤は細胞毒性を有する医薬品である。適用される特別な取扱い及び廃棄手順に従わなければならない。

溶解方法

- 各投与サイクル開始時の患者の体重に基づき、本剤の必要投与量（mg）を算出する（前回の投与から体重が 10%超変動した場合は、より頻回に算出する）。
- 必要数のバイアルを室温（20～25℃）に戻す。
- 滅菌シリンジを用いて 1 バイアルに 20 mL の塩化ナトリウム 9 mg/mL（0.9%）注射液をゆっくり注入する。調製後の濃度は 10 mg/mL となる。
- バイアルをゆっくりと回して混和し、最長 15 分間かけて溶解する。振とうはしないこと。投与前に粒子状物質及び変色の有無を目視で確認すること。溶液は目に見える微粒子がなく、澄明かつ黄色でなければならない。溶解後の液に濁り又は変色が認められる場合は使用しないこと。
- 速やかに使用し、点滴静注用希釈液を調製する。

希釈方法

- 患者の体重に応じた投与量を得るために必要な溶解液量を算出する。
- 本剤の濃度範囲 1.1～3.4 mg/mL で適切な用量を送達するための輸液の最終容量を決定する。
- 最終の輸液バッグから、必要な溶解液量と同量の塩化ナトリウム 9 mg/mL（0.9%）注射液を抜き取り廃棄する。
- シリンジを用いて必要量の溶解液をバイアルから抜き取る。バイアルに残った溶解液は廃棄すること。
- 必要量の溶解液を輸液バッグ（ポリ塩化ビニル、ポリオレフィン［ポリプロピレン及び／又はポリエチレン］又はエチレン酢酸ビニル製）に、泡立ちを最小限に抑えるためゆっくり注入する。内容物を振とうしないこと。
- 必要に応じて、塩化ナトリウム 9 mg/mL（0.9%）注射液を用いて輸液バッグ内の液量を調整し、1.1～3.4 mg/mL の濃度にする。溶解液は塩化ナトリウム 9 mg/mL（0.9%）注射液のみを使用すること。他の輸液を使用した場合の希釈後の安定性は確認できていない。
- 直ちに使用しない場合、希釈溶液が入った輸液バッグは遮光して 2～8℃で最長 24 時間の冷蔵保存が可能である。凍結させないこと。冷蔵保存後、希釈溶液は 25℃以下の室温で 8 時間以内（点滴時間を含む）に投与すること。

投与方法

- 本剤は点滴静注すること。輸液バッグを遮光すること。本剤投与中は、投与が完了するまで輸液バッグを覆うこと。点滴中に点滴チューブを覆ったり、遮光チューブを使用する必要はない。
- 輸液ポンプを使用してもよい。
- 他剤と混注したり、他剤とともに点滴静注したりしないこと。
- 点滴静注終了後、静脈ラインを 20 mL の塩化ナトリウム 9 mg/mL（0.9%）注射液で洗い流すこと。

廃棄

未使用の医薬品又は廃棄物は現地の要件に従って廃棄すること。

7. 製造販売業者

Gilead Sciences Ireland UC
Carrigtohill
County Cork, T45 DP77
Ireland

8. 製造販売承認番号

EU/1/21/1592/001

9. 初回承認日/承認更新日

初回承認日：2021 年 11 月 22 日

10. 本文改訂日

本医薬品の詳細情報は欧州医薬品庁のウェブサイト http://www.ema.europa.eu に掲載されている。