NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942] Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

Contents:

The following documents are made available to consultees and commentators:

The **final scope** and **final stakeholder list** are available on the NICE website.

1. **Company submission** from Gilead
2. **Clarification questions and company responses**
3. **Patient group, professional group and NHS organisation submission** from:
   a. Breast Cancer Now
   b. NCRI-ACP-RCP-RCR
4. **Evidence Review Group report** prepared by Warwick Evidence
5. **Evidence Review Group – factual accuracy check**
6. **Technical engagement response** from **Gilead**
7. **Technical engagement responses & expert statements from experts:**
   a. Dr Alicia Okines, Consultant Medical Oncologist – clinical expert, nominated by NCRI-ACP-RCP-RCR
8. **Technical engagement response from consultees and commentators:**
   a. Breast Cancer Now
   b. Royal College of Radiologists
9. **Evidence Review Group critique of company response to technical engagement** prepared by Warwick Evidence
10. **Evidence Review Group addendum** prepared by Warwick Evidence

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

ID3942: Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after two or more therapies

Document B
Company evidence submission
September 2021

File name	Version	Contains confidential information	Date
ID3942 Gilead Sacituzumab govitecan mTNBC Evidence Submission Document B_ACiC_14Sep2021	1.0	Yes	14 September 2021

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Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse events
AFT	Accelerate time to failure
AIC	Akaike Information Criterion
ASCO	American Society of Clinical Oncology
BC	Breast cancer
BIC	Bayesian Information Criterion
BMI	Body mass index
BSA	Body surface area

CBR	Clinical benefit rate
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CT	Computed tomography
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ESME	Epidemiological Strategy and Medical Economics
ESMO	European Society for Medical Oncology
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratios
IRC	Independent Review Committee
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
LY	Life years
LYG	Life-years gained
MBC	Metastatic breast cancer
MID	Minimum important difference
MIMS	Monthly Index of Medical Specialties
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
MRU	Medical resource use
mTNBC	Metastatic triple-negative breast cancer
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis

ORR	Objective response rate
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PARP	Poly-ADP ribose polymerase
PAS	Patient access scheme
PD	Progressive disease
PF	Progression free
PFS	Progression-free survival
PH	Proportional hazard
PR	Progesterone receptor
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SG	Sacituzumab govitecan hziy
TEAE	Treatment-emergent adverse events
TNBC	Triple-negative breast cancer
TPC	Treatment of physician’s choice
TTD	Time-to-treatment discontinuation
VBA	Visual Basic for Applications

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

The submission covers the technology's full marketing authorisation for this indication. Sacituzumab govitecan hziy ([SG]; 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 lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease.(1)

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Table 1: The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	Adults with unresectable locally advanced or metastatic triple-negative breast cancer who have had at least two prior therapies, including at least one for locally advanced or metastatic disease	Adults with unresectable locally advanced or metastatic triple-negative breast cancer who have had at least two prior therapies, including at least one for locally advanced or metastatic disease	As per NICE final scope and in line with NICE reference case
Intervention	Generic name: Sacituzumab govitecan hziy Brand Name: Trodelvy	Generic name: Sacituzumab govitecan hziy Brand Name: Trodelvy	As per NICE final scope and in line with NICE reference case
Comparator(s)	• capecitabine • vinorelbine • eribulin	• capecitabine • vinorelbine • eribulin • gemcitabine	Defining specific comparators at certain stages of the mTNBC treatment pathway is challenging, as the choice of treatment is heavily dependent on a number of individualised factors, such as prior therapies received, the patient's fitness level with regard to what they can tolerate, and an individual patient's preferences. In particular, for patients diagnosed at and treated for early-stage disease, the most effective therapies (anthracyclines, taxanes, alkylating agents, and platinum compounds) are used in the neoadjuvant setting, meaning they are not available for metastatic disease. However, after consultation with clinical experts, Gilead's view is that the use of eribulin, vinorelbine and capecitabine is an appropriate reflection of clinical practice in England for the population outlined above and are well represented in the TPC arm of the ASCENT trial. Of the three comparators, clinical expert feedback suggests

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
			that eribulin may be described as “best alternative care”. Gemcitabine was also used in a small proportion of patients in the TPC arm (15%) in the ASCENT trial. Subgroup analysis by treatment agent showed similar survival benefits as the other three agents in the TPC arm. Therefore, inclusion of gemcitabine in the TPC arm is not expected to bias outcomes of the ASCENT trial in favour of sacituzumab govitecan. UK clinical expert feedback supports that the TPC arm is a pragmatic and appropriate comparator, consisting mostly of therapies that are commonly used in England.
Outcomes	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.	The outcome measures to be considered include: • overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.	As per NICE final scope and in line with NICE reference case
Special considerations including issues related to equity or equality	None	We do not envisage any equality issues arising from the scope. However, it should be noted that the prevalence of TNBC is higher among people of African ancestry than among white people. Consequently, guidance that restricts the use of sacituzumab govitecan may disproportionately impact black people with TNBC.	

B.1.2 Description of the technology being appraised

A description of the technology being appraised, SG is presented in Table 2.

Table 2: Description of SG

UK approved name and brand name	Sacituzumab govitecan-hziy (TRODELVY®)
Mechanism of action	Sacituzumab govitecan-hziy is a first-in-class Trop-2–directed antibody and topoisomerase inhibitor conjugate. Sacituzumab is a humanised antibody that recognises Trop-2. The small molecule, SN-38, is a topoisomerase I inhibitor, which is covalently attached to the antibody by a linker.(1) Trop-2 is a transmembrane calcium signal transducer,(2, 3) that is highly expressed in many tumour types.(4) This includes breast cancer, where Trop-2 membrane expression has been linked to poor disease prognosis,(5, 6) and specifically TNBC where overexpression of Trop-2 is found in 80% of patients.(7) Trop-2 therefore provides a novel target in TNBC, a disease area lacking the conventional breast cancer targets of the HER2, oestrogen and progesterone receptors.(7) Sacituzumab govitecan binds to Trop-2-expressing cancer cells and is internalised 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 decreased tumour growth in mouse xenograft models of triple-negative breast cancer. Anti-tumour effects may also be observed in cells adjacent to those expressing Trop-2 through the bystander effect, due to the membrane permeability of free SN-38 and pH dependent hydrolysis of sacituzumab govitecan-hziy in the tumour extracellular environment.(3, 8)
Marketing authorisation/CE mark status	Marketing authorisation was granted on 8th September 2021 by UK MHRA
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	The licensed indication for sacituzumab govitecan-hziy is for: the treatment of unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease.
Method of administration and dosage	The recommended dose of sacituzumab govitecan-hziy 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
Additional tests or investigations	N/A
List price and average cost of a course of treatment	[redacted]

Patient access scheme (if applicable)	A PAS is currently being considered by PASLU. Discounted Price: [redacted] per 180 mg vial Assuming normal distribution of patients around a mean weight of 68.4 kg, cost per 3-week treatment cycle is estimated at [redacted](excluding value-added tax [VAT])

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Disease overview

Breast cancers are a group of malignancies originating from breast tissue; most often occurring in ducts or lobules.(9) Locally advanced breast cancer occurs when the tumour has spread into nearby tissue and lymph nodes around the breast, but not to other organs.(10) Metastatic breast cancer (MBC) is defined by spread of the tumour to another organ and is the stage of disease associated with the poorest prognosis.(11, 12) Common sites of metastases in breast cancer include the liver, brain, bones, and lungs.(11)

Breast cancer is the most common cancer in the UK, representing 15% of all new cancer cases in 2017 (date of last available official statistics), with 99% of these cases in females and 1% in males.(13) In England, 46,109 new cases of breast cancer were diagnosed in 2017.(13) Breast cancer is generally more common in older people with nearly a quarter (24%) of new cases of breast cancer diagnosed in those aged ≥75 years in the UK between 2015 to 2017.(13) In 2018, 9,640 deaths were attributed to breast cancer in England, and breast cancer accounted for 7% of all cancer deaths in the UK that year.(14)

Breast cancer is characterised by the presence or absence of molecular markers for oestrogen and progesterone receptors as well as HER2.(15) The TNBC subtype is defined as tumours lacking hormone receptor expression (i.e. oestrogen receptor [ER]- and progesterone receptor [PR]-negative) and without overexpression of human epidermal growth factor receptor 2 (HER2).(16, 17)

Epidemiology data specific to TNBC in England is limited, however, it is estimated to account for approximately 10% to 15% of breast cancer cases.(18-21) This equates to between 4,500 and 6,750 new cases of TNBC per year in England.

B.1.3.2 Burden of disease

TNBC is a heterogeneous and aggressive disease which, compared with other breast cancer subtypes, has faster growing, less differentiated tumours of a higher histologic grade that tend to be larger at diagnosis.(16, 17, 22-24) TNBC impacts younger women at a higher proportion than other breast cancer subtypes(16, 17, 22) with studies reporting that >10% of patients with TNBC are diagnosed at age 40 years or younger.(25, 26) According to an analysis of the French Epidemiological Strategy and Medical Economics (ESME) registry of MBC patients between 2008 to 2016, the median onset of diagnosis of mTNBC is 56 years compared with 61 years for MBC overall.(27)

Black and Hispanic women and patients carrying *BRCA1/2* mutations are at higher risk of developing TNBC than White women.(16, 17, 22) In an analysis of nearly 300,000 women with a breast cancer diagnosis from 2010 to 2011 in a national US database, 11.6% of all White women were diagnosed with the TNBC subtype compared with 23.7% of all Black women ($p<0.001$ versus all White women) and 14.8% of Hispanic women.(28) Another US review of 6,370 women with TNBC and 44,704 women with other breast cancer subtypes (1999 to 2003) reported that women with TNBC were significantly more likely to be Black (odds ratio [OR]: 1.8), Hispanic (OR: 1.2) or under the age of 40 (OR: 1.5) compared with other breast cancer subtypes.(25)

Patients with TNBC have a poorer prognosis, including faster progression and a higher likelihood of developing distant metastases, than patients with other breast cancer subtypes.(22) The risk of early relapse following (neo)adjuvant chemotherapy, particularly within the first 2 years of diagnosis, is higher in patients with TNBC compared with HR+ breast cancer.(22) A Canadian database review of 1,601 women diagnosed with breast cancer found that women with TNBC had a significantly higher risk of distant recurrence in their first five years of diagnosis compared with other breast cancer types (hazard ratio [HR]: 1.5; 95% CI: 1.1, 2.0; $p<0.02$).(29) Patients with TNBC are also more often diagnosed in advanced stages of the disease compared with patients with other breast cancer subtypes.(25) TNBC metastases occur more frequently in visceral organs including lungs, liver, and

central nervous system and less frequently in bone, which also confers a poor disease prognosis.(16, 22, 24)

B.1.3.3 Outcomes for mTNBC

TNBC is difficult to target for treatment due to a lack of hormone and HER2 receptors.(24) Patients with mTNBC often progress rapidly through multiple lines of chemotherapy, particularly after reaching second line.(30-32) This impacts survival rates, which are lower for TNBC than other breast cancer subtypes, leading to TNBC accounting for 25% of breast cancer deaths despite comprising between 10% and 20% of cases.(24, 33)

While treatment innovations have improved OS for some patients with MBC (e.g., HER2+ patients) in recent years, survival outcomes have remained consistently poor for patients with mTNBC.(34) Data from the French ESME registry of MBC patients between 2008 to 2016 showed the median overall survival (OS) for patients with mTNBC (n=2,963) was 15 months from diagnosis of metastatic disease, compared with 43 months in patients with HR+ (n=13,656) and 50 months in HER2+ (n=4,017) breast cancer at a median follow up of 51.8 months.(27)

OS worsens as patients with mTNBC progress through treatment lines, highlighting the importance of using the most effective treatments early in the treatment pathway.(30) Among 135 patients with mTNBC from a German retrospective chart review (2012 to 2015), OS in patients receiving first-line therapy was 13 months compared with 7 months at second- and third-line therapy.(30) OS has also been assessed in a pooled analysis from two phase III clinical trials, EMBRACE and Study 301, in patients with locally advanced or mTNBC who had received 0 to ≥2 treatments for advanced disease (88% of pooled population had received ≥1 prior treatment for advanced disease).(35) The median OS was 13 months with eribulin and 8 months with capecitabine or treatment of physician's choice (TPC).(35) In another phase III trial in mTNBC after ≥1 prior line of therapy in the metastatic setting, median OS in patients treated with TPC (including eribulin, capecitabine, gemcitabine and vinorelbine) was 7 months.(36, 37)

Real-world data on the outcomes of patients with TNBC in England are lacking. However, a retrospective review of medical records from 186 patients diagnosed with mTNBC at the Royal Marsden NHS Trust between 2011 and 2016 found that as patients progressed through systemic treatment lines, treatment response and outcomes diminished.(32) For example, progression-free survival (PFS) worsened from 3.7 months at first-line treatment to 3.5 months, 2.5 months and 2.1 months at second-, third- and fourth-line treatment, respectively.(32)

B.1.3.4 Clinical care pathway

B.1.3.4.1 Introduction

The primary aim of treatment for advanced breast cancer is not curative but rather to improve quality of life and prolong survival.(38)

When breast cancer is initially diagnosed, systemic treatment is guided by disease stage, molecular subtype, prognostic biomarkers, tumour grade and patient age, among other factors.(39, 40) Subsequent therapy is then typically chosen based on patients treatment history and which treatment options the patient is yet to receive.(41)

In contrast with HR+ disease, patients with TNBC do not benefit from classical targeted breast cancer treatments such as endocrine therapy or anti-HER2 therapy.(16) The checkpoint inhibitor, atezolizumab has recently been recommended for use in combination with nab-paclitaxel in mTNBC patients with tumours expressing PD-L1 and who have not had previous chemotherapy for metastatic disease.(42) However, only 40% to 50% of patients with TNBC express this biomarker, and use of this combination is restricted to first-line use due to low response rates in later lines of mTNBC treatment.(41-43) As such, for most patients with mTNBC the principal systemic treatment option, particularly for second-line therapy and beyond, is cytotoxic chemotherapy.(40-42, 44)

Clinical expert feedback indicates that combinations of effective chemotherapy regimens, including taxanes, carboplatin, anthracyclines and capecitabine, are widely used in the neoadjuvant and adjuvant setting to reduce the possibility of

relapse and improve prognosis in early TNBC.(45) However, this leaves limited treatment options for patients following progression to mTNBC, which is of concern as these patients already have fewer treatment options compared with patients with HR+ and HER2+ breast cancers.

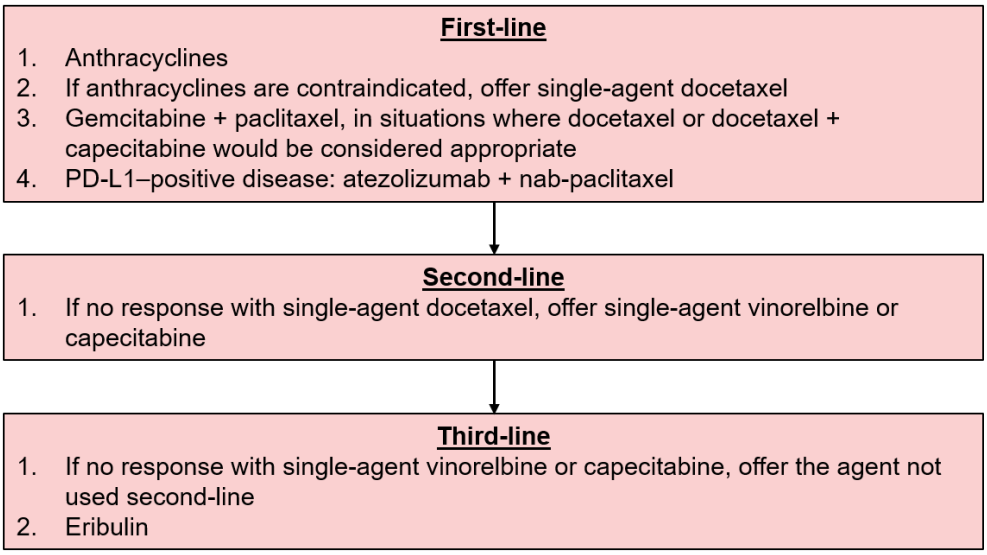
B.1.3.4.2 NICE guidelines

The treatment of TNBC is not addressed in the National Institute for Health and Care Excellence (NICE) guideline for advanced breast cancer: diagnosis and treatment (CG81).(46) However, the NICE pathway detailing the management of advanced breast cancer (March 2021) includes specific TNBC recommendations.(42)

According to the NICE pathway and ESMO guidelines, patients with advanced (stage 4) TNBC, defined as unresectable locally advanced and metastatic disease, should be offered systemic sequential single-agent chemotherapy on disease progression.(41, 42) Single-agent chemotherapy regimens are the preferred standard of care in mTNBC, demonstrating similar survival benefits with less toxicity and improved quality of life compared with combination regimens.(15)

The NICE treatment pathway for managing mTNBC is shown in Figure 1. Both NICE and ESMO recommend anthracycline- and taxane-based chemotherapy for first-line mTNBC.(41, 42) Second- and third-line treatments recommended by NICE include vinorelbine, capecitabine and eribulin.(42)

Figure 1: NICE treatment pathway for managing mTNBC(42)



B.1.3.4.3 UK clinical practice

There is no established standard of care for pretreated mTNBC, with generally poor outcomes across the available chemotherapy agents. Instead, treatments are chosen on an individual basis depending on which treatment options the patient is yet to receive.(41)

A retrospective analysis of treatment patterns in patients with advanced/mTNBC in the UK showed that most patients received treatment regimens inconsistent with the current NICE clinical pathway described above, and that treatment options are highly variable.(32) This study evaluated the treatment of patients with mTNBC at the Royal Marsden NHS Foundation Trust between 2011 and 2016.(32) First line treatment of 186 patients with mTNBC was dominated by fluoropyrimidine use (43.5%) with only 7.5% of patients receiving anthracycline-based regimens and 17.7% of patients receiving taxanes.(32) Platinum-based regimens were most commonly used in second line treatment (31.4%), eribulin in third line treatment (37.1%) and platinum-based regimens in fourth line treatment (30.0%).(32)

UK clinical expert feedback indicates that single-agent chemotherapy is the preferred treatment modality for second-line mTNBC and beyond, which is in line with NICE and ESMO guidance.(41, 42) Clinicians typically use capecitabine, vinorelbine or eribulin, with eribulin cited as the most effective option. This is particularly true for the majority of patients with mTNBC who have relapsed from early stage disease (approximately 80% vs. 20% diagnosed with *de novo* metastatic disease)(47), since these patients have typically already been treated with anthracyclines, taxanes and platinum-containing therapies.

B.1.3.5 Summary of unmet clinical need

More than 45,000 women in England are diagnosed with breast cancer each year, between 4,500 and 9,200 of them with TNBC.(13, 15, 19, 23, 24) TNBC is an aggressive, fast-progressing breast cancer subtype which sadly affects a higher proportion of young, working-age women aged <40 years than other breast cancer subtypes.(16, 17, 22)

Breast cancer causes more than 9,500 deaths in England each year.(14) A diagnosis of mTNBC can be particularly devastating for patients and their families, as it is associated with worse survival outcomes and more limited treatment options compared with other MBC subtypes; with survival of approximately 15 months from diagnosis of metastatic disease compared with >4 years for metastatic HR+ and HER2+ breast cancer.(27)

Unfortunately, patients with TNBC do not benefit from endocrine therapy or anti-HER2 therapy, which have been established as highly effective treatments for ER+/PR+ and HER2+ tumours, respectively.(16) As such, while treatment innovations have improved OS for patients with HER2+ MBC, survival outcomes have remained consistently poor for patients with mTNBC with available cytotoxic treatments, including eribulin, capecitabine, gemcitabine and vinorelbine.(34-37) Survival further diminishes as patients progress to second-line therapy and beyond.(30) Of patients treated with single-agent chemotherapy in the 2L+ setting, only ~23% are alive and progression free at 3 months.(37)

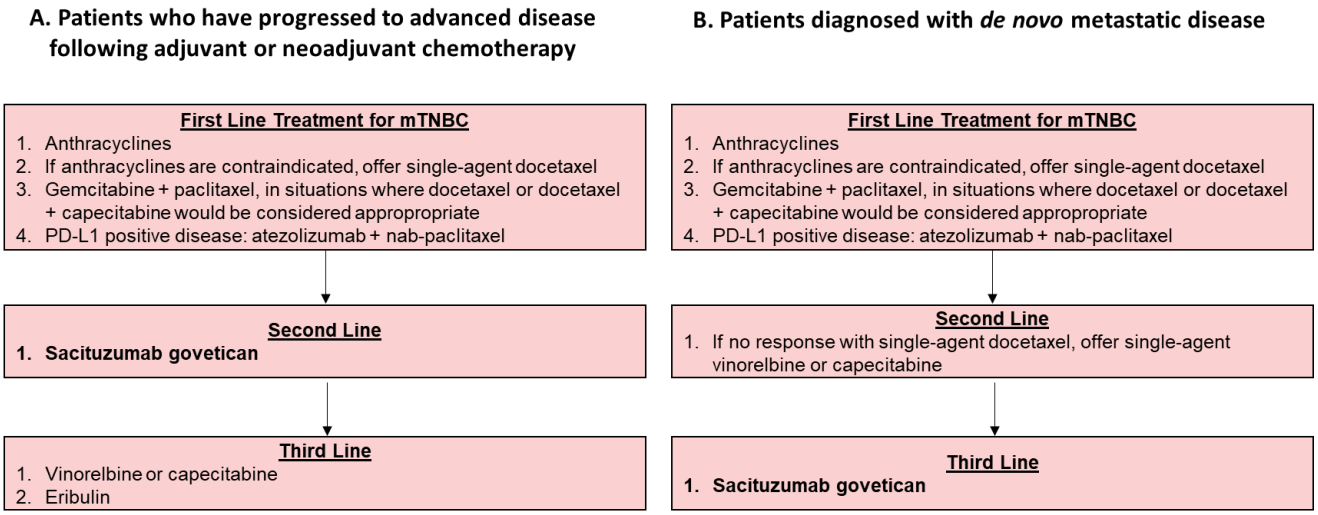
TNBC is known to have a higher frequency of early relapse than other breast cancer subtypes and the choice of treatments for patients that have progressed to mTNBC from early stage disease (approximately 80% of mTNBC patients) is further limited by the early extensive use of neoadjuvant chemotherapy as treatment is typically dictated by which agents the patient is yet to receive.(41, 45) Therefore, there remains a clear need for additional effective second-line and beyond treatments for patients with mTNBC that can broaden their treatment options and prolong life in disproportionately young patients with breast cancer who are likely to have dependent families and would otherwise look forward to a longer future.

B.1.3.5.1 Proposed positioning of SG in mTNBC treatment pathway

The current NICE clinical practice treatment pathway for TNBC is presented in Figure 2 showing the proposed positioning of SG for unresectable locally advanced or mTNBC in patients who have received two prior lines of systemic therapy, at least one of them given for unresectable locally advanced or metastatic disease.(1) The anticipated licensed indication includes both unresectable locally advanced and

mTNBC. However, the population eligible for SG is expected to consist primarily of patients with metastatic disease; while limited treatment pattern data are available for patients with relapsed locally advanced disease, only 2.8% of patients enrolled in the ASCENT trial had prior systemic therapy for locally advanced TNBC.(48)

Figure 2: NICE treatment pathway for managing TNBC with proposed positioning for SG in patients with mTNBC(42)



Note: Adjuvant or neoadjuvant therapy for localised disease is considered a prior systemic therapy, and therefore patients who progress following early stage therapy would be eligible for SG in the second-line metastatic setting per the licensed indication

mTNBC = metastatic triple-negative breast cancer; NICE = National Institute for Health and Care Excellence; PD-L1 = programmed death-ligand 1; SG = sacituzumab govitecan

B.1.4 Equality considerations

No equality issues relating to SG have been identified. However, reimbursement decisions and guidance related to TNBC will disproportionately impact Black and Hispanic women with breast cancer, who are at greater risk of this breast cancer subtype compared with White women,(25) as well as Ashkenazi Jewish women, who are at higher risk of a *BRCA* mutation, which is associated with TNBC.(49, 50)

B.2 Clinical effectiveness

B.2.1 Identification and selection of relevant studies

See Appendix D for full details of the process and methods used to identify and select the clinical evidence relevant to the technology being appraised.

B.2.2 List of relevant clinical effectiveness evidence

Sacituzumab govitecan has been studied in patients with mTNBC in a phase I/II study and a pivotal phase III study, both of which have been completed (Table 3).(36, 51-55) The phase I/II IMMU-132-01 study (NCT01631552) found that SG had a manageable safety profile and that SG treatment was associated with a durable objective response in a small cohort of patients with pretreated mTNBC. These findings were confirmed in the pivotal phase III study, ASCENT.(51, 54, 55) Data from the ASCENT study are the primary source of evidence for the patient population included in the product label, as well as the cost-effectiveness model included in this submission.

IMMU-132-01 phase I/II trial

IMMU-132-01 was a phase I/II, single-arm, open-label, dose-escalation study of the efficacy and safety of SG in advanced epithelial cancers, including mTNBC.(51, 56) In the phase II dose expansion phase of the study, patients with mTNBC initially received either SG 8 mg/kg (n=14) or 10 mg/kg (n=39) on Days 1 and 8 of 21-day cycles.(57) Following results from the phase II expansion, the 10 mg/kg dose was selected for use in the pivotal phase III ASCENT study based on improved efficacy and good therapeutic index compared with the 8 mg/kg dose.(57)

At a median follow-up of 9.0 months, a total of 108 patients with mTNBC received SG at a dose of 10 mg/kg.(51, 56) In this cohort of patients, the objective response rate (ORR) for SG was 33.3% with a median duration of response (DOR) of 9.1 months (95% CI: 4.6, 11.3).(56) Median OS was 13.0 months (95% CI: 11.2 to 14.0) and median PFS was 5.6 months (95% CI: 4.8, 6.6).(56) After a mean of 18.7 doses of SG, the most common adverse events (AEs) were nausea (67%), neutropenia

(64%) and diarrhoea (62%).(51) The most common Grade ≥3 adverse events were neutropenia (26%) and anaemia (11%).(51) AEs leading to treatment discontinuation were low (3% of patients) and treatment disruption occurred in less than half of patients (44%).(51) Overall, IMMU-132-01 showed SG to have a durable objective response and manageable safety profile in patients with pretreated mTNBC at a dose of 10 mg/kg.(51, 56)

ASCENT (IMMU-132-05) phase III trial

ASCENT (IMMU-132-05; NCT02574455) was an international, multicentre, open-label, randomised, phase III confirmatory study comparing SG with single-agent treatment of physician's choice (TPC) in patients with unresectable, locally advanced or mTNBC who were refractory or had relapsed after receiving ≥2 prior standard-of-care chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease.(37, 52, 53, 55) Adjuvant or neoadjuvant therapy for more localised disease was considered as one of the two required regimens if progression to unresectable, locally advanced or metastatic disease occurred within 12 months of completing chemotherapy.(55) All patients must also have received previous taxane treatment in either the adjuvant, neoadjuvant or advanced stage.(37, 55)

Table 3: Clinical effectiveness evidence

Study	ASCENT (IMMU-132-05)(37, 55)	IMMU-132-01(36, 51, 57)
Study design	Phase III, open-label, RCT of the efficacy and safety of SG in locally advanced or mTNBC	Phase I/II, single-arm trial of the efficacy and safety of SG in advanced epithelial cancers, including mTNBC
Population	Patients with locally advanced or mTNBC who were either refractory or had relapsed after ≥2 prior standard-of-care chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease[a], and had received previous taxane treatment in either the adjuvant, neoadjuvant or advanced stage	Patients with mTNBC who were either refractory to or had relapsed after ≥1 prior standard-of-care chemotherapy regimen and without brain metastasis (unless treated and without progression)
Intervention	SG: 10 mg/kg SG was administered via slow IV infusion on Days 1 and 8 of a 21-day treatment cycle Treatment was continued until detection of disease progression or unacceptable toxicity/AEs	SG: During the dose expansion phase, either 8 mg/kg or 10 mg/kg SG was administered IV on Days 1 and 8 of a 21-day treatment cycle. Following this, the 10 mg/kg dose was chosen for further development based on improved efficacy and good

Study	ASCENT (IMMU-132-05)(37, 55)					IMMU-132-01(36, 51, 57)				
						therapeutic index compared with 8 mg/kg Treatment was continued until there was no longer clinical benefit or until disease progression or unacceptable toxicity/AEs				
Comparator(s)	One of the following single-agent treatments was selected by investigator before randomisation (TPC): <u>Eribulin:</u> 1.4 mg/m^2 (NA sites) or 1.23 mg/m^2 (European sites) was administered IV over 2-5 minutes on Days 1 and 8 of a 21-day cycle <u>Capecitabine:</u> 1,000 to 1,250 mg/m^2 was administered orally twice daily for 2 weeks with a 1-week rest period over a 21-day cycle <u>Gemcitabine:</u> 800 to 1,200 mg/m^2 was administered IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle <u>Vinorelbine:</u> 25 mg/m^2 was administered IV over 6-10 minutes weekly All TPC was continued until disease progression or occurrence of unacceptable AEs					-				
Indicate if trial supports application for marketing authorisation	Yes	✓	Indicate if trial used in the economic model	Yes	✓	Yes	✓	Indicate if trial used in the economic model	Yes	
	No			No		No			No	✓
Rationale for use/non-use in the model	Most relevant clinical evidence for the efficacy of SG versus TPC in locally advanced or mTNBC					Single-arm study; more recent and robust data from phase III trial available				
Reported outcomes specified in the decision problem	The outcome measures considered include: ▪ OS ▪ PFS (BM-ve patients and ITT population) ▪ ORR ▪ AEs ▪ HRQoL as measured by EORTC-QLQ C30					-				

Study	ASCENT (IMMU-132-05)(37, 55)	IMMU-132-01(36, 51, 57)
All other reported outcomes	▪ DOR ▪ CBR ▪ TTR ▪ TTP	▪ AEs ▪ ORR ▪ DOR ▪ Clinical benefit ▪ OS ▪ PFS

[a] Adjuvant or neoadjuvant therapy for more localised disease was considered as one of the two required regimens if progression to unresectable, locally advanced or metastatic disease occurred within 12 months of completing chemotherapy

AE = adverse event; CBR = clinical benefit rate; DOR = duration of response; EORTC-QLQ C30 = European Organisation for Research and Treatment of Cancer - Quality of life Questionnaire Core 30 HRQoL = health-related quality of life; ITT = intent-to-treat; IV = intravenous(ly); mTNBC = metastatic triple negative breast cancer; NA = North American; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; RCT = randomised controlled trial; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTP = time to progression; TTR = time to response

B.2.3 Summary of methodology of the relevant clinical effectiveness evidence

B.2.3.1 Study design

Patients in ASCENT were randomised 1:1 to receive SG or single-agent TPC.(55) Randomisation was stratified by the number of prior treatments for advanced disease (2-3 versus >3), geographic location (North America versus rest of world) and known stable brain metastasis at baseline (yes or no).(55)

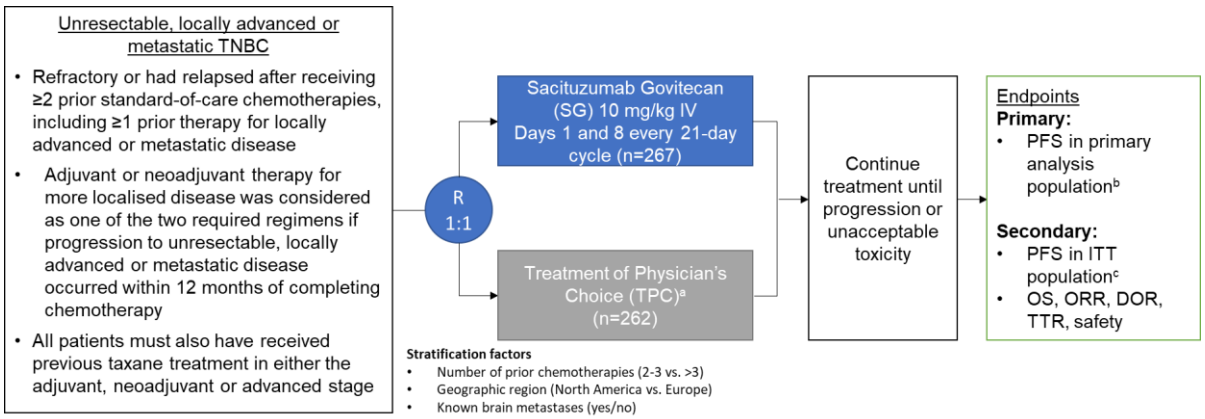
Single-agent TPC was the active comparator for this study because there is no accepted current standard of care for pretreated patients with TNBC.(37) TPC consisted only one of the following single-agent treatments:(55)

- Eribulin
- Capecitabine
- Gemcitabine
- Vinorelbine (except if the patient had Grade ≥2 neuropathy)

UK clinical expert feedback supports that the TPC arm is a pragmatic and appropriate comparator, consisting mostly of therapies that are commonly used in England.

Patients were treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal or death, whichever came first.(55) An overview of the ASCENT study design is presented in Figure 3.

Figure 3: Overview of the ASCENT study design (IMMU-132-05)(52, 55)



[a] TPC: eribulin, vinorelbine, gemcitabine or capecitabine

[b] PFS measured by an independent, centralised, and blinded group of radiology experts (IRC) in BM-ve patients

[c] The full population includes all randomised patients (with and without brain metastases at baseline)

BM-ve = brain metastasis negative (no brain metastases at baseline); DOR = duration of response; IRC = independent review committee; ITT = intent-to-treat; IV = intravenous; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; R = randomisation; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; TTR = time to response

Tumour response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI) every 6 weeks (same imaging method throughout the study) for 36 weeks and then every 9 weeks thereafter until the occurrence of progression of disease requiring discontinuation of further treatment.(37, 55) All available CT or MRI scans were reviewed by the Independent Review Committee (IRC) for this study, using modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 to assess disease progression and response to treatment.(37, 55) The decision to discontinue a patient for progressive disease (PD) was made by the investigator.(37)

B.2.3.1.1 Study objectives

The primary objective of ASCENT was to compare SG and TPC for progression-free survival (PFS) by IRC assessment in the brain metastasis-negative (BM-ve) patient population (primary analysis population).(55)

The secondary objectives of the study were to compare SG with TPC for the following endpoints:(37, 55)

- PFS in ITT population
- Overall survival (OS)
- Objective response rate (ORR)
- Clinical benefit rate (CBR)
- Duration of response (DOR)
- Time to onset of response (TTR)
- Time to progression (TTP)
- Quality of life (QoL)
- Adverse events (AEs)

B.2.3.1.2 Patient eligibility

Patients in ASCENT had unresectable, locally advanced or mTNBC and were refractory or had relapsed after receiving ≥2 prior standard-of-care chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease.(37, 52, 53, 55) Adjuvant or neoadjuvant therapy for more localised disease was considered as one of the two required regimens if progression to unresectable, locally advanced or metastatic disease occurred within 12 months of completing chemotherapy.(37, 55) All patients must also have received previous taxane treatment in either the adjuvant, neoadjuvant or advanced stage.(37, 55) Patients who either had a contraindication or were intolerant to taxanes were enrolled if they had received at least 1 cycle of a taxane,(55) with either the contraindication or intolerance during or at the end, of the first taxane cycle.(36) Poly-ADP ribose polymerase (PARP) inhibitors were allowed as 1 of 2 prior standard-of-care chemotherapies for patients with a documented germ-line *BRCA1/BRCA2* mutation.(55)

The inclusion criteria for patients with known brain metastases was amended during the conduct of the study. In the original protocol for ASCENT, patients were screened for brain metastases and those with brain metastases were excluded unless treated, non-progressive and off high-dose steroids (>20 mg prednisone or equivalent) for at least 4 weeks prior to study entry.(58) Following a protocol

amendment, only patients with known brain metastases at baseline required a brain MRI at screening and were eligible to enrol in the trial as long as their central nervous system (CNS) disease was treated and stable for at least 4 weeks prior to randomisation (as defined in Table 4).(58) The proportion of patients with known brain metastasis at baseline was limited to ≤15% and this subgroup was not included in the primary efficacy analysis population.(55)

Table 4 summarises the key inclusion and exclusion criteria for the ASCENT study.

Table 4: ASCENT study inclusion and exclusion criteria (IMMU-132-05)(37, 55)

Inclusion criteria
Patients had to meet all of the following criteria to be included: ▪ Age ≥18 years ▪ ECOG PS 0 or 1 ▪ mTNBC based on most recent biopsy or other pathology specimen ▪ Unresectable, locally advanced or mTNBC who were refractory or had relapsed after receiving ≥2 prior chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease o No cap on the number of prior chemotherapies for locally advanced or metastatic disease o Adjuvant or neoadjuvant therapy for more localised disease was considered as one of the two required regimens if progression to unresectable, locally advanced or metastatic disease occurred within 12 months of completing chemotherapy o For patients with a documented germline *BRCA1/BRCA2* mutation who received an approved PARP inhibitor, the PARP inhibitor could be used to meet the criteria for 1 of 2 prior standard of care chemotherapies o All patients must have been previously treated with a taxane, regardless of disease stage (adjuvant, neoadjuvant or advanced) when it was given. Patients who had contraindications or were intolerant to taxanes were eligible if they had received at least 1 cycle of a taxane and showed contraindications or intolerance during or at the end of that taxane cycle ▪ Eligible for one of the TPC chemotherapy options (eribulin, vinorelbine, gemcitabine or capecitabine) ▪ Adequate haematologic, hepatic, and renal function ▪ Measurable disease[a] by CT or MRI (per RECIST v1.1) ▪ At least 2 weeks beyond prior anticancer treatments and recovered from all acute toxicities to Grade ≤1 (except alopecia and peripheral neuropathy which could be Grade ≤2) ▪ At least 2 weeks beyond high-dose systemic corticosteroids ▪ Brain MRI should have been performed for patients with brain metastasis; patient must have had stable central nervous system disease for at least 4 weeks, with stable defined as follows: o Prior local treatment by radiation, surgery or stereotactic surgery o Imaging – stable or decreasing size after such local treatment o Clinically stable signs and symptoms o ≥2 weeks from discontinuation of anti-seizure medication ▪ If needed, the corticosteroid dose was either stable or decreasing for at least 2 weeks

before randomisation. Steroid dose was ≤20 mg of prednisone/prednisolone daily or equivalent for a different steroid. ▪ A life expectancy of 3 months or greater in the opinion of the investigator
Exclusion criteria
Patients meeting any of the following criteria were excluded: ▪ Pregnancy or lactation (and women of childbearing potential or fertile men unwilling to use highly effective contraception during study and up to 3 months after treatment discontinuation in women of child-bearing potential and 6 months in males post last study drug) ▪ Prior malignancies within 3 years, except nonmelanoma skin cancer or carcinoma in situ of the cervix ▪ Gilbert's disease ▪ Positivity for HIV, HBV or HCV within 6 months ▪ Known history of unstable angina, MI or CHF within 6 months or a clinically-significant cardiac arrhythmia (other than stable atrial fibrillation) requiring anti-arrhythmia therapy ▪ Infection requiring antibiotic use within 1 week of randomisation ▪ Known history of clinically significant active COPD or other moderate-to-severe chronic respiratory illness present within 6 months ▪ Prior history of clinically-significant bleeding, intestinal obstruction or GI perforation within 6 months of randomisation ▪ Active chronic inflammatory bowel disease (ulcerative colitis, Crohn's disease) and patients with a history of bowel obstruction ▪ Received a live vaccine within 30 days of randomisation ▪ Previously received irinotecan ▪ Rapid deterioration during screening prior to randomisation (e.g., significant change in PS, ≥20% decrease in serum albumin levels, unstable pain symptoms requiring modifications in analgesic management) ▪ Other concurrent medical or psychiatric conditions that were likely to confound study interpretation or prevent completion of study procedures and follow-up examinations (based on Investigator's opinion)

[a] Bone-only disease was not permitted

BRCA = Breast Cancer Gene; CT = computed tomography; CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease; ECOG = Eastern Cooperative Oncology Group; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MI = myocardial infarction; MRI = magnetic resonance imaging; mTNBC = metastatic triple negative breast cancer; PARP = poly (ADP-ribose) polymerase; PS = performance status; RECIST = response evaluation criteria in solid tumours; TPC = treatment of physician's choice

B.2.3.1.3 Administration of study drug

SG was administered at a dose of 10 mg/kg by slow intravenous (IV) infusion on Days 1 and 8 of a 21-day treatment cycle.(37, 55) Deviations in the treatment schedule of up to 7 days were allowed for holidays, vacations or personal reasons.(37) The dose of 10 mg/kg was based on data from the phase I/II study, IMMU-132-01.(37) Dosing was based on patient body weight on Day 1 of each cycle or at each dosing day if change in body weight >10%.(37)

The initial infusion rate was ≤50 mg/hr for the first 15 minutes, and if vital signs were stable, the rate was advanced 50 mg/hr every 15-30 minutes up to a maximum of 500 mg/hr.(37) Infusion was slowed, interrupted or terminated in response to changes in vital signs or infusion reactions.(37)

The doses of single-agent TPC (either eribulin, capecitabine, gemcitabine or vinorelbine) were based on approved labelling.(55)

B.2.3.1.4 Prior and concomitant therapy

Prior to the administration of either SG or TPC, patients were administered a 2- or 3-drug combination regimen (e.g., dexamethasone with either a 5-HT3 receptor antagonist or a NK1 receptor antagonist and other drugs as indicated) for prevention and treatment of chemotherapy-induced nausea and vomiting.(55) All patients were given additional medications for prevention and treatment of nausea, vomiting and diarrhoea for use at home.(37)

Premedication, including antipyretics, H1 and H2 blockers or corticosteroids (50 mg hydrocortisone or equivalent orally or IV), was strongly recommended to prevent infusion reactions with SG.(55)

The following concomitant therapy were prohibited in ASCENT:(37, 55)

- Any anticancer therapy or any other chemotherapeutic agents for a minimum of 2 weeks before the start of SG administration
- High-dose systemic corticosteroids within 2 weeks of study entry
- Strong inhibitors or inducers of CYP3A4 because of the known interaction with irinotecan

The following concomitant therapies were permitted in ASCENT:(55)

- Palliative and/or supportive medications such as bone-modifying medications, and/or procedures such as radiation and surgery, at investigator's discretion
- Premedication for prevention of infusion reactions with SG
- Appropriate premedication for prevention and treatment of chemotherapy-induced nausea and vomiting
- Appropriate premedication for any patient who had an excessive cholinergic response to SG

- Haematopoietic growth factors or blood transfusions
- Low dose, stable doses of corticosteroids ≤20 mg prednisone or equivalent daily were permitted if the patient entered the study on low-dose steroids for treatment of brain metastasis
- Topical steroids and corticosteroid inhalers

B.2.3.2 Summary of methodology

A summary of the methodology used in ASCENT is presented in Table 5.

Table 5: Summary of ASCENT trial methodology (IMMU-132--05)(37, 55)

Trial	ASCENT (IMMU-132-05)
Location	Multicentre: 88 sites Belgium (5 sites), Canada (3 sites), France (10 sites), Germany (3 sites), Italy (1 site) Spain (10 sites), United Kingdom (6 sites), United States (50 sites)
Trial design	Phase III, randomised, open-label, multicentre study
Eligibility criteria for participants	Eligible patients were ≥18 years of age with locally-advanced or mTNBC, were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens, including ≥1 prior therapy for locally advanced or metastatic disease. Adjuvant or neoadjuvant therapy for more localised disease was considered as one of the two required regimens if progression to unresectable, locally advanced or metastatic disease occurred within 12 months of completing chemotherapy. All patients must also have received previous taxane treatment in either the adjuvant, neoadjuvant or advanced stage
Settings and locations where the data were collected	Belgium, Canada, France, Germany, Italy, Spain, United Kingdom of Great Britain and Northern Ireland, United States of America
Trial drugs (the interventions for each group with sufficient details to allow replication, including how and when they were administered) **Intervention(s) (n=267) and comparator(s) (n=262)**	The study treatment was SG; the active comparator was single-agent TPC, consisting of either eribulin, capecitabine, gemcitabine or vinorelbine. Prior to administration of SG or TPC, patients were administered a 2- or 3-drug combination regimen for prevention and treatment of chemotherapy-induced nausea and vomiting; patients were also given medications for nausea and vomiting for use at home. For all groups, treatment was continued until progression of disease required discontinuation or occurrence of unacceptable AEs. ▪ SG was administered at a dose of 10 mg/kg as an IV infusion on Days 1 and 8 of a 21-day treatment cycle. Dosing was based on patient body weight on Day 1 of each cycle or at each dosing day if change in body weight >10%. The initial infusion rate was ≤50 mg/hr, and if vital signs were stable, the rate was advanced 50 mg/hr every 15-30 minutes up to a maximum of 500 mg/hr. Infusion was slowed, interrupted or terminated in response to changes in vital signs or infusion reactions ▪ Eribulin was administered at a dose of 1.4 mg/m^2 (NA sites) or 1.23 mg/m^2 (European sites) as an IV injection over 2-5 minutes on Days 1 and 8 of a 21-day cycle. Patients with

	moderate hepatic impairment were administered 0.7 mg/m^2 (NA) or 0.62 mg/m^2 (Europe) on the same schedule Capecitabine was administered orally at a dose of 1,000-1,250 mg/m^2 twice daily for 2 weeks followed by a 1-week rest period ▪ Gemcitabine was administered at a dose of 800-1,200 mg/m^2 via IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle ▪ Vinorelbine was administered at a dose of 25 mg/m^2 as an IV injection on Day 1 weekly over 6-10 minutes. Patients with ≥grade 2 neuropathy were excluded from this TPC
Permitted and disallowed concomitant medication	The following medications/treatments were not permitted during the study: ▪ Any anticancer therapy/other chemotherapeutic agents for 2 weeks before the start of SG administration ▪ High-dose systemic corticosteroids within 2 weeks of study entry ▪ Strong inhibitors or inducers of CYP3A4 due to known SG interaction with irinotecan The following concomitant medications were permitted during the study: ▪ Palliative and/or supportive medications such as bone-modifying medications, and/or procedures such as radiation and surgery, at investigator's discretion ▪ Premedication for prevention of infusion reactions with SG ▪ Appropriate premedication for prevention and treatment of chemotherapy-induced nausea and vomiting ▪ Appropriate premedication for any patient who had an excessive cholinergic response to SG ▪ Haematopoietic growth factors or blood transfusions ▪ Low dose, stable doses of corticosteroids ≤20 mg prednisone or equivalent daily were permitted if the patient entered the study on low-dose steroids for treatment of brain metastasis ▪ Topical steroids and corticosteroid inhalers
Primary outcomes (including scoring methods and timings of assessments)	PFS by IRC in BM-ve patients Defined as the time from randomisation until objective tumour progression by RECIST v1.1 or death. CT/MRI scans were obtained at baseline, every 6 weeks through Week 36, and then every 9 weeks until disease progression.
Other outcomes used in the economic model/specified in the scope	▪ PFS by IRC in the ITT population ▪ OS, defined as the time from the start of the study treatment to death from any cause ▪ ORR by IRC and investigator assessment, defined as the percentage of patients who had either a confirmed CR or PR ▪ TTR by IRC and investigator assessment, defined as the time from randomisation to first recorded CR or PR ▪ DOR by IRC and investigator assessment, defined as the number of days between the first date showing a documented CR or PR and the date of progression or death ▪ CBR by IRC and investigator assessment, defined as the percentage of patients with CR, PR or SD with a duration of ≥6 months

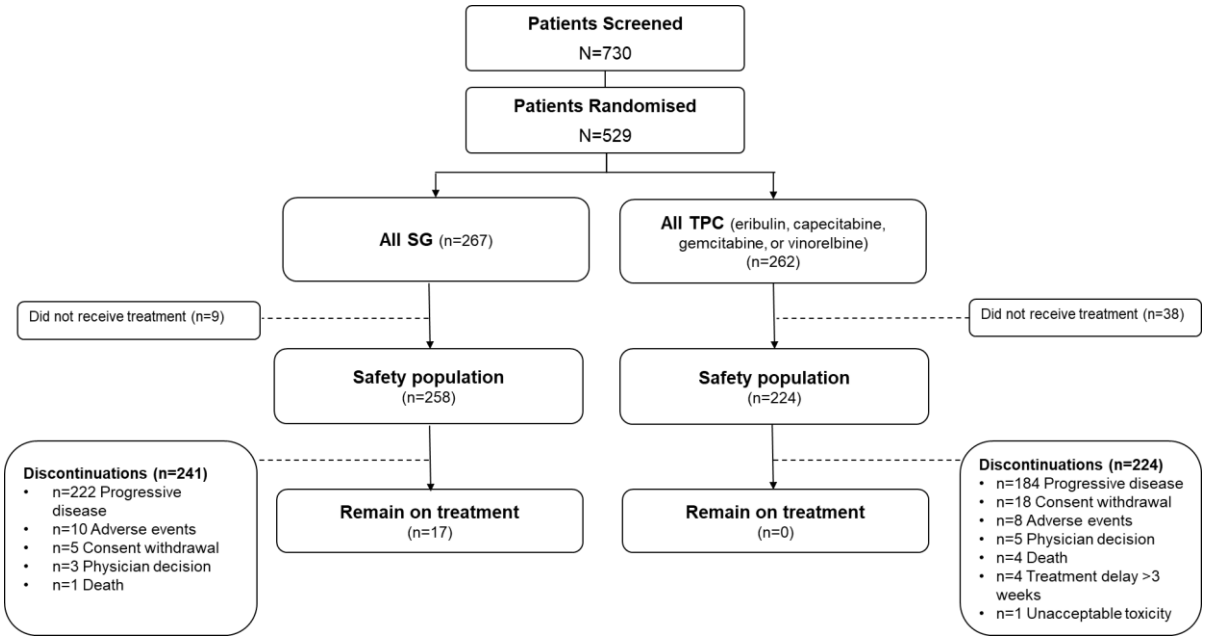
	▪ QOL using EORTC-QLC-C30 at baseline, beginning of every cycle, and final study visit (i.e., four weeks after the last dose of study drug or in the event of premature study termination) ▪ AEs recorded at every study visit
Pre-planned subgroups	▪ Age (<65, ≥65 years) ▪ Race (White, Black, Asian) ▪ Prior therapies (2-3, and >3) ▪ Region (North America, rest of world) ▪ Original diagnosis TNBC (yes, no) ▪ Prior breast cancer surgery (yes, no) ▪ Prior cancer radiotherapy ▪ *BRCA1* status (positive, negative) ▪ *BRCA1* and *BRCA2* status (positive, negative) ▪ Prior PD-L1/PD-1 use (yes, no) ▪ Trop-2 status (percentage of membrane cells with 2+ or 3+ <85% staining, percentage of membrane cells with 2+ or 3+ staining ≥85%) ▪ Liver metastasis at baseline (yes, no) ▪ *UGT1A1* status (*1/*1, *1/*28, *28/*28, other)

AE = adverse event; BM-ve = brain metastasis negative (no brain metastases at baseline); *BRCA* = Breast Cancer gene; CBR = clinical benefit rate; CR = complete response; CT = computed tomography; CYP3A4 = Cytochrome P450 3A4; DOR = duration of response; EORTC-QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; IRC = Independent Review Committee; ITT = intention-to-treat; MRI = magnetic resonance imaging; mTNBC = metastatic triple negative breast cancer; NA = North America; ORR = objective response rate; OS = overall survival; PD-1 = Programmed cell death protein 1; PD-L1 = Programmed death-ligand 1; PFS = progression-free survival; PR = partial response; QOL = quality of life; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease; SG = Sacituzumab govitecan; TPC = treatment of physician's choice; TTR = time to onset of response; *UGT1A1* = uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1

B.2.3.3 Baseline patient and disease characteristics

Of 730 patients screened for the study, a total of 529 patients were randomised in ASCENT (SG, n=267; TPC, n=262) across 88 sites and included in the ITT population (Figure 4).(37, 55) The most frequent reasons for screening failure were lack of stable CNS disease (12.9%) and inadequate renal and hepatic function (12.4%).(37) A smaller percentage of patients in the SG group compared with the TPC group were randomised but not treated (3.4% and 14.5%, respectively).(37) Communication with the sites suggests that some patients in the TPC group elected not to participate in the study when they were not randomised to the SG group (number not reported).(37)

Figure 4: Patient disposition in ASCENT (IMMU-132-05)(48)



SG = sacituzumab govitecan; TPC = treatment of physician's choice

In the ITT population, most patients were female and <65 years old with 36% of patients aged less than 50 years.(37) Most patients had an original diagnosis of TNBC, did not have either a *BRCA1* or *BRCA2* mutation, and had normal renal and hepatic function.(37) The majority of patients had no brain metastases at baseline (235 patients in the SG group and 233 patients in the TPC group).(37) Median number of prior systemic regimens was 4 in both the SG and TPC groups, ranging from 2 to 17 prior systemic regimens in the SG group and 2 to 14 prior systemic regimens in the TPC group; some of the prior regimens included hormonal therapies in patients who converted to TNBC after an initial diagnosis of hormone receptor positive breast cancer (25.1% and 29.0%, respectively).(37, 48) The most frequent prior systemic therapies in the SG and TPC groups were cyclophosphamide (82.8% and 82.4%), paclitaxel (76.4% and 80.2%, respectively), carboplatin (61.4% and 68.3%, respectively) and capecitabine (64.0% and 69.8%, respectively).(48) Overall, 29.6% and 28.2% of the patients in the SG and TPC groups, respectively, had received prior PD-1/PD-L1 therapy.(48) Clinical expert feedback agreed that the baseline characteristics of patients in ASCENT are broadly reflective of the mTNBC population in England, including the proportion of patients with *BRCA* mutation and

prior checkpoint inhibitor therapy (estimated to be 10% and 30% of mTNBC patients in England, respectively).

Table 6 summarises the key characteristics of patients in ASCENT in the ITT population.

Table 6: Characteristics of patients in ASCENT across treatment groups in ITT population (IMMU-132-05)(37, 48)

Characteristic	SG (N=267)	TPC (N=262)	Total (N=529)
Age, years, n (%)			
< 50	96 (36.0)	89 (34.0)	185 (35.0)
50-64	122 (45.7)	121 (46.2)	243 (45.9)
≥ 65	49 (18.4)	52 (19.8)	101 (19.1)
Mean (SD)	54.0 (11.34)	54.0 (11.69)	54.0 (11.50)
Median	54.0	53.0	54.0
Range	27 to 82	27 to 81	27 to 82
Sex, n (%)			
Male	2 (0.7)	0	2 (0.4)
Female	265 (99.3)	262 (100.0)	527 (99.6)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	13 (4.9)	9 (3.4)	22 (4.2)
Black	28 (10.5)	34 (13.0)	62 (11.7)
Native Hawaiian or Other Pacific Islander	0	0	0
White	215 (80.5)	203 (77.5)	418 (79.0)
Other	11 (4.1)	16 (6.1)	27 (5.1)
BMI (kg/m^2)[a]			
Mean (SD)	26.82 (6.481)	26.74 (6.200)	26.78 (6.337)
Median	25.41	25.97	25.82
Range	15.0 to 49.3	14.6 to 48.2	14.6 to 49.3
Body surface area (m^2)[b]			
Mean (SD)	1.79 (0.231)	1.77 (0.207)	1.78 (0.219)
Median	1.76	1.75	1.75
Range	1.3 to 2.5	1.3 to 2.4	1.3 to 2.5
Number of prior chemotherapies for randomisation stratification, n (%)[c]			
2-3	184 (68.9)	181 (69.1)	365 (69.0)
>3	83 (31.1)	81 (30.9)	164 (31.0)
Prior PD-1/PD-L1 therapy, n (%)			
Yes	79 (29.6)	74 (28.2)	153 (28.9)
No	188 (70.4)	188 (71.8)	341 (71.1)
Number of prior systemic therapies			
Mean (SD)	4.5 (2.05)	4.6 (2.14)	4.5 (2.09)

Characteristic	SG (N=267)	TPC (N=262)	Total (N=529)
Median	4.0	4.0	4.0
Range	2 to 17	2 to 14	2 to 17
Frequent prior systemic therapies[d]			
Cyclophosphamide	221 (82.8)	216 (82.4)	437 (82.6)
Paclitaxel	204 (76.4)	210 (80.2)	414 (78.3)
Carboplatin	164 (61.4)	179 (68.3)	343 (64.8)
Capecitabine	171 (64.0)	183 (69.8)	354 (66.9)
Doxorubicin	142 (53.2)	141 (53.8)	283 (53.5)
Gemcitabine	85 (31.8)	106 (40.5)	191 (36.1)
Docetaxel	101 (37.8)	83 (31.7)	184 (34.8)
Eribulin	88 (33.0)	85 (32.4)	173 (32.7)
Region for randomisation stratification, n (%)[c]			
North America	175 (65.5)	172 (65.6)	347 (65.6)
Rest of World	92 (34.5)	90 (34.4)	182 (34.4)
Original diagnosis TNBC, n (%)			
Yes	192 (71.9)	180 (68.7)	372 (70.3)
No	75 (28.1)	82 (31.3)	157 (29.7)
Time from diagnosis of stage 4 to study entry (months)[e]			
Mean (SD)	21.74 (21.202)	22.35 (20.353)	22.04 (20.768)
Median	16.82	15.82	16.23
Range	0.1 to 202.9	-0.4 to 140.1	-0.4 to 202.9
Presence of known brain metastases at study entry for randomisation stratification, n (%)[c]			
Yes	32 (12.0)	29 (11.1)	61 (11.5)
No	235 (88.0)	233 (88.9)	468 (88.5)
***UGT1A1* genotype (SG only), n (%)**			
*1/*1	113 (42.3)	-	-
*1/*28	96 (36.0)	-	-
*28/*28	34 (12.7)	-	-
Other	7 (2.6)	-	-
Missing	17 (6.4)	-	-
***BRCA1/BRCA2* Mutational Status, n (%)[f]**			
Negative	150 (56.2)	146 (55.7)	296 (56.0)
Positive	20 (7.5)	23 (8.8)	43 (8.1)
Screening ECOG performance status, n (%)			
0: Normal Activity	121 (45.3)	108 (41.2)	229 (43.3)
1: Symptoms but Ambulatory	146 (54.7)	154 (58.8)	300 (56.7)
Baseline serum bilirubin, n (%)			
Normal (≤ULN)	253 (94.8)	218 (83.2)	471 (89.0)
>1 and ≤1.5× ULN	5 (1.9)	4 (1.5)	9 (1.7)
>1.5× ULN	0	1 (0.4)	1 (0.2)
Baseline creatinine clearance (mL/min)			
Mean (SD)	110.952 (38.2121)	110.210 (38.3305)	110.584 (38.2364)

Characteristic	SG (N=267)	TPC (N=262)	Total (N=529)
Median	101.000	106.575	104.000
Range	60.17 to 255.50	53.00 to 260.00	53.00 to 260.00
Frequent (≥5% in either group) tumour locations based on IRC, n (%)			
Abdominal lymph node	9 (3.4)	13 (5.0)	22 (4.2)
Axillary lymph node	59 (22.1)	78 (29.8)	137 (25.9)
Bone	62 (23.2)	63 (24.0)	125 (23.6)
Brain	15 (5.6)	18 (6.9)	33 (6.2)
Breast	45 (16.9)	50 (19.1)	95 (18.0)
Chest wall	51 (19.1)	68 (26.0)	119 (22.5)
Hilar lymph node	32 (12.0)	37 (14.1)	69 (13.0)
Liver	107 (40.1)	114 (43.5)	221 (41.8)
Lung	131 (49.1)	115 (43.9)	246 (46.5)
Mediastinal lymph node	61 (22.8)	68 (26.0)	129 (24.4)
Pleura	26 (9.7)	18 (6.9)	44 (8.3)
Pleural effusion	17 (6.4)	21 (8.0)	44 (8.3)
Retroperitoneal lymph node	14 (5.2)	14 (5.3)	28 (5.3)
Skin	14 (5.2)	12 (4.6)	26 (4.9)
Subcarinal lymph node	19 (7.1)	15 (5.7)	34 (6.4)
Thoracic lymph node	28 (10.5)	29 (11.1)	57 (10.8)
Thoracic vertebra	19 (7.1)	15 (5.7)	34 (6.4)
Treatment of physician choice, n (%)[g]			
Eribulin	115 (43.1)	139 (53.1)	254 (48.0)
Capecitabine	48 (18.0)	33 (12.6)	81 (15.3)
Gemcitabine	46 (17.2)	38 (14.5)	84 (15.9)
Vinorelbine	58 (21.7)	52 (19.8)	110 (20.8)

[a] BMI is calculated as BMI (kg/m^2) = (weight in kg)/(height in m)^2

[b] Body surface area is calculated using Mosteller's formula: $\sqrt{\frac{(height\ (cm))(weight\ (kg))}{3600}}$

[c] The randomisation strata are based on IxRS

[d] Therapies used by ≥30% of patient population

[e] Time from diagnosis is defined as number of days divided by 30.4375 from date of diagnosis to date of study entry

[f] Positive denotes patient is either *BRCA1* positive or *BRCA2* positive. Negative denotes patient is both *BRCA1* negative and *BRCA2* negative. Note that not all patients were screened for *BRCA* mutational status

[g] As specified by the investigator prior to randomisation.

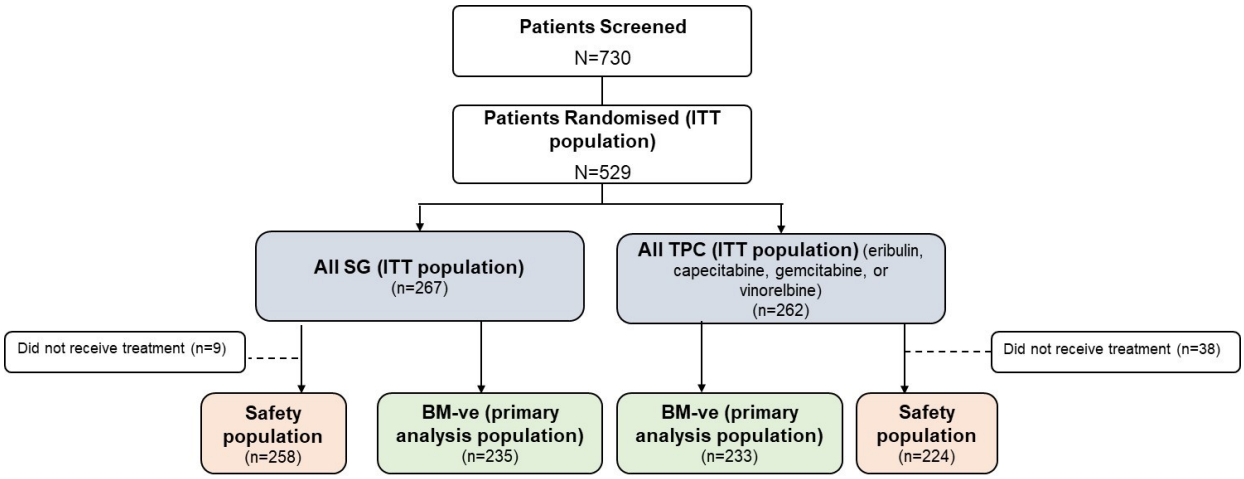
BMI = body mass index; *BRCA* = breast cancer gene; ECOG = Eastern Collective Oncology Group; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; ITT = intention-to-treat; IRC = Independent Review Committee; IxRS = Interactive Voice/Web Response System; SD = standard deviation; SG = Sacituzumab govitecan; TNBC = triple negative breast cancer; TPC = treatment of physician's choice; *UGT1A1* = uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1; ULN = upper limit of normal.

B.2.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.2.4.1 Study populations

The analysis populations in the ASCENT trial are summarised in Figure 5.

Figure 5: Patient analysis groups in ASCENT (IMMU-132-05)(52)



BM-ve = brain metastasis negative (no brain metastases at baseline); ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

ASCENT had a 95% power to detect a statistically significant improvement in PFS, with a 2-sided type 1 error rate of 5%, if data were analyses after 315 PFS events by IRC assessment (primary efficacy endpoint).(37) The primary efficacy analysis was conducted in the primary analysis population, consisting of all patients without brain metastases at baseline (BM-ve).(55) In this population, the study had approximately 90% power to detect an improvement in OS (HR=0.7) assuming 72% of the expected number of deaths (238) had occurred at the time of the interim analysis.(37) At the time of final analysis (data cut-off 11 March 2020), 316 PFS events and 340 OS events had occurred in the primary analysis population.(37)

Table 7 summarises the endpoints assessed in the four analysis populations evaluated in the ASCENT study.

Table 7: Analysis populations in ASCENT (IMMU-132-05)(37, 55, 59)

Population	Endpoints assessed	SG, n (%)	TPC, n (%)	Total, n (%)
Patients randomised (ITT population)	All secondary efficacy endpoints	267	262	529
Brain metastasis negative at baseline (BM-ve population)	All primary and secondary efficacy endpoints	235 (88.0)	233 (88.9)	468 (88.5)
Received at least one dose of study drug (safety population)	Adverse events	258 (96.6)	224 (85.5)	482 (91.1)
HRQoL evaluable population	HRQoL	236 (88.4)	183 (69.8)	419 (79.2)

BM-ve = brain metastasis negative (no brain metastases at baseline); HRQoL = health-related quality of life; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Several pre-specified subgroup analyses were performed evaluating the primary efficacy endpoint of PFS, OS and ORR:

- Age group (<65 versus ≥65 years)
- Race (White, Black, Asian)
- Prior therapies (2-3, and >3)
- Region (North America, rest of world)
- Original diagnosis TNBC (yes, no)
- Prior breast cancer surgery (yes, no)
- Prior cancer radiotherapy
- *BRCA1* status (positive, negative)
- *BRCA1* and *BRCA2* status (positive, negative)
- Prior PD-L1/PD-1 use (yes, no)
- Trop-2 status (percentage of membrane cells with 2+ or 3+ <85% staining versus percentage of membrane cells with 2+ or 3+ staining ≥85%)
- Liver metastasis at baseline (yes, no)
- *UGT1A1* status (*1/*1, *1/*28, *28/*28, other)

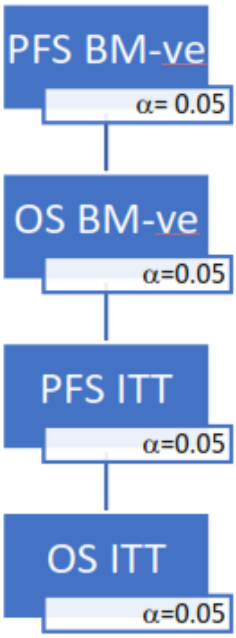
B.2.4.2 Statistical analysis

The primary efficacy endpoint was PFS by IRC assessment in the BM-ve population.(55) The null hypothesis (H0) was that there is no treatment difference in PFS hazard rates between the experimental arm and control arm or the PFS hazard rate is greater in the experimental arm.(58) The alternate hypothesis (HA) was that the PFS hazard rate in the experimental arm is lower than the PFS hazard rate in the control arm.(58)

To test the secondary endpoint of OS, the H0 was that there is no treatment difference in death rates between the experimental arm and control arm or the death rate is greater in the experimental arm.(58) The HA was that the death rate in the experimental arm is lower than the death rate in the control arm.(58)

In order to strongly control the type 1 error at 0.05, a hierarchical testing strategy was employed for testing the endpoints of IRC assessed PFS and OS,(55) where a given hypothesis was only declared statistically significant if all previous hypotheses in the hierarchy were also statistically significant (Figure 6).(37)

Figure 6: ASCENT statistical hierarchy (IMMU-132-05)(37)



BM-ve = brain metastasis negative (no brain metastases at baseline); ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival

Analysis comparing groups for the primary hypothesis was performed using a stratified log-rank test.(55) PFS was plotted over time using KM curves; median PFS and associated 95% CIs were determined by the Brookmeyer and Crowley method with log-log transformation.(55) OS, TTP, and DOR were analysed by the same method as PFS, while ORR and CBR were compared between groups using the Cochran-Mantel-Haenszel method with 2-sided CIs calculated by the Clopper-Pearson exact method.(37, 55)

A listing was generated for the ITT population reflecting group, date of randomisation, date of first dose, date of last dose, date and reasons of treatment and study discontinuation, survival follow-up status and information for each patient.(37) The following censoring rules for the primary analysis of PFS were applied:(37)

- Patients with no adequate response assessment after randomisation
    - Patients who died prior to second scheduled assessment were censored on the date of death
    - Patients who did not die or died after missing 2 or more scheduled assessments were censored at randomisation.
- Patients with continued scheduled response assessments until objective progressive disease or death
    - Patients who experienced progressive disease or death after missing 2 or more scheduled assessments were censored at date of last adequate response assessment before missed assessments.
    - Patients who died between scheduled assessments, or prior to missing 2 scheduled successive assessments were censored on the date of death
- Patients with continued scheduled response assessments without objective progressive disease or death
    - Patients who initiated other anti-cancer treatment were censored at date of last adequate response assessment with documented non-progression prior to starting other anti-cancer treatment.
    - Patients with no objective progressive disease or death were censored at date of last adequate response assessment.

Health-related quality of life (HRQoL) was assessed by the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30). Primary domains of interest were defined as including global health status/quality of life (QoL), physical functioning, role functioning, pain, and fatigue. These domains were selected as the primary domains of interest because they are:(59)

- More clinically relevant and important to the target population
- Used as the primary HRQoL domains of interest in other published studies(60-62)

All 15 domain scores range from 0 to 100. A higher score for global health status/QoL and functional domain represents a higher overall HRQoL or healthier level of functioning. A higher score for a symptom domain represents a higher level of symptomatology or problems.(59, 63)

HRQoL was assessed at baseline (i.e., ≤28 days of cycle 1 day 1 [C1D1]), day 1 of each cycle, and the final study visit (i.e., four weeks after the last dose of study drug or in the event of premature study termination).(59)

The following PRO/HRQoL endpoints were used to assess between-treatment differences in all the PRO/HRQoL domains in the HRQoL evaluable population:(59)

- Mean changes from baseline over the treatment phase (with a particular focus on the first five cycles of treatment [i.e., Day 1 of Cycles 2, 3, 4, 5, and 6] due to small sample size in the TPC arm thereafter)
    - Linear mixed-effect model for repeated measures (MMRM) was applied using on-treatment data for Cycle 2 to Cycle 6 (where n was ≥25 in both arms).
    - Analysis included random intercept and slope and the following covariates as fixed effects: treatment, visit (discrete), stratification factors (i.e., the number of prior treatments [2-3 vs. >3]; geographic location [North America vs. rest of the world]; and known brain metastasis [yes or no]), baseline score, baseline score-by-visit interaction, and treatment-by-visit interaction

- Proportion of subjects with a clinically meaningful HRQoL improvement or deterioration based on within-subject changes from baseline (with a particular focus on the first five cycles of treatment [i.e., Day 1 of Cycles 2, 3, 4, 5, and 6])
- Time to first HRQoL improvement/deterioration

Across all measures, the minimum important difference (MID) was defined as:

- Within-group change MID: the 10-point threshold(64)
- Between-group difference MID (i.e., non-inferiority margin): the lower threshold for small effect size of improvement or deterioration(65), as it is considered the most conservative set of thresholds among all published studies

B.2.5 Quality assessment of the relevant clinical effectiveness evidence

Table 8 summarises quality assessment results for ASCENT, covering appropriate randomisation, concealment of treatment allocation, study group similarity, imbalances in drop-outs between groups and reporting of outcome measures.

Table 8: Quality assessment results for ASCENT (IMMU-132-05)(37, 55)

Assessment	ASCENT (IMMU-132-05)	Risk of bias
Was randomisation carried out appropriately?	Yes, patients were randomised using IWRS. Randomisation was stratified by the number of prior treatments for advanced disease, geographic location, and known brain metastases at baseline.	Low
Was the concealment of treatment allocation adequate?	ASCENT was open label. Blinding of site personnel was not possible due to differences in treatment administration; however, potential bias was minimised by blinding the IRC, Sponsor's and contract research organisation's statisticians, and all medical monitors.	Low, as the blinded IRC assessed the primary PFS endpoint
Were the groups similar at the outset of the study in terms of prognostic factors?	There were no differences between the groups in demographics, stratification factors or disease characteristics at baseline.	Low
Were the care providers, participants and outcome assessors blind to treatment allocation?	No, ASCENT was open label, and only outcome assessors were blinded.	Low, as the blinded IRC assessed the primary PFS endpoint
Were there any unexpected imbalances in drop-outs between groups?	A larger percentage of patients in the TPC group compared with the SG group were randomised but not treated (14.5% and 3.4%,	High

Assessment	ASCENT (IMMU-132-05)	Risk of bias
	respectively). Communication with the study sites suggest that some patients in the TPC group elected not to participate in the study upon not being randomised to the SG group.	
Is there any evidence to suggest that the authors measured more outcomes than they reported?	None	Low
Did the analysis include an intent-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	All patients who were randomised, including 61 patients with brain metastasis at baseline were included in the ITT population. This population was used for efficacy analyses after the primary endpoint was tested in the primary analysis population.	Low, as the primary endpoint was also assessed in the ITT population with supportive results

BM-ve; brain metastasis negative (no brain metastases at baseline); IRC = independent review committee; ITT = intention-to-treat; IWRS = interactive web-based response system; SG = sacituzumab govitecan; TPC = treatment of physician's choice

B.2.6 Clinical effectiveness results of the relevant trials

B.2.6.1 Overview of efficacy results from the ASCENT phase III clinical trial

This section will primarily focus on results from the ITT analysis population as this population matches the decision problem and is used in the base case for the cost-effectiveness model. For completeness, results from the primary efficacy analysis in those without brain metastases are also presented below.

The clinical benefit of SG versus standard single-agent chemotherapy (TPC) was demonstrated in the results from ASCENT, confirming its potential as the new standard of care in pretreated locally advanced or mTNBC (Table 9).(37, 52, 55) In the primary analysis population, SG demonstrated a significant 59% reduction in the risk of progression or death over TPC (primary endpoint; (HR: 0.409; 95% CI: 0.323, 0.519; p<0.0001;), with a median PFS of 5.6 months for patients treated with SG compared with 1.7 months for those treated with TPC (HR: 0.409; 95% CI: 0.323 to 0.519; p<0.0001; further data for the primary analysis population are detailed below).(37, 55) The significant PFS benefit with SG versus TPC was supported by analyses in the ITT population, (median PFS: 4.8 versus 1.7 months; p<0.0001, Table 9).(55) OS in the ITT population was 11.8 months with SG treatment versus 6.9 months with TPC (HR: 0.51; 95% CI: 0.41, 0.62; p<0.0001).(37, 55)

Further, SG treatment demonstrated significant improvements versus TPC for objective response rate (ORR; 31% versus 4%; p<0.0001) and clinical benefit rate (CBR; 40% versus 8%; p<0.0001).(48, 55) The efficacy demonstrated by SG over TPC led to early halting of the study by unanimous recommendation of the Data Safety Monitoring Committee.(55)

Table 9: Summary of efficacy results for ASCENT in ITT population (IMMU-132-05)(37, 48, 55)

Endpoint		ITT population		Primary analysis population	
		SG	TPC	SG	TPC
PFS by IRC assessment	n	267	262	235	233
	Median, months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	5.6 (4.3, 6.3)	1.7 (1.5, 2.6)
	HR (95% CI); p-value	0.433 (0.347, 0.541); p<0.0001		0.409 (0.323, 0.519); p<0.0001	
OS	n	267	262	235	233
	Median, months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)	12.1 (10.7, 14.0)	6.7 (5.8, 7.7)
	HR (95% CI); p-value	0.508 (0.414, 0.624); p<0.0001		0.476 (0.383, 0.592); p<0.0001	
ORR (CR + PR) by IRC assessment	n	267	262	230	230
	% ORR (95% CI)	31.1 (25.6, 37.0)	4.2 (2.1, 7.4)	34.9 (28.8, 41.4)	4.7 (2.4, 8.3)
	OR (95% CI); p-value	10.994 (5.659, 21.358); p<0.0001		10.859 (5.590, 21.095); p<0.0001	
CBR (CR + PR + stable disease[a]) by IRC assessment	n	261	257	235	233
	% CBR (95% CI)	40.4 (34.5, 46.6)	8.0 (5.0, 12.0)	44.7 (38.2, 51.3)	8.6 (5.3, 12.9)
	OR (95% CI); p-value	8.067 (4.836, 13.456); p<0.0001		8.543 (5.055, 14.437); p<0.0001	
	n	83	11	82	11

Endpoint		ITT population		Primary analysis population	
		SG	TPC	SG	TPC
DOR (CR + PR) by IRC assessment	Median, months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, --)	6.3 (5.5, 9.0)	3.6 (2.8, --)
	HR (95% CI); p-value	0.390 (0.142, 1.066); p=0.0569		0.390 (0.142, 1.066); p=0.0569	
Time to response (CR + PR) by IRC assessment	n	83	11	82	11
	Median, months	1.54	1.45	1.54	1.45
Time to progression[b] by IRC assessment	n	[redacted]	[redacted]	[redacted]	[redacted]
	Median, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
	HR (95% CI); p-value	[redacted]		[redacted]	

[a] Stable disease for ≥6 months

[b] Time to progression was defined as the time from the date of randomisation to the date of the first evidence of disease progression

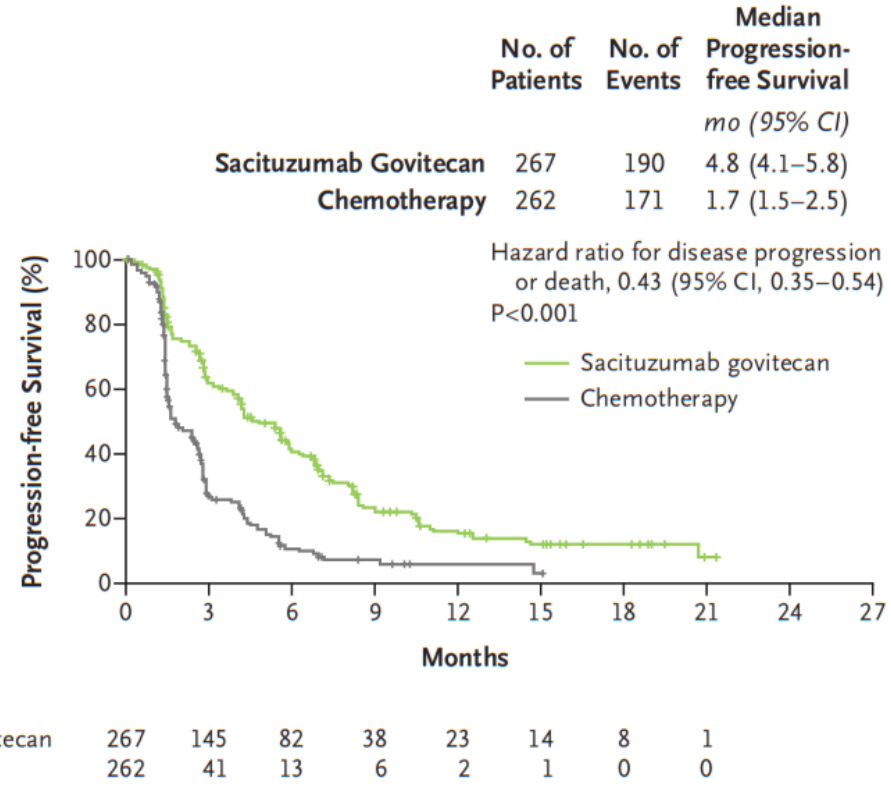
BM-ve = brain metastasis negative (no brain metastases at baseline); CBR = clinical benefit rate; CI = confidence interval; CR = complete response; DOR = duration of response; HR = hazard ratio; IRC = independent review committee; IRC = Independent Review Committee; ITT = intent-to-treat; OR = odds ratio; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; SG = sacituzumab govitecan; TPC = treatment of physician's choice

B.2.6.2 Progression-free survival by IRC assessment

ITT population

Analysis of PFS in the ITT population demonstrated that patients treated with SG had significantly longer median PFS versus TPC (4.8 versus 1.7 months) which was associated with a 57% reduction in the risk of disease progression or death compared with TPC (HR: 0.43; 95% CI: 0.35 to 0.54; p<0.001; Figure 7).(55) The proportion of patients alive and without progression was consistently higher in the SG versus TPC group at Months 3 (61.9% versus 27.1%), 6 (40.6% versus 10.7%), 9 (22.8% versus 7.2%) and 16.2 (17.2% versus 6.0%).(37)

Figure 7: Kaplan-Meier plot for PFS by IRC assessment (ASCENT; ITT population)(55)



CI = confidence interval; IRC = independent review committee; ITT = intent-to-treat; PFS = progression-free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Primary efficacy population

For the primary efficacy endpoint, patients in the primary analysis group treated with SG had significantly longer median PFS versus TPC (5.6 versus 1.7 months; p<0.0001) which was associated with a 59% reduction in the risk of disease progression or death (HR: 0.41; 95% CI: 0.32, 0.52).(55) The proportion of patients alive and without progression was consistently higher in the SG versus TPC group at Months 3 (64.6% versus 27.0%), 6 (44.2% versus 11.0%), 9 (24.6% versus 8.0%) and 12 (17.2% versus 6.7%).(37, 55)

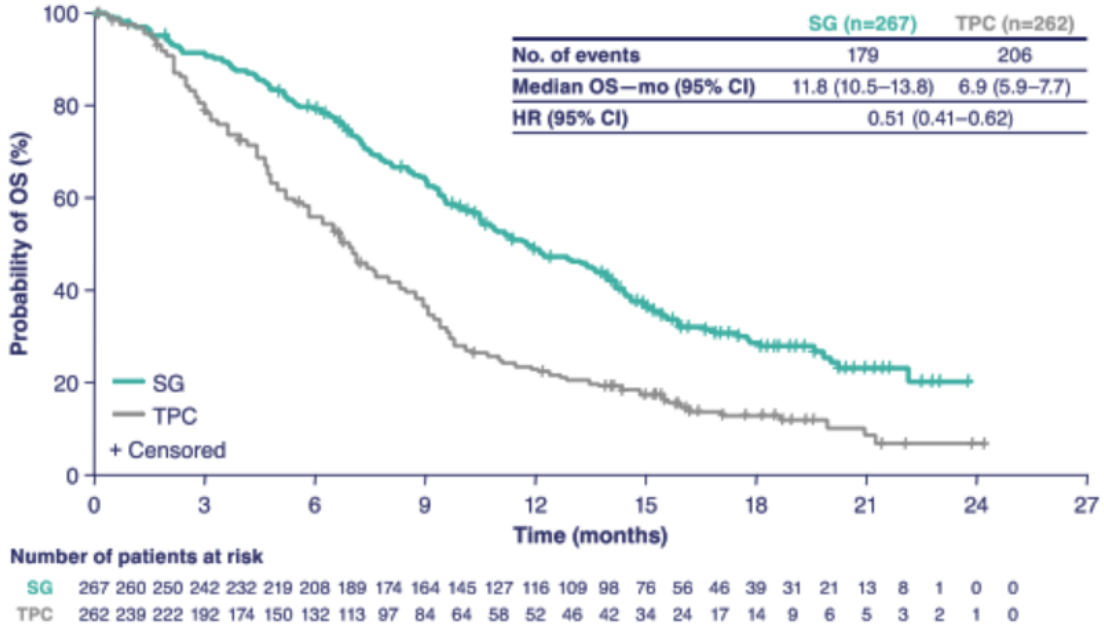
B.2.6.3 Overall Survival

ITT population

OS was significantly prolonged with SG compared with TPC treatment in the ITT population.(55) Among the patients evaluable for OS, 385 deaths occurred; 179 and 206 in the SG and TPC groups, respectively.(37)

The median OS was 11.8 months in the SG arm and 6.9 months in the TPC arm, which was associated with a 49% reduction in the risk of death and indicates an improved OS with SG (HR 0.51; 95% CI 0.41, 0.62; p<0.0001; Figure 8).(48, 55)

Figure 8: Kaplan-Meier plot for OS (ASCENT; ITT population)(55)



CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Primary analysis population

OS was also significantly prolonged with SG compared with TPC treatment in the primary analysis population.(37) Among the patients evaluable for OS, 340 deaths occurred in the primary analysis population (155 and 185 in the SG and TPC groups, respectively).(37)

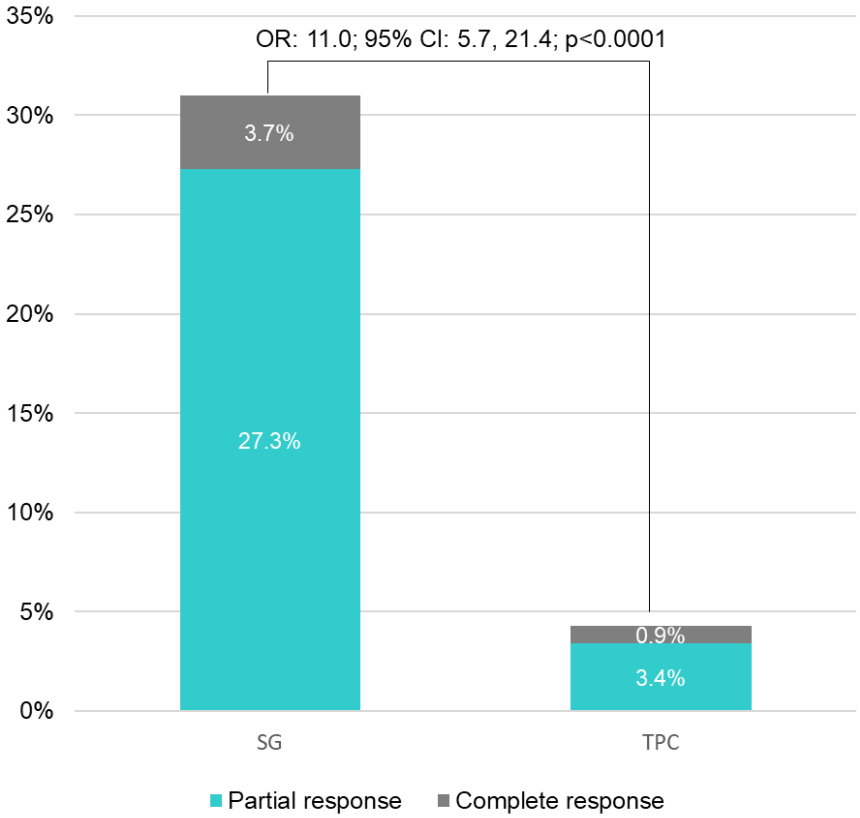
The median OS was nearly twice as long in the SG group versus TPC (12.1 versus 6.7 months; p<0.0001), which was associated with a 52% reduction in the risk of death (HR: 0.48; 95% CI: 0.38 to 0.59).(55)

B.2.6.4 Objective response rate by IRC assessment

The ORR, encompassing patients who achieved either a complete response (CR) or partial response (PR), in the ITT population was significantly higher in the SG group

than in the TPC group (31.1% versus 4.2%, respectively; OR: 10.99 [95% CI: 5.66, 21.36]; p<0.0001; Figure 9).(37, 55)

Figure 9: ORR by IRC assessment (ASCENT; ITT population)(37, 55)



CI = confidence interval; IRC = independent review committee; ITT = intent-to-treat; ORR = objective response rate; OR = odds ratio; SG = sacituzumab govitecan; TPC = treatment of physician's choice

[redacted]

Figure 10. Best percent change in size of the target lesion by IRC assessment (ASCENT; ITT population)(66)

IRC = independent review committee; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

B.2.6.5 Clinical benefit rate by IRC assessment

CBR (ORR + stable disease for ≥6 months) was significantly higher with SG treatment versus TPC (40.4% versus 8.0%; OR: 8.07 [95% CI: 4.84, 13.46]; p<0.0001).(48, 55)

B.2.6.6 Duration of response by IRC assessment

Among patients with a treatment response, the estimate of median DOR was longer with SG treatment versus TPC (6.3 versus 3.6 months; HR: 0.39 [95% CI: 0.14, 1.07]; p=0.057; Figure 11).(55, 66)

Figure 11: Kaplan-Meier plot for DOR by IRC assessment (ASCENT; ITT population)(66)

CI = confidence interval; DOR = duration of response; IRC = independent review committee; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

B.2.6.7 Time to onset of response by IRC assessment

For patients with a confirmed response, the median time to first response was similar between the SG and TPC groups (1.54 and 1.45 months, respectively) in the ITT population.(48)

B.2.6.8 Time to progression by IRC assessment

Time to progression was defined as the time from the date of randomisation to the date of the first evidence of disease progression.(37)

B.2.6.9 Health-related quality of life

HRQoL, functional status and severity of symptoms in both treatment arms were meaningfully worse at baseline than the general population in most EORTC QLQ-C30 domains, indicating substantial impairment in HRQoL, functioning, and symptoms at the study entry.(59)

In the analysis of observed changes from baseline, global health status/QoL was generally maintained over time, with a trend of slight improvement in the SG arm and slight worsening in the TPC arm, although neither arm reached the clinically meaningful change threshold. There was no statistically significant difference

between treatment arms across visits. At the final study visit (i.e., after the last dose or premature study termination), both arms had worsening in global health status/QoL, suggesting negative effect on HRQoL caused by disease progression or treatment toxicities. Similar results were observed in other primary domains, with generally maintained or slightly improved scores for patients treated with SG.(59)

MMRM LSM analysis found statistically significant ($p<0.05$) and clinically meaningful improvements from baseline in patients treated with SG versus TPC for all primary domains except role functioning (Table 10), where the improvement with SG was still statistically significant ($p<0.05$) but slightly below the clinically meaningful threshold (5.6 vs. 6.0).(59) Across the primary domains, the proportion of patients with meaningful improvement was consistently higher, and the proportion of patients with meaningful worsening was slightly lower, in the SG arm compared with the TPC arm.(59)

Across the secondary domains, SG demonstrated non-inferiority to TPC with the exception of nausea/vomiting and diarrhoea.(59) SG also showed statistically significantly and clinically meaningfully greater improvement in emotional functioning, dyspnoea, and insomnia versus TPC (Table 10).(59)

Table 10. MMRM LSM changes from baseline in EORTC QLQ-C30 scores (ITT population)

	SG Mean (95% CI)	TPC Mean (95% CI)	Difference in Means SG vs. TPC, Mean (95% CI)	Non-inferiority Margin
Primary domains				
Global health status/QoL	[redacted]	[redacted]	[redacted]	[redacted]
Physical functioning	[redacted]	[redacted]	[redacted]	[redacted]
Role functioning	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Pain	[redacted]	[redacted]	[redacted]	[redacted]

	SG Mean (95% CI)	TPC Mean (95% CI)	Difference in Means SG vs. TPC, Mean (95% CI)	Non-inferiority Margin
Secondary domains				
Emotional functioning	[redacted]	[redacted]	[redacted]	[redacted]
Cognitive functioning	[redacted]	[redacted]	[redacted]	[redacted]
Social functioning	[redacted]	[redacted]	[redacted]	[redacted]
Nausea/vomiting	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]
Appetite loss	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Financial difficulties	[redacted]	[redacted]	[redacted]	[redacted]

Statistically significant improvement in mean difference from baseline with SG are denoted in bold

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of life Questionnaire Core 30; ITT = intent-to-treat; LSM = least square mean; MMRM = mixed model for repeated measures; QoL = quality of life; SG = sacituzumab govitecan; TPC = treatment of physician's choice

The median time to improvement in the SG arm was significantly shorter than the TPC arm for physical functioning (72.1 days vs. not reached; HR: 1.66; p=0.001) and pain (7.4 vs. 10.1 days; HR: 1.41; p=0.01; Figure 12).(59) There were no significant differences between SG and TPC for median time to improvement in global health status, role functioning or fatigue.(59)

Figure 12. Time to first improvement in EORTC QLQ-C30 Pain score (ITT population)(59)

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of life Questionnaire Core 30; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

The median time to deterioration was substantially longer in patients treated with SG versus TPC across the domains of physical functioning (23.3 vs. 9.9 days; HR: 0.54; p<0.001), role functioning (11.4 vs. 6.7 days; HR: 0.60; p<0.001) fatigue (7.3 vs. 5.9 days; HR: 0.74; p=0.01) and pain (21.9 vs. 9.3 days; HR: 0.48; p<0.001; Figure 13).(59) There were no significant differences between SG and TPC for time to deterioration in global health status.(59)

Figure 13. Time to first deterioration in EORT QLQ-C30 domains (ITT population)(59)

CI = confidence interval; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer - Quality of life Questionnaire Core 30; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

B.2.7 Subgroup analysis

The improvements in PFS and OS with SG treatment versus TPC were consistent across key pre-planned subgroup analyses in the ITT population (Table 11). Several groups were affected by low patient numbers leading to wide confidence intervals, making statistical interpretation difficult.

Table 11: Summary of results from key prespecified subgroup analyses (ASCENT; ITT population)(37, 52, 55, 67)

Subgroup	SG vs. TPC		
	n	PFS by IRC assessment, HR (95% CI); p-value	OS, HR (95% CI); p-value
ITT population			
Age group <65 >65	[redacted]	[redacted]	[redacted]
Race White Black Asian	[redacted]	[redacted]	[redacted]
Prior systemic therapies[a] 2-3 >3	[redacted]	[redacted]	[redacted]
Brain metastases Yes No	[redacted]	[redacted]	[redacted]
Region North America Rest of World	[redacted]	[redacted]	[redacted]
Prior breast cancer surgery Yes No	[redacted]	[redacted]	[redacted]
Original diagnosis TNBC Yes No	[redacted]	[redacted]	[redacted]
Prior cancer radiotherapy Yes No	[redacted]	[redacted]	[redacted]

Subgroup	SG vs. TPC		
	n	PFS by IRC assessment, HR (95% CI); p-value	OS, HR (95% CI); p-value
BRCA1 status			
Positive			
Negative			
BRCA1 + *BRCA2* status			
Positive			
Negative			
Prior PD-L1/PD-1 use			
Yes			
No			
Trop-2 status:			
I2+I3 <85%			
I2+I3 ≥85%			
Liver metastases			
Yes			
No			

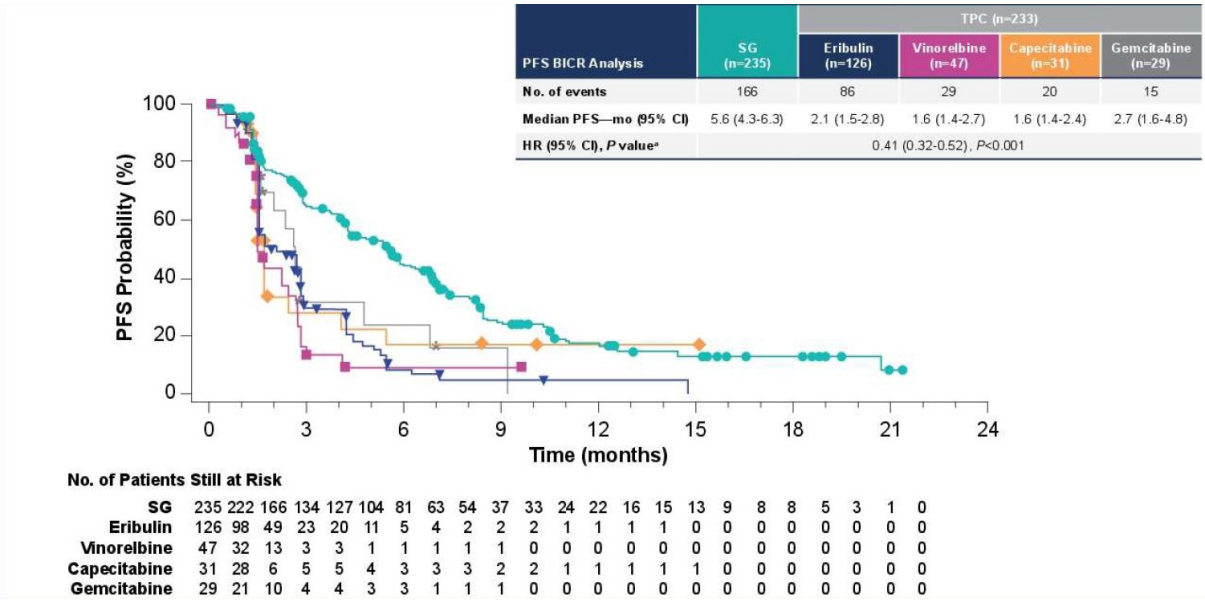
Values <1 favour SG treatment

[a] In metastatic or locally advanced setting

CI: confidence interval; HR: hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

Treatment benefits with SG were demonstrated regardless of the comparator treatment used in the TPC group, as demonstrated by a subgroup analysis in the primary analysis population whereby treatment with SG resulted in longer median PFS (Figure 14) and OS (Figure 15) versus eribulin, vinorelbine, capecitabine and gemcitabine.(68) These results also show that the survival benefits among the chemotherapy agents used in the TPC arm were similar and in line with expected outcomes in clinical practice for second-line therapy and beyond, as per clinical expert feedback. Therefore, no comparator treatment exhibited outstanding outcomes that may potentially bias the results in either direction, further supporting the use of a TPC arm comparator in the ASCENT trial.

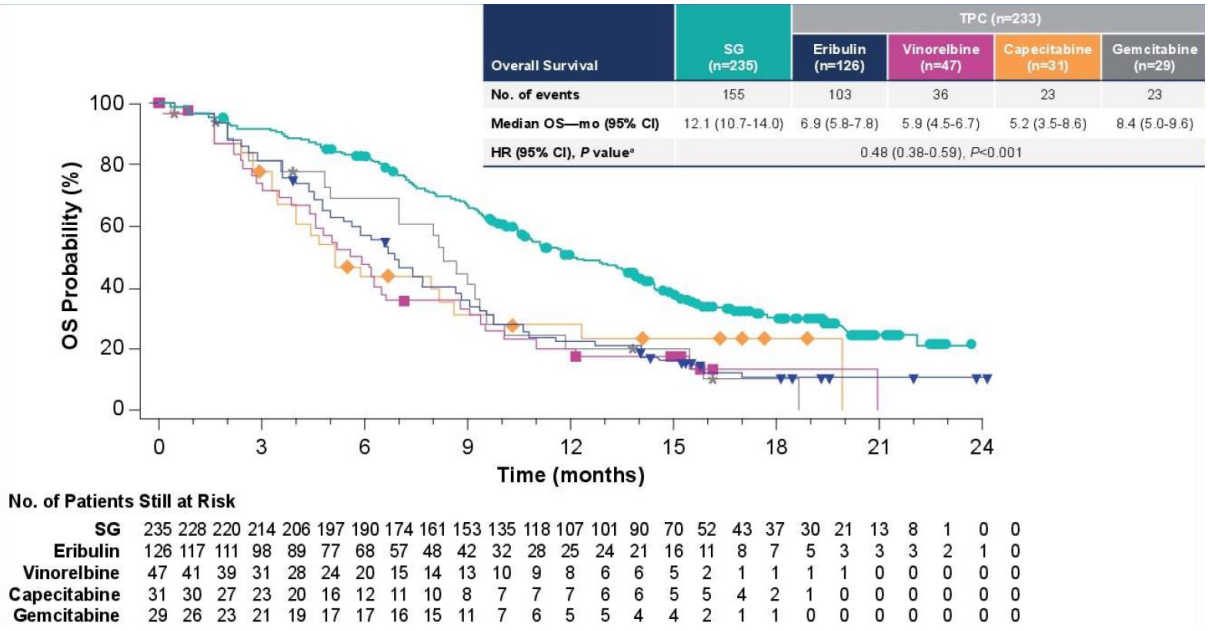
Figure 14. PFS by agent (ASCENT; primary analysis population)(68)



PFS was assessed by an IRC

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; SG = sacituzumab govitecan

Figure 15. OS by agent (ASCENT; primary analysis population)(68)



CI = confidence interval; HR = hazard ratio; OS = overall survival; SG = sacituzumab govitecan

SG also demonstrated prolonged PFS and OS in a subgroup of patients in the primary analysis population that had received one prior line of therapy in the metastatic setting and had progressed within <12 months of completing adjuvant or neoadjuvant therapy, i.e., patients on second-line mTNBC therapy (n=65; Table 12).(67) This demonstrates a clear survival benefit with SG treatment in the most

refractory second-line patients with mTNBC who would otherwise have an exceptionally poor prognosis. The OS and PFS benefit of SG in this subgroup was consistent with the overall treatment population.(67)

Table 12: OS and PFS in patients that had received one prior line of therapy in the metastatic setting and had progressed within <12 months of completing adjuvant or neoadjuvant therapy (ASCENT; primary analysis population)(67)

	SG	TPC
n	33	32
Median PFS[a], months (95% CI)	5.7 (2.6, 8.1)	1.5 (1.4, 2.6)
PFS HR (95% CI)	0.41 (0.22, 0.76)	
Median OS, months (95% CI)	10.9 (6.9, 19.5)	4.9 (3.1, 7.1)
OS HR (95% CI)	0.51 (0.28, 0.91)	

[a] PFS was assessed by an IRC

CI = confidence interval; HR = hazard ratio; IRC = Independent Review Committee; OS = overall survival; PFS = progression-free survival; SG = sacituzumab govitecan

B.2.8 Meta-analysis

Outcomes data from the ASCENT clinical trial were used in the economic model for this submission as indirect treatment comparisons (ITC) were not feasible for the population of interest. Following a systematic literature review that identified relevant clinical trials published from 2000 to January 2021, four trials met the inclusion criteria and were evaluated for NMA feasibility. However, there was heterogeneity in the distribution of chemotherapies used in the TPC arms of each trial and the TPC arms in each trial would be expected to perform differently based on the distribution of chemotherapies. Therefore, an NMA was not feasible as the TPC arms could not be combined into a single node to connect to the network.

In the absence of an NMA, alternate statistical approaches for indirect treatment comparisons including population-adjusted indirect comparison (PAIC) were considered. However, PAIC approaches were not considered feasible as patients with pretreated mTNBC were only reported as a subgroup across all the comparator trials and baselines characteristics were not reported for these subgroups.

B.2.9 Adverse reactions

B.2.9.1 Treatment-emergent adverse events (TEAEs) overall

AE information was collected at each study visit and at the final study visit (4 weeks after the last dose of study drug or in the event of early study termination).(37) Median treatment duration was substantially longer in the SG group (4.4 months) versus TPC (1.0 to 1.6 months).(55) In the safety population in the TPC group, 122 patients received eribulin, 22 capecitabine, 31 gemcitabine and 43 vinorelbine.(37)

In ASCENT, SG had a consistent and manageable safety profile in the treated population.(52) Most patients treated with SG or TPC had at least one TEAE after the start of treatment (99.6% and 97.8%, respectively; Table 13).(37) Higher rates of Grade ≥3 TEAEs were observed in patients treated with SG compared with TPC (71.4% versus 63.8%, respectively).(37, 55)

Treatment-related TEAEs were more common in the SG group versus TPC (97.7% versus 85.7%).(37, 55) The most common treatment related TEAEs in the SG and TPC groups were nausea (57.0% and 26.3%, respectively), fatigue (44.6% and 30.4%, respectively), diarrhoea (59.3% and 12.1%, respectively) and neutropenia (41.9% and 25.0%, respectively).(37, 55) The percentage of patients who discontinued treatment because of at least one TEAE was low for SG and TPC (4.7% and 5.4%, respectively).(37, 55)

No cases of severe cardiovascular toxicity, Grade >3 neuropathy or Grade >3 interstitial lung disease were reported.(52, 55) No treatment-related deaths were seen in the SG group, while 1 treatment-related death (neutropenic sepsis) was noted in the TPC group.(55)

Table 13: Summary of TEAEs (ASCENT; safety population)(37, 55)

	SG (n=258)	TPC (n=224)
Any TEAE, n (%)	257 (99.6)	219 (97.8)
Treatment-related TEAE, n (%)	252 (97.7)	192 (85.7)
Serious TEAE, n (%)	69 (26.7)	63 (28.1)
TEAEs leading to dose reduction, n (%)5)	56 (21.7)	59 (26.3)

TEAEs leading to drug interruption, n (%)	162 (62.8)	87 (38.8)
TEAEs leading to drug discontinuation, n (%)	12 (4.7)	12 (5.4)
Grade 3 TEAE, n (%)	132 (51.2)	100 (44.6)
Grade 4 TEAE, n (%)	52 (20.2)	43 (19.2)
TEAEs leading to death, n (%)	1 (0.4)	3 (1.3)

SG = sacituzumab govitecan; TEAE treatment-emergent adverse event; TPC = treatment of physician's choice

B.2.9.2 TEAEs by preferred term

The most frequently reported TEAEs (≥30%) for the SG group were diarrhoea (65%), nausea (62%), fatigue (52%), alopecia (47%), neutropenia (43%), anaemia (39%), constipation (37%), and vomiting (33%, Table 14).(37) The most frequently reported TEAEs (≥30%) for the TPC group were fatigue (40%) and nausea (30%).(37) The three most common grade 3 or 4 adverse events reported in patients treated with SG or TPC were neutropenia (35% and 20%, respectively) and neutrophil count decreased (21% and 15%, respectively).(37)

Table 14: TEAEs by preferred term (ASCENT; safety population)(37, 48)

TEAE	SG (n=258)			TPC (n=224)		
	All grades (≥10%)	Grade 3	Grade 4	All grades (≥10%)	Grade 3	Grade 4
Any TEAE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Alopecia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutropenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Constipation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Decreased appetite	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neutrophil count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cough	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dyspnoea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Back pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypokalaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asthenia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pyrexia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Urinary tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
WBC count decreased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Arthralgia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypomagnesaemia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rash	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

TEAE	SG (n=258)			TPC (n=224)		
	All grades (≥10%)	Grade 3	Grade 4	All grades (≥10%)	Grade 3	Grade 4
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AST increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALT increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pruritus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Stomatitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Oedema peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Neuropathy peripheral	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All data given as n (%).

ALT = alanine aminotransferase; AST = aspartate aminotransferase; SG = sacituzumab govitecan; TEAE treatment-emergent adverse event; TPC = treatment of physician's choice; WBC = white blood cell

B.2.9.3 TEAEs of special interest

B.2.9.3.1 Diarrhoea, nausea and vomiting

Diarrhoea (65.1% versus 17.0%), nausea (62.4% versus 30.4%) and vomiting (33.3% versus 16.1%) occurred in a higher percentage of patients in the SG group than in the TPC group.(37) The majority of these events in both the SG and TPC groups were grade 1 or 2 and were considered nonserious.(37) Diarrhoea led to a dose reduction for 4.7% of the SG group and 0.4% of the TPC group. Nausea and vomiting led to dose reductions in 1.9% and 0.4% of the SG group, respectively, and no dose reductions in the TPC group.(37) Treatment interruptions due to diarrhoea (5.4% SG group versus 0.4% TPC group), nausea (1.9% SG group only) and vomiting (1.2% SG group only) were low, and no patients discontinued treatment because of nausea or vomiting, with only 1 patient in the SG group discontinuing due to diarrhoea.(37)

B.2.9.3.2 Neutropenia, febrile neutropenia, thrombocytopenia, and anaemia

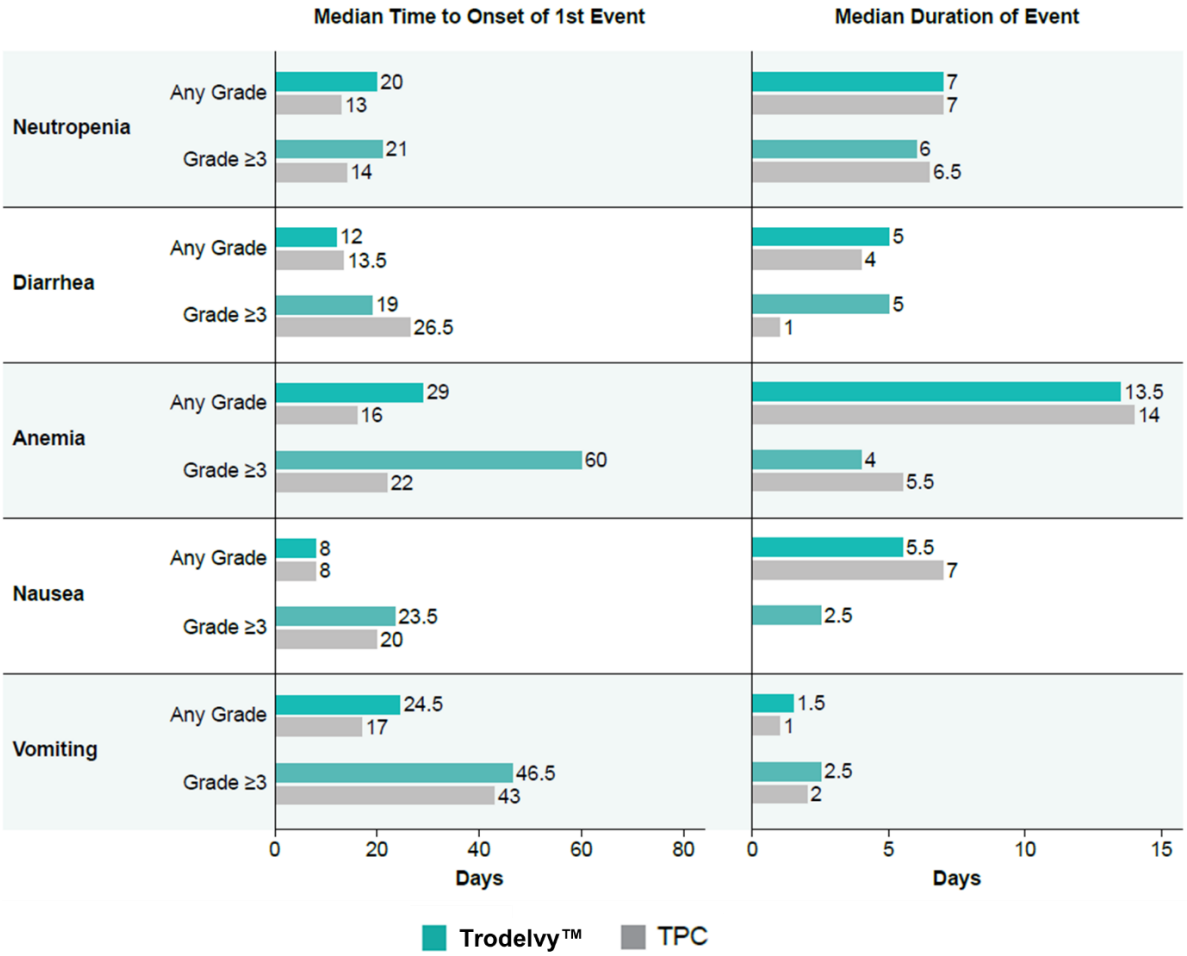
[redacted]. During the study, neutropenia was managed by dose reduction and/or dose delay, and with growth-factor support after Day 1 of Cycle 1.(55) [redacted]. Concomitant growth-factor support was given to 49% of the patients treated with SG and 23% of those with TPC.(55) [redacted].

[redacted]

[redacted]

In general, the median time to onset of first event for Grade ≥3 treatment-related AEs was longer for patients in the SG group than in the TPC group (Figure 16).(69)

Figure 16: Time to onset and duration of selected Grade ≥3 treatment-related AEs (ASCENT; safety population)(69)



TPC = treatment of physician's choice

B.2.10 Ongoing studies

NCT04319198 is an ongoing, phase III rollover study which aims to evaluate the long-term safety of SG in patients with metastatic solid tumours who are benefiting from ongoing SG treatment in another company-sponsored study (including ASCENT).(70) The primary completion date for this rollover study is estimated for April 2024.(70)

B.2.11 Innovation

Targeted treatment for TNBC is challenging due to a lack of hormone and HER2 receptor expression.(24) Therefore, in contrast with HR+ and HER2+ disease, patients with TNBC do not benefit from effective targeted breast cancer treatments such as endocrine therapy or anti-HER2 therapy and generally rely on cytotoxic chemotherapy.(16) This contributes to the poor prognosis of TNBC, which has faster progression through lines of therapy and lower survival rates than other breast cancer types.(30-32)

The already poor outcomes associated with TNBC worsen as patients' disease progresses to mTNBC and through lines of therapy, highlighting the importance of early and effective treatment options.(32) As such, combinations of five to six effective chemotherapy regimens, including taxanes, carboplatin, anthracyclines and capecitabine, are widely used in the neoadjuvant and adjuvant setting to improve prognosis in early TNBC.(45) However, this leaves limited treatment options for patients following progression to mTNBC, which is of concern as these patients already have fewer and less effective treatment options compared with patients with HR+ and HER2+ breast cancers.

The checkpoint inhibitor, atezolizumab has recently been recommended for use in combination with nab-paclitaxel in previously untreated mTNBC with tumours expressing PD-L1.(42) However, only 40% to 50% of patients with TNBC express this biomarker, and this combination is restricted to first-line use due to low response rates in later lines of mTNBC treatment.(41-43) Therefore, for most patients with mTNBC, the principal systemic treatment option, particularly for second- and third-line therapy, remains cytotoxic chemotherapy.(40-42, 44)

SG is an innovative first-in-class humanised antibody-drug conjugate and the only targeted treatment option to potentially be available for patients with previously treated mTNBC, representing a landscape change for this subpopulation.(1, 42) Sacituzumab is a humanised monoclonal antibody that binds to the novel target, Trop-2, allowing for the concentrated delivery of the topoisomerase inhibitor, SN-38, directly to tumour cells.(1) Therefore, as well as offering a much needed additional therapy option for patients with previously treated mTNBC, SG also offers a novel mechanism of action that is not restricted by biomarker expression.(1) Most significantly, SG offers substantially improved efficacy, including improvement in quality of life and overall survival of approximately 5 months and a reduction in the risk of death of 49%, which represents a step change from current disease management with cytotoxic chemotherapies and a significantly prolonged life for patients.(37, 55, 59)

B.2.12 Interpretation of clinical effectiveness and safety evidence

ASCENT was the first phase III study of an antibody-drug conjugate in patients with pretreated[1] locally advanced or mTNBC.(55) The clinical benefit of SG versus single-agent treatment with eribulin, capecitabine, vinorelbine or gemcitabine (TPC) was demonstrated in the results from ASCENT, confirming its potential as the new standard of care in pretreated locally advanced or mTNBC.(37, 55) SG demonstrated a significant 57% reduction in the risk of progression or death over single-agent chemotherapy, with a median PFS of 4.8 months for patients treated with SG compared with 1.7 months for those treated with TPC ($p<0.0001$).(37, 55) OS was 11.8 months with SG treatment versus 6.9 months with TPC (HR: 0.51; 95% CI: 0.41, 0.62; $p<0.0001$).(37, 55) Improvements in PFS and OS with SG were irrespective of the comparator chemotherapy used.(68) In addition, comparator chemotherapies performed similarly to each other, with no individual agent showing unexpected outcomes that could bias the analysis.(68) UK clinical expert feedback supports that the TPC arm is a pragmatic and appropriate comparator, consisting mostly of therapies that are commonly used in the UK and demonstrating outcomes

[1] Patients were refractory or had relapsed after receiving ≥2 prior standard-of-care chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease

that would be expected in clinical practice. Improvements in PFS and OS consistent with the ITT population were also demonstrated in early-relapsing patients on second-line treatment for mTNBC, indicating that SG shows compelling efficacy in this particularly refractory subpopulation.(66-68) Taken together, these data represent a large step forwards for patients with mTNBC, who have an extremely poor prognosis compared with other breast cancer types and require early and effective treatment due to their rapid progression through lines of therapy.(30-32) Further, SG treatment demonstrated significant improvements versus TPC for objective response rate (ORR; 31% versus 4%; $p<0.0001$), offering patients a much greater chance of tumour shrinkage than they would otherwise have had with available chemotherapies, leading to relief of symptoms such as insomnia, dyspnoea and pain, as demonstrated by the HRQoL analysis.(48, 55, 59)

Improving quality of life for patients with mTNBC is a high priority as the disease substantially impairs HRQoL and physical functioning due to a debilitating impact of symptoms and tumour burden.(59) Treatment with SG leads to statistically significant and/or clinically meaningful benefits across all primary domains of the EORTC QLQ-C30 compared with TPC, fulfilling a great unmet need in this patient population.(59) SG also prolonged time to deterioration in most HRQoL domains, including pain and fatigue, and significantly shortened time to improvement in physical functioning and pain.(59) Therefore, not only does SG provide progression-free and overall survival benefits, treatment also improves both HRQoL of patients versus the current standard of care and the duration that patients experience a reduced symptom burden.

Treatment-related TEAEs were more common in the SG group versus TPC (97.7% versus 85.7%), which should be placed in the context that median treatment duration was substantially longer in the SG group (4.4 months) versus TPC (1.0 to 1.6 months).(37, 55) However, the percentage of patients who discontinued treatment because of at least one TEAE was low for SG and TPC (4.7% and 5.4%, respectively), which is suggestive of a manageable safety profile and patient-experienced benefits exceeding patient-experienced harms.(37, 55)

Overall, the ASCENT study demonstrates how the introduction of SG in pretreated mTNBC can significantly and meaningfully improve the very poor prognosis, response rates and HRQoL for this group of patients compared with the limited range of single-agent chemotherapy options currently available.

B.2.13 End-of-life criteria

Table 15: End-of-life criteria

Criterion	Data available	Reference in submission (section and page number)
The treatment is indicated for patients with a short life expectancy, normally less than 24 months	Data from the French ESME registry of MBC patients between 2008 to 2016 showed the median OS for patients with mTNBC (n=2,963) was 15 months from diagnosis of metastatic disease.(27) Among 135 patients with mTNBC from a German retrospective chart review (2012 to 2015), OS in patients on first-line therapy was 13 months compared with 7 months at second- and third-line therapy.(30) OS has also been assessed in a pooled analysis from two phase III clinical trials, EMBRACE and Study 301, in patients with locally advanced or mTNBC who had received 0 to ≥2 treatments for advanced disease (88% of pooled population had received ≥1 prior treatment for advanced disease).(35) The median OS was 13 months with eribulin and 8 months with capecitabine or (TPC).(35) In the phase III ASCENT trial ITT population, median OS in patients treated with TPC (including eribulin, capecitabine, gemcitabine and vinorelbine) was 7 months.(37, 56) In the base-case of the cost-effectiveness analysis the mean OS with TPC treatment was 10.5 months (median 6.7 months)	Section B1.3.3, Page 12 Section B.2.6.3, Page 45
There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared with current NHS treatment	In the phase 3 ASCENT trial, the median OS with SG treatment was 4.9 months longer than single-agent chemotherapy in the ITT population (11.8 months vs 6.9 months, respectively; HR 0.51; 95% CI 0.41, 0.62; p<0.0001).(37, 55) In the base-case of the cost-effectiveness analysis SG improved mean OS by a mean of 6.9 months compared with TPC (median 5.1 months)	Section B.2.6.3, Page 45

ESME = Epidemiological Strategy and Medical Economics; ITT = intention to treat; MBC = metastatic breast cancer; mTNBC = metastatic triple-negative breast cancer; NHA = National Health Service; OS = overall survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice;

B.3 Cost effectiveness

B.3.1 Published cost-effectiveness studies

A systematic search of cost-effectiveness studies associated with locally advanced TNBC or mTNBC was conducted to identify cost effectiveness analyses relevant to the decision problem. Details of the methods used to identify and select the relevant studies are described in Appendix G. A total of 12 studies were identified, including 3 studies relevant to the UK perspective; these studies are summarized in Table 16.

The NICE technology appraisals of eribulin (TA423(71) and TA515(72)) were not captured by the systematic search as they were not conducted specifically for locally advanced or mTNBC patients. However, the modelling approach used in these appraisals also informed the approach for the SG analysis (Table 17).

Table 16: Summary of published UK cost-effectiveness studies in locally advanced TNBC or mTNBC

Study	Year	Patient population	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Atezolizumab						
NICE TA639 (18)	2020	PD-L1-positive 1L locally advanced TNBC or mTNBC	Cost-effectiveness analysis using a partitioned survival model Study objective: To evaluate cost-effectiveness of atezolizumab + nab-paclitaxel vs weekly paclitaxel or docetaxel for patients with untreated locally advanced TNBC or mTNBC (PD-L1 positive) Horizon: 15 years Discount rate: 3.5% Currency/year (perspective): GBP/NR (healthcare system [NHS])	Atezolizumab + nab-paclitaxel vs paclitaxel ▪ QALY gain: NR ▪ LY gain: 1.05 Atezolizumab + nab-paclitaxel vs docetaxel ▪ QALY gain: NR ▪ LY gain: 0.97	Atezolizumab + nab-paclitaxel ▪ Total cost: NR Paclitaxel ▪ Total cost: £16,489 Docetaxel ▪ Total cost: £10,818	Atezolizumab + nab-paclitaxel vs weekly paclitaxel ▪ Using list price: NR ▪ Using PAS price: £51,145 Atezolizumab + nab-paclitaxel vs weekly docetaxel ▪ Using list price: NR ▪ Using PAS price: £63,859
SMC2267 (73)	2020	PD-L1-positive 1L locally advanced TNBC or mTNBC	Cost-effectiveness analysis using a partitioned survival model Study objective: To evaluate cost-effectiveness of atezolizumab + nab-paclitaxel vs weekly paclitaxel for patients with untreated unresectable	Atezolizumab + nab-paclitaxel vs paclitaxel ▪ QALY gain: NR ▪ LY gain using PAIC for weekly paclitaxel: 1.070 ▪ LY gain using nab-paclitaxel as proxy for weekly paclitaxel: 0.636	NR	Atezolizumab + nab-paclitaxel vs weekly paclitaxel ▪ Using PAIC for weekly paclitaxel and PAS price: £28,187 ▪ Using nab-paclitaxel as proxy for weekly paclitaxel and PAS price: £34,132

Study	Year	Patient population	Summary of model	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
			locally advanced TNBC or mTNBC (PD-L1 positive) Horizon: 15 years Discount rate: NR Currency/year (perspective): GBP/NR (NR)			
Eribulin						
Wex et al. (74)	2018	2L+ locally advanced TNBC or mTNBC	Cost-effectiveness analysis using a partitioned survival model Study objective: To determine the cost-effectiveness of eribulin vs capecitabine or TPC in patients with locally advanced TNBC or mTNBC Horizon: Lifetime Discount rate: 3.5% Currency/year (perspective): GBP/2017 (NR)	Eribulin vs capecitabine or TPC ▪ LY gain: 0.3 ▪ QALY gain: 0.2	Eribulin vs capecitabine or TPC ▪ Incremental cost: NR	Eribulin vs capecitabine or TPC ▪ <£50,000

1L = first line; 2L+ = second line or later; GBP = British pound sterling; ICER = incremental cost effectiveness ratio; LY = life-year; mTNBC = metastatic triple-negative breast cancer; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; NR = not reported; PAIC = population-adjusted indirect comparison; PAS = patient access scheme; PD-L1 = Programmed death-ligand 1; QALY = quality-adjusted life-year; SMC = Scottish Medicines Consortium; TPC = treatment of physician's choice; UK = United Kingdom

B.3.2 Economic analysis

No published cost effectiveness studies directly relevant to the SG technology appraisal were identified. A *de novo* cost-effectiveness model was developed to assess the incremental cost-effectiveness of SG versus relevant comparators and inform decision making.

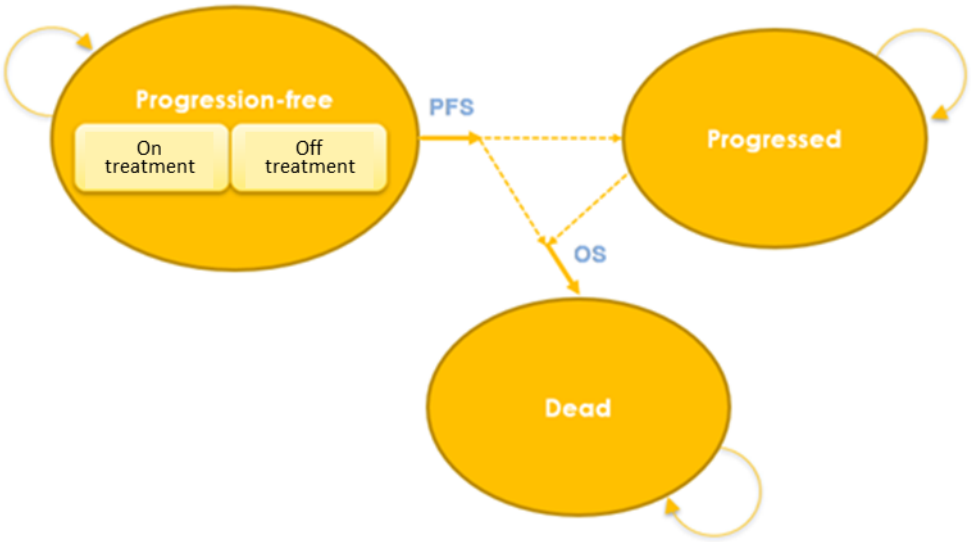
B.3.2.1 Patient population

The modelled population in the economic evaluation reflects that of the ITT population in the phase III ASCENT trial.(37, 55) Inclusion and exclusion criteria for ASCENT are described in Section B.2.3.

B.3.2.2 Model structure

A three-health state partitioned survival model was developed to follow patients over time from the beginning of treatment until death.(75) Figure 17 illustrates the three health states used to model patients' survival outcomes over the time horizon: progression free (PF), progressed disease (PD), and death. Patients who are eligible for treatment enter the model, initiate treatment, and experience an interval of PFS. Patients who are alive but whose disease has progressed continue to the PD health state and may receive subsequent treatments. Patients may die at any time point in the model.

Figure 17: Model diagram



A partitioned survival approach does not directly calculate transitions between health states, but rather partitions the modelled population into groups. Patients' progression and death were tracked using treatment specific and independent PFS and OS curves. The method postulates that at any time point the proportion of patients falling under the PFS curve is in the PF health state, the proportion of patients falling above the OS curve is in the Dead health state, and whoever remains must be in the PD health state.

Time on treatment is modelled independently from PFS, allowing patients to discontinue treatment despite not having progressed. Treatment-related costs (including drug acquisition, administration, concomitant medications, and AE costs) are accrued based on the time on treatment, assuming that patients receive treatment up until discontinuation in line with the expected use of SG in clinical practice. Following treatment discontinuation, a proportion of eligible patients can switch to an active anti-cancer subsequent treatment, modelled as a basket of treatments defined by a weighted distribution. These costs are accrued, however, no additional adjustment on survival is required as any survival benefit attributable to subsequent treatment is implicitly captured in the OS data.

Additionally, in line with standard practice for developing partitioned survival models in oncology, the following constraints are applied in the model to ensure logical patient flow at each cycle:

- The risk of death in the modelled population cannot be lower than the all-cause mortality of the general population at each model cycle, determined by published life tables.(76) This ensures that at any given cycle, the mortality risk of the modelled population is equal to or greater than that of the general population (matched on age and gender).
- PFS is constrained by OS, such that the number of patients who are PF cannot exceed the total number of patients alive.

Costs were assigned to each health state, and utilities were applied according to patients' disease progression status and type of treatment received. As the model progresses cycle by cycle for the duration of the time horizon, cost and utility data were summed per treatment arm, allowing for the calculation of differences in accumulated costs and effectiveness between comparators at model completion.

The model aggregates the health outcomes and costs from each health state and reports the following outcomes:

- Total life years (LY), incremental LYs
- Total quality-adjusted LYs (QALY), incremental QALYs
- Total costs, including drug acquisition and administration costs, subsequent treatment costs, disease management and monitoring costs, AE management costs, and incremental costs
- Incremental cost-effectiveness ratios (ICER): cost per incremental LYs gained, costs per incremental QALYs gained

B.3.2.2.1 Model features

The base case analysis was conducted from the perspective of the UK NHS and Personal Social Services, considering only direct medical costs.

A 10-year time horizon was used in the base case and could be considered a lifetime horizon. This time horizon was deemed to be appropriate to capture the long-term clinical and economic impacts of mTNBC on the targeted population with median age of 54 years, given their poor prognosis. A prior appraisal (TA423 eribulin in 3L+ MBC treatment) used 5 years as the time horizon(72), while TA639 (atezolizumab + nab-paclitaxel in 1L mTNBC), which is for an earlier line of treatment, used a 15-year time horizon.(18) Alternative (five-year and 15-year) time horizons are tested in sensitivity analyses.

A one-week model cycle was implemented to accommodate the various cycle length of treatment comparators considered and is short enough to accurately capture differences in cost or health effects between cycles. Half-cycle correction was

considered in the model allowing for a better approximation of the area under the curve. For each cycle, instead of using the output calculated for a specific cycle, the average of the output at the current and previous cycles was taken.

Costs and health-related outcomes were discounted by 3.5% annually.

B.3.2.2.2 Justification of the chosen structure

The strengths of the partitioned survival approach are well-documented (NICE Decision Support Unit [DSU] Technical Support Document [TSD]19).(75) This approach is flexible, and is able to adequately quantify the primary objectives of treating patients with mTNBC, particularly as it is not necessary to model multiple lines of subsequent therapy given the limited treatment options for patients in this setting and it directly uses trial-based time-to-event endpoints (OS, PFS, TTD]). The partitioned survival model structure is a widely accepted approach that has been used in previous NICE health technology assessments in breast cancer.(18, 71, 72)

Moreover, the survival data from ASCENT trial are mature, and therefore subject to less uncertainty than in other cases where the models rely heavily on extrapolations post-trial period.

A modeling advisory board meeting was held on April 28, 2021 with external health economic experts and clinician oncologists with expertise in TNBC. The experts were consulted and made recommendations on the model structure, functionality, underlying assumptions, data sources, and inputs (treatment-related AEs, health utilities).

The selected approach is also consistent with previous NICE technology appraisals for atezolizumab in a broader unresectable locally advanced or mTNBC indication and for eribulin in 2L+ locally advanced or metastatic BC were considered, where relevant, to inform the approach taken in the cost-effectiveness analysis for SG. A comparison is presented in Table 17.

Table 17: Comparison of current and previous NICE appraisals relevant to TNBC

Factor	Previous appraisals			Current appraisal	
	TA639 (atezolizumab + nab-paclitaxel)(18)	TA423 (eribulin)(71)	TA515 (eribulin)(72)	Chosen values	Justification
Model approach/ structure	Three-state PartSA	Three-state PartSA	Three-state PartSA	Three-state PartSA	Flexible, directly uses trial-based time-to-event endpoints, and consistent with previous appraisals
Patient population	Adults with unresectable locally advanced or mTNBC whose tumors have PD-L-1 expression ≥1% and who have not received prior chemotherapy for metastatic disease	Adults with locally advanced or metastatic BC that has progressed after 1 chemotherapy regimen	Adults with locally advanced or metastatic BC that has progressed after 2 or more chemotherapy regimens	Adults with either locally advanced or mTNBC who were either refractory or had relapsed after at least 2 prior standard-of-care chemotherapy regimens	Population reflects that of the phase III ASCENT trial, which may not fully capture a broad 2L indication, but is aligned with the best evidence of the efficacy of SG
Comparators	• Paclitaxel • Docetaxel • Anthracycline-based chemotherapy (relevant but not included in the CEA due to lack of evidence)	TPC (vinorelbine, gemcitabine, paclitaxel, doxorubicin, docetaxel)	• Capecitabine • Vinorelbine (in sensitivity analysis)	TPC (including eribulin, vinorelbine, gemcitabine, and capecitabine)	Consistent with NICE treatment pathway for managing mTNBC, which recommends vinorelbine, capecitabine and eribulin for 2L and 3L treatment(42) Gemcitabine was used in a small proportion of patients in the TPC arm (15%) and subgroup analysis showed similar survival benefits as the other three agents in the TPC arm

Factor	Previous appraisals			Current appraisal	
	TA639 (atezolizumab + nab-paclitaxel)(18)	TA423 (eribulin)(71)	TA515 (eribulin)(72)	Chosen values	Justification
Time horizon	15 years	5 years	5 years	10 years	Deemed appropriate to capture the long-term clinical and economic impacts of mTNBC on the targeted population with median age of 54 years, given later line of therapy and the poor prognosis of patients in 2L and 3L of therapy. Alternative (five-year and 15-year) time horizons are tested in scenario analyses.
Cycle length	One week	One month	One month	One week	Accommodates the various cycle length of comparators and is short enough to accurately capture differences in cost or health effects between cycles
Half-cycle correction	Applied	Not applied	Not applied	Applied	Allows for a better approximation of the area under the curve (i.e., helps avoid over- or underestimating it)

Factor	Previous appraisals			Current appraisal	
	TA639 (atezolizumab + nab-paclitaxel)(18)	TA423 (eribulin)(71)	TA515 (eribulin)(72)	Chosen values	Justification
Source of clinical efficacy data	Trial data and NMA (NMA results not recommended by ERG)	Within-trial comparison only, no ITCs used PFS data were mature and therefore no extrapolation was applied.	Within-trial comparison only, no ITCs used	Within-trial comparison only, no ITCs possible	A feasibility assessment determined it is not feasible to conduct a clinically and methodologically valid ITC/NMA (Section B.2.8)
Source of utilities	EQ-5D-5L mapped to EQ-5D-3L from IMpassion130 trial; literature	EORTC-QLQ C30 in the Study 301 trial mapped to EQ-5D-3L via published algorithm(77) Note: ERG considered it inappropriate as it was based on trial results from untreated locally advanced BC with good baseline health status	Same utility mapping algorithm and same ERG comments received as in submission TA423 (3L)	EORTC-QLQ C30 in the ASCENT trial mapped to EQ-5D-3L via published algorithm (Longworth)(78)	Allows utility calculation from the same population from which efficacy data were derived; aligned with NICE DSU TSD 10(79)
Source of costs	NHS reference costs; PSSRU; BNF/eMIMS; literature; expert opinion	NHS reference costs; PSSRU; BNF/eMIMS; literature; expert opinion	NHS reference costs; PSSRU; BNF/eMIMS; literature; expert opinion	NHS reference costs; PSSRU; BNF/eMIT/MIMS; literature; expert opinion	Sources were verified as reasonable and appropriate by UK clinicians

3L = third line; BC = breast cancer; BNF = British National Formulary; CEA = cost-effectiveness analysis; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ERG = evidence review group; ITC = indirect treatment comparison; MIMS = Monthly Index of Medical Specialties; mTNBC = metastatic triple-negative breast cancer; N/A = not applicable; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PartSA = partitioned survival approach; PD-L1 = programmed death-ligand 1; PSSRU = Personal Social Services Research Unit; TA = technology appraisal; TPC = treatment of physician's choice

Alternative model structures were considered; however, they were ultimately deemed less appropriate for addressing the decision problem, as discussed below:

- A patient-level discrete event simulation model may capture detailed changes along the clinical pathway more accurately (e.g., sequencing of subsequent lines of treatment), however, that is not a key aspect of this decision problem, given the 2L+ settings.
- Markov models require estimates of transition probabilities between health states. This process involves competing risks and multi-state modelling, consideration of selection effects and dependent censoring. It can consider mortality post progression explicitly; however, given the maturity of the ASCENT trial data, partitioned survival structure can satisfy the needs in a clear and transparent way, without necessitating the use of a complex Markov structure.

B.3.2.3 Intervention technology and comparators

SG was compared to TPC in the base case analysis. In the ASCENT trial comparator arm, TPC—eribulin, vinorelbine, gemcitabine, or capecitabine—was administered as a single-agent regimen that was selected by the investigator before patient randomization.(55) The ITT population in the TPC arm of ASCENT was composed of 53.1% eribulin, 19.8% vinorelbine, 14.5% gemcitabine, and 12.6% capecitabine.(48)

Despite gemcitabine being rarely used in the patient population of interest in the UK (and therefore not included in the final scope), clinicians advised that using pooled efficacy of TPC from the ASCENT trial would be reasonable assuming that gemcitabine was not associated with significantly different outcomes compared to other components of the TPC arm. [redacted].

Table 18: KM estimates of OS for single-agent treatment within TPC in ITT population

Planned single-agent treatment within TPC	Event/total	Median (95% CI)[a]	Hazard ratio (95% CI)[b]	Covariate level p-values	P-value
					[redacted]
TPC-capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	
TPC-eribulin	[redacted]	[redacted]	[redacted]	[redacted]	
TPC-gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	
TPC-vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	

[a] Kaplan-Meier method

[b] Cox model

[c] Logrank test

[d] Wald Chi-Square test

CI = confidence interval; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; TPC = treatment of physician's choice

Figure 18. KM estimates of OS for single-agent treatment within TPC in ITT population

CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; TPC = treatment of physician's choice

Table 19. KM estimates of PFS by IRC assessment for single-agent treatment within TPC in ITT population

Planned single-agent treatment within TPC	Event/total	Median (95% CI)[a]	Hazard ratio (95% CI)[b]	Covariate level p-values	P-value
					[redacted]
TPC-capecitabine	[redacted]	[redacted]	[redacted]	[redacted]	
TPC-eribulin	[redacted]	[redacted]	[redacted]	[redacted]	
TPC-gemcitabine	[redacted]	[redacted]	[redacted]	[redacted]	
TPC-vinorelbine	[redacted]	[redacted]	[redacted]	[redacted]	

[a] Kaplan-Meier method

[b] Cox model

[c] Logrank test

[d] Wald Chi-Square test

CI = confidence interval; IRC = independent review committee; ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; TPC = treatment of physician's choice

Figure 19. KM estimates of PFS by IRC assessment for single-agent treatment within TPC in ITT population

CI = confidence interval; HR = hazard ratio; IRC = independent review committee; ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; TPC = treatment of physician's choice

B.3.3 Clinical parameters and variables

The key efficacy inputs in the model are PFS, OS, and time-to-treatment discontinuation (TTD). The ASCENT trial was used as the main source of efficacy data.(55)

Parametric survival analyses were conducted by fitting survival functions to patient-level survival data collected in ASCENT to make long-term extrapolations for the model. Six parametric distributions—Weibull, log-normal, log-logistic, exponential, Gompertz, generalized gamma—were fitted to the time-to-event data. The methods used to extrapolate outcomes followed the guidance outlined in NICE DSU TSDs 14(80) and 18(81) for the analysis of survival outcomes for economic evaluations alongside clinical trials for projection. This approach formally accounts for censored observations and uses statistical distributions that can account for the typically skewed distributions of time-to-event variables.

For each outcome, an assessment of the fitted models was conducted to determine which parametric survival models were most appropriate. For each outcome, an assessment of the fitted models was conducted to determine which parametric survival models were most appropriate. The following factors were considered:

- Statistical goodness of fit, as determined by the curve with the lowest Akaike Information Criterion (AIC)/Bayesian Information Criterion (BIC)
- Visual fit to KM plots, with consideration given to the entire trial period for which data are available.
- Clinical plausibility of model extrapolations for OS

Relevant and clinically plausible best-fitting models were selected for the base case; alternative models were considered in sensitivity analysis.

For each of the time-to-event analyses (PFS, OS, and TTD), a best parametric fitting approach was used in the base case to estimate outcomes across the model time horizon (trial period and post-trial period). Additional estimation approaches explored in scenario analyses included use of KM data for the trial duration, followed with best parametric fittings for the post-trial period, and use of KM data only.

B.3.3.1 Population characteristics

The model target population reflects adults with unresectable locally advanced or mTNBC who have received two or more prior systemic therapies, at least one of them for metastatic disease, based on the population enrolled in the ASCENT trial.

Baseline characteristics for patients in the model are shown in Table 20. Age is used in the model to assign age-stratified general mortality, which serves as the minimum all-cause mortality boundary, while the weight and body surface area (BSA) are used to calculate treatment costs for those treatments with weight or BSA-based regimen. To better reflect a UK population in terms of these characteristics, values were calculated from 187 patients recruited from ex-US and mostly European countries into the ASCENT trial.

Table 20: Target population baseline characteristics (ex-US population)

Parameter	Mean	SD	Source
Age (years)	52.4	11.4	ASCENT Clinical Study Report – post hoc analysis for body surface area and weight(37)
Weight (kg)	68.4	15.8	
Body surface area (m^2)	1.75	0.21	

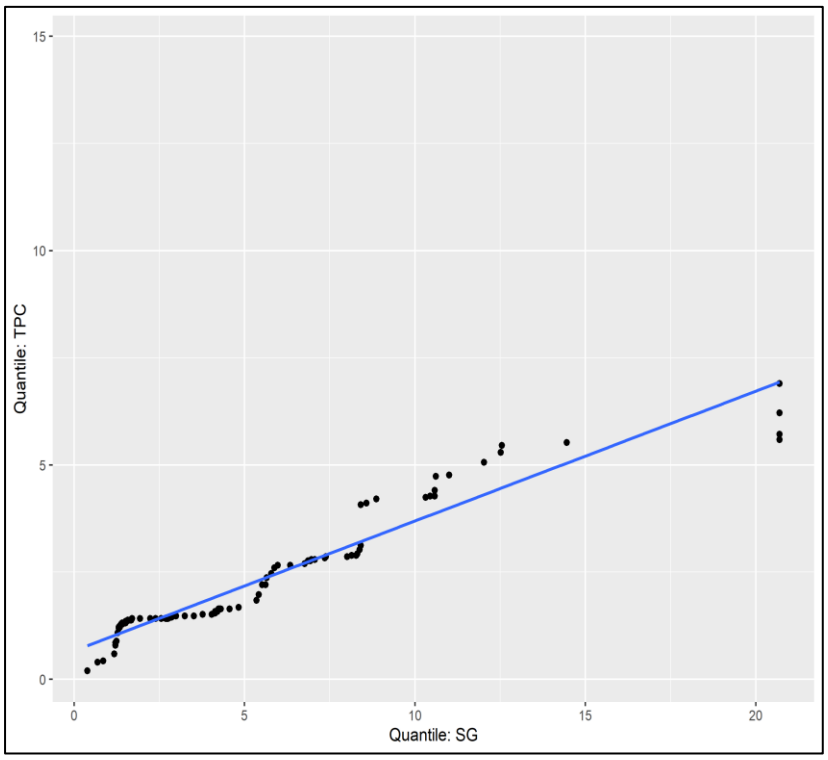
SD = standard deviation; US = United States

B.3.3.2 Progression-free survival

PFS data in the ASCENT trial were mature; [redacted].

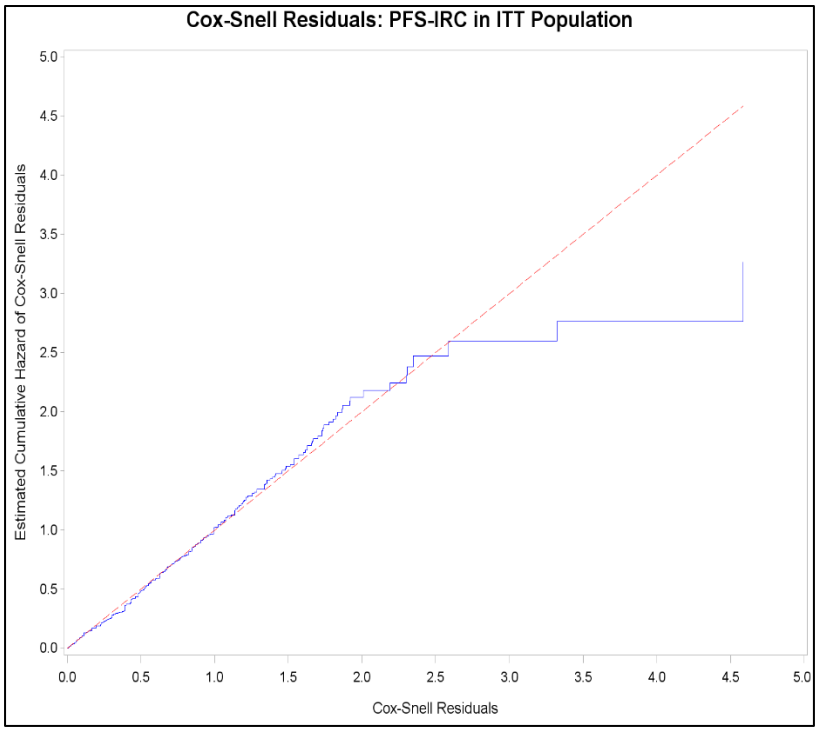
Parametric fittings suggested that the two treatment arms in ASCENT should be fitted separately, since the diagnostic plots indicated violation of the accelerate time to failure (AFT) and proportional hazard (PH) assumptions. As shown in Figure 20, slight deviation of QQ-plot points from a straight line, suggesting that the AFT assumption may be violated. Similarly, the deviation from the diagonal line in the Cox-Snell residual plot (Figure 21) indicate that the PH assumption may be violated as well (p=0.2649 based on Schoenfeld residual plot; Figure 22). This latter finding was further supported by non-parallel lines in the log-log plot for the SG and TPC treatment arms (Figure 23).

Figure 20: PFS by IRC assessment in the ITT population: QQ-plot



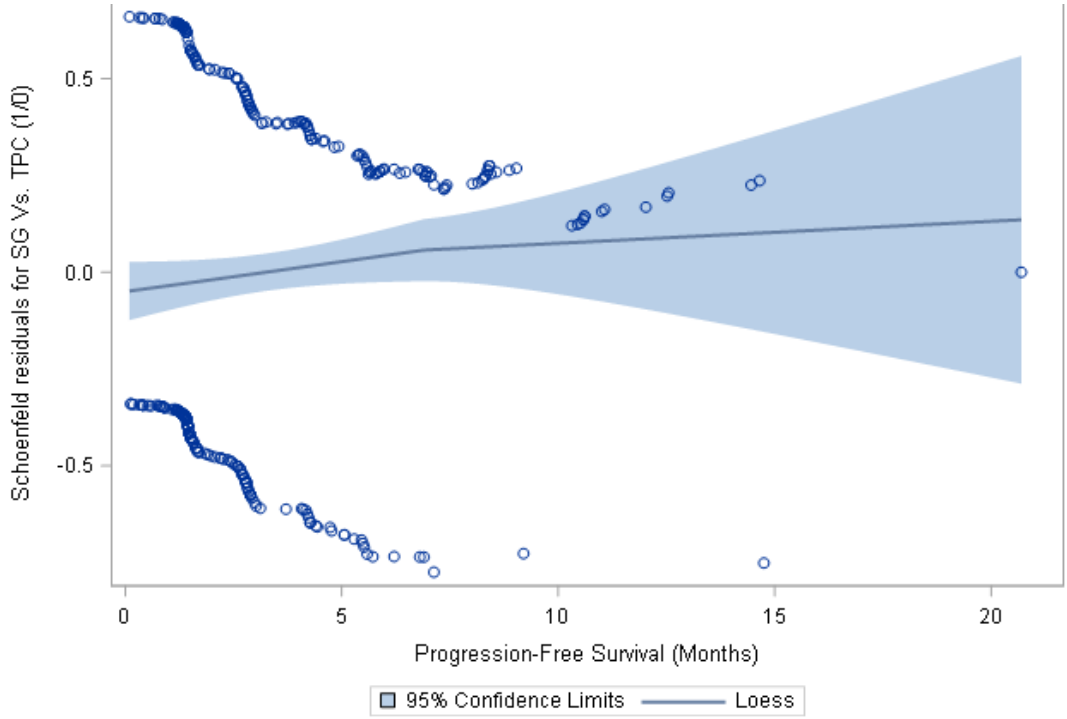
IRC = independent review committee; ITT = intention-to-treat; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 21: PFS by IRC assessment in the ITT population: Cox-Snell residual plot



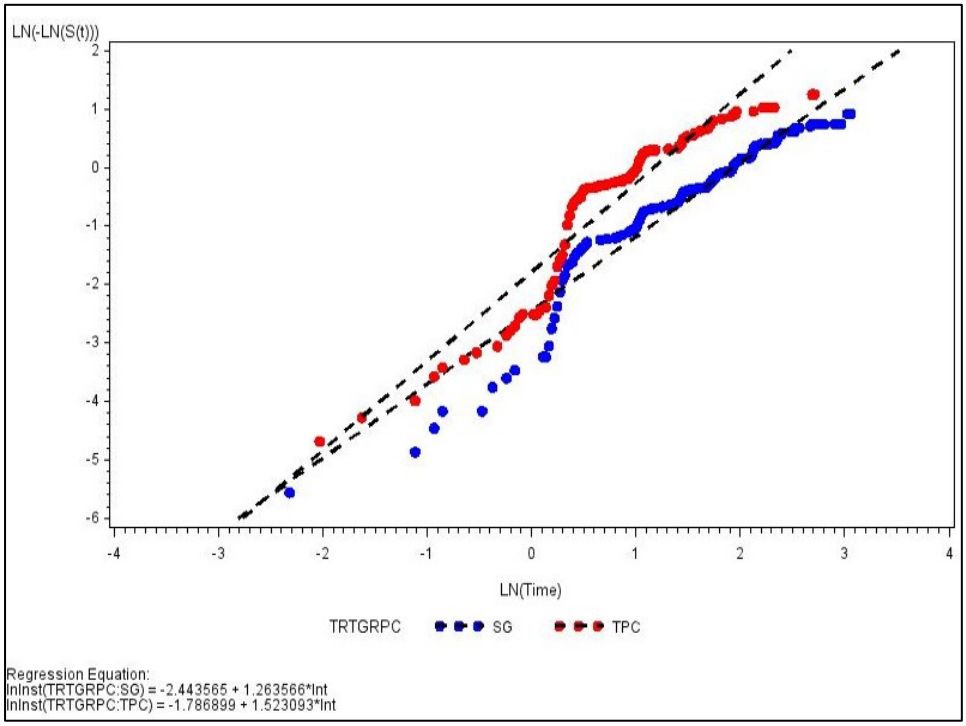
IRC = independent review committee; ITT = intention-to-treat; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 22: PFS by IRC assessment in the ITT population: Schoenfeld residual plot



IRC = independent review committee; ITT = intention-to-treat; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

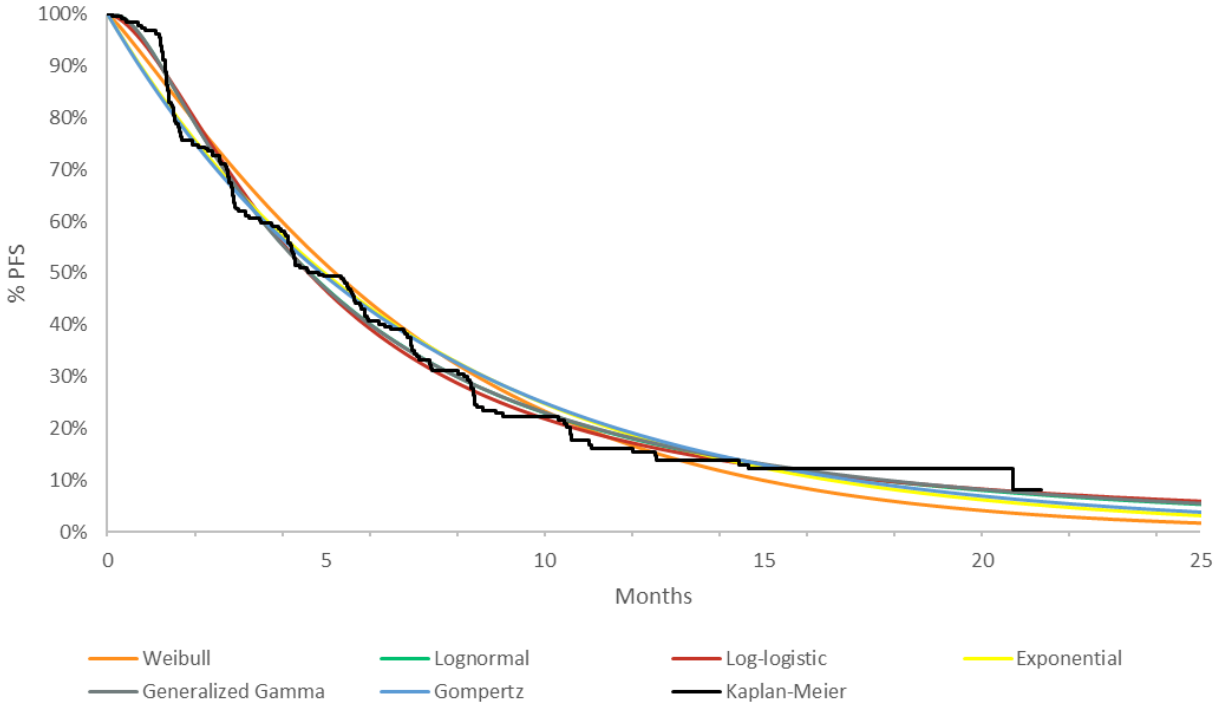
Figure 23: PFS by IRC assessment in the ITT population: log-log residual plot



IRC = independent review committee; ITT = intention-to-treat; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

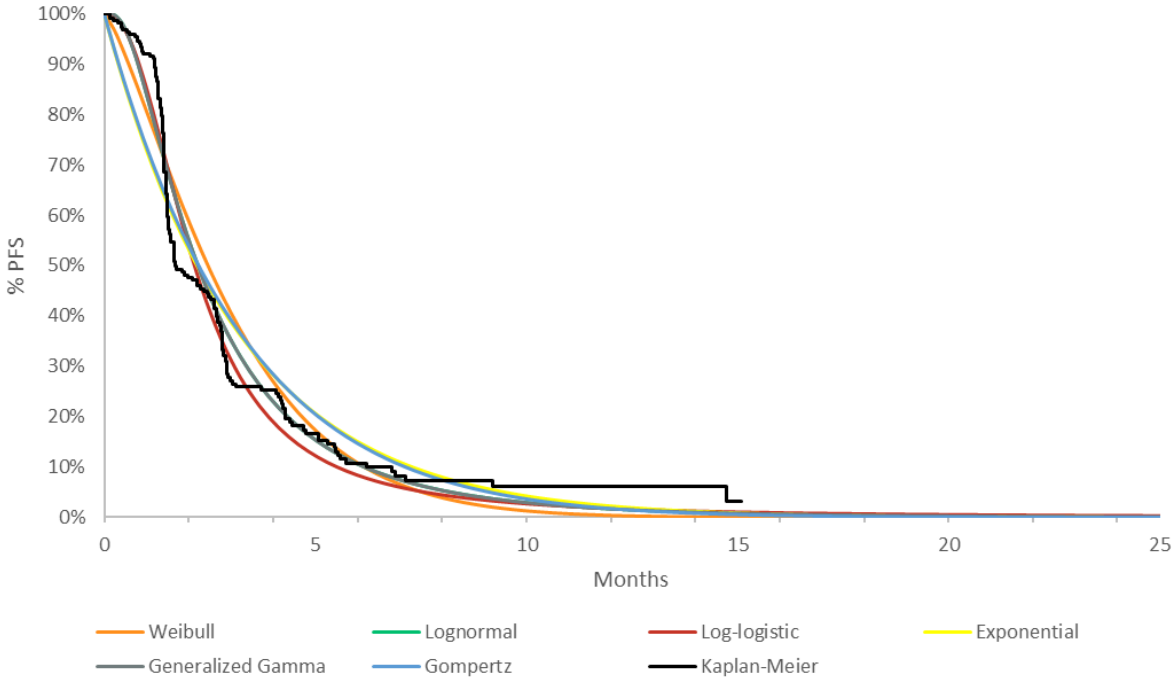
In addition, based on the goodness-of-fit statistics (AIC and BIC), the separately fitted distributions provided better fit compared to jointly fitted distributions with treatment arm as predictor. Thus, PFS curves were fitted separately for SG (Figure 24) and TPC (Figure 25).

Figure 24: PFS in the ITT Population: observed vs. predicted PFS for SG



ITT = intention-to-treat; PFS = progression-free survival; SG = sacituzumab govetican

Figure 25: PFS in the ITT Population: observed vs. predicted PFS for TPC



ITT = intention-to-treat; PFS = progression-free survival; TPC = treatment of physician's choice

The fit statistics of each distribution are shown in Table 21. Statistically, the log-normal distribution and the log-logistic distribution provided the best fit to the PFS observed data for SG and TPC, respectively.

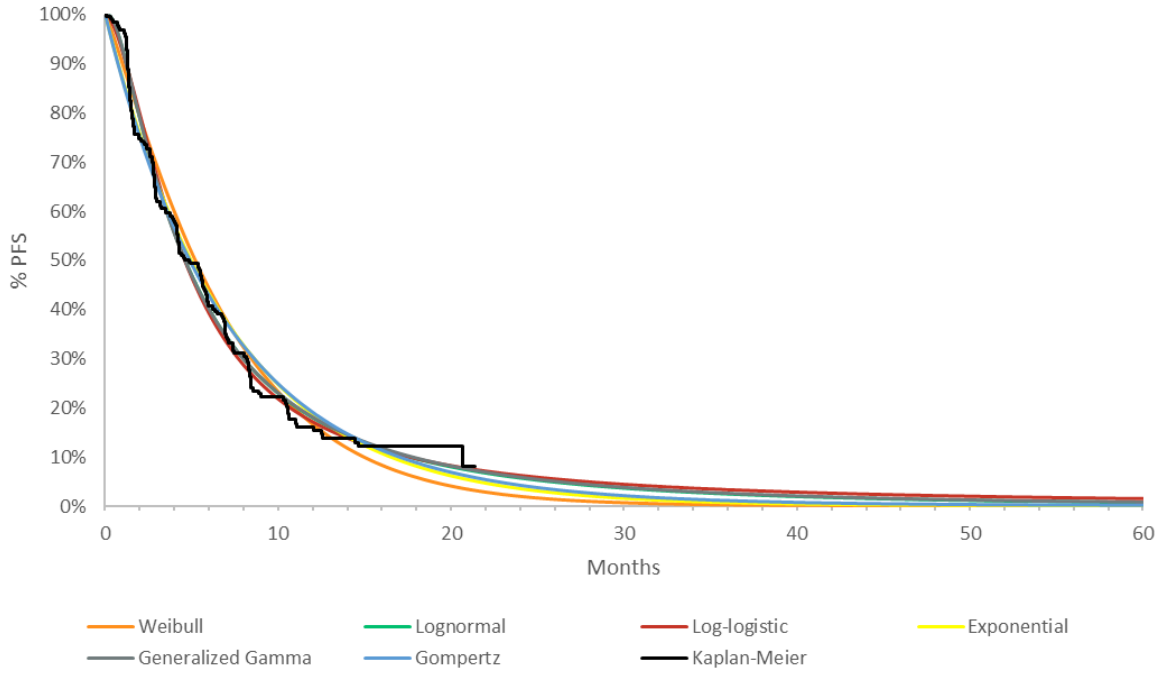
Table 21: AIC and BIC values for parametric models for PFS

Distribution	SG (Stratified)		TPC (Stratified)	
	AIC	BIC	AIC	BIC
Weibull	1126.2	1133.4	720.0	727.0
Log-normal	**1103.5**	**1110.6**	**682.4**	**689.5**
Log-logistic	1106.4	1113.5	670.1	677.2
Exponential	1129.2	1132.8	738.7	742.2
Generalized gamma	1105.5	1116.1	684.4	695.0
Gompertz	1131.0	1138.2	740.5	747.5

AIC = Akaike information criterion; BIC = Bayesian information criterion; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

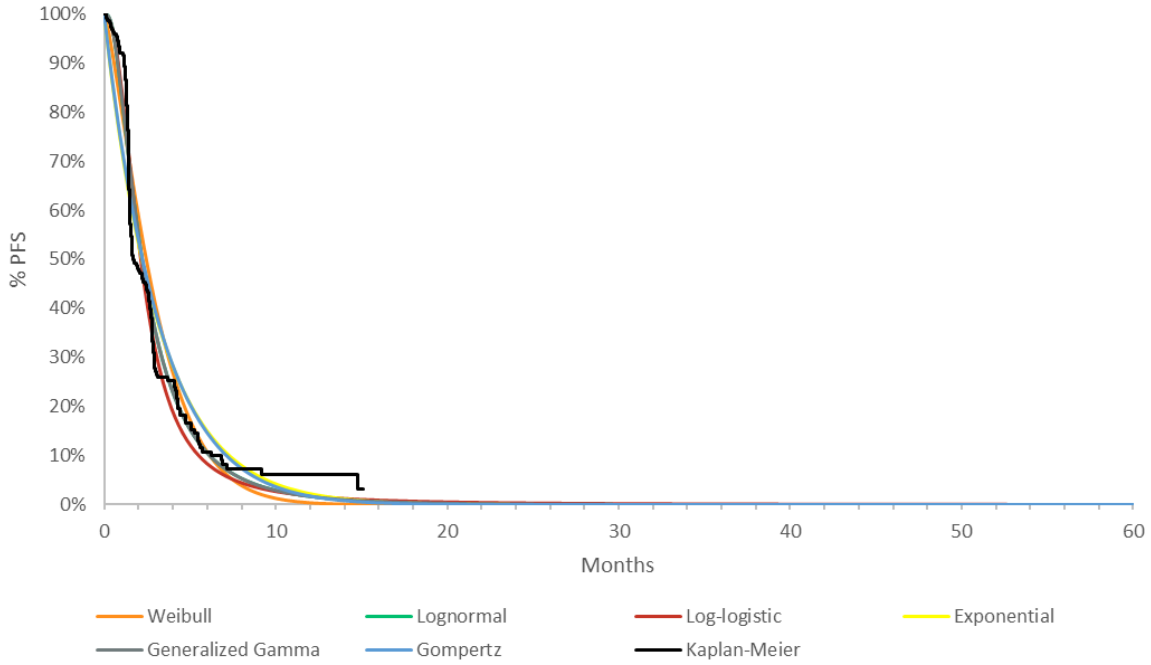
Figure 26 and Figure 27 present the long-term projections for PFS for both SG and TPC, respectively. Sole assessment of the visual and statistical fit of the PFS curves was deemed acceptable to determine the distribution for PFS, given the maturity of the patient-level data from ASCENT and reasonably similar extrapolations across distributions.

Figure 26: PFS in the ITT population: long-term projections for SG



ITT = intention-to-treat; PFS = progression-free survival; SG = sacituzumab govetican

Figure 27: PFS in the ITT population: long-term projections for TPC



ITT = intention-to-treat; PFS = progression-free survival; TPC = treatment of physician's choice

Table 22 and Table 23 detail the median PF months for all distributions, along with the percentage of those who were PF at one, two, three, five and 10 years for the SG and TPC arms. Log-normal was selected as the appropriate option for the

prediction of PFS in patients treated with SG, and log-logistic was selected as the most appropriate option of the prediction of PFS in patients treated with TPC.

Table 22: PFS in the ITT population: predictions by distribution in the SG treatment arm

Distribution	Median (months)	Mean (months)	1-Year PFS	2-Year PFS	3-Year PFS	5-Year PFS	10-Year PFS
KM (ASCENT) (55)	4.8						
Weibull	5.20	6.80	16.56%	1.90%	0.19%	<0.01%	<0.01%
Log-normal	**4.62**	**7.68**	**17.94%**	**5.66%**	**2.42%**	**0.68%**	**0.09%**
Log-logistic	4.59	8.16	17.08%	6.18%	3.27%	1.44%	0.46%
Exponential	4.95	7.08	18.64%	3.47%	0.65%	0.02%	<0.01%
Generalized gamma	4.60	7.68	18.06%	5.83%	2.56%	0.76%	0.11%
Gompertz	4.88	7.33	19.01%	4.17%	1.04%	0.09%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; SG = sacituzumab govetican

Table 23: PFS in the ITT population: predictions by distribution in the TPC treatment arm

Distribution	Median (months)	Mean (months)	1-Year PFS	2-Year PFS	3-Year PFS	5-Year PFS	10-Year PFS
KM (ASCENT) (55)	1.7						
Weibull	2.46	2.99	0.41%	<0.01%	<0.01%	<0.01%	<0.01%
Log-normal	2.22	3.00	1.72%	0.14%	0.02%	<0.01%	<0.01%
Log-logistic	**2.14**	**2.85**	**1.81%**	**0.37%**	**0.14%**	**<0.01%**	**<0.01%**
Exponential	2.20	3.14	2.27%	0.05%	<0.01%	<0.01%	<0.01%
Generalized gamma	2.22	3.00	1.71%	0.14%	0.02%	<0.01%	<0.01%
Gompertz	2.24	3.15	1.78%	0.01%	<0.01%	<0.01%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; TPC = treatment of physician's choice

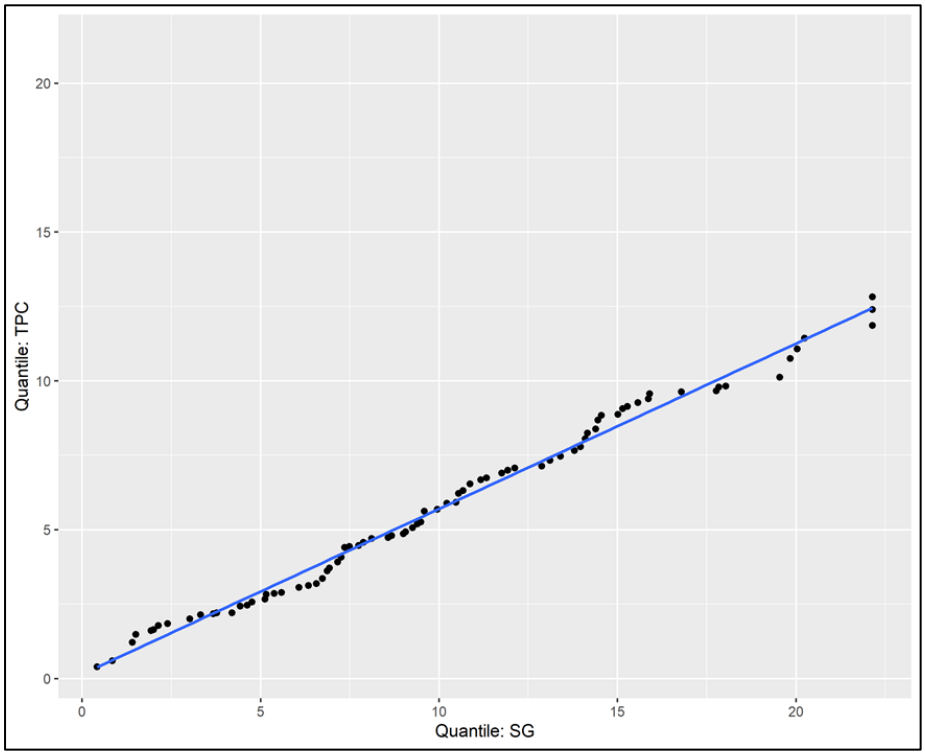
B.3.3.3 Overall survival

OS data from ASCENT trial were mature; [redacted].

To evaluate whether jointly or separately fitted (stratified) distributions were more appropriate for modeling OS, diagnostic plots were constructed to determine if the AFT or PH assumptions hold between the two treatment arms. The points forming a relatively straight line in the QQ-plot (Figure 28) suggested that both sets of observed quantiles in the SG and TPC treatment arms came from the same AFT

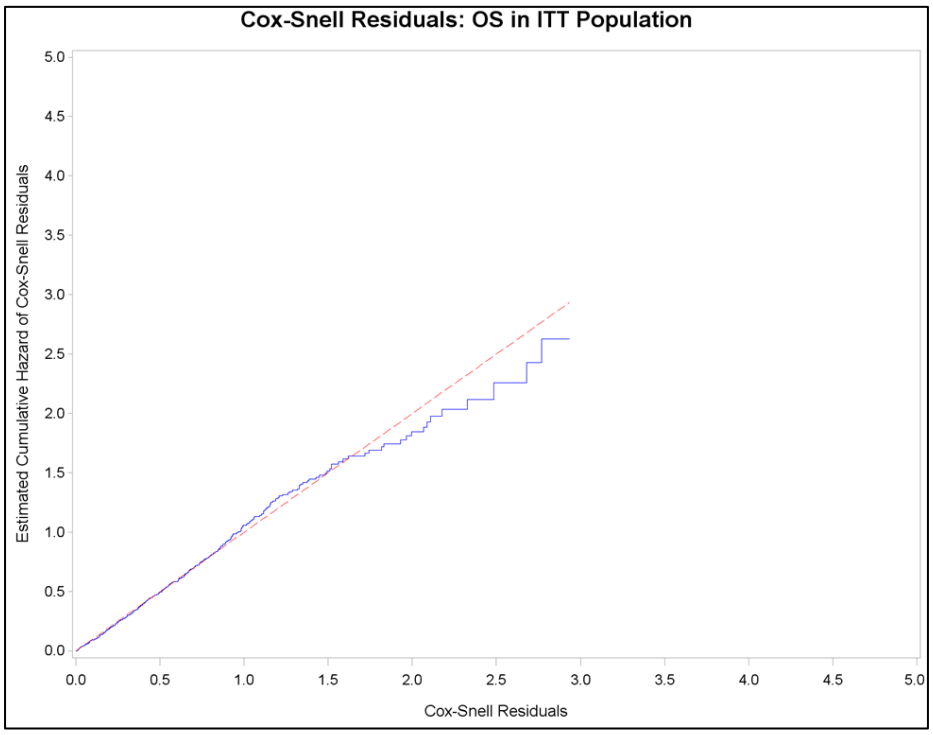
distribution and that the AFT assumption holds. Additionally, the deviation of the residuals from the diagonal line in the Cox-Snell residual plot (Figure 32) indicated that the PH assumption might be slightly violated (p=0.2089 based on Schoenfeld residual plot; Figure 30). This finding was further supported by the log-log plot (right panel in Figure 34), where points representing observations in the SG and TPC treatment arms were overlapping over the first two months after randomization, then became parallel and started to converge slightly at the tail.

Figure 28: OS in the ITT population: QQ-plot



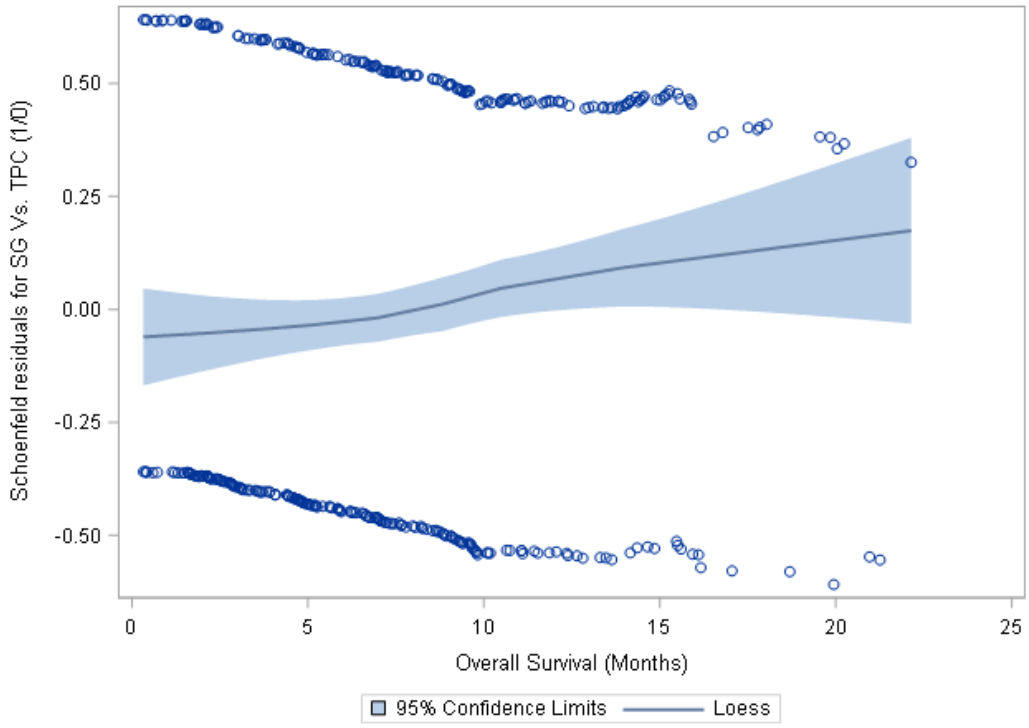
ITT = intention-to-treat; OS = overall survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 29: OS in the ITT population: Cox-Snell residual plot



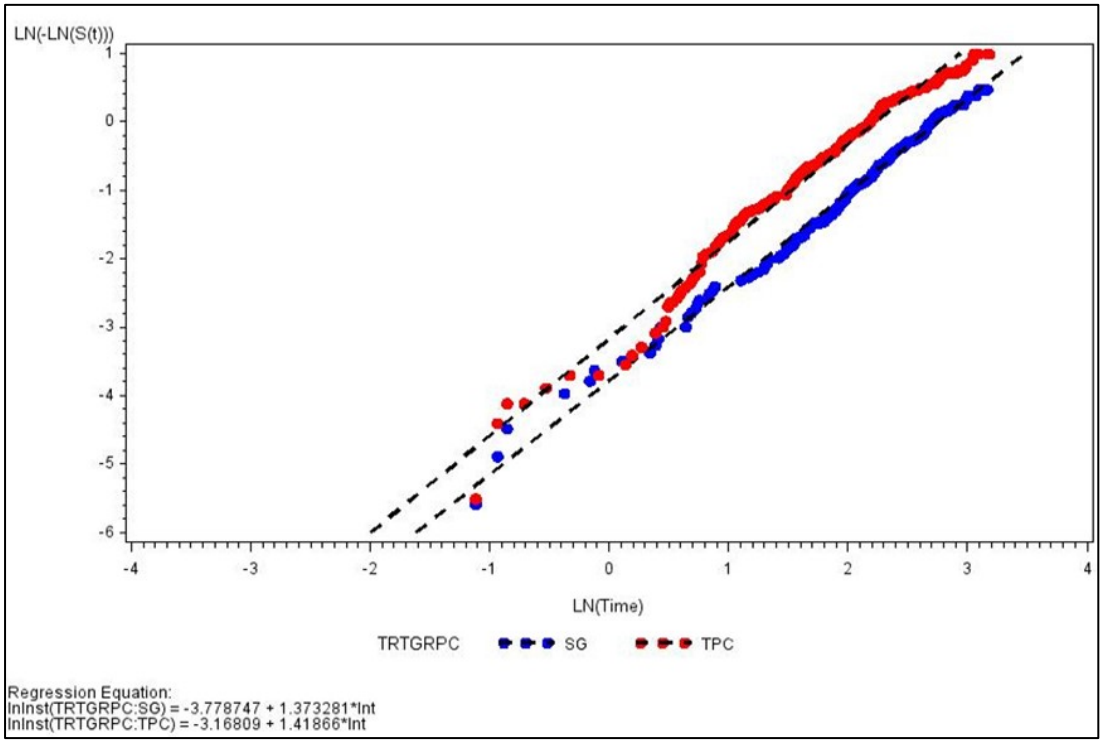
ITT = intention-to-treat; OS = overall survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 30: OS in the ITT population: Schoenfeld residual plot



ITT = intention-to-treat; OS = overall survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 31: OS in the ITT population: Schoenfeld residual plot

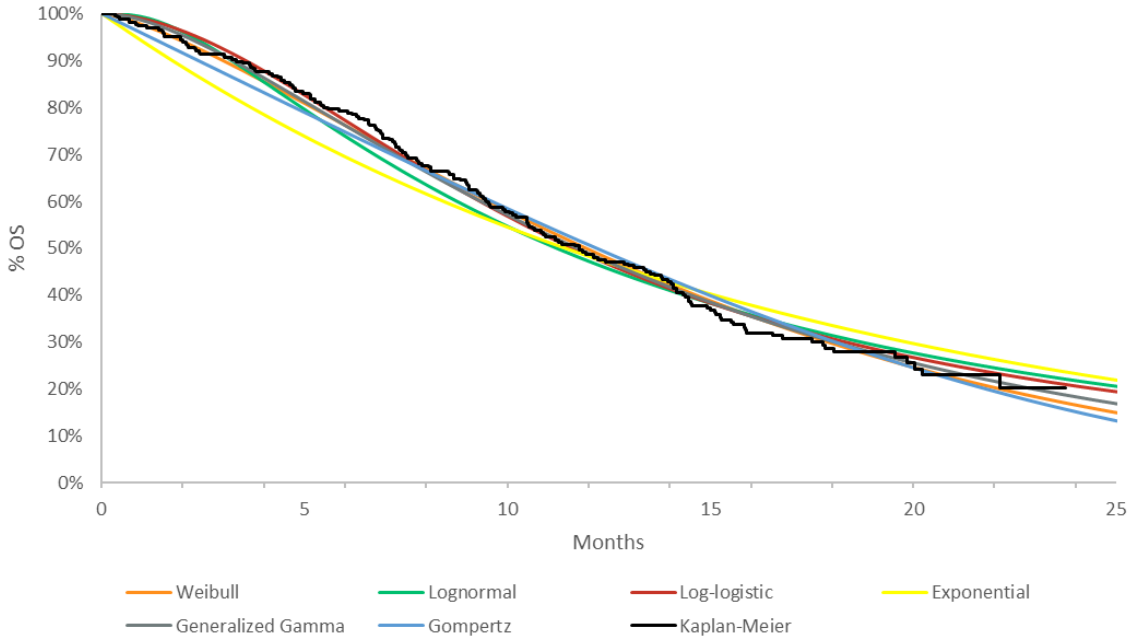


ITT = intention-to-treat; OS = overall survival; SG = sacituzumab govetican; TPC = treatment of physician's choice

The statistical tests suggested that the PH assumption might be slightly violated, and the AFT assumption holds; therefore, jointly fitted AFT distributions with treatment arm as predictor were used in the base case.

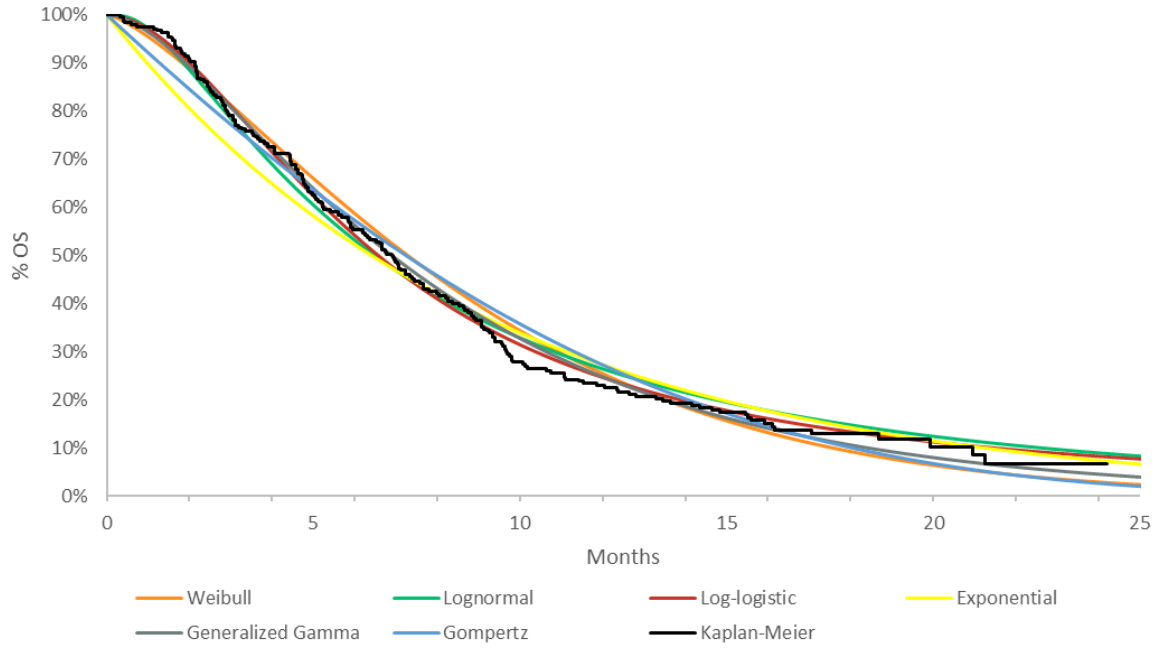
The curves for the seven parametric models fitted to the OS data for SG and TPC are shown in Figure 32 and Figure 33.

Figure 32: OS in the ITT population: observed vs. predicted OS for SG



ITT = intention-to-treat; OS = overall survival; SG = sacituzumab govetican

Figure 33: OS in the ITT population: observed vs. predicted OS for TPC



ITT = intention-to-treat; OS = overall survival; TPC = treatment of physician's choice

The goodness-of-fit statistics (AIC and BIC) of all distributions fitted jointly with treatment arm used as a predictor are presented in Table 24. Based on the goodness-of-fit statistics, among all distributions, the log-logistic and generalized gamma distributions provided the best fit to the observed data.

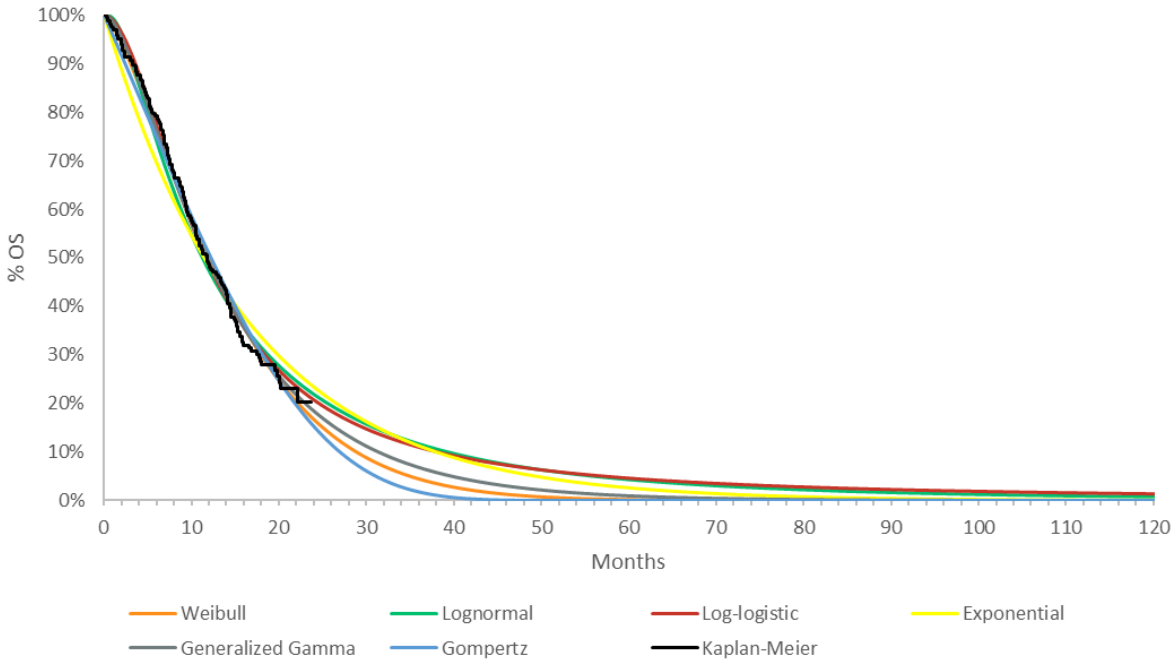
Table 24: OS in the ITT population: Goodness-of-fit statistics with treatment arm as predictor

Distribution	AIC	BIC
Weibull	2649.7	2662.4
Log-normal	2662.3	2675.1
Log-logistic	**2642.8**	**2655.6**
Exponential	2694.1	2702.6
Generalized gamma	2644.8	2661.8
Gompertz	2672.6	2685.4

AIC = Akaike information criterion; BIC = Bayesian information criterion; ITT = intention-to-treat; OS = overall survival

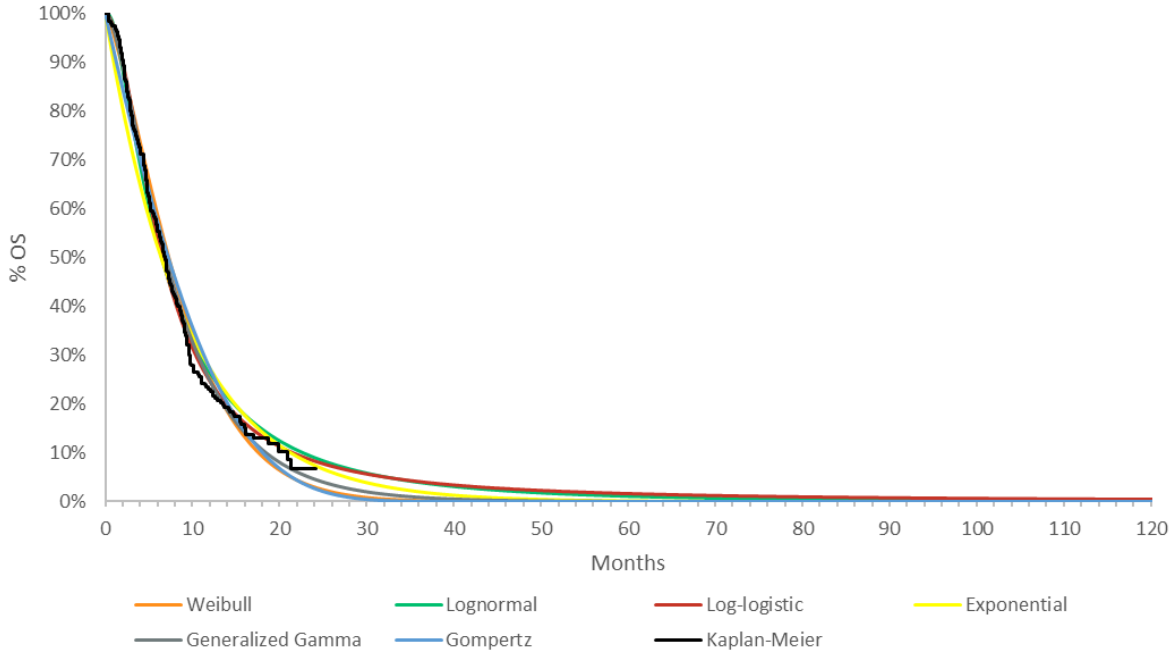
Extrapolation of OS is a key driver of the model and as such the clinical plausibility of long-term predictions have been thoroughly explored and externally validated. Visual inspection of observed vs. predicted OS curves above showed similar and good fit during the observed follow-up for both log-logistic and generalized gamma distributions, whereas the long-term projections from these two distributions differed substantially. Long-term projections from the log-logistic distribution were significantly longer compared to projections from the generalized gamma distribution (Figure 34 and Figure 35).

Figure 34: OS in the ITT population: long-term projection for SG



ITT = intention-to-treat; OS = overall survival; SG = sacituzumab govetican

Figure 35. OS in the ITT population: long-term projection for TPC



ITT = intention-to-treat; OS = overall survival; TPC = treatment of physician's choice

Table 25 and Table 26 show the predicted median survival for all distributions, along with the percentage of those who remained alive at one, two, three, five and 10 years for the SG and TPC arms.

Log-logistic distribution was selected for SG and TPC based on the best overall statistical fit and long-term survival projections, which were consistent with a small number of patients remaining alive at 10 years. Long-term survival of a very limited number of patients with mTNBC, which has been observed in real-world studies and aligns with the baseline disease characteristics from the ASCENT trial, was deemed clinically plausible and supported by input from UK clinicians.(27, 37, 82) Additionally, patients receiving SG in ASCENT were more likely to receive eribulin as a subsequent treatment than patients receiving TPC (Section B.3.5.2), which may support the plausibility of slightly improved long-term survival with SG relative to TPC.

Table 25: OS in the ITT population: predictions by distribution in the SG treatment arm

Distribution	Median (months)	Mean (months)	1-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
KM (ASCENT) (55)	11.8						
Weibull	11.94	14.24	49.75%	16.65%	4.45%	0.20%	<0.01%
Log-normal	11.22	17.61	47.26%	21.84%	11.66%	4.32%	0.77%
Log-logistic	**11.6**	**18.24**	**48.42%**	**20.63%**	**10.93%**	**4.55%**	**1.30%**
Exponential	11.43	16.34	48.31%	23.34%	11.28%	2.63%	0.07%
Generalized gamma	11.72	15.01	48.93%	18.40%	6.82%	0.99%	0.01%
Gompertz	12.2	13.63	50.74%	15.20%	1.78%	<0.01%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; SG = sacituzumab govetican

Table 26: OS in the ITT population: predictions by distribution in the TPC treatment arm

Distribution	Median (months)	Mean (months)	1-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
KM (ASCENT) (55)	6.9						
Weibull	7.29	8.69	25.49%	2.99%	0.23%	<0.01%	<0.01%
Log-normal	6.49	10.19	26.51%	9.07%	4.00%	1.15%	0.14%
Log-logistic	**6.57**	**10.34**	**24.69%**	**8.32%**	**4.11%**	**1.64%**	**0.46%**
Exponential	6.41	9.17	27.33%	7.47%	2.04%	0.15%	<0.01%
Generalized gamma	6.9	8.84	24.82%	4.62%	0.90%	0.04%	<0.01%
Gompertz	7.24	8.65	27.30%	2.72%	0.04%	<0.01%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; TPC = treatment of physician's choice

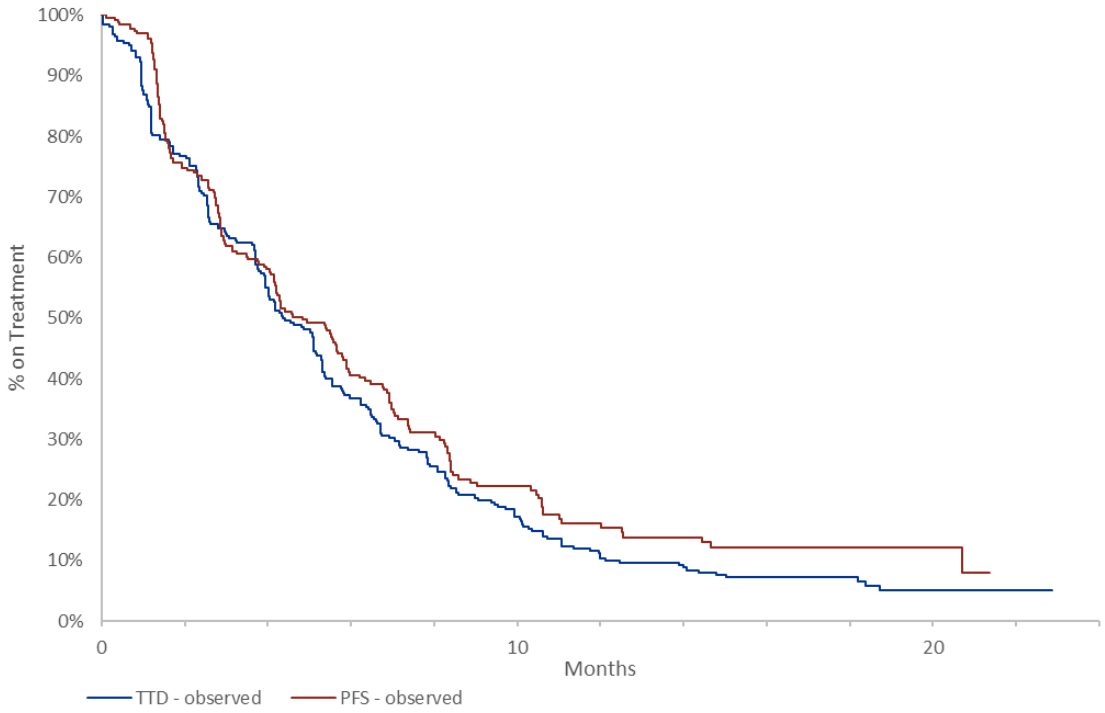
B.3.3.4 Treatment duration

Treatment duration is a key driver of costs and, thus, cost-effectiveness; therefore, the model was designed to project the average time on treatment for each comparator. In reality, there is a high positive correlation between TTD and efficacy, particularly PFS. In the model, treatment duration was modeled independently from efficacy, although the input parameters of the PFS and TTD curves are naturally correlated. TTD KM curves in the safety population were almost fully observed over the duration of the trial.

For long-term projection of TTD, parametric fitting was selected as the most appropriate approach based on input from clinical advisors. This approach was chosen over parametric fitting capped by PFS or treat to progression per PFS curve, due to consistency (as the PFS curves are also based on trial data) and utilization of

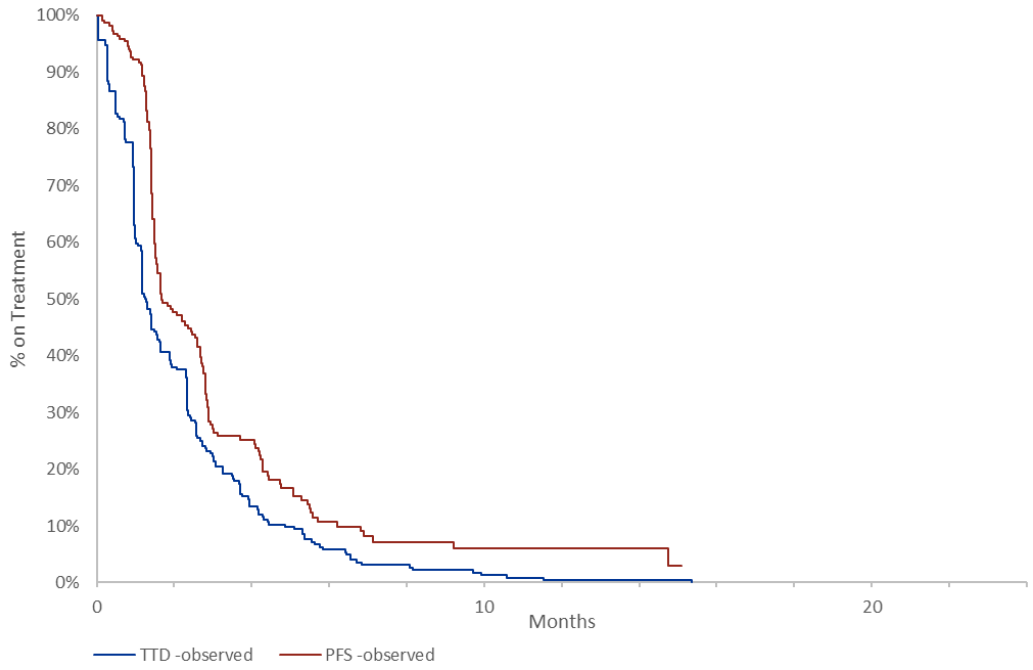
patient-level data to reflect the expected duration, including potential early discontinuation for reasons other than disease progression. Comparison of the TTD and the ASCENT PFS KM curves for SG and TPC supported the use of parametric fitting for TTD (Figure 36 and Figure 37).

Figure 36: PFS and TTD KM curves in the SG arm



KM = Kaplan-Meier; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to deterioration

Figure 37: PFS and TTD KM curves in the TPC arm



KM = Kaplan-Meier; PFS = progression-free survival; TPC = treatment of physician's choice; TTD = time to deterioration

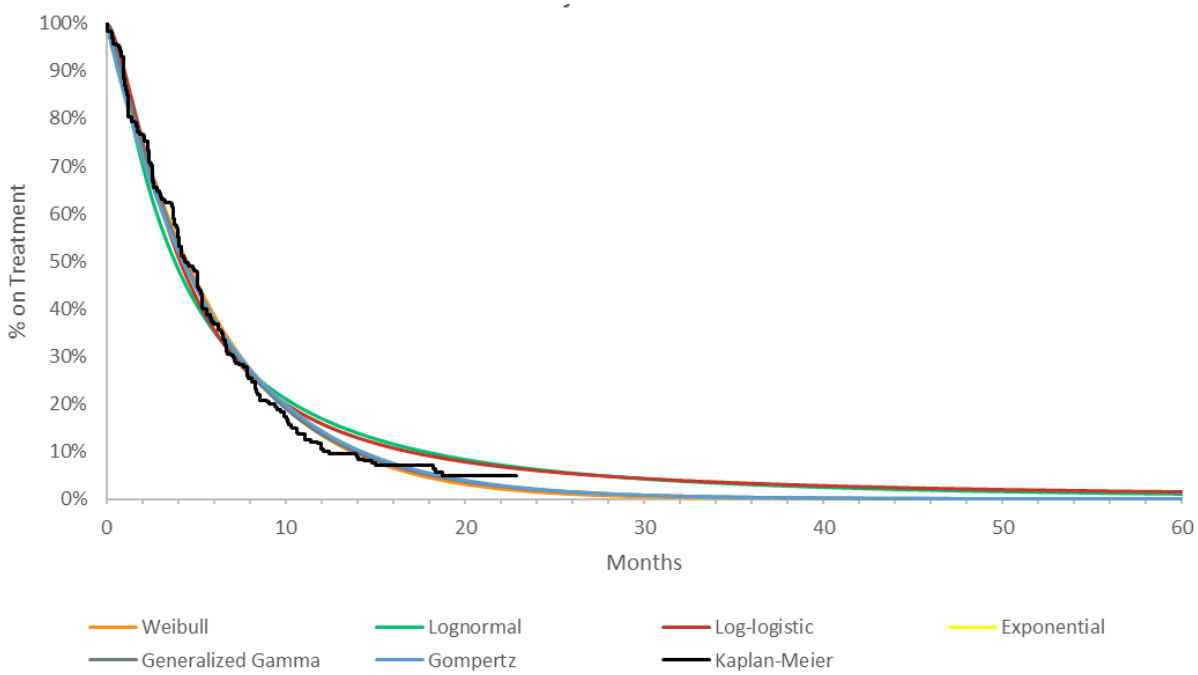
The goodness-of-fit statistics (AIC and BIC) of the separately fitted distributions in the safety population are presented in Table 27. Observed vs. predicted TTD curves are presented for both treatment arms in Figure 38 and Figure 39. Based on the goodness-of-fit statistics and visual inspection of the predicted vs. observed TTD curves, Weibull, exponential, and generalized gamma distributions provided good and almost identical fit. From these three distributions, the exponential distribution was selected for simplicity.

Table 27: TTD in the safety population: mean time on treatment and goodness-of-fit statistics for SG and TPC

Distribution	Mean Time on Treatment - SG	AIC	BIC	Mean Time on Treatment - TPC	AIC	BIC
Weibull	6.07	1361.4	1368.5	2.12	790.6	797.4
Log-normal	7.46	1390.8	1397.9	2.44	823.0	829.7
Log-logistic	7.81	1368.1	1375.2	2.55	803.0	809.7
Exponential	**6.12**	**1361.4**	**1364.9**	**2.11**	**789.3**	**792.7**
Generalized Gamma	6.12	1361.8	1372.4	2.11	790.9	801.1
Gompertz	6.19	1363.4	1370.5	2.17	791.2	797.9

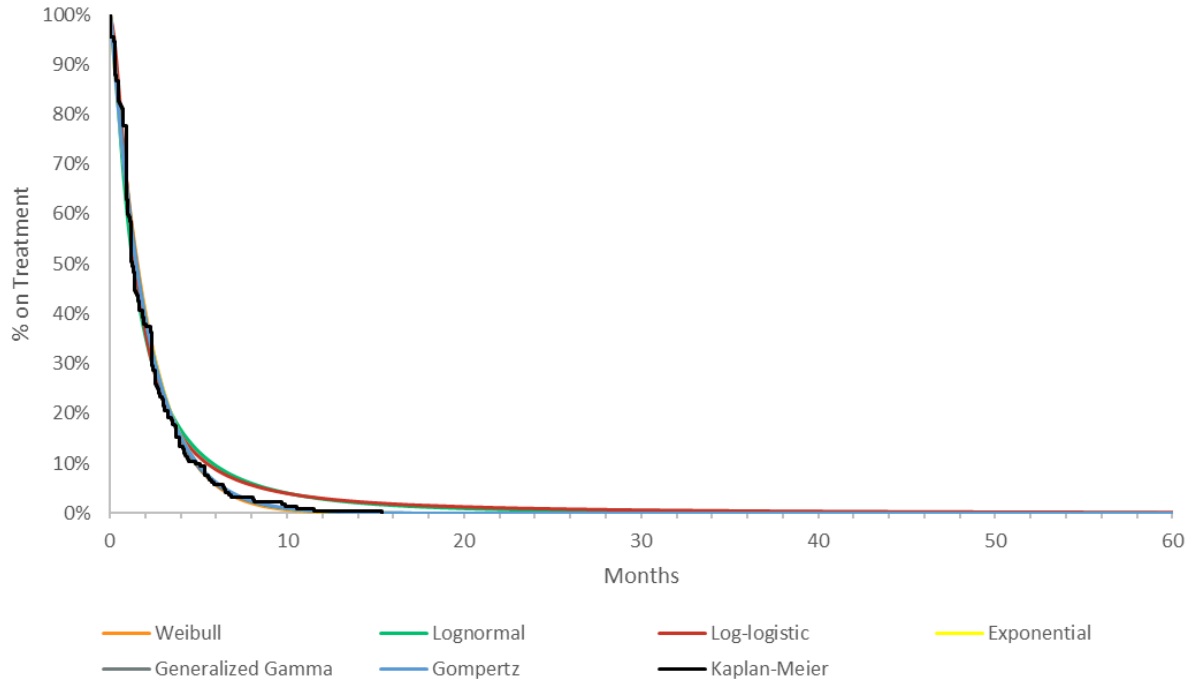
AIC = Akaike information criterion; BIC = Bayesian information criterion; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 38: TTD in the safety population: observed vs. predicted TTD for SG



SG = sacituzumab govetican; TTD = time to treatment discontinuation

Figure 39: TTD in the safety population: Observed vs. predicted TTD for TPC



TTD = time to treatment discontinuation; TPC = treatment of physician's choice

B.3.3.5 Safety inputs

AEs affect both costs and HRQoL of patients receiving treatment. A list of grade 3 and 4 AEs was compiled from the ASCENT CSR for each of the comparator treatments.(37) The AEs that were reported as occurring in at least 3% of patients in at least one of the comparator treatments were considered in the model (Table 28). This inclusion rule was considered appropriate and sufficient to capture AEs that would impact patients in a real-world setting where AEs are monitored in a less strict manner compared with a clinical trial setting.

The incidence rates of AE for SG and TPC were obtained from the ASCENT CSR based on the safety population. Only AEs associated with initial (i.e., current line) treatment were considered.

Table 28: Percentage of patients experiencing AEs

AEs	SG	TPC
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		

Source: ASCENT CSR Table 14.3.1.3(48)
AE = adverse event; SG = sacituzumab govetican; TPC = treatment of physician's choice

B.3.4 Measurement and valuation of health effects

Utility values were applied to each health state in the model to capture patient QoL associated with treatment and disease outcomes. Specifically, the model assigns utility values to PFS by treatment, and a single utility value to PD applicable for all treatments, assuming the QoL of the patients post progression does not differ based

on initial treatment received. SG and TPC have treat-to-progression regimens, and therefore for the PFS, there is no need to differentiate among utility values based on patients being on or off treatment.

The utilities used in the model are based on data from the ASCENT trial, discussed in more detail below. Trial data were preferred as a source of utility inputs given that this allowed utility and efficacy data to be derived from the same population.

B.3.4.1 Health-related quality-of-life data from clinical trials

The ASCENT clinical trial collected data from the EORTC QLQ-C30—a validated 30-item questionnaire containing both single- and multi-item measures. These include a Global Health Status/QoL scale, five functional scales (i.e., physical, role, emotional, cognitive, and social functioning), and nine symptom scales (i.e., fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). Scores for each scale are averaged and transformed linearly to a score ranging from 0 to 100. A high score for Global Health Status/QoL and for functional scales represents better functioning ability or HRQoL, whereas a high score for symptom scales represents significant symptomatology.

In the ASCENT clinical trial, EORTC QLQ-C30 questionnaires were completed by all patients at baseline, on day 1 of each cycle (until disease progression warranting discontinuation or unacceptable toxicity), and at final study visit (four weeks after the last dose of study drug or in event of premature study termination).

Preference-based measures such as the EQ-5D(83) were not administered in the ASCENT study. In accordance with NICE guidance, which recommends EQ-5D as a preferred elicitation tool, mapping from the EORTC QLQ-C30 to EQ-5D was performed to estimate utilities for patients enrolled in the ASCENT clinical trial.

B.3.4.2 Mapping

EORTC QLQ-C30 measurements collected in the ASCENT trial were mapped onto the EQ-5D-3L using the Longworth mapping algorithm.(78)

All patients in the ITT population who had an EQ-5D-3L utility score observation available at baseline and at least one other observation on a later date were considered as eligible for the utility analysis. An analytical dataset was created including one record per patient per visit, including a time-dependent variable indicating the patients' health status at the time of the utility measurement.

The ASCENT clinical trial database included 479 patients with at least one EORTC observation (3,014 in total). Mapping from EORTC to EQ-5D-3L utility scores failed for 43 patients (65 EORTC observations) due to incomplete EORTC dimensions. After the mapping, the 479 patients (256 in SG and 223 in the TPC treatment arm) had at least one EQ-5D-3L utility score observation available. A total of 411 out of 479 patients (with 2,907 utility observations) had utility observation available at baseline and (at least) at another visit after baseline. These 411 patients (233 in SG and 178 in the TPC arm) were considered eligible for inclusion in the utility regression analysis. Across all scheduled visits, the total number of utility observations used as response variable in the regression models was 2,496. The mean utility at baseline was 0.662 (95% CI: 0.641, 0.683); this value was applied when centering the baseline utility to be used for adjustments in the regression models.

The extent of missing HRQoL data over time was assessed and the impact of treatment differences on change scores for each domain of the EORTC QLQ-C30 was formally analysed by repeated measures analysis using a linear mixed-effects regression model (MMRM).

B.3.4.3 Health-related quality-of-life studies

An SLR was conducted to identify health-related quality-of-life studies in locally advanced TNBC or mTNBC relevant to the decision problem for SG. Details of the methods used to identify and select the relevant studies are described in Appendix H. A total of 9 studies were identified, of which 8 were economic models. Utility values from the remaining study, a NICE appraisal of atezolizumab with nab-paclitaxel for PD-L1-positive locally advanced or mTNBC, are summarized in Table 29. Potentially relevant utility values from two additional studies (a NICE appraisal of

eribulin in locally advanced or metastatic BC, and a study of UK-based utilities for MBC) that were not captured by the TNBC-specific search parameters are also included in Table 29.

Table 29: Utility values in published studies

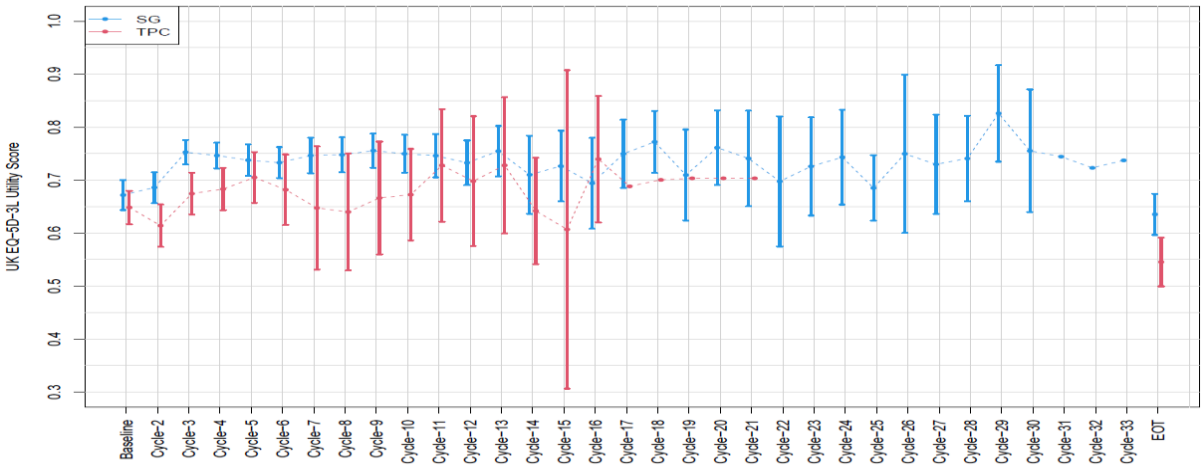
Study	PFS	PD	Comment
TA423(71)	• Eribulin: 0.705 • TPC: 0.701	• 0.679 • 0.59 (revised estimate, in line with committee assumptions)	Utilities were obtained by mapping EORTC QLQ-C30 into EQ-5D using the Crott algorithm.(77) The committee commented that small decrease between stable disease and PD that was not plausible and noted that the Crott algorithm had been developed using data from people with locally advanced but not metastatic breast cancer, and who had good baseline health status.
TA639(18)	• Both treatment arms: 0.726 • Atezolizumab: 0.741 • TPC: 0.710	• 0.653	Utilities were derived by mapping EQ-5D-5L scores collected from the trial to the EQ-5D-3L using the Van Hout algorithm. Treatment was not a significant factor in the prediction of utility. A consistent utility value for PFS and PD was used across treatment arms in the base case analyses.
Lloyd, 2006(84)	• Baseline SD: 0.715	• 0.496	The ERG recommend using PD value from this study for eribulin in 3L NICE assessment (TA423)(84)

3L = third line; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; ERG = evidence review group; PD = progressed disease; PF = progression free; SD = standard deviation; TPC = treatment of physician's choice

B.3.4.4 Health-related quality-of-life data used in the cost-effectiveness analysis

The mean utility scores and associated 95% CIs throughout the ASCENT trial are presented in Figure 40 by treatment arm. Note that, according to the study design of the ASCENT clinical trial, patients who discontinued their treatment were no longer assessed at scheduled cycle visits; instead, these patients were further assessed at the EOT visit.

Figure 40: Mean EQ-5D utility scores in ASCENT by visit



CI = confidence interval; EOT = end of treatment

In the SG treatment arm, the mean utility at baseline was 0.672 (95% CI: 0.644, 0.700). The mean utility at all scheduled cycle visits was consistently higher than at baseline, and the mean utility at the EOT visit was 0.635 (95% CI: 0.597, 0.674). In the TPC treatment arm, the mean utility at baseline was 0.649 (95% CI: 0.617, 0.680); the mean utility at the EOT visit was 0.546 (95% CI: 0.500, 0.592).

Comparing the SG and TPC treatment arms, patients receiving SG stayed substantially longer on treatment than patients receiving TPC. In general, the mean utility observed at baseline and at scheduled cycle visits in the SG treatment arm was higher than in the TPC treatment arm. The actual utility decrements due to declining heath states were quantified by the regression models below.

EQ-5D utility scores from all visits were analysed using mixed-effects linear regression with a random intercept for each patient to account for the clustering of multiple observations. The utility models investigated the potential effect on EQ-5D utilities of treatment arm and progression status (PD vs. PF), one at a time (univariate models) and in combinations (multivariate models). In addition, all models were adjusted for baseline utility (centered at the mean value of the eligible population) to consider between-patient differences in utilities at baseline. Therefore, the intercept term in the model refers to an “average” patient in the ASCENT clinical trial in terms of baseline utility.

Univariate utility models indicated significantly higher utility in the SG arm vs the TPC arm (0.085; p<0.001), with a significant effect of treatment arm and progression status on the mean utility of patients. The mean predicted utility in the SG treatment and TPC arm was 0.693 (95% CI: 0.672, 0.713) and 0.607 (95% CI: 0.583, 0.632), respectively. When analysed by progression status, utility decreased significantly by 0.058 (p<0.001) due to progression; the mean predicted utility in PF and PD health states was 0.676 (95% CI: 0.66, 0.693) and 0.619 (95% CI: 0.6, 0.638), respectively.

In multivariate utility models, the effect of treatment arm and progression status was investigated when applied simultaneously as covariates. Multivariate utility analyses including both treatment arm and progression status as predictors indicated significantly higher utility in the SG treatment arm vs. TPC and significant disutility due to progression. According to this model, utility increased significantly by 0.084 (p<0.001) in the SG treatment arm vs. TPC treatment arm, whereas utility decreased significantly by 0.056 (p<0.001) due to progression. The mean predicted utility in the PF health state was 0.710 (95% CI: 0.690, 0.730) and 0.626 (95% CI: 0.601, 0.651) in the SG and TPC treatment arms, respectively. The mean predicted utility in the PF health state was 0.653 (95% CI: 0.631, 0.676) and 0.569 (95% CI: 0.543, 0.596) in the SG and TPC treatment arms, respectively.

Multivariate regression analyses indicated that treatment arm and progression status affected the EQ-5D utility significantly. Therefore, the multivariate utility model adjusting for treatment arm and progression status was recommended to be used in the CEM.

The utility estimates used in the model are provided in Table 30. According to the multivariate model, utility was significantly improved in the SG treatment arm vs. the TPC arm in the progression-free state (0.084; p<0.001). Within each treatment arm utility decreased significantly by 0.056 (p<0.001) due to disease progression. Treatment is considered to be significant factor of utility in PFS and therefore utilities by treatment arms were used in the base case. UK clinicians considered the 0.08 difference in progression-free utility to be clinically plausible, due to improved HRQoL observed with SG vs TPC (statistically significant and clinically meaningful improvement in most functional and symptom domains of the EORTC-QLQ-C30);

this difference was attributed to higher, durable response rates with SG vs. TPC driving better symptom control (e.g., pain) (Section B.2.6.7 and B.2.6.10). Post-progression utilities also remained higher in the SG arm, which can be attributed to a lower tumour burden for patients at the time of progression and the availability of eribulin for a larger proportion of patients after progression.

Table 30: Utility model including treatment arm and progression status as predictors

Health state	Health state	Utility value	SE	95% CIs
Progression-free	SG	0.710	0.010	0.690-0.730
	TPC	0.626	0.013	0.601-0.651
Progressed disease	SG	0.653	0.012	0.631-0.676
	TPC	0.569	0.013	0.543-0.596

CI = confidence interval; SE = standard error; SG = sacituzumab govetican; TPC = treatment of physician's choice

HRQoL will be impacted by the occurrence of grade 3/4 AEs. In the base case, it was assumed that any disutilities due to AEs would already be incorporated into the health state trial-derived utilities and incorporating an additional disutility could be considered double-counting.

In scenario analyses including AE disutilities, the model estimated the average QALY loss due to AEs for each treatment by considering the treatment-specific AE rates, the mean utility decrements associated with these AEs and the mean duration of each AE episode. Only grade 3/4 AEs occurring in ≥3% of study subjects were included. The total mean QALY loss associated with AEs for each treatment was determined by calculating the sum of individual QALY loss associated with each AE. The total QALY loss due to AEs was applied once at the start of the model, assuming that AEs occurred within the early period of treatment. Utility decrements associated with AEs were not explicitly collected in the ASCENT study, these values were sourced from previous NICE appraisals in BC (TA495) and the published literature (Table 31). Where there were no data for certain AEs, utility decrements were assumed to be equivalent to the greatest decrement identified in the literature across the other AEs.

Table 31: AE disutilities

Grade 3/4 AE	Disutility	Duration (weeks)	Source
Neutropenia	-0.124	1	NICE TA423(71)
Diarrhea	-0.103	1	Lloyd et al.(84)
Leukopenia	-0.003	1	NICE TA423(71)
Anaemia	-0.01	1	NICE TA423(71)
Febrile neutropenia	-0.15	1	Lloyd et al.(84)
Fatigue	-0.115	1	Lloyd et al.(84)
Dyspnea	-0.027	1	NICE TA423(71)
Hypophosphatemia	-0.15	1	No data. Assumed the same as the greatest decrement
Pneumonia	-0.15	1	No data. Assumed the same as the greatest decrement
Nausea	-0.103	1	Lloyd et al.(84)
Pulmonary embolism	-0.15	1	No data. Assumed the same as the greatest decrement
Pleural effusion	-0.15	1	No data. Assumed the same as the greatest decrement

AE = adverse event; NICE = National Institute for Health and Care Excellence

B.3.5 Cost and healthcare resource use identification, measurement and valuation

Disease- and treatment-related costs are important considerations in the model and were applied for each model health state and event. Cost categories included: drug acquisition and administration costs applied for the duration of active treatment (determined by dosing regimen and treatment duration data from clinical trial); medical resource use (MRU) costs; and the costs of unplanned events, such as AEs, co-medications, and terminal care costs.

Unit costs of drug acquisition, administration, resources use, and AE management were based on standard costing sources. The types and frequencies of resources associated with disease management, monitoring, and terminal care were derived based on previous NICE appraisals and based on input from UK clinicians.

Appendix I describes how relevant cost and healthcare resource use data for England were identified.

B.3.5.1 Intervention and comparators' costs and resource use

The dosing regimen used in the model for each treatment option is reported in Table 32. Dosing information for SG and each treatment option in TPC were drawn from the ASCENT trial.(55) Dose regimens are used in the model to inform the cost of treatment.

Table 32: Dosing regimen

Drug	Dosing Regimen
SG	10 mg/kg was administered as a slow IV infusion on Days 1 and 8 of a 21-day treatment cycle.
Eribulin	Administered as an IV injection over 2 to 5 minutes at a dose of 1.4 mg/m^2 at North American sites and 1.23 mg/m^2 at European sites [1.23 mg/m^2 used in the model] on Days 1 and 8 of a 21-day cycle.
Vinorelbine	25 mg/m^2 was administered as a weekly IV injection over 6 to 10 minutes
Gemcitabine	1200 mg/m^2 was administered as an IV injection over 30 minutes on Days 1, 8 and 15 of a 28-day cycle
Capecitabine	1,250 mg/m^2 was orally administered in a 21-day cycle, twice daily for 2 weeks followed by 1-week rest period

Source: ASCENT CSR Chapter 9.4(37)
IV = intravenous; SG = sacituzumab govetican

Drug costs for the treatment options in the model used the MIMS (Monthly Index of Medical Specialties) and pharmaceutical electronic market information tool (eMIT) prices and are detailed in Table 33.

Table 33: Drug acquisition costs

Drug	Dose/vial concentration	Pack size/vial volume	Cost per pack/vial	Cost per weekly model cycle	Adminis-tration route	Source
SG	10 mg/ml	18 ml	[redacted]	[redacted]	IV	Assumption
Eribulin	0.44 mg/ml	2 ml	£361.00	£607.24	IV	MIMS(85)
	0.44 mg/ml	3 ml	£541.50		IV	
Vinorelbine	10 mg/ml	1 ml	£5.25	£19.49	IV	eMIT(86)
	10 mg/ml	5 ml	£15.77		IV	
Gemcitabine	100 mg/ml	10 ml	£10.20	£17.01	IV	
	100 mg/ml	20 ml	£20.66		IV	
Capecitabine	150 mg	60	£4.28	£8.03	Oral	
	500 mg	120	£25.02		Oral	

eMIT = electronic market information tool; IV = intravenous; MIMS = Monthly Index of Medical Specialties; SG = sacituzumab govetican

For treatments that are dependent on weight or BSA there is a potential that some of the drug will be wasted if perfect vial sharing is not practiced (for IV-based drugs). When vial sharing is used, the model calculates the exact dose needed for the patients, depending on their weight or BSA, and multiplies it by the per milligram cost of the drug. When vial sharing is not allowed, drug wastage was calculated using the method of moments assuming normal distribution of patients around the mean weight of 68.4 kg and BSA of 1.75 m^2 and the standard deviation (obtained from the baseline characteristics of ex-US patients in the ASCENT trial).(55) To ensure the best use of available data from ASCENT trial, the weight distribution for SG was not based on the assumption of normal distribution but directly informed by the observed data from ASCENT trial ex-US population. In TA523 (also referenced by TA704), a clinical expert confirmed that "in clinical practice drug wastage is recognised and efforts are made to minimise it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain". Therefore, a same assumption was made in the model following the previous appraisals to reflect the uncertainty where vial sharing may not be always feasible in practice. In the absence of further data, 50% wastage is assumed, with scenarios considering 0% and 100% wastage.

B.3.5.1.1 Dose intensity

As in the real world, patients in clinical trials do not always receive the full doses of their assigned treatments. Data from clinical trials, therefore, may best reflect the efficacy of the received dose rather than the intended dose. To account for this, dose intensity is considered in the model and is used to adjust the drug cost in proportion to the doses received in the trial.

The model considers dose intensity in the drug cost calculation. Patients' exposure to the regimen during the on-treatment period is reflected via relative dose intensity. Relative dose intensity is calculated as the actual dose received divided by the standard calculated dose during the trial period. Applying this factor in the calculation of drug cost ensures that the drug exposure is consistent with the efficacy data from the ASCENT trial.(55)

Some dose reductions and dose interruptions were observed for SG in the ASCENT trial and the overall relative dosing intensity was reported as 94.2% in the ASCENT CSR.(37) Dosing intensity of TPC was not reported and was assumed to be 94.2%, for consistency with the SG treatment arm, with alternative values explored in scenario analyses. When applied in the model, dose intensity impacts the drug cost, but not efficacy.

B.3.5.1.2 Drug administration costs

Administration costs were applied to IV drugs, which differ by the time of administration (initial vs. subsequent attendance during the treatment cycle). Pharmacist time per administration is applied to those medications that are orally administered. Unit costs for all categories of administration were based on National Schedule of NHS Costs and are presented in Table 34. Total administration costs by drug are presented in Table 35.

Table 34: Administration unit costs

Administration category	Cost	Source
Simple parenteral chemotherapy at first attendance	£221.35	National Schedule of NHS Costs 2019/2020(87)
Subsequent elements of a chemotherapy cycle	£253.77	
Pharmacist time (12 minutes pharmacist time every 4 weeks)	£9.60	PSSRU 2020(88)

NHS = National Health Service; PSSRU = Personal Social Services Research Unit

Table 35: Drug administration costs

Drug	Cost per weekly model cycle
SG	£158.37
Eribulin	£158.37
Vinorelbine	£221.35
Gemcitabine	£182.22
Capecitabine	£3.20

SG = sacituzumab govetican

B.3.5.1.3 Co-medication costs

Co-medication drug costs are calculated separately based on the ASCENT trial for both SG and TPC arms. Table 36, Table 37, and Table 38 detail the proportion of patients receiving each of the co-medications and their associated dosing and unit costs from the ASCENT trial.

Table 36: Proportion of patients taking co-medication

Treatment class	Antiemetics and antinauseants	Drugs for peptic ulcer and GERD	Corticosteroids for systemic use	Antihistamines for systemic use	Antipropulsives
Representative treatment	Ondansetron	Pantoprazole	Dexamethasone	Loratadine	Loperamide hydrochloride
SG	83.1%	67.0%	63.7%	63.7%	53.6%
TPC	53.8%	40.5%	35.1%	16.4%	8.8%

Source: ASCENT trial Table 14.1.6.5(48)
GERD = Gastroesophageal Reflux Disease; SG = sacituzumab govetican; TPC = treatment of physician's choice

Table 37: Co-medication dosing regimens

	Dose	Administration route	Administration per treatment cycle	Treatment cycle length
Antiemetics and antinauseants (ondansetron)(89)	8 mg	Oral	42	3 weeks
Drugs for peptic ulcer and gastroesophageal reflux disease (pantoprazole)(90)	20 mg	Oral	21	3 weeks
Corticosteroids for systemic use, plain (dexamethasone)(91)	8 mg	Oral	21	3 weeks
Antihistamines for systemic use (loratadine)(92)	10 mg	Oral	21	3 weeks
Antipropulsives (loperamide hydrochloride)(93)	2 mg	Oral	6	3 weeks

IV = intravenous

Table 38: Co-medication unit costs

Medication	Strength per unit	Unit per pack	Cost per pack	Cost per weekly model cycle	Source
Antiemetics and antinauseants (ondansetron)	8 mg	10	£0.81	£1.13	eMIT(86)
Drugs for peptic ulcer and gastroesophageal reflux disease (pantoprazole)	20 mg	28	£0.59	£0.15	eMIT(86)
Corticosteroids for systemic use, plain (dexamethasone)	2 mg	50	£2.68	£1.50	eMIT(86)
Antihistamines for systemic use (loratadine)	10 mg	30	£0.26	£0.06	eMIT(86)
Antipropulsives (loperamide hydrochloride)	2 mg	10	£0.29	£0.06	eMIT(86)

eMIT = electronic market information tool

The total concomitant medication cost for SG was £2.06 per week and for TPC it was £1.21 per week.

B.3.5.2 Subsequent treatment costs

The costs of subsequent treatment after progression are included in the model. Two approaches were considered for subsequent treatment cost calculation: micro-costing and fixed cost per week.

In the micro-costing approach, the subsequent treatment compositions and usage were derived from the ASCENT trial follow-up analysis, with 70.5% and 66.4% of patients in the SG and TPC arms receiving subsequent treatment, respectively. Based on input from UK clinicians, subsequent treatment composition and duration values were applied separately for the SG and TPC treatment arms. Eribulin use was expected to be lower after TPC than SG, given that patients receiving prior eribulin were not likely to be rechallenged with eribulin in a subsequent line of therapy.

Per clinician feedback, interchangeability was assumed between doxorubicin and epirubicin (used in the UK), with cost calculations based on epirubicin, and distribution and treatment duration based on observed doxorubicin use in ASCENT. Single-agent gemcitabine and cyclophosphamide were omitted from the subsequent treatment list based on clinician input.

The total costs of subsequent treatments were calculated based on the average treatment distribution, duration, and unit cost of subsequent treatments, which is presented in Table 39, Table 40, and Table 41.

Table 39: Composition of subsequent treatment

	Input	Eribulin	Paclitaxel	Carboplatin	Capecitabine[b]	Epirubicin	Vinorelbine[b]
SG	%	66.0%	0.7%	7.9%	8.6%	8.2%	8.6%
	Duration (weeks)	10.7	13.1	9.9	11.4	14.0	6.6
TPC	%	46.9%	8.4%	5.3%	14.0%	9.9%	15.5%
	Duration (weeks)	12.9	17.8	11.7	16.0	12.0	10.1

[a] subsequent treatments ≥5% in either arm were included

[b] to ensure a total of 100% for the composition distribution, additional percentage was assigned to capecitabine and vinorelbine as they are more widely used than paclitaxel in later lines.

Source: ASCENT trial subsequent treatment analysis (data on file) and composition basket distribution is based on UK clinicians' opinion to reflect standard practice.

ITT = intention-to-treat; SG = sacituzumab govetican; TPC = treatment of physician's choice

Table 40: Subsequent treatment dosing regimens

Treatment	Dose	Administration route	Administration per treatment cycle	Treatment cycle length	Source
Eribulin	Consistent with current-line treatments in Table 32				
Capecitabine					
Vinorelbine					
Paclitaxel	175 mg/m^2	IV	1	3 weeks	SmPC(94)
Carboplatin	400 mg/m^2	IV	1	4 weeks	SmPC(95)
Epirubicin	75 mg/m^2	IV	1	3 weeks	SmPC(96)

IV = intravenous; SmPC = summary of product characteristics

Table 41: Subsequent treatment unit costs

Treatment	Strength per unit	Unit per pack	Cost per pack	Cost per weekly model cycle	Source
Eribulin	Consistent with current-line treatments in Table 33				
Capecitabine					
Vinorelbine					
Paclitaxel	100 mg	1	£7.22	£81.16	eMIT(86)
Carboplatin	450 mg	1	£13.76	£60.69	
Epirubicin	200 mg	1	£347.55	£149.89	BNF(97)

BNF = British National Formulary; eMIT = electronic market information tool

B.3.5.3 Health-state unit costs and resource use

Medical resource use (MRU) costs include those incurred by recurrent disease management and monitoring, and those by one-off procedures.

B.3.5.3.1 Disease management and monitoring costs

For disease management (routine follow-up), MRU costs can be calculated with two approaches, namely aggregate cost approach or micro-costing approach. Disease management costs used in the model can be differentiated by health state and treatment arm. The micro-costing approach was used in the current model analysis.

With the micro-costing approach, overall MRU costs were calculated by multiplying the frequencies of use (monthly use) and unit costs for each resource use item. Items considered in the current model analysis include general practitioner visit, oncology consultant visit, community nurse, and clinical nurse specialist. In the current analysis, frequencies of use were adapted from previous NICE appraisals; the percentage of patients who used each medical resource was assumed to be 100% for both arms. Table 42 presents an overview of unit costs and frequency of resource use by health state.

Table 42: Disease management frequency by heath state and unit cost

	Unit cost	Frequency per month (PFS)	Frequency per month (PD)
Oncologist visit	£200.20	1	1
GP visit (surgery)	£39.23	1	1
Clinical nurse specialist	£99.30	1	1
Community nurse	£43.46	0.5	0.68
Source	National Schedule of NHS Costs(87); PSSRU: Unit Costs of Health and Social Care 2020(88)	NICE TA639(18); NICE TA423(71)	

GP = general practitioner; NHS = National Health Service; NICE = National Institute for Health and Care Excellence; PD = progressed disease; PFS = progression-free survival; PSSRU = Personal Social Services Research Unit

B.3.5.3.2 Monitoring

Table 43 details the frequencies and unit costs of monitoring used in the model. In the PF state, the frequency and type of monitoring tests were specific to each intervention. Considering the unit costs of these tests, the total monitoring costs were calculated as £10.80 per week in the SG group compared with £17.19 in the TPC group. For patients with PD, monitoring costs continued to be accrued at each model cycle for the duration that patients remained alive. Monitoring costs were £16.80 per week for all patients in this health state. Frequency of full blood count and exclusion of ECF and metabolic panel were based on feedback from UK clinicians.

Table 43: Monitoring frequency and unit costs

	CT scan	Full blood count	Liver function	Renal function	ECG	Source
Unit Cost	£120.55	£2.53	£9.60	£12.00	£61.80	National Schedule of NHS Costs 2019/2020(87)
Frequency per month - PFS						
SG	0.33	2.67	-	-	-	TRODELVY® SmPC(1)
TPC	0.33	2.67	0.33	0.33	0.33	Xeloda SmPC(98); Halaven SmPC(99); Gemcitabine SmPC(100); Vinorelbine SmPC(101)
Frequency per month - PD						
All Treatments	0.33	2	0.33	0.33	0.33	Assumption

CT = computed tomography; ECG = electrocardiogram; NHS = National Health Service; PD = progressed disease; PFS = progression-free survival; SG = sacituzumab govetican; SmPC = summary of product characteristics; TPC = treatment of physician's choice

B.3.5.4 Adverse reaction unit costs and resource use

The costs of managing the AEs that were considered in the model are presented in Table 44. AE costs were accrued at the start of the model for the current-line treatment. This includes grade 3/4 AEs occurring in ≥3% of study subjects in either SG or TPC arm of the ASCENT trial.

Table 44: AE management costs

Adverse event	Cost per event	Source	Code
Neutropenia[a]	£705.82	National Schedule of NHS Costs 2019/2020(87)	SA35 Agranulocytosis, non-elective short stay
Diarrhea	£581.93		FD10 Non-malignant gastrointestinal tract disorders with single intervention or without intervention, non-elective short stay
Leukopenia	£614.78		SA08 Other haematological or splenic disorders, non-elective short stay
Anaemia	£500.48		SA09 Other Red Blood Cell Disorders with CC Score 0-5, non-elective short stay
Febrile neutropenia[a]	£1,785.62		SA35 Agranulocytosis, non-elective short stay and long stay
Fatigue	£39.00		PSSRU 2020: 1hr community nurse visit per day for duration of adverse event(88)
Dyspnea	£370.86		DZ19N Other Respiratory Disorders without Interventions, with CC Score 0-4, non-elective short stay
Hypophosphatemia	£714.44		KC04 Inborn Errors of Metabolism with CC Score 0-2, non-elective short stay
Pneumonia	£792.30		DZ11 Lobar, Atypical or Viral Pneumonia, non-elective short stay
Nausea	£581.93		FD10 Non-malignant gastrointestinal tract disorders with single intervention or without intervention, non-elective short stay
Pulmonary embolism	£663.02		DZ09 Pulmonary Embolus with or without intervention, non-elective short stay
Pleural effusion	£623.36		DZ16 Pleural Effusion without Interventions, non-elective short stay

[a] Per UK clinician feedback, it is assumed that the AE costs for neutropenia and febrile neutropenia include G-CSF costs (£50 per day)

AE = adverse event; G-CSF = granulocyte-colony stimulating factor; NHS = National Health Service

B.3.5.5 Miscellaneous unit costs and resource use

Terminal care cost per patient who dies during pre-progression or post-progression is accrued as a one-off at the time of death. Typical costs associated with hospitalization and palliative care toward the end of life were included (Table 45). The total terminal care cost in the model was £7,752.90.

Table 45: Terminal care costs

	Cost	% Patients
Hospital	£8,515.00	40%
Hospice	£21,574.00	10%
Home	£4,379.00	50%
Source	PSSRU: Unit Costs of Health and Social Care 2020(88)	NICE TA639(18)

NICE = National Institute for Health and Care Excellence; PSSRU = Personal Social Services Research Unit

B.3.6 Summary of base case analysis inputs and assumptions

B.3.6.1 Summary of base case analysis inputs

A summary of inputs used in the model base case is provided in Table 46.

Table 46: Summary of variables applied in the economic model

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Model Settings			
Time horizon	10 years	Scenario analysis	B.3.2.2
Discount rate	3.5% for health and cost outcomes	Scenario analysis	B.3.2.2
Perspective	Payer (NHS)	—	B.3.2.2
Population	Locally advanced or mTNBC with two or more prior systemic therapies	—	B.3.2.1
TPC composition	Eribulin: 53.1%, vinorelbine: 19.8%; gemcitabine: 14.5%, capecitabine: 12.6%	—	B.3.2.3
Clinical Inputs			
OS estimation approach	Best fit parametric (jointly fitted)	Scenario analysis	B.3.3.3
PFS estimation approach	Best fit parametric (stratified)	Scenario analysis	B.3.3.2
TTD estimation approach	Best fit parametric (stratified)	Scenario analysis	B.3.3.4

Variable	Value	Measurement of uncertainty and distribution	Reference to section in submission
Treatment duration approach	TTD curve	Scenario analysis	B.3.3.4
OS parametric fitting distribution	SG: Log-logistic TPC: Log-logistic	Scenario analysis	B.3.3.3
PFS parametric fitting distribution	SG: Log-normal TPC: Log-logistic	Scenario analysis	B.3.3.2
TTD parametric fitting distribution	Exponential	Scenario analysis	B.3.3.4
Cost Inputs			
Wastage	Include (50%)	Scenario analysis	B.3.5.1
Dose intensity	Considered based on ASCENT trial data for SG (94.2%) and assumed equivalent for TPC	Scenario analysis	B.3.5.1.1
Comedication	Include	—	B.3.5.1.3
Subsequent treatment	Micro-costing	—	B.3.5.2
Disease management and monitoring	Micro-costing	—	B.3.5.3
Utility Inputs			
Utility during PFS	SG: 0.710 TPC: 0.626	SG: SE 0.010 (95% CI 0.690-0.730) TPC: SE 0.013 (95% CI 0.601-0.651)	B.3.4.4
Utility during PD	SG: 0.653 TPC: 0.569	SG: SE 0.012 (95% CI 0.629-0.677) TPC: SE 0.013 (95% CI 0.544-0.594)	B.3.4.4
AE disutility	Exclude	—	B.3.4.4

AE = adverse event; CI = confidence interval; NHS= National Health Service; OS = overall survival; PD = progressed disease; PFS = progression-free survival; SE = standard error; SG = sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to treatment discontinuation

B.3.6.2 Assumptions

Table 47 outlines the assumptions made in the model.

Table 47: Model assumptions and justification

Area	Assumption	Justification
Time horizon	10 years	Deemed appropriate to capture the long-term clinical and economic impacts of mTNBC on the targeted population with median age of 54 years, given their poor prognosis
Cycle length	1 week	Can accommodate the various cycle length of treatment comparators considered and is short enough to accurately capture differences in cost or health effects between cycles
Discount	Both health benefits and costs were discounted at an annual rate of 3.5%	NICE-recommended discount rates
Modelling approach	PartSA model	Flexible, directly uses trial-based time-to-event endpoints, and consistent with previous appraisals
Extrapolation	OS, PFS, and TTD curves were extrapolated. Curve selection based on statistical fit and clinical face validity of predictions	Per DSU guidance
Treatment duration approach	Treatment discontinuation modelled via TTD curve	Better captures early discontinuers due to non-progression reasons progression (e.g., severe AEs or loss of follow-up)
Composition of TPC	Eribulin: 53.1%, Vinorelbine: 19.8%; Gemcitabine: 14.5%, Capecitabine: 12.6%	Aligned with TPC composition of ASCENT ITT population
Estimation approach	Best fit parametric (OS: jointly fitted; PFS/TTD stratified)	Commonly accepted estimation approach; for PFS, the AFT assumption and PH assumption may both be violated, and thus treatment arms were fitted separately; for OS, the PH assumption might be slightly violated, while the AFT assumption holds, so jointly fitted AFT distributions with treatment arm as predictor was selected; for TTD, stratified fitting was selected as the most appropriate approach based on clinical input
OS parametric fitting distribution	Log-logistic for SG and TPC	Based on best overall statistical fit and long-term survival projections, which were consistent with a small number of patients remaining alive at 10 years
PFS parametric fitting distribution	Log-normal for SG and log-logistic for TPC	Best fits based on goodness-of-fit statistics
TTD parametric	Exponential	Best fits based on goodness-of-fit statistics

Area	Assumption	Justification
fitting distribution		
Subsequent treatments	Micro-costing approach	Subsequent treatment composition and treatment duration derived from ASCENT (separately for SG and TPC treatment arms, per clinician input)
Disease management	Micro-costing	Frequencies of use and unit cost for each MRU item is better to capture the disease management cost
Comedication	Include	Based on feedback from UK clinicians
Utilities	The model uses different utilities by treatment arm for PF and PD	Derived from EQ-5D-3L analysis with ASCENT trial data. Treatment is considered to be a significant factor of utility in PFS, and therefore utilities may differ by treatment arm; UK clinical experts agreed that the 0.08 difference in progression-free utility was plausible.
AE disutilities	Not included	It was assumed that any disutilities due to AEs have already been incorporated into the health state trial-derived utilities and incorporating an additional disutility could be considered double-counting
Dose intensity	Included for SG based on observed relative dose intensity in ASCENT (94.2%); assumed to be the same for TPC	Adjustment to account for efficacy of received dose of treatment vs intended dose
Wastage	Included (50%)	It was assumed that some of the drug will be wasted if perfect vial sharing is not practiced

AFT = accelerate time to failure; AE = adverse event; ITT = intention to treat; MRU = medical resource utilisation; National Institute for Health and Care Excellence; OS = overall survival; PD = progressed disease; PF = progression-free; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to treatment discontinuation;

B.3.7 Base case results

B.3.7.1 Base case incremental cost-effectiveness analysis results

Base case results of the model with the above-described assumptions and inputs are presented in Table 48 for PAS price. In the base case analysis, SG was associated with greater discounted LYs and discounted QALYs than TPC. SG was also associated with higher costs, driven primarily by the drug acquisition cost, which is strongly influenced by the longer time on treatment for patients on SG. The resulting ICER for SG versus TPC was £49,651/QALY at PAS price (Table 49; Figure 41).

Table 48: Base case results (PAS price)

Outcomes	SG	TPC
Health outcomes		
Total LYs	[redacted]	[redacted]
LYs in PFS	[redacted]	[redacted]
LYs in PD	[redacted]	[redacted]
Total QALYs	[redacted]	[redacted]
QALYs in PFS	[redacted]	[redacted]
QALYs in PD	[redacted]	[redacted]
Cost outcomes		
Drug acquisition	[redacted]	[redacted]
Drug administration	[redacted]	[redacted]
Concomitant medication	[redacted]	[redacted]
Subsequent treatment	[redacted]	[redacted]
Disease management	[redacted]	[redacted]
PFS	[redacted]	[redacted]
PD	[redacted]	[redacted]
Terminal care	[redacted]	[redacted]
Monitoring	[redacted]	[redacted]
PFS	[redacted]	[redacted]
PD	[redacted]	[redacted]
AE management	[redacted]	[redacted]
Total costs	[redacted]	[redacted]

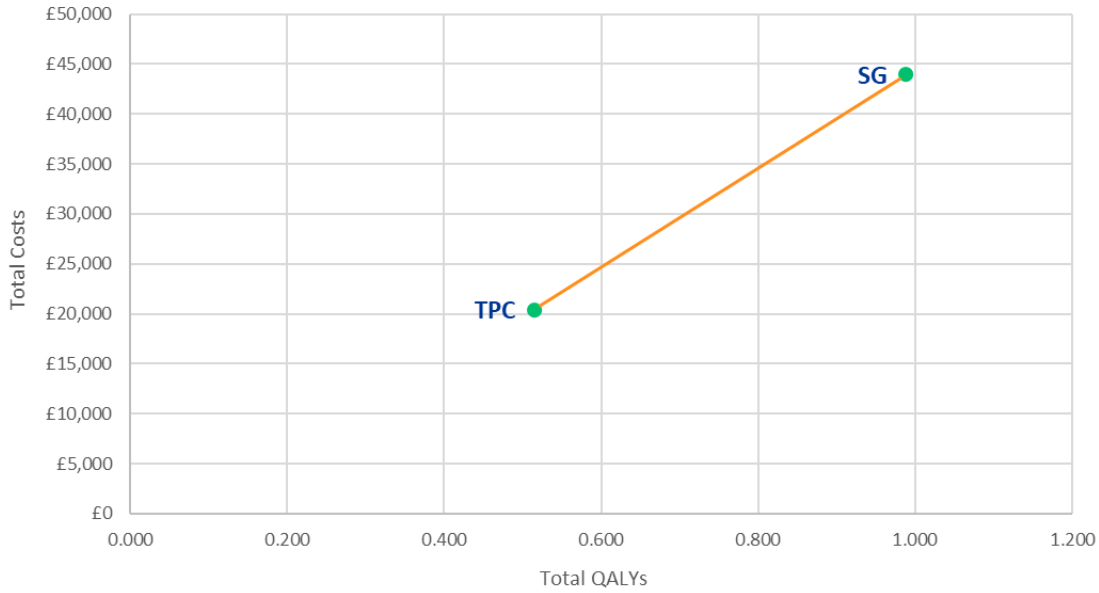
AE = adverse event; ICER = incremental cost-effectiveness ratio; LY = life year; PAS = patient access scheme; PD = progressed disease; PFS = progression-free survival; QALY = quality-adjusted life year; SG = sacituzumab govetican; TPC = treatment of physician's choice

Table 49: Incremental cost-effectiveness results (PAS price)

Incremental outcomes	SG vs TPC
Incremental costs	[redacted]
Incremental LYs	[redacted]
Incremental QALYs	[redacted]
ICER (cost per LY gained)	£40,706
ICER (cost per QALY gained)	£49,651

ICER = incremental cost-effectiveness ratio; LY = life year; PAS = patient access scheme; QALY = quality-adjusted life year; SG = sacituzumab govetican; TPC = treatment of physician's choice

Figure 41: Base case cost-effectiveness plane and efficacy frontier



PAS = patient access scheme; QALY = quality-adjusted life year; SG = sacituzumab govetican; TPC = treatment of physician's choice

B.3.8 Sensitivity analyses

B.3.8.1 Probabilistic sensitivity analysis

To account for the joint uncertainty of the underlying parameter estimates, a second-order stochastic sensitivity analysis (i.e., PSA) was performed. Distributions built in a PSA are beta, gamma, log-normal, and normal, per conventions in economic analyses.(102)

- The beta distribution is confined by the interval 0 to 1 and is typically used for inputs such as proportions and utility values.
- The gamma distribution is confined by the interval 0 to ∞ and is typically used for costs.
- The normal distribution allows any value from ∞ to ∞, and is typically used for parameters that follow the central limit theorem.
- The log-normal distribution is a normal distribution on the log scale, and is typically used for sampling relative risks, odds ratios, and HRs.

The model also included Cholesky decomposition matrix calculation fields for modeling pairs of input parameters for which the covariance structure between two variables was known. For example, all survival curve function parameters (OS, PFS, and TTD) were varied using this method to account for the correlation between the scale and shape parameters of the two-parameter survival functions. The variance and covariance matrix of the survival function parameters were obtained from the curve-fitting procedure. The parameters included in the PSA and how they were varied are shown in Table 50.

Table 50: Model parameters varied in the PSA

Parameter	PSA distribution
Weight (kg)	Normal distribution
BSA (m^2)	
PFS	Normal distribution (Cholesky decomposition)
OS	
TTD	
HRs of PFS and OS (if used for the out-of-trial placeholder comparators)	Log-normal distribution
Relative dosing intensity	Beta distribution
Cost components: Subsequent treatment costs Disease management and monitoring costs AE management costs	Gamma distribution
Utility	Beta distribution

AE = adverse event; BSA = body surface area; HR = hazard ratio; PFS = progression-free survival; PSA = probabilistic sensitivity analysis; OS = overall survival; TTD = time to treatment discontinuation

Based on the results of 1,000 simulations (in which incremental costs and incremental QALYs were varied over replications of SG vs TPC), the PSA results were consistent with the base case results (Table 51). The mean ICER was £49,648 (£49,651 in the base case).

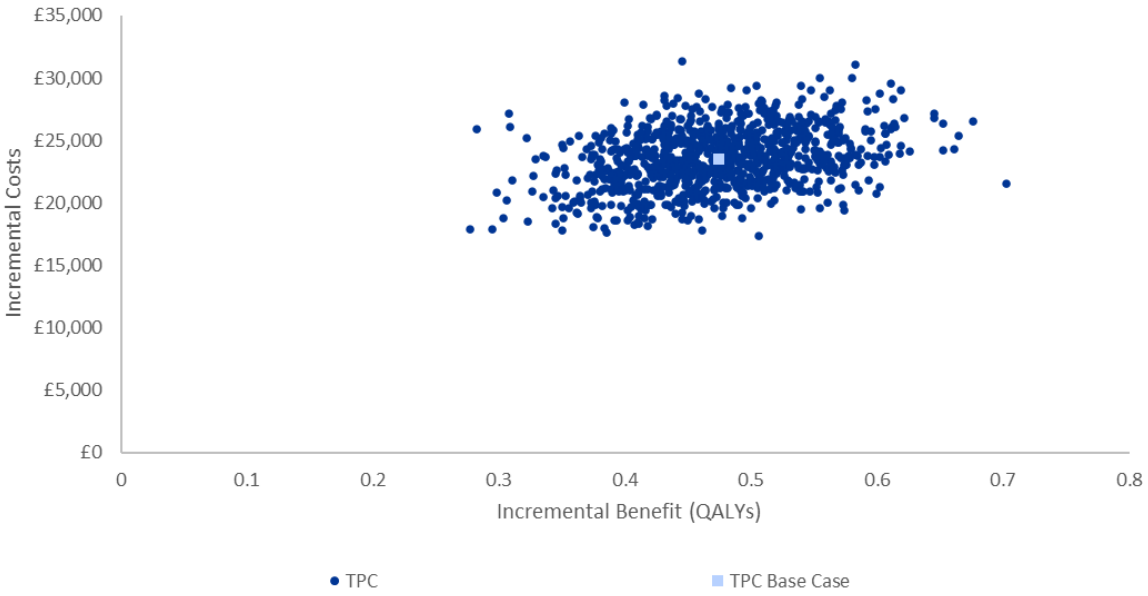
Table 51: Probabilistic sensitivity analyses results (PAS price)

Incremental outcomes	SG vs TPC
Incremental costs	[redacted]
Incremental LYs	[redacted]
Incremental QALYs	[redacted]
ICER (cost per LY gained)	£40,757
ICER (cost per QALY gained)	£49,648

ICER = incremental cost-effectiveness ratio; LY = life year; PAS = patient access scheme; QALY = quality-adjusted life year; SG = sacituzumab govetican; TPC = treatment of physician's choice

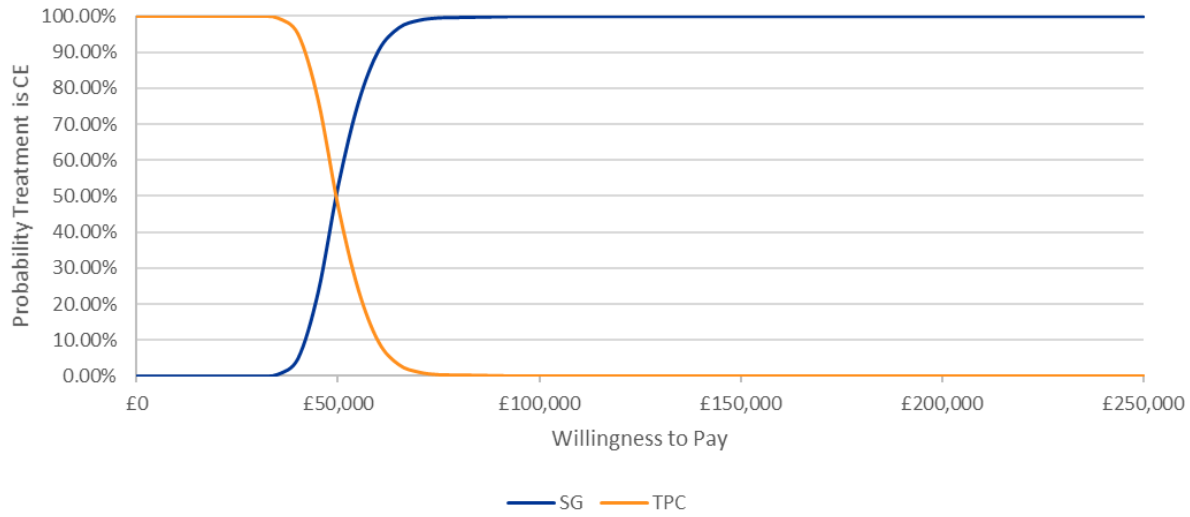
The PSA results are illustrated below on a cost-effectiveness plane (Figure 42) and a cost-effectiveness acceptability curve (CEAC) (Figure 43). Using the iterations performed for the PSA, the CEAC is generated by plotting the fraction of simulations, for which the treatment arm therapy is more cost-effective than the control arm therapy, over a range of cost/QALY willingness-to-pay thresholds. Therefore, a CEAC is a way to summarize the impact of the overall model parameter uncertainty in the cost-effectiveness estimates. The CEACs indicate that at a willingness-to-pay threshold of £50,000, SG had a 53% probability of being cost-effective compared with TPC (Figure 43). This rapidly increased such that SG had a 91% chance of being cost-effective compared with TPC at a threshold of £60,000.

Figure 42: Probabilistic results on the cost-effectiveness plane (PAS price)



LY = life year; PAS = patient access scheme; TPC = treatment of physician's choice

Figure 43: Cost-effectiveness acceptability curves for SG vs TPC (PAS price)



CE = cost-effective; PAS = patient access scheme; SG = sacituzumab govetican; TPC = treatment of physician's choice

B.3.8.2 Deterministic sensitivity analysis

All major model variables for which values were uncertain were tested in a one-way sensitivity analysis to identify model drivers and examine key areas of uncertainty. Where possible, CIs or published ranges were used as alternative values. In the absence of CIs or published ranges, upper and lower bounds tested in the one-way sensitivity analysis were calculated as ± 20% of the mean value. The parameters tested in the one-way sensitivity analyses and how they were varied are shown in Table 52.

Table 52: Model parameters varied in DSA

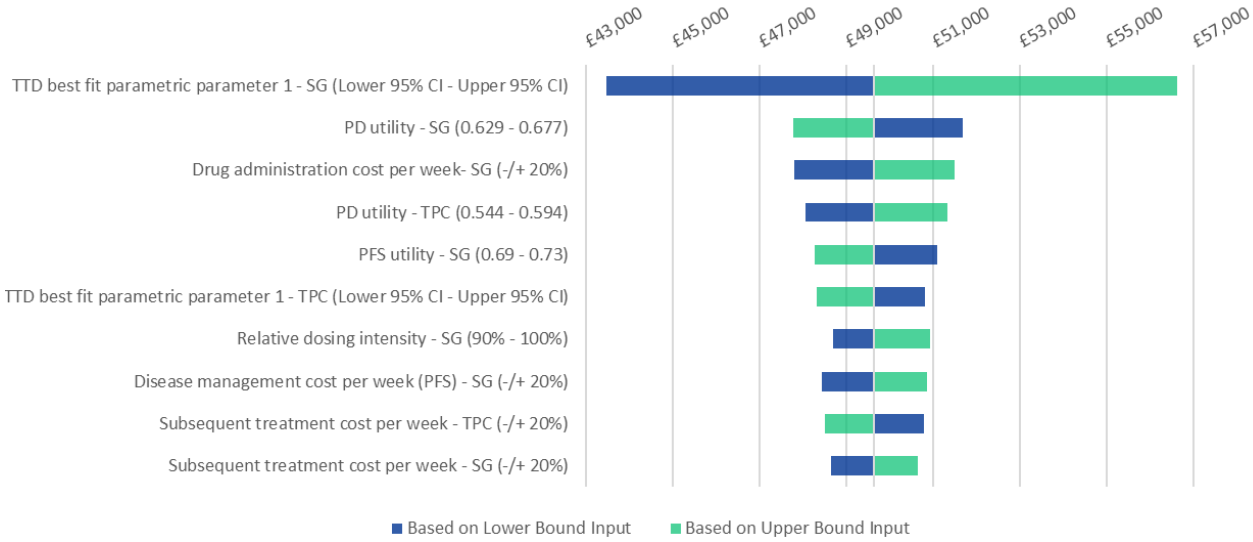
Variable	Base case	Lower	Upper	Rationale
Starting age (years)	52	51.48 (lower 95% CI)	53.42 (upper 95% CI)	Used variability around the mean from trial
Weight (kg)	68.35	66.09 (lower 95% CI)	70.61 (upper 95% CI)	Used variability around the mean from trial
BSA (m^2)	1.75	1.72 (lower 95% CI)	1.78 (upper 95% CI)	Used variability around the mean from trial
Efficacy: PFS best fit parametric parameters - SG	See Section B.3.3.2	Lower 95% CI	Upper 95% CI	Varied within bounds
Efficacy: PFS best fit parametric parameters - TPC		Lower 95% CI	Upper 95% CI	Varied within bounds
Efficacy: OS best fit parametric parameters - SG		Lower 95% CI	Upper 95% CI	Varied within bounds

Variable	Base case	Lower	Upper	Rationale
Efficacy: OS best fit parametric parameters - TPC	See Section B.3.3.3	Lower 95% CI	Upper 95% CI	Varied within bounds
Efficacy: TTD best fit parametric parameters - SG	See Section B.3.3.4	Lower 95% CI	Upper 95% CI	Varied within bounds
Efficacy: TTD best fit parametric parameters - TPC		Lower 95% CI	Upper 95% CI	Varied within bounds
Relative dosing intensity of SG	94.2%	90.0%	100.0%	Alternative values
Relative dosing intensity of TPC	94.2%	90.0%	100.0%	Alternative values
Drug administration cost per week- SG	£158	-20%	+20%	Extreme values
Drug administration cost per week - TPC	£155	-20%	+20%	Extreme values
Concomitant treatment cost per week - SG	£2	-20%	+20%	Extreme values
Concomitant treatment cost per week - TPC	£1	-20%	+20%	Extreme values
Subsequent treatment cost per week - SG	£4,076	-20%	+20%	Extreme values
Subsequent treatment cost per week - TPC	£3,567	-20%	+20%	Extreme values
Disease management cost per week (PFS) - SG	£83	-20%	+20%	Extreme values
Disease management cost per week (PFS) - TPC	£83	-20%	+20%	Extreme values
Disease management cost per week (PD)	£85	-20%	+20%	Extreme values
Terminal cost	£7,753	-20%	+20%	Extreme values
Monitoring cost per week (PFS) - SG	£11	-20%	+20%	Extreme values
Monitoring cost per week (PFS) - TPC	£17	-20%	+20%	Extreme values
Monitoring cost per week (PD)	£17	-20%	+20%	Extreme values
AE management cost - SG	£778	-20%	+20%	Extreme values
AE management cost - TPC	£472	-20%	+20%	Extreme values
PFS utility - SG	0.710	0.690 (lower 95% CI)	0.730 (upper 95% CI)	Varied within bounds
PFS utility - TPC	0.626	0.601 (lower 95% CI)	0.651 (upper 95% CI)	Varied within bounds
PD utility - SG	0.653	0.629 (lower 95% CI)	0.677 (upper 95% CI)	Varied within bounds
PD utility - TPC	0.569	0.544 (lower 95% CI)	0.594 (upper 95% CI)	Varied within bounds

AE = adverse event; BSA = body surface area; CI = confidence interval; PD = progressed disease; PFS = progression-free survival; OS = overall survival; SG = sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to treatment discontinuation

The parameter that had the greatest impact on the ICER was the SG TTD curve parameter, which determines the treatment duration of SG (Figure 44). Other parameters that had less of an effect on the ICER included the PD utility of SG, SG drug administration cost, PD utility of TPC, and PFS utility of SG.

Figure 44: Deterministic sensitivity analysis of SG vs TPC (PAS price) – tornado diagram



CI = confidence interval; PAS = patient access scheme; PD = progressed disease; PFS = progression-free survival; SG = sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to treatment discontinuation

B.3.8.3 Scenario analysis

Scenario analyses were conducted to test the impact of clinical assumptions and cost and utility estimation scenario. The results of the scenario analyses are presented in Table 53. The majority of scenarios examined increased or decreased the base case ICER by <5%, indicating that results of the model are relatively robust. Changes to the clinical inputs for OS and PFS produced the largest impact on the resulting ICER; scenario results are described in more detail below.

Table 53: Scenario analysis variables and results

Variable	Base case	Alternative	Rationale	ICER (PAS price)	% change from base case
Base case				£49,651	—
Model settings					
Time horizon	10 years	5 years	Equal to the time horizon used in eribulin NICE TA423(71)	£53,707	8.17%
		15 years	Longer time horizon ensures that all patients will be deceased. Equal to the time horizon used in atezolizumab NICE TA639(18)	£48,516	-2.29%
Discounting	3.5% for both costs and outcomes	1.5% for both costs and outcomes	NICE HTA guidance(103)	£48,671	-1.97%
Clinical Inputs					
PFS extrapolation	Stratified fit model: log-normal for SG and log-logistic for TPC (best statistical fit)	Stratified fit model: Weibull for SG and TPC (pessimistic assumption for long-term estimation)	Test of alternative survival projections to explore their influence on outcomes	£50,768	2.25%
		Stratified fit model: log-logistic for SG and log-normal for TPC (2nd best statistical fit)		£49,473	-0.36%
		KM + parametric fit (Stratified fit model: log-normal for SG and log-logistic for TPC)		£50,668	2.05%
OS extrapolation	Joint fit model: log-logistic for both SG and TPC (best statistical fit)	Joint fit model: generalized Gamma for both SG and TPC (pessimistic assumption for long-term estimation and 2nd best statistical fit)	Test of alternative survival projections to explore influence on their outcomes	£56,105	13.00%
		KM + Parametric fit (Joint fit model: log-logistic for both SG and TPC)		£49,422	-0.46%

Variable	Base case	Alternative	Rationale	ICER (PAS price)	% change from base case
Treatment duration	Based on TTD parametric fitting model separately fitted to trial observed data: exponential for both SG and TPC (best statistical fit)	Based on TTD parametric fitting model separately fitted to trial observed data: KM + Parametric fit (exponential for both SG and TPC)	Test of alternative survival projections to explore influence on outcomes	£50,856	2.43%
		Based on TTD parametric fitting model separately fitted to trial observed data: Weibull for both SG and TPC (second best statistical fit)		£49,271	-0.77%
Other Inputs					
Relative dosing intensity	94.2% for SG; assumed the same for TPC	84% for TPC	Equal to the relative dosing intensity presented in eribulin NICE TA423(71)	£50,314	1.34%
		100% for SG and TPC	Test of extreme assumption	£50,462	1.63%
Wastage	50% of wastage	100% of wastage	Test of extreme assumption; aligns with approach to scenario analysis in trastuzumab NICE TA704(104)	£52,232	5.20%
		0% of wastage	Aligns with base case presented in atezolizumab NICE TA639(18)	£47,069	-5.20%
Utility analysis mapping algorithm from EORTC QLQ-C30 collected in ASCENT trial to EQ-5D-3L	Longworth et al. 2014(78)	Crott et al. 2010(77)	Test potential impact of different approaches to mapping utilities. Aligns with base case presented in eribulin NICE TA423(84)	£46,102	-7.15%
AE disutility	Exclude	Include	Included in eribulin NICE TA423 base case(71) and in scenario analysis in atezolizumab NICE TA639(18)	£49,724	0.15%

AE = adverse event; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; PFS = progression-free survival; OS = overall survival; PAS = patient access scheme; SG = sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to treatment discontinuation

B.3.8.3.1 Clinical input scenarios

Using the second-best statistical fits for extrapolation of PFS (log-logistic for SG or log-normal for TPC), or using the Weibull distribution, considered a pessimistic assumption for estimation of long-term PFS, had little impact on the ICER. Extrapolating PFS using KM + parametric fit, instead of best fit parametric, increased the ICER by a small amount to £50,668.

Altering the OS extrapolation method to the KM + parametric fit also had a small impact on the ICER (decreased to £49,422). Use of the generalized gamma distribution for OS extrapolation of both SG and TPC, however, increased the ICER to £56,105. While generalized gamma provided the second-best statistical fit, it was considered to be a pessimistic assumption for long-term estimation of OS, predicting 1.00% survival at 5 years and <0.01% survival at 10 years. This assumption is not consistent with real-world data or baseline disease characteristics from the ASCENT trial, which support long-term survival of a limited number of patients.(27, 37, 82).

Scenario analyses exploring the method of estimating treatment duration had small impact on the ICER (ranged from £49,271 to £50,856). Instead of using the predicted parametric fitting curve, a scenario using trial observed curve was explored to ensure the best use of available data. KM estimates of TTD were applied until the endpoint of the follow-up in safety population (i.e., 22.87 months for SG and 15.34 months for TPC), which was then followed by a parametric fitting curve using an exponential distribution (i.e., best statistical fit). It modestly increased the ICER (to £50,856). Likewise applying the Weibull distribution to estimate treatment duration for both SG and TPC had a minimal effect on the ICER (to £49,271).

B.3.8.3.2 Model settings and other inputs

Scenario analyses that varied the model settings, extending the time horizon to 15 years or reducing discounting of costs and outcomes, generally improved the ICER. Changes to dosing assumptions had a small impact on the ICER (e.g., 0% or 100% wastage increased or decreased the ICER by 5.2%, respectively; adjustments to relative dosing intensity increased the ICER by 1.3-1.6%).

Use of the Crott mapping algorithm for mapping utilities reduced the ICER by 7.15% to £46,102. This algorithm was developed based on data from patients with locally advanced breast cancer, rather MBC, which impacts the relevance of its use to the decision problem. The use of the Longworth algorithm in the base case can therefore be described as a conservative approach to utility mapping.

B.3.9 Validation

B.3.9.1 Validation of cost-effectiveness analysis

Upon completion of model programming, a rigorous and comprehensive quality check of the model was conducted to ensure the completed model contained no errors and worked as intended.

A series of tests and checks were also conducted on the model engine. Among other reviews, the validator:

- Confirmed that all model inputs were correctly linked to the engine
- Checked all cells with “IF logic” in detail, confirming that the statements provided the correct value for each condition
- Traced all links between the calculation sheets and results sheet to make sure that the proper outputs were displayed in the correct location
- Thoroughly reviewed and debugged all Visual Basic for Applications (VBA) code
- Searched for common Microsoft Excel® errors (e.g., !#REF errors, unused named ranges, broken links, links to external workbooks, copy/paste errors) and resolved them as needed
- Checked all text and formatting to ensure that there were no typographical errors or formatting irregularities

Finally, an extreme-value sensitivity analysis was conducted on all applicable model inputs. While conducting the analysis, the validator noted the direction and magnitude of change for each extreme value tested, and confirmed that this aligned with the expected result (e.g., if all drug cost inputs are set to 0, the model should

output total drug costs of 0 as well). The model validation process uncovered minimal discrepancies and no impactful model calculation errors. Feedback from the validation was addressed in the model, and the refined post-validation model was used to generate the results included in this report.

External validation of the modelling approach and key assumptions was carried out in several stages. Firstly, an advisory board was held in April 2021, with external health economic experts and clinician oncologists with expertise in TNBC. The aim of this advisory board was to gain insight into the TNBC treatment pathway, as well as input and recommendations on the model structure, functionality, underlying assumptions, data sources, and inputs. Second, an online platform was utilized to obtain feedback from clinicians on specific questions related to the plausibility of long-term survival extrapolations. Finally, an advisory board was held two months prior to submission, attended by two UK-based health economists and two UK-based expert clinicians, to validate and finalise model assumptions.

B.3.10 Interpretation and conclusions of economic evidence

As described throughout Section B.3, the methods to evaluate the cost effectiveness of SG are based on the best currently available evidence from the ASCENT trial. The range of economic analyses presented in this submission indicate that the findings of the SG cost-effectiveness analysis are relatively robust. In the base case analysis, SG was cost-effective versus TPC, with an ICER of £49,651/QALY at PAS price. Probabilistic sensitivity analyses showed that these results are robust with respect to parameter uncertainty, producing a mean ICER of £49,648. At a willingness-to-pay threshold of £50,000, SG was more likely to be cost-effective than TPC.

Treatment duration and OS extrapolations are key drivers of the model results, and as such have been externally validated and explored in sensitivity and scenario analyses. Model results were also driven by utility estimates, which were confirmed by UK clinicians to be clinically plausible; notably, scenario analyses testing use of an alternate utility mapping algorithm resulted in a lower ICER (£46,102/QALY), indicating that the base case considers a conservative approach to mapping utility.

The appropriateness of the modelling approach, clinical inputs, and assumptions were tested via consultation with UK clinical experts. Survival extrapolations were validated using a combination of statistical fit, expert opinion, and external data sources, when available.

This cost-effectiveness analysis has several strengths:

- The clinical pathways upon which the model was based reflect current UK clinical practice for second-line or later locally advanced or metastatic TNBC.
- The model structure, projection approaches, and assumptions were validated by clinical experts to ensure accuracy and completeness.
- The modeling approach was based on a thorough review of published economic modeling approaches, considered critiques from previous NICE appraisals in MBC, and was vetted by a panel of expert health economists. Overall, the model provides extensive flexibility in how to estimate OS and in data options, which are key areas of uncertainty.
- The model approach and programming were well validated.
- The model is flexible in terms of how to inform treatment duration, PFS, and OS assumptions; considering combinations of these clinical factors is important for clinical plausibility.

Limitations of this cost-effectiveness analysis include the following:

- EQ-5D was not collected in the ASCENT trial, and therefore EORTC QLQ-C30 measurements collected in the ASCENT trial were mapped to the EQ-5D-3L using the Longworth mapping algorithm,(78) which could introduce uncertainty in the estimated utility values.
- Treatment of physician's choice was selected prior to randomization from 1 of the 4 allowed regimens, and efficacy is reported for the treatment basket and not for individual drugs (eribulin, gemcitabine, capecitabine, or vinorelbine). This comparator does not fully reflect clinical practice in the UK, as single agent gemcitabine is not a standard therapy for 2L or 3L mTNBC. Further analysis of ASCENT data found no significant differences in OS or PFS between treatments in the TPC arm, indicating the inclusion of gemcitabine is unlikely to influence results of the trial or model in favour of SG. Moreover, <15% of patients in the TPC arm received gemcitabine.

- There were no data available to establish external validity of the OS long-term estimates; however, given the maturity of the trial data, this is not likely to impact the results.

Overall, results of the economic analyses demonstrate that SG is a highly effective, life-extending treatment for patients with mTNBC, a population with an extremely poor prognosis and limited treatment options. In a patient population with an estimated OS of only 7 months (30), SG is predicted to provide [redacted] additional LYs and [redacted] additional QALYs vs standard of care therapy.

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after two or more therapies [ID3942]

Clarification questions

October 2021

File name	Version	Contains confidential information	Date
Clarification Questions ERG	3	yes	28.10.2021

Section A: Clarification on effectiveness data

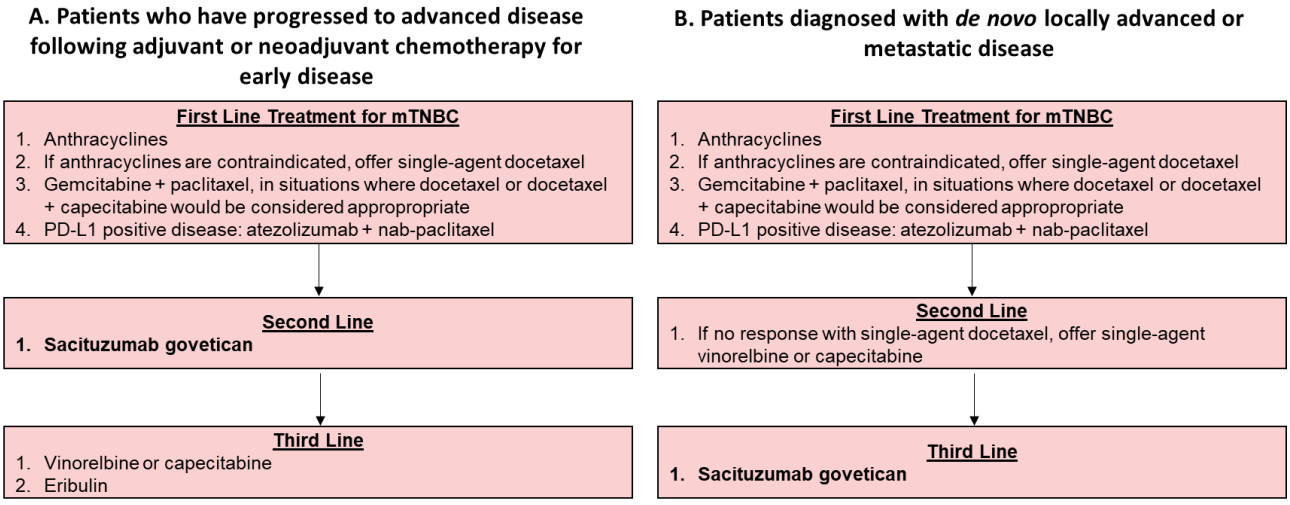
Document B

A1. **Table, page 9: the population includes Adults with unresectable locally advanced or metastatic triple-negative breast cancer who have had at least two prior therapies, including at least one for locally advanced or metastatic disease. Does this mean that of those who received 'at least two prior therapies' some may have received only one prior therapy and had progressed within 12 months*?***

The indication licensed in Great Britain for SG is for the treatment of adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received two or more prior lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease.(1) This means all patients receiving SG within its Marketing Authorisation are on second-line mTNBC therapy or beyond.

All patients on third-line mTNBC or beyond can receive SG (Figure 1B).(2) Patients on second-line treatment receiving SG will have been diagnosed with TNBC at an earlier disease stage before progressing to mTNBC and must have received one systemic regimen in the locally advanced or metastatic setting and at least one systemic regimen (i.e, as a pre-surgery neoadjuvant therapy or post-surgery adjuvant therapy) prior to locally advanced or metastatic recurrence (Figure 1A).(2)

Figure 1. NICE treatment pathway for managing TNBC with proposed positioning for SG in patients with mTNBC(2)

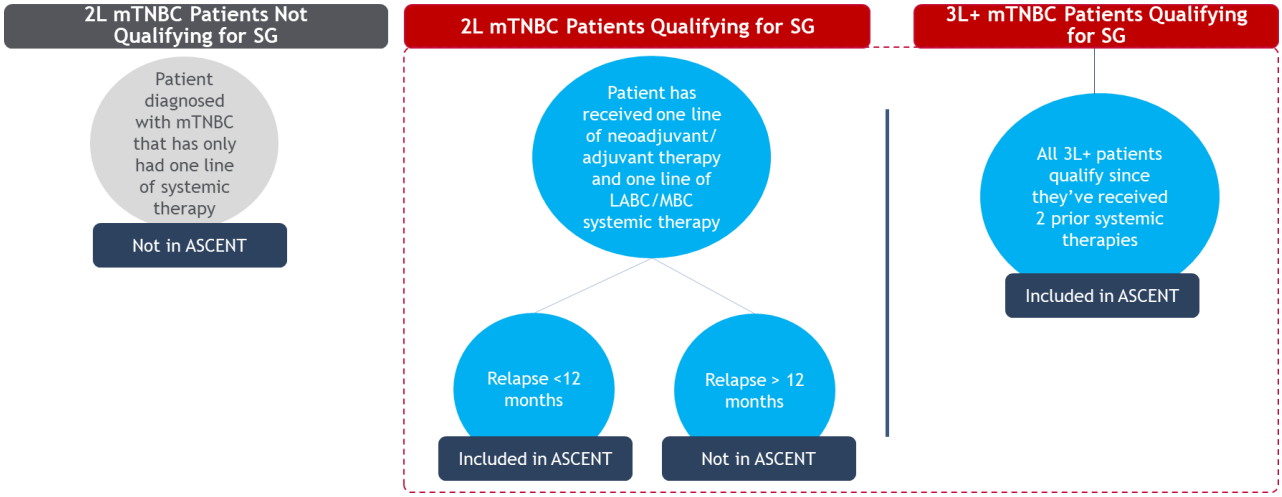


Note: Adjuvant or neoadjuvant therapy for localised disease is considered a prior systemic therapy, and therefore patients who progress following early stage therapy would be eligible for SG in the second-line metastatic setting per the licensed indication

mTNBC=metastatic triple-negative breast cancer; NICE=National Institute for Health and Care Excellence; PD-L1=programmed death-ligand 1; SG=sacituzumab govitecan

The full licensed population described above is the one for which reimbursement is being sought. Figure 2 illustrates the licensed patient populations for SG and the included patient population in ASCENT.(1, 3)

Figure 2: Overview of licensed population for SG in mTNBC and trial population in ASCENT(1, 3)



Red dashed lines indicate the licensed patient populations for SG

3L+=third-line and beyond; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; mTNBC=metastatic triple-negative breast cancer; SG=sacituzumab govitecan

A2. Figure 2, page 19:

A2.1. The difference between A and B populations is the stage at diagnosis (A=locally advanced vs. B=metastatic)?

Not quite – the difference between the A and B populations is defined by prior treatment which is, in turn, largely defined by disease stage at diagnosis, but the terminology suggested in the question is not correct. Population A includes patients who were initially diagnosed with early-stage, potentially curable breast cancer whilst population B is, essentially, comprised of patients whose disease was locally advanced or metastatic and hence, incurable, at the the time of doagnosis.

Figure 2 (page 19) in Document B presents the earliest possible use of SG in the mTNBC treatment pathway according to its licensed indication in Great Britain.(1) Per our response to question A.1, Figure 2A refers to patients who were diagnosed with early stage TNBC before progressing to a locally advanced or metastatic

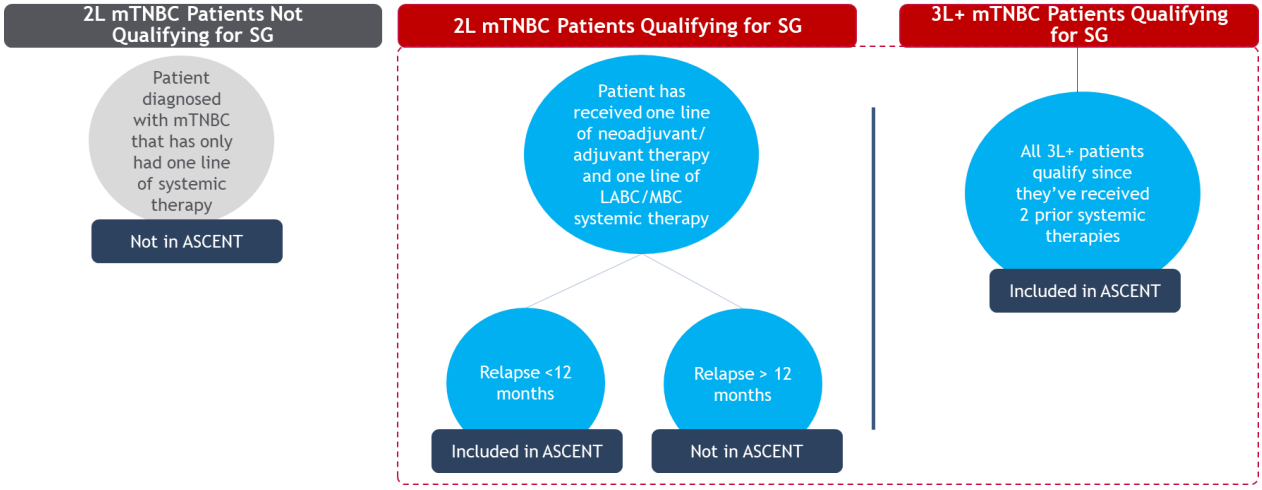
disease stage as they would have likely received neoadjuvant and/or adjuvant chemotherapy and surgery as potentially curative treatment, followed by one line of systemic therapy in the metastatic setting. Therefore, Figure 2A presents the treatment pathways for patients receiving SG in the second-line mTNBC setting. Figure 2B shows patients who have received two prior lines of systemic therapy for mTNBC. These patients may have been diagnosed with *de novo* locally advanced or metastatic disease and therefore would have had both of the required two prior lines of systemic therapy in the locally advanced or metastatic setting. In summary, the main difference between the populations in Figure 2A and Figure 2B is the stage of disease at diagnosis of TNBC as the treatment pathways differ between these two groups.

A2.2. Is the company positioning sacituzumab govitan (SG) as second and third line treatment?

Reimbursement is being sought for the full licensed population as per the label for Great Britain which indicates SG for the treatment of adult patients with unresectable locally advanced or mTNBC who have received two or more prior lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease.(1) Therefore, reimbursement is sought for all patients on third-line mTNBC treatment or beyond as well as patients on second-line treatment for mTNBC who have also received at least one systemic regimen for early (operable) TNBC (i.e., as neoadjuvant or adjuvant therapy given as an adjunct to surgery) at any time prior to progression to locally advanced or mTNBC.

Figure 3 illustrates the licensed patient populations for SG which are all covered by the submission and how those relate to the population in the ASCENT trial.

Figure 3: Overview of licensed population for SG in mTNBC(1, 3)



Red dashed lines indicate the licensed patient populations for SG
1L=first-line; 2L=second-line; 3L+=third-line and beyond; LABC=locally advanced breast cancer; MBC=metastatic breast cancer; mTNBC=metastatic triple-negative breast cancer; SG=sacituzumab govitecan

A3. Please provide the baseline characteristics of UK only patients in ASCENT trial

Table 1 summarises the key characteristics of UK only patients in ASCENT in the ITT population.

Table 1: Characteristics of UK only patients in ASCENT across treatment groups in ITT population

Characteristic	SG [redacted]	TPC [redacted]	Total [redacted]
Age, years, n (%)			
< 50	[redacted]	[redacted]	[redacted]
50-64	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Sex, n (%)			
Male	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]
Race, n (%)			
American Indian or Alaska Native	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]
Black	[redacted]	[redacted]	[redacted]
Native Hawaiian or Other Pacific Islander	[redacted]	[redacted]	[redacted]
White	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]
BMI (kg/m^2)[a]			

Characteristic	SG	TPC	Total
Mean (SD)			
Median			
Range			
Body surface area (m^2)[b]			
Mean (SD)			
Median			
Range			
Number of prior chemotherapies for randomisation stratification, n (%)[c]			
2-3			
>3			
Prior PD-1/PD-L1 therapy, n (%)			
Yes			
No			
Number of prior systemic therapies			
Mean (SD)			
Median			
Range			
Region for randomisation stratification, n (%)[c]			
Rest of World			
Original diagnosis TNBC, n (%)			
Yes			
No			
Time from diagnosis of stage 4 to study entry (months)[d]			
Mean (SD)			
Median			
Range			
Presence of known brain metastases at study entry for randomisation stratification, n (%)[c]			
Yes			
No			
***UGT1A1* genotype (SG only), n (%)**			
*1/*1			
*1/*28			
*28/*28			
Other			
Missing			
***BRCA1/BRCA2* Mutational Status, n (%)[e]**			
Negative			
Positive			
Screening ECOG performance status, n (%)			
0: Normal Activity			
1: Symptoms but Ambulatory			
Baseline serum bilirubin, n (%)			
Normal (≤ULN)			
>1 and ≤1.5× ULN			

Characteristic	SG [redacted]	TPC [redacted]	Total [redacted]
>1.5× ULN	[redacted]	[redacted]	[redacted]
Baseline creatinine clearance (mL/min)			
Mean (SD)	[redacted]	[redacted]	[redacted]
Median	[redacted]	[redacted]	[redacted]
Range	[redacted]	[redacted]	[redacted]
Tumour locations based on IRC, n (%)[f]			
Adrenal gland	[redacted]	[redacted]	[redacted]
Axillary lymph node	[redacted]	[redacted]	[redacted]
Bone	[redacted]	[redacted]	[redacted]
Brain	[redacted]	[redacted]	[redacted]
Chest wall	[redacted]	[redacted]	[redacted]
Hilar lymph node	[redacted]	[redacted]	[redacted]
Liver	[redacted]	[redacted]	[redacted]
Lung	[redacted]	[redacted]	[redacted]
Lymph node	[redacted]	[redacted]	[redacted]
Mediastinal lymph node	[redacted]	[redacted]	[redacted]
Pleura	[redacted]	[redacted]	[redacted]
Pleural effusion	[redacted]	[redacted]	[redacted]
Retroperitoneal lymph node	[redacted]	[redacted]	[redacted]
Skin	[redacted]	[redacted]	[redacted]
Subcarinal lymph node	[redacted]	[redacted]	[redacted]
Thoracic lymph node	[redacted]	[redacted]	[redacted]
Treatment of physician choice, n (%)[g]			
Eribulin	[redacted]	[redacted]	[redacted]
Capecitabine	[redacted]	[redacted]	[redacted]
Gemcitabine	[redacted]	[redacted]	[redacted]
Vinorelbine	[redacted]	[redacted]	[redacted]

[a] BMI is calculated as BMI (kg/m^2) = (weight in kg)/(height in m)^2

[b] Body surface area is calculated using Mosteller's formula: $\sqrt{\frac{(height\ (cm))(weight\ (kg))}{3600}}$

[c] The randomisation strata are based on IxRS

[d] Time from diagnosis is defined as number of days divided by 30.4375 from date of diagnosis to date of study entry

[e] Positive denotes patient is either *BRCA1* positive or *BRCA2* positive. Negative denotes patient is both *BRCA1* negative and *BRCA2* negative. Note that not all patients were screened for *BRCA* mutational status

[f] Includes both target and non-target lesions

[g] As specified by the investigator prior to randomisation.

BMI=body mass index; *BRCA*=breast cancer gene; ECOG=Eastern Collective Oncology Group; ITT=intention-to-treat; IRC=Independent Review Committee; IxRS=Interactive Voice/Web Response System; PD-1=programmed death protein 1; PD-L1=programmed death-ligand 1; SD=standard deviation; SG=sacituzumab govitecan; TNBC=triple negative breast cancer; TPC=treatment of physician's choice; *UGT1A1*=uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1; ULN=upper limit of normal.

A4. Table 3, page 21-23:

The list of endpoints in Doc B were as the following: overall survival (OS), progression-free survival (PFS), objective response rate (ORR), adverse events (AEs), health-related quality of life (HRQoL), duration of response (DOR), clinical benefit rate (CBR), time to response (TTR), and time to progression (TTP). The company states the following*: "Median treatment duration was substantially longer in the SG group (4.4 months) versus TPC (1.0 to 1.6 months)."*

A4.1. **Please explain why no additional data on treatment duration or time-to-treatment discontinuation (TTD) were provided in the clinical effectiveness section of document B. In the cost section the company states that TTD was one of the main clinical inputs in the economic model.**

The clinical effectiveness section of Document B focuses on pre-defined and established clinical efficacy and safety endpoints used in oncology clinical trials. TTD is not a clinical efficacy endpoint and is rarely, if ever, a prospectively defined endpoint in oncology trials. Rather, TTD is recorded as a matter of course in oncology trials and is useful for informing economic models. Consequently, we believe that the TTD parameter is best detailed in the cost-effectiveness section of Document B.

A4.2. **Please provide the following data:**

- **For treatment duration (means, standard deviations (SDs), mean differences with corresponding 95% confidence intervals (CIs), the proportions on treatment)**

The table below summarises treatment duration by treatment type and the proportion of patients remaining on treatment at 6, 12 and 18 months. Data on the mean differences in treatment durations for each individual component of TPC was not available in the clinical summary report for the ASCENT trial.(4)

Table 2: Treatment durations by treatment type in ASCENT (safety population)(4)

	SG (n=258)	Eribulin (n=122)	Capecitabine (n=22)	Gemcitabine (n=31)	Vinorelbine (n=43)
Treatment duration (months)					
n	258	122	22	31	43
Mean	5.767	2.270	2.156	2.250	1.732
SD	4.9046	2.1827	2.5623	2.0067	2.3122
Median	4.386	1.643	1.183	1.413	0.953
Minimum	0.03	0.03	0.33	0.23	0.03
Maximum	22.87	15.34	10.58	8.08	11.53
Patients remaining on therapy over time, n (%)					
≥6 months	95 (36.8%)	7 (5.7%)	2 (9.1%)	2 (6.5%)	2 (4.7)
≥12 months	26 (10.1%)	1 (0.8%)	0	0	0
≥18 months	10 (3.9%)	0	0	0	0

SD=standard deviation; SG=sacituzumab govitecan

- ***For TTD (hazard ratios (HRs) with 95% CIs, Kaplan Meier (KM) curves for TTD) separately for intention-to-treat (ITT) and primary efficacy populations?***

Hazard ratios of TTD for ITT and primary efficacy (brain metastases negative [BM-ve]) populations are shown in Table 3. KM plots are shown in Figure 4 and Figure 5.

Table 3: KM estimates of TTD for ITT and primary efficacy (BM-ve) populations

	Event/Total	Median (95% CI)[1]	Hazard Ratio (95% CI)[2]	Covariate Level P-values	P-value
ITT population					
Actual Treatment for Period 01					[redacted]
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
BM-ve population					
Actual Treatment for Period 01					[redacted]
SG	[redacted]	[redacted]	[redacted]	[redacted]	
TPC	[redacted]	[redacted]	[redacted]	[redacted]	

[1]Kaplan-Meier method; [2]Cox model; [3]Logrank test; [4]Wald Chi-Square test;

BM-ve=brain metastases negative; CI=confidence interval; ITT=intention-to-treat; KM=Kaplan Meier; SG=sacituzumab govitecan; TPC=treatment physician choice; TTD=time to treatment discontinuation

Figure 4: KM estimates of TTD in ITT population

CI=confidence interval; HR=hazard ratio; TTD=time to treatment discontinuation

Figure 5: KM estimates of TTD in BM-ve population

BM-ve=brain metastases negative; CI=confidence interval; HR=hazard ratio; TTD=time to treatment discontinuation

A5. **Please provide the breakdown of both treatment effect and adverse events by the number of treatment doses.**

As discussed during the clarification call on 12th October, treatment effect is closely associated with the number of treatment doses, due to the fact that, for all therapies used in the ASCENT trial, treatment is administered until disease progression. Consequently, as agreed on the call, we are limiting this response to AE data only.

Due to the heterogeneous nature of the control arm, i.e. multiple different drugs with different dosing regimens, it is not possible to provide adverse event data by the number of treatment doses. Instead, the table below shows adverse event data alongside total drug exposure time and incidence rates adjusted for exposure.

The adjusted incidence rates can be interpreted as the number of patients with a particular type of AE per person-year of treatment exposure.

[redacted]

Table 4: Adverse events adjusted by treatment exposure

	SG (N=258)			TPC (N=224)		
	# patients with events	**Total Exposure Time in Years**	**Adjusted Incidence Rate (95% CI)**	**# patients with events**	**Total Exposure Time in Years**	**Adjusted Incidence Rate (95% CI)**
TEAEs						
Worst CTCAE Grade	[redacted]					
5						
4						
3						
2						
1						

	SG (N=258)			TPC (N=224)		
	# patients with events	**Total Exposure Time in Years**	**Adjusted Incidence Rate (95% CI)**	**# patients with events**	**Total Exposure Time in Years**	**Adjusted Incidence Rate (95% CI)**
Treatment-related TEAEs						
Worst CTCAE Grade	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TE Serious AE						
Worst CTCAE Grade	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment-related TE Serious AE						
Worst CTCAE Grade	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	SG (N=258)			TPC (N=224)		
	# patients with events	**Total Exposure Time in Years**	**Adjusted Incidence Rate (95% CI)**	**# patients with events**	**Total Exposure Time in Years**	**Adjusted Incidence Rate (95% CI)**
Dose reductions, treatment interruptions and deaths						
TEAEs Leading to Dose Reduction	[redacted]					
TEAEs Leading to Study Drug Interruption	[redacted]					
TEAEs Leading to Study Drug Discontinuation	[redacted]					
Treatment-related TEAEs Leading to Study Drug Discontinuation	[redacted]					
TEAEs Leading to Death	[redacted]					
Treatment-related TEAEs Leading to Death	[redacted]					

AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events; SG=sacituzumab govitecan; TEAE=treatment-emergent adverse event; TPC=treatment physician choice;

The exposure-adjusted TEAE rate is defined as the number of subjects with a specific event divided by the total exposure-time (in years) in the treatment group. For subjects with the specific event(s), exposure-time was calculated from first dose date up to the first onset of the event. For subjects without the specific event, exposure-time was calculated from first dose date up to data cutoff date if the subjects was on study drug, or up to the earliest date among 30 days after last dose, data cutoff date, and death date (if applicable) if the subject discontinued study drug. The total exposure-time is the sum of the exposure-time over all subjects in the treatment group.

***A*6. *Patient eligibility, page 25 – 26*: "Following a protocol amendment, only patients with known brain metastases at baseline required a brain MRI at screening and were eligible to enrol in the trial as long as their central nervous system (CNS) disease was treated and stable for at least 4 weeks prior to randomisation"**

A6.1. **Please define known brain metastases.**

"Known" BM were known to or suspected by the investigator prior to enrolment into the ASCENT study(5), usually because they became symptomatic and were then diagnosed and treated.

A6.2. **How was brain metastasis diagnosed/determined?**

Patients with mTNBC and BM at baseline would have been diagnosed with BM prior to enrolment and diagnosis was not determined as part of the ASCENT study.(5) Only patients with known BM prior to enrolment were required to have a brain MRI at screening to confirm that the existing central nervous system (CNS) disease was stable.(5)

Diagnostic investigations for brain metastases often occur because a patient is experiencing symptoms consistent with CNS involvement of their cancer.(6) Presence of BM is usually subsequently determined by a CT or MRI scan.(7) Patients were not screened for asymptomatic brain metastases prior to study entry This is consistent with routine clinical practice where patients are only investigated for possible CNS disease in response to symptoms suggesting this possibility.

A6.3. **Were all patients examined for the brain metastases*?***

Patients enroled in ASCENT were not routinely examined for BM.(5) Only patients with known BM at screening were required to have brain MRI to confirm that the existing CNS disease was stable.(5)

A6.4. **Why were only patients with known brain metastases at baseline required to have a brain MRI at screening? Please provide a rational.**

In oncology clinical practice, patients are usually only examined for the presence of BM if they appear to be symptomatic for CNS involvement of their cancer.(7) In the ASCENT trial, patients with known BM at baseline were required to have MRI scans at screening in order to establish whether they met the inclusion criteria for stable BM.(5)

A6.5. **Table 6, page 35: the company states that n=468 patients (primary efficacy analysis sample) were free of brain metastases; how was this determined? Did they undergo an MRI?**

Patients who were defined as BM negative encompassed all patients who did not have a diagnosis of BM prior to enrolment.(5) These patients were not examined for the presence of BM at screening.(5) Therefore, it is likely that some patients in the BM negative subpopulation had asymptomatic, undetected BM. As stated in Question A.6.4, this reflects clinical practice in the UK, where typically patients only undergo examination for brain metastases if they are symptomatic.

A7. **Table 6, page 35: Treatment of physician choice (TPC) n (%) variable: The table indicates that patients in SG arm (n=267) also received TPC (at least at baseline) which is not prior treatment. Does this mean that SG arm constitutes patients who received combination of SG and TPC in the ASCENT trial*?***

SG was exclusively administered as monotherapy in the ASCENT trial.(8)

A TPC treatment was chosen by the investigator for each patient in the trial prior to randomisation.(8) Therefore, all patients were assigned a TPC but only patients that then went on to be randomised into the TPC arm actually received this treatment. Table 6 in Document B summarises the TPC chosen for patients in each arm prior to randomisation, i.e., the treatment they would have received had the patients in the SG arm been randomised into the TPC arm instead.(8)

A8. **Section B.2.6.2, page 44:** ***"The proportion of patients alive and without progression was consistently higher in the SG versus TPC group at Months 3 (61.9% versus 27.1%), 6 (40.6% versus 10.7%), 9 (22.8% versus 7.2%) and 16.2 (17.2% versus 6.0%).(37)".*** **Please confirm that 16.2 months is correct value?**

The '16.2' is a typographical error, the correct value is 12 months. The sentence should read as, 'the proportion of patients alive and without progression was consistently higher in the SG versus TPC group at Months 3 (61.9% versus 27.1%), 6 (40.6% versus 10.7%), 9 (22.8% versus 7.2%) and **12** (17.2% versus 6.0%)'.(8)

A9. **Page 49 – 50 and table 10: Assessment of EORTC QLQ-C30 observed mean scores and changes from baseline. The company used two types of analysis*:***

- **Assessment of observed scores and changes from baseline**
- **Linear mixed-effect model for repeated measures (MMRM)**

A9.1. **Please clarify the statistical test/analyses used for the observed mean change scores? Were any adjustments applied?**

For the observed mean change scores, we presented descriptive statistics of the change from baseline scores. Mean EORTC QLQ-C30 data was calculated for patients at baseline and at their final study visit for the SG and TPC arms.(8) Paired t tests were used for testing within-group change and independent t test for between-group differences. No adjustments were applied to the observed mean change scores.(8)

A9.2. **Please clarify why the**

[redacted]

The observed mean changes are just arithmetic averages of the observed values, while the MMRM least square (LS) mean changes are adjusted for the covariates (including baseline HRQoL scores and the stratification factors, i.e. number of prior treatments, geographic location and brain metastasis). With missing data, LS mean changes are different from observed mean changes by adjusting for the average values or weights of the covariates. Please also note that Table 10 provides the treatment difference in the overall LS mean changes, i.e. LS mean changes across visits.

The observed change at a given post-baseline only included those with non-missing change scores at a given post-baseline visit. As subjects dropped out of the study

quickly, especially in TPC arm, the statistical power was considerably reduced. This is different with MMRM in which all HRQoL evaluable population were included in the estimation under the missing at random assumption. Thus, the statistical power was greater with MMRM to detect the difference in LS mean change between arms.

A10. **Subgroup analysis, page 54: The company states that there were no subgroup effects of SG, i.e., the improvements in PFS/OS with SG treatment versus TPC were consistent across key pre-planned subgroup analyses in the ITT population.**

ERG confirmed on clarification call on 12/10/21 that this question is an error and should be disregarded.

A11. **Page 66: Treatment-related TEAEs were more common in the SG group versus TPC (97.7% versus 85.7%), which may be explained by substantially longer median treatment duration in the SG group (4.4 months) versus TPC (1.0 to 1.6 months).**

A11.1. **Is the ERG right to think that treatment duration was not adjusted which may partially explain higher incidence of TEAEs in SG vs. TPC arm?**

The ERG's assumption is correct that adverse event data as presented in the company submission have not been adjusted for treatment duration/drug exposure. Please refer to Question A.5 for new data showing AEs by exposure time and adjusted AE incidence rates. In this analysis, SG has a numerically lower rate of overall TEAEs of all severities when adjusted for exposure, though treatment-related TEAEs were similar. Moreover, dose reduction and drug discontinuation are also numerically lower with SG compared with TPC following adjustment for exposure.

A12. **Please provide the ASCENT Kaplan Meier data for the ITT population for PFS, OS, and TTD, split by treatment arm. This will allow the ERG to fit the parametric survival models in sections B.3.3.2-4.**

Number at risk for OS, PFS and TTD by treatment arm is provided in the table below.

Table 5: Number at risk for OS, PFS and TTD by treatment arm

Timepoint	N at risk (ITT population)					
	OS		PFS (IRC)		TTD	
	SG	TPC	SG	TPC	SG	TPC
Month 0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Month 17	[redacted]	[redacted]	[redacted]		[redacted]	
Month 18	[redacted]	[redacted]	[redacted]		[redacted]	
Month 19	[redacted]	[redacted]	[redacted]		[redacted]	
Month 20	[redacted]	[redacted]	[redacted]		[redacted]	
Month 21	[redacted]	[redacted]	[redacted]		[redacted]	
Month 22	[redacted]	[redacted]	[redacted]		[redacted]	
Month 23	[redacted]	[redacted]			[redacted]	
Month 24	[redacted]	[redacted]				
Month 25		[redacted]				
Month 26						

IRC=independent review committee; ITT=intention-to-treat; OS=overall survival; PFS=progression-free survival; SG=sacituzumab govitecan; TPC=treatment physician choice; TTD=time to treatment discontinuation

Table 6: Primary reason for end of study in ITT population(4)

Treatment arm	Patients randomized (ITT population)	Patients who discontinued from study	Primary Reason for End of Study				
			Lost to follow-up	Consent withdrawal	Death	Study end	Sponsor's Decision
SG	267	185	3	8	174	NR	0
TPC	262	228	4	27	197	NR	0

ITT=intention-to-treat; NR=not reported; SG=sacituzumab govitecan; TPC=treatment physician choice

A13. Section B.3.3.3, OS modelling: long-term survival extrapolation was validated against real-world evidence from figure 2 of Deluche et al 2020 (reference 27). Please clarify why the company did not use the observed PFS in figure 3 of Deluche et al 2020 to compare long-term PFS extrapolations in section B.3.3.2, and base the choice of curve on statistical fit.

Long-term extrapolation for OS was based on the best statistical fit and validated against external data sources as it has a noticeable impact on model results. Though it is not among the top 10 drivers in DSA, the scenario analysis of alternative OS extrapolation settings showed a range of -0.46% to 13% change from the base case, whilst the alternative PFS extrapolation settings have a minor impact, ranging from -0.36% to 2.25% change from the base case. The external validation process for OS extrapolation was in part done by comparison to published RWE in mTNBC patients (e.g., Deluche 2020).

The model predicted median OS in base case is 6.57 months and 10-year survival rate of 0.46% for TPC, comparing to 11.60 months and 1.30% for SG respectively. Deluche *et al.* 2020 reported median OS of 14.8 months and approximately 5% survival at 10-year for HR-/HER2- cohort. The generally longer long-term OS in Deluche *et al.* 2020 is likely due to the registry being conducted on patients newly diagnosed with mTNBC, with survival being measured from 1L therapy, as opposed to from 2nd or 3rd line therapy per the ASCENT population. Overall, there is a data gap in RWE of mTNBC and we could not identify any published study with data reported comparable to the model studied population of the decision problem. The validation against the Deluche 2020 was provided as supplementary supportive evidence.

PFS extrapolation was selected using the same approach as OS, mainly through the assessment of best statistical fit and consultation with UK clinicians. As with the OS data, the PFS data in Deluche *et al* 2020 is measured from first-line therapy, meaning it is of limited use to help validate PFS extrapolations for second- and third-line therapies. This fact, alongside it's minor impact on the ICER, led us to adopt UK clinicians' opinion as external validation.

A14. The ERG identified the following study in the scoping searches TOPiCS=NCT03901339.

A14.1. Please confirm the status of the trial.

Recruitment for TROPiCS-02 (NCT03901339) has completed and follow-up is ongoing.(9)

A14.2. Please confirm if the company will be using any data from the trial to support this submission; and

The full title of the TROPiCS-02 trial is "Phase 3 Study of Sacituzumab Govitecan (IMMU-132) Versus Treatment of Physician's Choice (TPC) in Subjects With Hormonal Receptor-Positive (HR+) Human Epidermal Growth Factor Receptor 2 (HER2) Negative Metastatic Breast Cancer (MBC) Who Have Failed at Least Two Prior Chemotherapy Regimens".(9) This study is being conducted in HR+ breast cancer patients, not TNBC patients, and so is not relevant to this appraisal.(9) If successful, this trial may form the basis of a new, entirely separate indication in the applicable patient population.

A14.3. Depending on the status of the trial, if the company anticipate data from this study to report during this submission process?

No. Data from the TROPiCS-02 trial is not applicable to this submission.(9)

A15. Figure 36-39, Pages 97-99: The company uses *'treatment duration' with time to deterioration' (TTD) and 'time to treatment discontinuation' interchangeably. The abbreviation list defines TTD 'time to treatment discontinuation',* but not 'time to deterioration' which are different parameters. Please clarify the inconsistencies for section B.3.3.4 Treatment duration.

This is a typographical error. In all instances throughout B.3.3.4, TTD should refer to ‘time to treatment discontinuation’.

Document B Appendix

A15. Figure 1, page 16:

A15.1. Full-text screening of these records identified 24 unique publications reporting data for 10 independent RCTs that were considered relevant. However, Table 7 (page 17-18) indicates 25 publications. Please confirm the correct number.

The number 24 (as shown in the PRISMA figure) is correct. One study, Winer 2021, was a duplicate and appeared twice (i.e., identified in hand searches in SLR 1 and then identified in the SLR update, SLR 2). There is a footnote for the table (footnote 'b') that explains this; because it is the primary publication for KEYNOTE-119 we felt it was important to show the study in both SLR 1 and 2 locations.

A15.2. The PRISMA flow chart: the numbers reported do not appear to align with the tables reporting in bibliographic database search strategies. Taking the clinical effectiveness review as an example, there appears to be a discrepancy of n=730 between the database search tables and the PRISMA (please see Table below).

The database search results were de-duplicated prior to providing outputs for the PRISMA diagram. In addition there was some overlap in articles captured in the SLR1 and SLR2 searches, so summing up the number of results from each database (SLR1 + SLR2) would overstate the number of unique references.

A15.3 **Please check the PRISMA charts for each of the four reviews to ensure that they are harmonised with the search strategies.**

Discrepancies in the number of hits reported in the PRISMA charts of other reviews result from the same issue described in A15.2 above (i.e., we report the already combined and de-duplicated number of hits in the PRISMA figures).

A15.4. Please provide detail on any changes that you might need to make in the reporting to align the tables with PRISMA. It would be helpful to include an explanation as to the cause of the differences in reporting.

As described above, the reason for the discrepancy in individual search results and records recorded in the PRISMA diagram is the de-duplication step. Calculations for each search are detailed below.

Table 7: Clinical SLR

Database	SLR1	SLR 2	Total	Records identified through database searching per your PRISMA
MEDLINE	583	86	669	-
Embase	1646	246	1892	-
CENTRAL	295	27	322	-
CDSR	2	0	2	-
Summary			**2885**	**2155 (following de-duplication)**

Table 8: Humanistic SLR

Database	SLR1	SLR 2	Total	Records identified through database searching per your PRISMA
MEDLINE	35	7	42	-
Embase	106	11	117	-
EconLit	0	0	0	-
NHS HEED	0	0	0	-
International HTA database	6	0	6	-
Summary			**165**	**132 (following de-duplication)**

Table 9: Economic SLR

Database	SLR1	SLR 2	Total	Records identified through database searching per your PRISMA
MEDLINE	16	4	20	-
Embase	89	8	97	-
CENTRAL	13	0	13	-
EconLit	0	0	0	-

Database	SLR1	SLR 2	Total	Records identified through database searching per your PRISMA
NHS HEED	0	0	0	-
International HTA database	6	0	6	-
Summary			**130**	**112 (following de-duplication)**

Section B: Clarification on cost-effectiveness data

Document B

B1. According to the marketing authorisation, SG 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 lines of systemic therapies, at least one of them given for unresectable locally advanced or metastatic disease (see section 5.1).

<u>For each of the groups / subgroups stated here below</u>

a. **overall trial population**
b. **by region (US, non-US)**
c. **by locally advanced patients and metastatic patients**
d. **by prior therapies: patients with 1 prior therapy post-metastasis diagnosis vs patients with 2+ therapies post-metastasis diagnosis**

Please provide the following:

B1.1. Number of patients in each trial arm x each subgroup of the above (a, b, c, d).

The number of patients with locally advanced disease was very small (10 in SG arm; 5 in TPC arm). This substantially limits the statistical validity of any comparisons between treatment arms for clinical outcomes (e.g, PFS and OS). Therefore, no further analyses for these subgroups are presented.

Table 10: Number of patients for key subgroups in each trial arm

Group	Subgroup	SG (N)	TPC (N)
A	ITT population	267	262
B	Country is USA (US)	172	170
	Country is not USA (Non-US)	95	92
C	Locally advanced disease patients*	10	5
	Metastatic patients*	258	260
D	Patients with 1 prior therapy post-metastasis diagnosis	35	34
	Patients with 2+ therapies post-metastasis diagnosis	223	226

*Data from Table 14.1.4.1 of the CSR post-text tables.(4) No further analyses have been run for these subgroups

ITT=intention-to-treat; KM=Kaplan Meier; SG=sacituzumab govitecan; TPC=treatment physician choice; USA=United States of America

Further data in response to B1.2 to B1.10 is provided are the attached Excel. Post-hoc analyses contained within the file should be reviewed with caution, as they are not sufficiently powered to allow for robust statistical interpretation.

B1.2. Patient mean weight (with SD, etc..) each trial arm x each subgroup of the above (a, b, c, d).

See Excel file above.

B1.3. Efficacy data (PFS, OS, TTD, AEs) for each subgroup of the above (a, b, c, d) [some breakdowns are already provided, for example Table 12 Document B; please provide KM plots and fitted curves plots if possible].

See Excel file above.

B1.4. KM data and fitted curves (where possible) for each subgroup of the above (a, b, c, d).

See Excel file above.

B1.5. Produce Figure 23 PFS and Figure 31 (OS) log-log residuals for each subgroup of the above (a, b, c, d).

See Excel file above.

B1.6. Produce Figure 12 and 13, document B: time to improvement or deterioration QOL (with numbers at risk) for each subgroup of the above (a, b, c, d).

See Excel file above.

B1.7. Produce Figure 14, 15, restricted to the three subgroups b, c and d. listed above.

See Excel file above.

B1.8 Provide EQ-5D analyses (mean changes from baseline over the treatment phase analysis) and specifically, a rerun of the analysis including random intercept and slope and the following covariates (as appropriate for the subgroup) as fixed effects: treatment, visit (discrete), stratification factors (i.e., the number of prior treatments [2-3 vs. >3]; geographic location [North America vs. rest of the world], where appropriate; and known brain metastasis [yes or no]), baseline score, baseline score-by-visit interaction, and treatment-by-visit interaction.

See Excel file above.

B1.9. SG drug dosing data for the on-treatment patient population (by each subgroup listed above a, b, c, d), including means of:

- **number of cycles delivered during the trial period.**
- **number of cycles for which the dose was reduced.**
- **number of cycles skipped number of cycles delayed and average number of days delayed.**

See Excel file above.

B1.10. Use of granulocyte colony stimulation factors by each subgroup listed above a, b, c, d.

See Excel file above.

B2. ***Page 39: "A listing was generated for the ITT population reflecting group, date of randomisation, date of first dose, date of last dose, date and reasons of treatment and study discontinuation, survival follow-up status and information for each patient.(8) The following censoring rules for the primary analysis of PFS were applied:(8)***

- ***Patients with no adequate response assessment after randomisation***
- ***Patients who died prior to second scheduled assessment were censored on the date of death.***
- ***<u>Patients who did not die or died after missing 2 or more scheduled assessments were censored at randomisation.</u>***

Please clarify how the last sentence (underlined) should be interpreted.

The highlighted statement refers to patients that had no adequate response assessment after randomisation, and may be clarified by this extract from section 9.3 (Efficacy Analysis) of the protocol:

> *"Patients without baseline tumor assessments* ***<u>or without additional follow-up data</u>*** *will be censored at the date of randomization. However, if such a patient dies no later than the time of the second scheduled assessment as defined in the protocol, this patient will be considered to have an event at the date of death."*

Patients without adequate response data were censored at randomisation, and consequently were effectively excluded from the progression-free survival analysis. These patients included those still alive after missing two or more scheduled response assessments, and those who died after missing two or more scheduled response assessments.

B3. Section B.3.4, page 102 states: ***"The ASCENT clinical trial database included 479 patients with at least one EORTC observation (3,014 in total). Mapping from EORTC to EQ-5D-3L utility scores failed for 43 patients (65 EORTC observations) due to incomplete EORTC dimensions. After the mapping, the 479 patients (256 in SG and 223 in the TPC treatment arm) had at***

least one EQ-5D-3L utility score observation available. A total of 411 out of 479 patients (with 2,907 utility observations) had utility observation available at baseline and (at least) at another visit after baseline. These 411 patients (233 in SG and 178 in the TPC arm) were considered eligible for inclusion in the utility regression analysis. Across all scheduled visits, the total number of utility observations used as response variable in the regression models was 2,496".

Based on the following flow, please clarify why the analysis was conducted on 2,496 observations:

479 patients (3014 observations):

Mapping failed for 43 patients, 25 did not have utilities at baseline + another reading

411 had 2,907 readings

The analysis is conducted on 2,496 reading – is the difference explained by missing predictors?

Please provide details on reasons for exclusion of observations from one stage to another.

The ASCENT clinical trial database included 479 patients with at least one EORTC QLQ-C30 observation and 3,104 observations in total. Mapping from EORTC QLQ-C30 to EQ-5D-3L utility scores failed for 43 patients (65 EORTC observations) due to incomplete EORTC dimensions. The remaining 3,039 EORTC observations were successfully mapped into EQ-5D-3L utility scores. After the mapping, the 479 patients (256 in the SG treatment arm and 223 in the TPC treatment arm) had at least one EQ-5D-3L utility score observation (utility observation) available. 411 (233 in the SG arm and 178 in the TPC arm) out of 479 patients (with 2,907 utility observations) had utility observation available at baseline and (at least) at another visit after baseline and were considered eligible for inclusion in the utility regression analysis. Of the 68 out of 479 patients who were not eligible for the utility analysis, 17 patients did not have utility observation available at baseline and 51 patients did not have utility observation available at another visit after baseline.

Since the baseline utility observations of the 411 patients were used in the utility regression analysis only for adjustment and not as a response variable, the total number of utility observations used as a response variable in the regression models was 2,496. The availability of any further information related to the utility observations, such as progression or treatment discontinuation status, was not considered in the summary above. Therefore, 2,496 represents the maximum number of utility observations that could be used in a regression model, depending on which covariates were considered for further adjustment. For instance, in case of 126 utility observations the progression status was not available at the date of observation, therefore in models with progression status covariate the remaining 2,370 utility observations of 402 patients were used.

Section C: Textual clarification and additional points

Searches and documents identification

C1. The ERG was unable to identify the following study (and study reports) as an included or excluded study in clinical effectiveness section despite the study (and some of the study reports) appear in document B. This below study is reported in available clinical evidence (document B) and four study reports are also cited in document B (references 36, 51, 56-57). Please clarify why the following are not included or excluded in the systematic review of clinical effectiveness;

- **Phase I/II IMMU-132-01 study (NCT01631552)**
- **REF 36: Bardia A, Mayer IA, Diamond JR, Moroose RL, Isakoff SJ, Starodub AN, et al. Efficacy and safety of anti-Trop-2 antibody drug conjugate sacituzumab govitecan (IMMU-132) in heavily pretreated patients with metastatic triple-negative breast cancer. J Clin Oncol. 2017;35(19):2141-8.**
- **REF 51: Bardia A, Mayer IA, Vahdat LT, Tolaney SM, Isakoff SJ, Diamond JR, et al. Sacituzumab govitecan-hziy in refractory metastatic triple-negative breast cancer. N Engl J Med. 2019;380(8):741-51.**

- **REF 56: Bardia A, Messersmith WA, Kio EA, Berlin JD, Vahdat L, Masters GA, et al. Sacituzumab govitecan, a Trop-2-directed antibody-drug conjugate, for patients with epithelial cancer: final safety and efficacy results from the phase I/II IMMU-132-01 basket trial. Annals of Oncology. 2021;32(6):746-56.**

- **REF 57: 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.**

- **The ERG was unable to locate a further study report in the submission (Starodub et al.): Starodub AN, Ocean AJ, Shah MA, Guarino MJ, Picozzi VJ Jr, Vahdat LT, Thomas SS, Govindan SV, Maliakal PP, Wegener WA, Hamburger SA, Sharkey RM, Goldenberg DM. First-in-Human Trial of a Novel Anti-Trop-2 Antibody-SN-38 Conjugate, Sacituzumab Govitecan, for the Treatment of Diverse Metastatic Solid Tumors. Clin Cancer Res. 2015 Sep 1;21(17):3870-8. doi: 10.1158/1078-0432.CCR-14-3321.**

Our PICOS criteria were selective for RCTs (see Table 6 in Appendices document for PICOS criteria), and this study was identified as a single-arm trial with no control arm. Single-arm studies were flagged for *potential* inclusion in the SLR if it was determined by our feasibility assessment that a MAIC was possible (see footnote 'b' in Table 6), but this was not the case after our assessment thus no single-arm trials were included in the final SLR screen. This study was identified by our search and flagged for potential inclusion, but ultimately excluded because of its design.

Because this was a publication containing data for SG, it was included in the submission despite not meeting SLR criteria and not being considered for an indirect treatment comparison.

C2. Please provide the search strategy which sets out how you identified the systematic literature reviews (SLR) referred to in "hand searches of reference lists from other recent SLRs (published within the last 2 years) in patients with advanced BC were undertaken to identify additional studies with a TNBC

subgroup that may not have been captured by our search terms" (Appendix D.1.1.1, Page 6*).*

There were no formal separate searches conducted to identify SLRs. For the most part we checked other SLRs in patients with TNBC that were ID'ed through our search because some RCTs are published in broader metastatic breast cancer patients but present a TNBC subgroup that is not mentioned in the title/abstract (thus these individual studies would not be ID'ed by our search terms, but the SLR was captured). Additional SLRs were consulted as a final check, based on experience and knowledge of the literature in the relevant therapy area.

C3. Please clarify how you searched for HRQoL/utility data, costs or economic data, and any background clinical data, in the broader breast cancer population were identified. Please clarify how you searched for this data and provide search strategies.

No separate search strategies were conducted, we flagged studies that were identified from our existing database search strategy and HTA searches that were too broad to fit our TNBC criteria, but provided some data for metastatic breast cancer in general. If relevant, these were briefly mentioned in the submission.

C4. Thank you for providing search strategies and details on the platform through which you have searched. Please also provide the following data for each individual search (including the original and update searches):

C4.1. Date each individual search was performed.

Dates of each search are provided in Table 11.

Table 11: Dates of SLR searches

SLR	Date	
	SLR1	SLR2
Clinical	20 January 2021	7 July 2021
Humanistic	21 January 2021	7 July 2021
Economic	21 January 2021	7 July 2021

SLR=systematic literature review

C4.2. Data parameters of the search platforms for each individual search. For instance, if I searched Ovid MEDLINE on Sept 24 2021, for instance the

following data parameters would be reported: 1946 to September 23, 2021. If I searched Cochrane CENTRAL (which we search via Wiley not like you on Ovid), I would report Issue 9 of 12, September 2021.

Data parameters of the search platforms are listed below:

- Embase: 1974 to 2021 Week 27
- Medline: 1946 to July 6, 2021
- CENTRAL: June 2021
- CDSR: 2005 to July 6, 2021
- EconLit: 1886 to July 7, 2021

Combining the January searches with the updates conducted on 7th July encompasses the full date range listed above.

C4.3. Clinical Study Report (Table 17, page 58). Given the PFS HR (SG vs. TPC) in the brain metastases negative population was 0.40 (95% CI: 0.32, 0.52) in favour of the SG arm, we would normally expect to see fewer disease progressions (or deaths) in the SG arm compared to TPC arm. This is the case for death (leading to study end) which is less frequent in the SG (64.3%) vs. TPC arm (76.0%). However, the frequency of disease progression (which led treatment discontinuation) is greater in the SG arm (84.7%) vs. TPC arm (71.2%). Can you please explain why there is this inconsistent trend for disease progression (i.e., more progression in SG arm vs. TPC arm) when PFS is in favour of SG arm?

The apparent imbalance in the frequency of disease progression between SG and TPC is due to the censoring rules applied to the PFS analyses. More patients in the TPC arm were censored at randomisation than in the SG arm, and these patients do not contribute to the event count. One of the main reasons for this censoring in the TPC arm was because significantly more patients in this arm did not receive therapy (and hence did not have a response assessment) than in the SG arm. More data regarding patient censoring is presented in Table 13.

A PFS sensitivity analysis of the safety population (xxxxxx.

Table 12) shows that event rates were [redacted] in those patients that received at least one dose of study drug, at around [redacted].

Table 12: Sensitivity analysis of PFS - independent review analysis 5 safety population

	SG (N=258)	TPC (N=224)	Treatment comparison
Patients with events (%)	[redacted]	[redacted]	
Patients without events (censored) (%)	[redacted]	[redacted]	
Median PFS (months)[a] (95% CI)	[redacted]	[redacted]	
Log-rank p-value (stratified)[b]			[redacted]
Stratified Cox regression analysis[b] Hazard Ratio (95% CI)			[redacted]
PFS rate (%) at 3 Months (95% CI)[c]	[redacted]	[redacted]	
PFS rate (%) at 12 Months (95% CI)	[redacted]	[redacted]	
PFS rate (%) at 9 Months (95% CI)	[redacted]	[redacted]	
PFS rate (%) at 12 Months (95% CI)	[redacted]	[redacted]	

CI=confidence interval; PFS=progression-free survival; SG=sacituzumab govitecan; TPC=treatment physician

Note: 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. See the SAP for the handling of censored cases and sensitivity analyses of PES.

[a] Median PFS is from Kaplan-Meier estimate. CI for median is computed using the Brookmeyer-Crowley method.

[b] Stratified log-rank test and stratified Cox regression adjusted for stratification factors: number of prior chemotherapies, presence of known brain metastases at study entry, and region.

[c] Estimate and CI for PFS rate at the specified time points are from Kaplan-Meier estimate.

High event rates in each arm are to be expected given the relative maturity of the data cut, with most patients having had documented progression. However, it should be noted that [redacted] censored patients in the SG arm are accounted for by those that are alive without disease progression compared with just [redacted] in the TPC arm (Table 13).

Table 13: Classification of events for primary PFS analysis ITT population

	SG (N=267)	TPC (N=262)	Total (N=529)
	n, (%)	n, (%)	n, (%)
Patients with PFS events (non-censored)	[redacted]	[redacted]	[redacted]
Death	[redacted]	[redacted]	[redacted]
Radiographic disease progression	[redacted]	[redacted]	[redacted]
Patients censored[a]	[redacted]	[redacted]	[redacted]
Alive without disease progression	[redacted]	[redacted]	[redacted]
Death after missing more than one visit of assessment interval	[redacted]	[redacted]	[redacted]
Death after starting new anti-cancer therapy	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]
No post-baseline evaluable tumor assessment	[redacted]	[redacted]	[redacted]
PD after missing more than one visit of assessment interval	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]

PFS=progression-free survival; PD=progressive disease; SG=sacituzumab govitecan; TPC=treatment physician

[a] A subject may qualify such as "Death after missing more than one visit of assessment interval" and “death after starting new anti-cancer therapy" at the same time, but is only counted once toward one of them.

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NICE National Institute for Health and Care Excellence

Patient organisation submission

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 10 pages.

About you

NICE National Institute for Health and Care Excellence

1.Your name	[redacted]
2. Name of organisation	Breast Cancer Now
3. Job title or position	[redacted]
4a. Brief description of the organisation (including who funds it). How many members does it have?	Breast Cancer Care and Breast Cancer Now merged on 1 April 2019 to create one charity – Breast Cancer Now. From research to care, our charity has people affected by breast cancer at its heart – providing support for today and hope for the future. United, we'll have the ability to carry out even more world-class research, provide even more life-changing support and campaign even more effectively for better services and care. All of our funding comes from the public and our partners.
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	In the last 12 months, Breast Cancer Now has received the following funding from manufacturers listed in the appraisal matrix. Please note, Breast Cancer Now does not receive any pharmaceutical funding for our Policy, Evidence and Influencing work. Our work on access to drugs is independent of any funding we may receive from the pharmaceutical industry and is based on the evidence of the clinical effectiveness of drugs. Gilead Sciences: £38,613 – Living With Secondary Breast Cancer Online Service Roche: £41,555 – Living With Secondary Breast Cancer Online Service

If so, please state the name of manufacturer, amount, and purpose of funding.	
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	None
5. How did you gather information about the experiences of patients and carers to include in your submission?	At Breast Cancer Now we utilise our various networks of those affected by breast cancer to gather information about patient experience. At the time of writing this submission (September 2021), we are running a campaign called 'Time for Trodelvy' calling on Gilead to agree an interim access arrangement with NHS England following licensing through Project Orbis to ensure all eligible women can access this treatment during the gap between licensing and a NICE decision. We know this is possible as it has happened for a number of other oncology drugs. As part of our campaign we have spoken to many women living with incurable secondary triple negative breast cancer and this has informed our submission.
Living with the condition	
6. What is it like to live with the condition? What do carers experience when caring for someone with the condition?	Locally advanced breast cancer is when the cancer spreads into the tissues around the breast and cannot be removed by surgery. Metastatic (also known as advanced, secondary or stage 4) breast cancer is when cancer originating in the breast has spread to other parts of the body; most commonly the lungs, brain, bones or liver. There is no cure for metastatic breast cancer, so the aim of treatment is to extend the length of life and to improve quality of life for patients. A patient can be diagnosed with metastatic

	cancer initially (de novo), or they can develop the condition years after treatment for their primary breast cancer has ended. Being diagnosed with locally advanced or metastatic breast cancer is extremely difficult to come to terms with both for patients and their family and friends. Everyone's experience of being diagnosed and living with secondary breast cancer is different. Many people will feel overwhelmed, upset and shocked or anxious, as well as angry and alone. The uncertainty of living with secondary breast cancer can be the hardest part for many people, with people telling us it has fundamentally changed their perspective on life and they feel they are living on borrowed time. These common feelings can have a huge impact on people's mental health. A diagnosis of secondary breast cancer can also affect people's relationship with those closest to them which can be particularly difficult to cope with. As well as the huge emotional toll of living with metastatic breast cancer, patients often have to cope with numerous practical concerns, such as managing their day to day activities, including working, household responsibilities and travelling to and from hospital appointments. A patient living with secondary triple negative breast cancer told us: "Every day I wake up and remember that I'm dying. I try to not let it get me down, and I'm actually a pretty cheerful person. I love my life and I love keeping busy and focusing on what I can do. But I'm aware of my tumours, so when a treatment isn't working or stops working then it's mental torture. Knowing there are so few treatments available for triple negative breast cancer is like holding a few matches in your hand and then striking another one out each time, knowing your hand will be empty soon. It's also very isolating. Triple negative breast cancer can feel like a totally different disease to other types of breast cancer. I am so envious of women who get to be declared 'stable' or whose treatments keep on working for years rather than months. My cancer is fast growing and unpredictable, it scares oncologists. Previous oncologists described my disease as 'scary' and described my secondary treatment as 'we're already chasing ghosts'. We all hope to be a cancer outlier, someone who dramatically outlives their prognosis. But that hope is in short supply with triple negative breast cancer. Trodelvy is the first real hope there has been in a long time, and to see that oncologists are excited about it is really powerful".

	Another patient told us: “Living with secondary triple negative breast cancer is like walking a tightrope everyday, at any moment I could take a turn for the worse and my treatment options are limited. Having brain metastases is especially frightening as the disease can take away who I am as a person as well as my physical abilities. I have to live in the moment and not plan too far ahead, I am grateful for every milestone reached, my daughters’ birthdays, start of a new school year, memories made, seeing friends – especially after lockdown has kept me isolated from so many loved ones during the last 18 months. I feel like I am in limbo, it’s so hard not having confidence in the future. I am unable to work or drive so my world has become smaller and I have a huge loss of independence. I am grounded and feel like my life is about hospital appointments, housework and dog walking! I am fairly well compared to others so I am grateful for the things I am able to do. I have felt a lot of pessimism from certain members of my medical team, although I do like to hear the facts and I do ask the difficult questions about prognosis etc. There is a sense of hopelessness and that my fate is sealed, I have almost been written off a couple of times but I have sought second opinions, researched trials and spoken with lots of other women online to establish what my options are. All of this has been driven by me and it has been a fight. She goes on to say: “When you are diagnosed with this disease it is like having a noose put around your neck. Some days it feels tighter than others. When I see women with hormone receptor positive or HER2 secondary breast cancer they have more options. Having TNBC is like having the one no one wants, the last one picked, the bruised apple, the green fruit pastille” Triple negative breast cancer can be more aggressive and harder to treat than other types of breast cancer, resulting in potentially poorer outcomes and short prognoses. It can be particularly upsetting and frightening to be diagnosed with this type of breast cancer.

	Triple negative breast cancer is more common in women under 40, black women and women who have inherited an altered BRCA gene. A woman living with this secondary triple negative breast cancer who is 35 explains from her perspective: "Triple negative breast cancer disproportionately affects younger women, more likely to be less financially secure. I am 35 with a mortgage and only a small amount of savings. I'm self-employed with no health insurance or anything else to fall back on. Trodelvy needs to be accessible to all women via the NHS to avoid widening the gap between those who can afford to pay for treatment and those who can't. It's not fair to ask people to make that choice, and it's not a choice for many of us". Patients are keen to find treatments that will halt progression and extend life for as long as possible. As patients' time is limited, people tell us that quality of life is just as important to take into account as length of life, as this enables them to spend quality time with their loved ones. Therefore, the type and severity of treatment side effects are also important for patients in their treatment decisions.
Current treatment of the condition in the NHS	
7. What do patients or carers think of current treatments and care available on the NHS?	Treatment for secondary triple negative breast cancer has remained unchanged for many years, with chemotherapy still the standard of care throughout the pathway. In 2020, atezolizumab in combination with nab-paclitaxel was recommended for routine use for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer. For the patient population in question in this appraisal, they may currently receive capecitabine, vinorelbine or eribulin. But patients have told us that the new treatment, sacituzumab govitecan, provides them with significant hope to spend more time with their family and

	doing the things that matter most as they are aware of the promising progression free and overall survival results when compared to chemotherapy. A patient told us: “The treatments feel very limited and it feels like a quick death sentence. I’m on my second line treatment and so far my treatments tend to only work for 2-3 months. At the moment, I’m waiting for scan results and I think my second line is failing”. Another patient told us: “The treatment options for secondary triple negative breast cancer are extremely limited and many younger women, many with young families are dying too soon.”
8. Is there an unmet need for patients with this condition?	Yes, there is a significant unmet need for patients living with incurable triple negative breast cancer. Around 15% of all breast cancers are triple negative, however, targeted and new clinically-effective treatments for triple negative breast cancer remains one of the greatest areas of unmet need in breast cancer. Triple negative breast cancer is often more aggressive as well as harder-to-treat than other types of breast cancer, often resulting in poor survival outcomes. Treatment options for this patient group have remained mostly unchanged for a significant number of years. Whilst we have seen the introduction of a number of new drugs for both hormone receptor positive and HER2 positive secondary breast cancer which can potentially slow disease progression and improve overall survival, treatment options remain limited for secondary triple negative breast cancer, with little improvement in outcomes seen over the years. Sacituzumab govitecan being introduced on the NHS would be a major step forward in the treatment options available for this group of patients.
Advantages of the technology	
9. What do patients or carers think are the advantages of the technology?	The phase 3 ASCENT trial showed a significant benefit of sacituzumab govitecan when compared with chemotherapy with respect to progression free survival and overall survival. Among all randomly assigned patients (those with or without brain metastases), the median progression free survival was 4.8 months with sacituzumab govitecan and 1.7 months with chemotherapy. For the same population, the median overall survival was 11.8 months with sacituzumab govitecan and 6.9

	months with chemotherapy. Efficacy in patients without brain metastases includes a median progression free survival of 5.6 months with sacituzumab govitecan compared to 1.7 months with chemotherapy. The median overall survival was 12.1 months with sacituzumab govitecan and 6.7 months with chemotherapy. For a patient group whose type of cancer is known to be particularly difficult to treat, these results are extremely promising and this treatment would be an major step-forward in the treatment options available for these women. We know patients value this extra time, as it can mean more quality time to spend with their relatives and friends. Maintaining a high quality of life for as long as possible is currently the best outcome for this patient group. Delaying progression can also have a positive impact on patient's emotional wellbeing and mental health, as it can mean patients can continue doing the activities they enjoy and what matters most to them. This can also bring some comfort to the family and friends. A patient with incurable secondary triple negative breast cancer told us: "I see the advantages of Trodelvy as being that it can be used after second line onwards – some other treatments are only available for use earlier, such as immunotherapy. It also has shown additional benefit for women with spread to the brain. I understand that the drug works is different to more traditional chemotherapies in that it is more targeted, which can only be a good thing in terms of effectiveness and side effects. The main thing it means for me is hope and another option when with women with triple negative breast cancer have so few and feel left behind. For me, accessing Trodelvy means more time to live more, and to stay with my husband a bit longer. I would love to be able to go to my youngest brother's wedding next year. It means time to set myself goals and make plans, rather than thinking 'what's the point?'. Another patient living with incurable secondary triple negative breast cancer told us: "Living with secondary breast cancer is bad enough but living with secondary triple negative breast cancer means I've drawn the short straw as I know that treatment options will be very limited. I have now exhausted those limited NHS treatments. I hope that bringing drugs like Trodelvy to the NHS as a treatment option might give me more time to spend making memories with my family. I know extra time is not guaranteed by any drug or treatment but as treatment options are so very limited surely those of us with secondary triple negative breast cancer deserve the chance to give it a go!"

	Whilst the primary endpoint was progression-free survival in patients without brain metastases, as stated above there has been some results in the overall population (with and without brain metastases) and the efficacy results are consistent with those of the primary endpoint. Brain metastases can be particularly difficult to treat and associated with a poor prognosis so the promising results of this treatment for patients whose breast cancer has spread to their brain is very welcome, with a small sub-group analysis showing improved PFS. A patient living with incurable triple negative secondary breast cancer which has spread to the brain told us: “I believe that Trodelvy can cross the blood brain barrier which would be a true systemic approach for me. It is more targeted than other treatments and could give people extra precious time with their loved ones”. To conclude this section, we would reiterate the significant hope that sacituzumab govitecan brings to this group of patients, hope of more time with their loved ones. A patient told us: “I was 4 days post giving birth to my twins by planned section when I was given the news. The shadow on my chest was breast cancer again. However, this time, it is stage 4. All I could think of was my babies and my 4-year-old. I’m now on my second line of treatment after the first stopped working and I’m consciously aware of the limited options a triple negative secondary breast cancer diagnosis has for treatment. “Juggling treatment, twins and a pre-schooler is difficult, but we muddle through. I married the love of my life earlier this year and we’ve bought a family home. I have too much to do and too many memories to make. Trodelvy gives someone like me hope, hope that I will see my twins’ first steps, that I’ll see my son at his first sports day. I’m 27. It’s not my time. I’m not ready.”

Disadvantages of the technology	
10. What do patients or carers think are the disadvantages of the technology?	Every treatment for breast cancer has some side effects and each patient's situation will be different, with side effects affecting some patients more than others. Sacituzumab govitecan is associated with some increased side effects compared to chemotherapy which may require careful monitoring and management. Patients' willingness to take treatments will vary, however, as long as all the side effects are clearly discussed with the patient, they will be able to make their own choice with the support of their clinician regarding treatment options. The most common side effects of any grade during the ASCENT trial included neutropenia (63% with sacituzumab govitecan versus 43% with chemotherapy), diarrhoea (59% with sacituzumab govitecan versus 12% with chemotherapy) and nausea (57% with sacituzumab govitecan versus 26% with chemotherapy). Clinicians are familiar with these side effects and are proficient at managing them as they are common side effects of other approved drugs. During the trial neutropenia was managed with dose reductions, dose delay or with growth factor support. Serious treatment related adverse events were reported in 15% of patients who received sacituzumab govitecan and 8% treated with chemotherapy. Patients in the trial were also given pre-medication to help prevent nausea and vomiting and additional medications for the prevention and treatment of nausea, vomiting and diarrhoea for us at home. A patient with incurable secondary triple negative breast cancer explained that: "I have tolerated my previous treatments with minimal side effects, so I don't think I would be put off having to balance potential risks versus benefits. For me, the potential benefit of more time with the people I love and who rely on me outweighs everything else." Another patient told us "like all chemotherapy based treatments, the side effects are the hardest to deal with. No one knows how your body will react as it is so individual so one can only hope it is tolerable and you are able to live as full a life as possible whilst on treatment". This treatment is given intravenously on days 1 and 8 of a 21-day treatment cycle so this would require time in hospital to receive this treatment. Whereas one of the comparators, capecitabine is given orally. However, for many patients any inconvenience in travel and time is outweighed by the benefits

	sacituzumab govitecan could bring them. Also in terms of administration method, eribulin which is another comparator to this treatment is also given intravenously on days 1 and 8 of a 21-day cycle.
Patient population	
11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	As mentioned previously, the promising results in those with brain metastases is very much welcome.
Equality	
12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	Triple negative breast cancer is more common in: - women who have inherited an altered BRCA gene (particularly BRCA1) - black women - women who have not yet reached the menopause - women under 40

Other issues	
13. Are there any other issues that you would like the committee to consider?	This treatment has been licensed through Project Orbis which aims to deliver faster patient access to innovative cancer treatments with potential benefits over existing therapies. The innovative nature of this treatment should be recognised, along with the unmet need for this patient group and the end of life criteria.

Key messages

14. In up to 5 bullet points, please summarise the key messages of your submission:

- Triple negative breast cancer is a harder-to-treat and often more aggressive type of breast cancer. Its management remains one of the greatest areas of unmet need and new treatment options are desperately needed.
- In the ASCENT trial, sacituzumab govitecan demonstrated longer progression free survival and overall survival when compared to chemotherapy. This is extremely important as it enables patients to spend quality time with their friends and families, as well as increasing the likelihood of people being able to continue with their daily activities, which can improve the emotional wellbeing of both patients and their families.
- There are some increased side effects from this treatment option compared to chemotherapy alone and it would also require frequent visits to hospital to receive the treatment. The benefits and risks of this treatment need to be clearly discussed with the patient to ensure they can make a decision that is right for them and for many patients any inconvenience of travel to the hospital and the potential of side effects would be outweighed by the benefits this treatment could bring them.
- Sacituzumab govitecan could offer a much-needed new treatment option for patients with metastatic (secondary) triple negative breast cancer and be a major step forward in the options available.

Thank you for your time.

NICE National Institute for Health and Care Excellence

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NICE National Institute for Health and Care Excellence

Professional organisation submission

Sacituzumab govitecan for treating locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

Information on completing this submission

- Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable
- We are committed to meeting the requirements of copyright legislation. If you intend to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs.
- Your response should not be longer than 13 pages.

About you	
1. Your name	[redacted]
2. Name of organisation	[redacted]

3. Job title or position	[redacted]
4. Are you (please tick all that apply):	☒ an employee or representative of a healthcare professional organisation that represents clinicians? ☐ a specialist in the treatment of people with this condition? ☐ a specialist in the clinical evidence base for this condition or technology? ☐ other (please specify):
5a. Brief description of the organisation (including who funds it).	**The NCRI Breast Research Group coordinates the development of a strategic portfolio of research within the field of breast cancer**
4b. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal matrix.]	**No**

If so, please state the name of manufacturer, amount, and purpose of funding.	
5c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	**No**
The aim of treatment for this condition	
6. What is the main aim of treatment? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability.)	Treatment for locally advanced or metastatic triple negative breast cancer is palliative; aiming to reduce symptoms from the disease, stop progression of the disease, maintain or improve quality of life and to prolong life.
7. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by	Reduction in the disease by 30% is used as a standard in clinical trials (RECIST criteria) and this usually correlates with improved symptoms, so is a useful correlate of a clinically significant response. However, more minor responses or stability of minimally symptomatic disease are also valuable to patients and meet the palliative aim of treatment, therefore clinical benefit rate (which includes both RECIST responses and stable disease) is also a clinically significant endpoint. Prolonged disease control and overall survival are by far the most important outcomes for most patients. Even an additional 3 months of disease control and survival is clinically meaningful.

x cm, or a reduction in disease activity by a certain amount.)	
8. In your view, is there an unmet need for patients and healthcare professionals in this condition?	Yes, triple negative breast cancer (TNBC) remains an area of significant unmet need. It has particularly aggressive biology and has no approved targeted therapies available. The survival of women diagnosed with metastatic TNBC is now hugely inferior to that for both ER-positive and HER2-positive subtypes (approximately 18 months compared to almost 5 years with other sub-types). It is an aggressive disease with a high rate of brain metastases (up to 50%) and consequently poor prognosis.
What is the expected place of the technology in current practice?	
9. How is the condition currently treated in the NHS?	First-line therapy is determined by PDL-1 status, where PDL-1 positive patients receive atezolizumab and nab-paclitaxel [TA639] and PDL-1 negative patients receive first-line chemotherapy. Chemotherapy regimens available to treat this disease include paclitaxel and epirubicin/cyclophosphamide (unless the patient recently received these for early breast cancer, which is frequently the case), capecitabine, 3rd line eribulin [TA423], gemcitabine-carboplatin and sometimes vinorelbine, although the latter drug has minimal efficacy and has been largely superceded by eribulin. Unfortunately, responses to these regimens are frequently short-lived, especially with later lines of treatment. For PDL-1 positive patients treated as above, median survival from initiation of first-line treatment was 21 months, compared to 18.7 months for PDL-1 negative patients in the Impassion-130 trial (Schmid P et al., Lancet Oncol 2020).

• Are any clinical guidelines used in the treatment of the condition, and if so, which?	The Advanced breast cancer Clinical Guidelines [CG81] include treatment of this condition but date from 2017. The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines (ABC5, 2020) are used for treatment of the condition. The American Society of Clinical Oncology (ASCO) also provide guidelines for the condition (Moy B et al., J Clin Oncol 2021)
• Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	The pathway is well-defined but the order that chemotherapy regimens are utilised depends upon prior treatment for early breast cancer (and timing of that prior treatment), patient co-morbidities and patient preferences (eg oral vs iv regimens, acceptability of hair loss)
• What impact would the technology have on the current pathway of care?	The technology would provide an urgently needed additional line of effective treatment for women living with advanced TNBC. The appraisal is for women who have received at least two lines of systemic therapy for advanced TNBC, the same indication as eribulin [TA423] and will usually be utilised before eribulin due to the more favourable median PFS reported with the technology (5.6 months compared to 3.7 months with eribulin in the Embrace trial; Cortes et al., Lancet 2011).
10. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	The technology is not currently available in the UK, but can easily be integrated into NHS clinical practice

• How does healthcare resource use differ between the technology and current care?	The treatment schedule for the technology is the same as for eribulin, so hospital visits and the use of blood tests and CT scans will be unchanged. However the preparation and infusion times for the technology are longer than for eribulin.
• In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	The technology must be supervised by an oncologist in a specialist clinic
• What investment is needed to introduce the technology? (For example, for facilities, equipment, or training.)	None
11. Do you expect the technology to provide clinically meaningful benefits compared with current care?	Yes, the ASCENT trial demonstrated clinically meaningful improvements in response rate, clinical benefit rate, progression-free and overall survival compared to current care.
• Do you expect the technology to increase length of life more than current care?	Yes, the improvement in median survival was from 6.7 to 12.1 months in the ASCENT trial.

• Do you expect the technology to increase health-related quality of life more than current care?	Yes, patients experience better quality of life if their disease is controlled. Although health-related QoL has not been reported for the ASCENT trial, prolonged disease control without significant additional toxicity can be reasonably expected to increase the duration of good health-related QoL
12. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, the biomarker analysis was unable to reliably confirm whether the technology was less effective in patients with low tumour Trop2 levels as the number of patients with Trop2 low was too small. No other clinical or tumour biomarkers predict benefit or lack of benefit. The exploratory subgroup analysis of patients with brain metastases did not show as high levels of efficacy as seen in the ITT population (Dieras V et al., SABCS 2020), but the data are limited by the small sample size, so patients with brain metastases should be excluded from receiving the technology. These patients have an inherently worse prognosis, but still had some benefit from the technology (numerically improved response rate and PFS).
The use of the technology	
13. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use (for example, any concomitant treatments needed, additional	The technology is associated with side-effects, but these do not differ significant from standard chemotherapy; grade 3 (severe) neutropenia in 34% of patients is slightly higher than expected for eribulin (21-25%) but can be managed with dose reduction if needed. The 10% rate of grade 3 (severe) diarrhoea is similar to the 5-8% expected with capecitabine. As such, it will not be more difficult for most patients. The technology requires pre-medication with anti-emetics, paracetamol and an anti-histamine and is given on day 1 and 8 of a 21 day cycle, so is not difficult to use for healthcare professionals.

clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed.)	
14. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	Adequate liver function is required to start the technology. Imaging response (usually on CT scan) will be used to determine when to stop treatment due to disease progression, as per standard therapy.
15. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation?	No

16. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met?	Yes. This is the first antibody-drug conjugate to demonstrate significant efficacy in TNBC. The prolongation of disease control and overall survival will be invaluable for patients living with this aggressive and poor prognosis condition.
• Is the technology a 'step-change' in the management of the condition?	Yes, the survival benefit is a step-change in the management of this condition
• Does the use of the technology address any particular unmet need of the patient population?	Yes, it provides an important and effective treatment for patients with advanced TNBC, who have a very poor prognosis with standard chemotherapy
17. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	As above, the side effects are manageable with supportive medications and dose reductions when needed. They are very unlikely to negatively impact on patients' QoL

Sources of evidence	
18. Do the clinical trials on the technology reflect current UK clinical practice?	Yes, the study population is representative of the UK TNBC population in terms of both demographics and previous treatments.
• If not, how could the results be extrapolated to the UK setting?	
• What, in your view, are the most important outcomes, and were they measured in the trials?	Overall response rate, clinical benefit rate, progression-free and overall survivals and safety are the most important outcomes and were all measured in the ASCENT trial
• If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes?	
• Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No

19. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
20. Are you aware of any new evidence for the comparator treatment(s) since the publication of NICE technology appraisal guidance [TA423]?	No. Eribulin was one of the comparator regimens permitted in the ASCENT trial, the others being vinorelbine, capecitabine or gemcitabine. No new data is available for these comparator regimens that I am aware of.
21. How do data on real-world experience compare with the trial data?	None currently available that I am aware of. The technology has only been available in the US since FDA approval in May 2020, so real-world data will likely follow in the next 12-18 months.
Equality	
22a. Are there any potential equality issues that should be taken into account when considering this treatment?	No

22b. Consider whether these issues are different from issues with current care and why.	

Key messages

23. In up to 5 bullet points, please summarise the key messages of your submission.

- Advanced TNBC has a very poor prognosis and few effective treatments
- SG is a well-tolerated novel antibody-drug conjugate
- SG improves response rate and clinical benefit rate compared to standard chemotherapy for TNBC
- SG is associated with a 3.9 months longer median PFS and 5.4 months longer median overall survival than standard chemotherapy
- SG is a real breakthrough for patients living with advanced TNBC

Thank you for your time.

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Evidence Review Group's Report

Title: ID3942: Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after two or more therapies

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None

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Rider on responsibility for report
The views expressed in this report are those of the authors and not necessarily those of the NIHR Systematic Reviews Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Lena Al-Khudairy (Associate Professor) coordinated the project, conducted the critique of the decision problem in the company submission and reviewed clinical effectiveness evidence. Emanuela Castelnuovo (Health Economist) conducted, reviewed and critiqued the cost-effectiveness evidence. Kate Evans (Research Associate), conducted the critique of reviewing methods, quality assessed and cross-checked data from key trials. Alexander Tsertsvadze (Senior Research Fellow) reviewed and critiqued clinical effectiveness evidence. Chris Cooper (Information Specialist) conducted the critique of the company's searches and conducted additional ERG searches. Mubarak Patel (Research Associate) conducted the critique of statistical analysis including the network meta-analysis of the company submission. All authors contributed to the writing and formatting of the report.

Please note that: Sections highlighted in yellow and underlined are 'academic in confidence' (AIC). Sections highlighted in aqua and underlined are 'commercial in confidence' (CIC). Figures that are CIC have been bordered with blue. Depersonalised Data (DPD) is highlighted in pink.

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Abbreviations

ADC	Antibody-drug conjugate
AE	Adverse events
AFT	Accelerate time to failure
AIC	Akaike Information Criterion
ASCEND	
ASCO	American Society of Clinical Oncology
BC	Breast cancer
BIC	Bayesian Information Criterion
BM-ve	Brain Metastasis-negative
BMI	Body mass index
BRCA	Breast Cancer gene
BSA	Body surface area
CBR	Clinical benefit rate
CEAC	Cost-effectiveness acceptability curve
CI	Confidence interval
CHF	Congestive Heart Failure
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CS	Company Submission
CT	Computed tomography
DOR	Duration of response
DSA	Deterministic sensitivity analysis
DSU	Decision Support Unit
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
ERG	Evidence Review Group
ESME	Epidemiological Strategy and Medical Economics
ESMO	European Society for Medical Oncology
GI	Gastrointestinal
G-CSF	Granulocyte Colony-Stimulating Factor
HBV	Hepatitis B Virus

HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratios
IRC	Independent Review Committee
ITC	Indirect treatment comparisons
ITT	Intention-to-treat
IV	Intravenous
IWRS	Iterative Web-Based Response System
KM	Kaplan-Meier
LD	Longest Diameter
LY	Life years
LYG	Life-years gained
MBC	Metastatic breast cancer
MI	Myocardial Infarction
MID	Minimum important difference
MIMS	Monthly Index of Medical Specialties
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
MRU	Medical resource use
mTNBC	Metastatic triple-negative breast cancer
NHS	National Health Service
NICE	The National Institute for Health and Care Excellence
NMA	Network meta-analysis
ORR	Objective response rate
OS	Overall survival
PAIC	Population-adjusted indirect comparison
PARP	Poly-ADP ribose polymerase
PAS	Patient access scheme
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1

PF	Progression free
PFS	Progression-free survival
PH	Proportional hazard
PR	Progesterone receptor
PRO	Patient Reported Outcome
PSA	Probabilistic sensitivity analysis
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life-year
QoL	Quality of life
RDI	Relative Dose Intensity
RECIST	Response Evaluation Criteria in Solid Tumors
SD	Standard Disease
SG	Sacituzumab govitecan hziy
TEAE	Treatment-emergent adverse events
TNBC	Triple-negative breast cancer
TPC	Treatment of physician’s choice
TTD	Time-to-treatment discontinuation
TTP	Time to Progression
TTR	Time to Response
VBA	Visual Basic for Applications

1 Executive summary

This summary provides a brief overview of the key issues identified by the evidence review group (ERG) as being potentially important for decision making. It also includes the ERG's preferred assumptions and the resulting incremental cost-effectiveness ratios (ICERs).

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the ICER. Sections 1.3 to 1.5 explain the key issues in more detail. Background information on the condition (1.62), technology and evidence and information on non-key issues are in the main ERG report (2.2, 3, 4).

All issues identified represent the ERG's view, not the opinion of NICE.

The company's submission of the comparative clinical effectiveness and safety evidence for Sacituzumab Govitecan (SG) is based on a single pivotal confirmatory phase-III open-label randomised controlled clinical trial (the ASCENT study) comparing SG to TPC in patients with locally advanced or mTNBC with ≥2 prior therapies.

Indirect comparison and/or multiple comparison analyses (including population-adjusted indirect comparison) was not possible due to infeasibility of such analyses in light of the absence of relevant evidence (lack of subgroup data on baseline patient characteristics and outcomes for endpoints in comparator trials) and/or violation of transitivity-consistency assumption.

The ASCENT study demonstrated clinical benefits of SG compared to TPC across multiple efficacy endpoints in pre-treated patients with TNBC. PFS and OS assessed by Independent Review Committee were significantly longer with SG than TPC in both BM-ve and ITT populations.

All issues identified represent the ERG's view, not the opinion of NICE.

1.1 *Overview of the ERG's key issues*

Table 1. Summary of key issues

ID	Summary of issue	Report sections
Issue 1	• Variation in prior therapy	3.2.6
Issue 2	• Long term effectiveness/safety data uncertainties	3.2.6
Issue 3	• Imbalance in the randomised but untreated patients across groups	**3.2.6**
Issue 4	• Differential attrition for the EORTC QLQ-C30 score	3.2.4
Issue 5	• Frequency of high grade neutropenia was more frequent in the SG	3.2.6 3.6.1
Issue 6	• Tumour location in the lymph node was higher in the TPC arm	3.2.5 3.2.6
Issue 7	• Early stopping of the trial	3.2.6
Issue 8	• Log-logistic OS parametric extrapolations overestimate survival	4.9.2
Issue 9	• Pre-progression utilities with SG may not be higher than utilities with TPC	5.2
Issue 10	• Evidence does not support higher post-progression utilities for women who received SG instead than TPC	5.2 5.5
Issue 11	• Post-progression therapy costs applied to TPC assume a very high proportion of people receiving eribulin, clinically incompatible with rates of prior and within trial eribulin, and assume more intensive therapy for longer, compared with SG.	5.4.5
Issue 12	• Acquisition and administration costs of SG and TPC are incorrectly underestimated	4.9.8 4.9.8.3
Issue 13	• The relative dose intensity (RDI) applied to the cost of SG and TPC may not be calculated correctly	5.4.3
Issue 14	• Wastage, for drugs used in this appraisal, is not part of the NHS perspective	5.4.4
Issue 15	• The model uses different weight distributions for the cost calculation of SG and TPC	5.4.2

The key differences between the company's preferred assumptions and the ERG's preferred assumptions are that in the absence of an appropriate analysis of utility data, SG does not confer higher utility than TPC during the initial treatment period, there is no difference in utility between the two groups after SG has been stopped, the costs of therapies post-progression must be commensurate to the time spent in post-progression, that RDI and wastage adjustments should not be applied in the model and that overall survival with SG and TPC are best modelled using a Weibull

distribution (SG) and a generalised gamma distribution (TPC). Taking these changes into account, the ICER initially submitted by the company (£49,651) is increased to £88,546.

1.2 *Overview of key model outcomes*

NICE technology appraisals compare how much a new technology improves length (overall survival) and quality of life in a quality-adjusted life year (QALY). An ICER is the ratio of the extra cost for every QALY gained.

Overall, the technology is modelled to affect QALYs by:

- Longer survival with SG compared with TPC. The model uses efficacy data from the ASCENT trial to this effect, which showed a difference in survival of about 4.9 months (median OS: SG=11.8 months, TPC=6.9 months). This result translated in a modelled improvement in survival of about 5.2 months.
- The model also incorporated longer progression free survival and longer time to treatment discontinuation with SG (4.8 months and 4.4 months respectively, with SG and 1.7 and 1.4 months with TPC).

Overall, the technology is modelled to affect costs by:

- An increased initial cost of therapy, compared with the cost components of TPC (eribulin, gemcitabine, vinorelbine and capecitabine), due to longer time on therapy and higher cost. SG is given intravenously, resulting in higher associated drug administration costs. SG is also associated with higher cost of post-progression therapy (made up by eribulin in largest proportion).

The modelling assumptions that have the greatest effect on the ICER are:

- An assumed improvement in utility due to SG, independently from treatment duration, compared with other drugs used in the comparator, as well as the longer period spent in pre-progression, during which such utility benefit is enjoyed;
- An assumed improvement in utility due to SG that carries over post-progression when women stop SG and are given another course of therapy, regardless of the time spent in post-progression, and compared with utility for women that received any of the drugs in the comparator during the pre-progression period;
- The assumption that women who initially receive TPC are treated more intensively after progression than women who received SG;

- The assumption that the log-logistic extrapolation curves are the best fitting curves in the model, translating in slightly less than 21% of women treated with SG to survive for 2 years after initial treatment, compared with 8% of women treated with TPC.

1.3 *The decision problem: summary of the ERG's key issues*

The CS decision problem matched the NICE scope. However, the trial evidence may be more relevant to the use of SG in mTNBC setting because only 2.8% of patients had prior systemic therapy for locally advanced TNBC. The comparator (TPC) included gemcitabine which is not used in the UK (not in treatment pathway) because of poor efficacy as a single agent in breast cancer (ERG clinical advisor). The ERG critique is available in section 2.2 of this report.

1.4 *The clinical effectiveness evidence: summary of the ERG's key issues*

Issue 1: Variation in prior therapy	
Report section	3.2.6
Description of issue and why the ERG has identified it as important	*Variation in prior therapy.* The number and types of prior therapies that patients received varied across the countries that participated in the trial. This limits the generalisability of ASCENT trials results to the UK setting
What alternative approach has the ERG suggested?	Produce a sub-group (population) that is UK relevant
What is the expected effect on the cost-effectiveness estimates?	This issue impacts on applicability (generalisability) of clinical effectiveness and cost-effectiveness estimates.
What additional evidence or analyses might help to resolve this key issue?	To tabulate a sub-group that is relevant to UK clinical practice and assess the implications on the results.

Issue 2: Long term effectiveness/safety data uncertainties	
Report section	3.2.6
Description of issue and why the ERG has identified it as important	*Long term effectiveness/safety data uncertainties.* Lack of longer-term effectiveness/safety data. The median (range) of ASCENT study follow-up was 8.38 (0-24) months
What alternative approach has the ERG suggested?	No alternative approach is required. The ERG critiqued and interpreted the submitted evidence accordingly
What is the expected effect on the cost-effectiveness estimates?	The uncertainties in longer-term effectiveness directly contribute to uncertainties in cost effectiveness estimates
What additional evidence or analyses might help to resolve this key issue?	Data from longer follow-up might resolve this issue.

Issue 3: Imbalance in the randomised but untreated patients across groups	
Report section	3.2.6 3.6.1
Description of issue and why the ERG has identified it as important	*Imbalance in the randomised but untreated patients across groups.* There was a notably higher proportion of randomised but untreated patients (consent withdrawals) in TPC (14.5%) vs. SG (3.4%) treatment group. The ERG is uncertain how the company handled these data in terms of follow-up, inclusion, imputation, or censoring matters.
What alternative approach has the ERG suggested?	Provide baseline characteristics and/or sensitivity analysis to this group
What is the expected effect on the cost-effectiveness estimates?	Depending on how these observations were handled in the efficacy analyses, this imbalance might lead to biased endpoint effect estimates (e.g., for PFS, OS, and other endpoints).
What additional evidence or analyses might help to resolve this key issue?	Sensitivity analysis or baseline patient characteristics h would help the ERG team in gauging the magnitude and direction of potential bias due to this sample attrition.

Issue 4: Differential attrition for the EORTC QLQ-C30 score	
Report section	3.2.4
Description of issue and why the ERG has identified it as important	*Differential attrition for the EORTC QLQ-C30 score.* There was a differential attrition of ITT sample due to missing values for EORTC QLQ-C30 score at a follow-up in the SG arm (11.7%) and TPC arm (30.2%).
What alternative approach has the ERG suggested?	Provide the reasons for this missing information.
What is the expected effect on the cost-effectiveness estimates?	The differential sample attrition might have led to biased treatment effect estimates for HRQoL. In the absence of reasons for such missing data, it is not possible to estimate the magnitude and direction of bias in the effect estimates.
What additional evidence or analyses might help to resolve this key issue?	To provide reasons for the differential attrition and missing values across arms to better assess the effect estimates for HRQoL.

Issue 5: Frequency of high grade neutropenia was more frequent in the SG	
Report section	3.2.6 3.6.1
Description of issue and why the ERG has identified it as important	*Frequency of high grade neutropenia was more frequent in the SG.* High grade neutropenia was more frequent in the SG (47.20%) vs. TPC (19.80%) arm. Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the TPC arm the treatment was discontinued and no G-CSF was administered (potentially dropped out).
What alternative approach has the ERG suggested?	Clinical validation that account for the costs and clinical implications of G-CSF
What is the expected effect on the cost-effectiveness estimates?	The model included higher adverse event costs with SG, including higher cost for neutropenia (rates: SG 55.4%, TPC: 35.3%, costed as one short hospital stay, £706) and higher costs for febrile neutropenia (SG: 5.8%, TPC:2.7%, cost of hospitalisation £1,786). More importantly, differential treatment of AEs in the trial may, perhaps, be associated with attrition rates, with an impact on quality-of-life data. Another potential effect of differential treatment is that quality of life in the SG arm may have been higher because of the treatment received; this bias could result in the overestimation of treatment effect with SG. Finally, better treatment in the SG arm may have resulted in a difference in the ability of women to remain on treatment; this could translate in the overestimation of PFS with SG. These three factors would have the effect of increasing the ICER although it is not possible to quantify the uncertainty.
What additional evidence or analyses might help to resolve this key issue?	Consider validation of the explicit costs

Issue 6: Tumour location in the lymph node was higher in the TPC arm.	
Report section	3.2.5 3.2.6
Description of issue and why the ERG has identified it as important	*Tumour location in the lymph node was higher in the TPC arm.* There were more patients who had tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.
What alternative approach has the ERG suggested?	Propose to include lymph node presence as a covariate in the model analysis. Currently the model analysis include group as the only covariate.
What is the expected effect on the cost-effectiveness estimates?	The results of this analysis may change the efficacy results.
What additional evidence or analyses might help to resolve this key issue?	To present a sub-group analysis (for PFS and OS) for with and without lymph node presence. Or To adjust for lymph node presence as a covariate in the model analysis.

Issue 7: Early stopping of the trial	
Report section	3.2.6
Description of issue and why the ERG has identified it as important	*Early stopping of the trial.* Caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment
What alternative approach has the ERG suggested?	None
What is the expected effect on the cost-effectiveness estimates?	Uncertainties in the effectiveness directly contribute to uncertainties in cost- effectiveness estimates
What additional evidence or analyses might help to resolve this key issue?	No additional evidence or analyses are required. This issue is flagged up to emphasise the importance of caution when interpreting the results of the trial.

1.5. The cost-effectiveness evidence: summary of the ERG's key issues

Issue 8: Log-logistic OS parametric extrapolations overestimate survival	
Report section	4.9.2
Description of issue and why the ERG has identified it as important	The use of the log-logistic distribution for OS overestimates (overall) survival in the model, which extends the period over which SG accrues a survival benefit compared with TPC.
What alternative approach has the ERG suggested?	The ERG prefers the Weibull distribution for SG, which provides the best fit, and the generalised gamma for TPC. However, because the model only gives the option to choose distributions modelled jointly, the joint generalised gamma distribution is the only available option in the cost-effectiveness model at this time. This distribution is preferred in the absence of 'stratified' curves, because, of all joint models, it projects more realistic survival estimates.
What is the expected effect on the cost-effectiveness estimates?	Overall shorter survival increases the ICER (see Section 1.6)
What additional evidence or analyses might help to resolve this key issue?	• Stratified parametric distributions for OS should be incorporated in the model to allow choosing the best fits.

Issue 9: Pre-progression utilities with SG may not be higher than utilities with TPC	
Report section	5.2
Description of issue and why the ERG has identified it as important	The cost-effectiveness model incorporates pre-progression utilities for SG of [redacted], 0.084 higher than those used for TPC, [redacted], with the difference being attributable to treatment with SG. EQ-5D utilities were obtained from a mapping algorithm which used EORTC QLQ C-30 scores from ASCENT. An analysis was presented which shows that the difference is statistically significant for utilities, despite the conclusion in the ASCENT CSR that EORTC QLQ C30 are, essentially, similar for SG and TPC. The EORTC QLQ data were strongly affected by attrition (in excess of 30% of the initial sample in TPC but far lower in SG section 3.2.4) No exploration of how attrition affected the comparability of the two groups whose QLQ values were mapped to obtain utility values. If attrition caused patient characteristics, prognostic factors or other treatment effect modifiers to become unbalanced between the SG and the TPC groups, then the difference seen in utility values between the two comparators may not be due to treatment but to imbalances in important determinants of benefit.
What alternative approach has the ERG suggested?	In the absence of robust demonstration that SG is associated with an independent treatment effect on utility scores, the ERG preferred approach is to use the same utility values for SG and TPC, consistently with prior appraisals (TA639, TA423) where no treatment effect was demonstrated on the utility scale.[1, 2] SG would still have higher utility compared with TPC, due to longer time spent in pre-progression.
What is the expected effect on the cost-effectiveness estimates?	Higher EQ-5D pre-progression utilities with SG are an important driver in the cost-effectiveness. The effect of using same utility values pre-progression is to increase the ICER (see Section 1.6).

What additional evidence or analyses might help to resolve this key issue?	• A complete, and thorough, description of the effect of attrition on baseline utilities for the SG and TPC groups • An exploration is required of whether potential imbalances affect prognostic factors and / or treatment effect modifiers (relative to utility values) • If imbalances of importance are found, utility data should be analysed taking attrition into account. The best approach for this analysis requires a feasibility assessment where patterns of missingness are analysed. If missingness is not at random, then utility analyses should account for patterns of missingness, to rebalance the comparison. • A range of approaches options should be considered: o Appropriate missing values imputation models o and / or, if appropriate, adjustments in the regression models used At this point, in the absence of information on the nature of dropouts, the selection of the best approach remains uncertain. This depends on whether imbalances are found, on the nature of potential imbalances identified and consequently, which is the most efficient approach to reanalyse utility data.

Issue 10: Evidence does not support higher post-progression utilities for women who received SG instead than TPC	
Report section	5.2 5.5
Description of issue and why the ERG has identified it as important	The cost-effectiveness analysis incorporates higher post-progression utilities with SG compared with TPC (by the same factor (0.084) used for pre-progression utility. The evidence for this utility gain with SG after SG has been stopped is unclear. EORTC QLQ data collection in ASCENT was stopped just after progression. Women receive a similar mix of therapies in SG and TPC in ASCENT.
What alternative approach has the ERG suggested?	Post-progression utilities should be the same for SG and TPC. As these data were not collected in ASCENT, the ERG replaced post-progression utilities using data from prior appraisals.
What is the expected effect on the cost-effectiveness estimates?	The use of the same post-progression estimates increases the ICER (see Section 1.6).
What additional evidence or analyses might help to resolve this key issue?	n/a

Issue 11: Post-progression therapy costs applied to TPC assume a very high proportion of people receiving eribulin, clinically incompatible with rates of prior and within trial eribulin, and assume more intensive therapy for longer, compared with SG.	
Report section	5.4.5

Description of issue and why the ERG has identified it as important	The costs of post-progression therapies applied in the model are not consistent with the time left in the model before death. The duration of post-progression treatment applied to SG (10.6 weeks on average) is generally shorter than that applied to TPC (13.2 weeks on average). This is implausible, because women treated with SG live longer in the post-progression state (average 25 weeks) compared with TPC (average 19 weeks). This translates in 14 weeks off treatment before death with SG and 6 weeks off treatment with TPC. This assumption implies that women receiving TPC are treated to end of life, whilst in SG, therapies are interrupted well before time of death. In addition, the mix of therapies applied to TPC is inconsistent with therapies received by women in the ASCENT trial, both before recruitment (prior therapies) and during the trial (allocated treatment). Post-progression costs for TPC are assumed to be made up by eribulin for 66% of women. This is incompatible with trial data, as approximately 33% of women (both arms) received eribulin before the study and 53% (TCP arm) during the study, leaving approximately 15% eribulin-naïve. The company's proportions implicitly assume that in the TPC arm, up to 50% of the cohort is treated with eribulin (the most expensive treatment) twice. Post-progression therapy proportions favour SG.

What alternative approach has the ERG suggested?	The ERG applied post-progression therapy for half the period after progression, based on time left to live for each comparator. An alternative would require a rather more sophisticated model structure, where the time spent on subsequent therapy is tracked for each model cycle when transitions to post-progression occur. Although more accurate, this approach is probably too onerous for the added precision and is therefore not preferred in the context of this appraisal, given the very short time spent in post-progression states for this cohort. With regards to eribulin rates post-progression, there are two possible approaches: • To realign post-progression therapies with clinical trial data. The ERG implemented this scenario decreasing the proportion of eribulin in TPC to 14% (similar to data from ASCENT); the remainder of the treated population was split equally between other components of post-progression therapy. This approach preserves the face validity of clinical assumptions incorporated in the cost-effectiveness, given the ASCENT trial data; whilst in principle effort could be spent to determine accurate proportions of the remaining post-progression therapies, their unit costs are so low that the impact of these proportions would be, essentially, minor. • To generate a cost-effectiveness scenario using trial data restricted to women who did not receive eribulin prior to being recruited to the trial (first line eribulin). This approach would allow to assess cost-effectiveness of SG within the UK clinical pathway, also allowing for a higher proportion of eribulin used post-progression. Restricting trial analyses to women not treated with eribulin first line may imbalance the data because type of prior therapy was not a randomisation stratification factor, although imbalances may not occur if use of first line eribulin overlaps with other randomisation stratification factors (i.e. if first line eribulin overlaps with US / ex-US geography). Approaches should be explored to assess whether trial rebalancing is needed, for this second scenario.
What is the expected effect on the cost-effectiveness estimates?	The effect of more balanced post-progression therapy costs is to increase the ICER. A lower proportion of post-progression eribulin in TPC increases the ICER (see Section 1.6). The effect of restricting the cost-effectiveness to women who did not receive eribulin first line is very uncertain at this point.

What additional evidence or analyses might help to resolve this key issue?	• Post-progression therapy proportions form ASCENT should be recalculated for women who did not receive eribulin first line • Additional clinical validation should be focussed on rates of eribulin; other explorations are unlikely to resolve uncertainty because of the low cost of post-progression therapies other than eribulin • In the case of the UK, where clinical opinion supports the positioning of eribulin mainly after TPC, i.e. in third or further treatment lines should be done compatibly with maintaining clinical plausibility.

Issue 12: Acquisition and administration costs of SG and TPC are incorrectly underestimated	
Report section	4.9.8 4.9.8.3
Description of issue and why the ERG has identified it as important	Acquisition and administration costs are applied in the model as a cost per (model) cycle (equal to 1 week), calculated as the total cost per therapy cycle (generally over 3 weeks) divided by 3. However, this approach underestimates acquisition and administration costs because costing by model cycle does not assign a proportion of the costs to people that die in (model) cycle 2 and 3 of every therapy cycle. Overall, the model generates underestimates of therapy costs, however the underestimates differ by therapy due to differences in prices, in administration patterns and costs and by type of prescriptions (oral vs IV).
What alternative approach has the ERG suggested?	The correction of this bias is rather simple and involves assigning a cost by 'transition' instead than by state: all people are costed in the proportion entering a cycle when the dose (or the pack, for oral drugs) is dispensed, and the relevant acquisition cost is supported by the NHS.
What is the expected effect on the cost-effectiveness estimates?	The use of the appropriate costing methodology increases the ICER (see Section 1.6).
What additional evidence or analyses might help to resolve this key issue?	Corrections have been implemented in the model; no additional evidence required.

Issue13: The relative dose intensity (RDI) applied to the cost of SG and TPC may not be calculated correctly	
Report section	5.4.3
Description of issue and why the ERG has identified it as important	The methods used to calculate the RDI applied in the model are not described. The use of the safety / exposure RDI may underestimate treatment costs because doses discarded result in lower exposure but not in lower costs.
What alternative approach has the ERG suggested?	In the absence of a correctly quantified RDI, the RDI has been reset to 100%. The relevant RDI, with all cost components accounted for, should be recalculated and RDI calculation methods should be provided and thoroughly described.
What is the expected effect on the cost-effectiveness estimates?	The use of the appropriate RDI increases the ICER (see Section 1.6).
What additional evidence or analyses might help to resolve this key issue?	Recalculating the correct RDI; a description of methods that can be validated.

Issue 14: Wastage, for drugs used in this appraisal, is not part of the NHS perspective	
Report section	5.4.4
Description of issue and why the ERG has identified it as important	The cost-effectiveness assumes that a fraction of drugs used for IV are 'redeployed' to other patients. However, all drugs used in this appraisal are prescribed in packs classified as 'special containers', as such, they are reimbursed as full vials, in the minimum quantity required to fulfil the prescribed dose, regardless as to whether wastage is discarded or redeployed. Therefore, the NHS perspective is not maintained when the cost of vials is reduced below the amount paid by the NHS at the point of filling the prescription. For oral drugs classified as packaged as 'special containers', the whole pact is dispensed and cannot be fractioned. For this reason, pack should be costed at the point of dispensing, not as pills are gradually consumed and regardless of whether the whole pack is consumed or not.
What alternative approach has the ERG suggested?	Wastage has been set to 100% in the cost-effectiveness
What is the expected effect on the cost-effectiveness estimates?	The use of costing consistently with the NHS perspective increases the ICER (see Section 1.6).
What additional evidence or analyses might help to resolve this key issue?	N/a

Issue 15: The model uses different weight distributions for the cost calculation of SG and TPC	
Report section	5.4.2
Description of issue and why the ERG has identified it as important	The cost of SG is calculated using a non-parametric distribution directly calculated using percentiles of weight from the ASCENT trial (non-US) population. This distribution is slightly skewed towards lower weight percentiles compared with the parametric (using the same mean and standard deviation) normal distribution used for TPC.
What alternative approach has the ERG suggested?	One weight distribution, derived from mean weight and SD from ASCENT has been replaced to the (hard-coded) non parametric distribution in SG.
What is the expected effect on the cost-effectiveness estimates?	The use of the weight distribution slightly increases the ICER (see Section 1.6).

What additional evidence or analyses might help to resolve this key issue?	n/a

Issue 16: Other minor issues	
Report section	4.9.8.3
Description of issue and why the ERG has identified it as important	The cost of vinorelbine and capecitabine were incorrectly calculated. The cost of vinorelbine used a distribution of doses with erroneous values. The cost of capecitabine used a fixed cost, whilst in practice, capecitabine is weight-based. The model used a half-cycle correction for costs. In general, this is not correct, however, in this model, an initial cost at cycle 0 was also added, resulting de facto in doubling up the cost of the first cycle.
What alternative approach has the ERG suggested?	The error in the vinorelbine cost computation has been corrected. Dose by weight tables are provided in the capecitabine SMPC; these have been used to recalculate the cost of this oral treatment. The cost calculation is rather laborious (although not complicated) for a minimal difference in the cost-effectiveness overall. And although the recalculated cost is twice the original cost, the acquisition cost of capecitabine remains low because of the low proportion of people receiving this drug. The half-cycle correction was taken out as part of the cost by cycle modification (see issue 12)
What is the expected effect on the cost-effectiveness estimates?	Cost calculation corrections affect the ICER very slightly (see Section 1.6).
What additional evidence or analyses might help to resolve this key issue?	n/a

1.5 *Other key issues: summary of the ERG's view*

- The evidence base directly informing the decision problem is limited to one RCT. No pair-wise/network meta-analysis, or population-adjusted analysis for indirect comparison was feasible to compare the effectiveness and safety profiles of SG and relevant comparator treatments as specified in the NICE scope.

- The ASCENT study was an open-label trial because blinding of study personnel and study participants was not possible due to differences in the administration of study treatments. This may have impacted the ascertainment of patient-reported outcomes such as HRQoL and inflated the clinical benefits shown for the mean EORTC QLQ-C30 score changes in the SG arm even if the outcome assessors were independent and blinded. QOL endpoints were patient or investigator rated therefore fully open to biased assessment. Open-label design may differentially affect the quality of care across the study treatment arms
- There is uncertainty if the primary analysis population (BM negative patients) was truly free of BM (only those patients with 'known BM' were MRI-ed and excluded from the primary analysis). The presence of BM is a strong predictor for disease progression and poorer prognosis (as shown in the subgroup analysis of the ASCENT study and previous research findings) and its imbalanced distribution between the SG and TPC study arms could bias the SG treatment effect estimates for PFS and OS.

1.6 *Summary of ERG's preferred assumptions and resulting ICER*

Scenario	**Incremental cost**	**Incremental QALYs**	**ICER**	**ICER, incremental % change from base case**
Company's revised base case	[redacted]	[redacted]	£50,070	
RDI set to 100%, both SG and TPC	[redacted]	[redacted]	£50,883	+2%
Patients weight distribution equal for SG and TPC, based on normal distribution	[redacted]	[redacted]	£51,878	+4%
Drug wastage set to full wastage	[redacted]	[redacted]	£54,118	+8%
Cost of subsequent therapies, eribulin assumed for eribulin naïve patients for both comparators	[redacted]	[redacted]	£59,125	+18%
Utility values, no utility difference for post-progression therapies (SG and TPC equal utility)	[redacted]	[redacted]	£66,334	+32%
Utility values, no SG treatment effect on utility during treatment	[redacted]	[redacted]	£70,021	+40%
OS distributions, using joint generalised gamma	[redacted]	[redacted]	£79,131	+58%
OS distributions, using Weibull (SG) and generalised gamma (TPC)	[redacted]	[redacted]	£88,546	+77%
ERG's preferred base case	[redacted]	[redacted]	£88,546	

Modelling errors identified and corrected by the ERG are described in Table 2 below. Overall, the base case submitted by the company was revised slightly.

Table 2. Modelling errors identified and corrected

Scenario	Incremental cost	Incremental QALYs	ICER
Company's base case	[redacted]	[redacted]	£49,651
Correction of error in Vinorelbine cost calculation	[redacted]	[redacted]	£49,673
No half cycle correction for drug acquisition cost, administration cost and concomitant drugs cost	[redacted]	[redacted]	£49,202
Costing using treatment cycles	[redacted]	[redacted]	£50,070
Company's base case, after corrections			£50,070

For completeness, sensitivity analyses were conducted to assess the effect of alternative distributional assumptions for PFS and time to treatment discontinuation (TTD) and are presented in Table 3 below.

Table 3. Additional sensitivity analyses, PFS and TTD extrapolations

Scenario	Incremental cost	Incremental QALYs	ICER
ERG's preferred base case + log-logistic distribution for PFS (SG and TPC)	[redacted]	[redacted]	£88,586
ERG's preferred base case + generalised gamma distribution for PFS (SG and TPC)	[redacted]	[redacted]	£88,648
ERG's preferred base case + generalised gamma distribution for TTD (SG and TPC)	[redacted]	[redacted]	£88,807

1.7. End of life criteria

The technology meets NICE criteria for end-of-life treatments. The expected survival for women with TNBC is between 7 and 12 months, as modelled in the cost-effectiveness analysis and using data from ASCENT. The number of women expected to present with a diagnosis of TNBC is between 4,500 and 6,750 new cases per year in England (Document B, Section B1.3.1).

2. INTRODUCTION AND BACKGROUND

2.1. Introduction

This single technology appraisal (STA) focuses on the use of sacituzumab govitecan (SG) for treating adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have had at least two prior therapies, including at least one for locally advanced or metastatic disease.

2.2. Background

Breast cancer is one of the most common cancer in the UK with over 60,000 people being diagnosed every year.[3] Breast cancer is mainly prevalent among women, however more than 300 men are diagnosed with breast cancer each year.[3] Breast cancer can spread locally within the breast, and in several lymph nodes or other tissues nearby.[3] This is known as locally advanced breast cancer. Breast cancer that spreads further from the breast to distant organs such as the bones, lungs, or other parts of the body is known as metastatic breast cancer (MBC).[4] In order to complete the prognosis and treatment plan, breast cancer cells are tested for the presence or absence of molecular markers of estrogen receptors (ER) or progesterone receptors (PR) and human epidermal growth factor 2 (ERBB2; formerly HER2).[5, 6] Hormone receptor-positive cells (cells that have one or both estrogen or progesterone receptors) can be treated with hormone therapy drugs. They tend to grow more slowly than hormone receptor-negative cells, and patients have a better short-term outlook, though the cancer can sometimes come back years after treatment.[5] Cells that are hormone receptor-negative have neither estrogen nor progesterone receptors and thus cannot be treated by hormone therapy drugs. Typically, these cancerous cells grow faster than hormone receptor-positive cancers and if they return it is usually within the first few years after treatment.[5] Triple-negative breast cancer (TNBC) lacks all 3 standard molecular markers and effects approximately 15% of all breast cancer patients.[6] Compared to the other two subtypes, the survival time is shorter with a mortality rate of 40% within the first 5 years after diagnosis and mortality rates as high as 75% 3 months after reoccurrence.[7] The time to relapse is also higher at 19–40 months in TNBC patients compared to 35–67 months in non-TNBC patients.[7] TNBC has high invasiveness and high metastatic potential affecting approximately 46% of TNBC patients and most commonly involving the brain and

visceral organs.[3, 7] The recurrence rate for metastatic triple-negative breast cancer (mTNBC) in patients after surgery is 25% and the median survival time after metastasis is 13.3 months.[7] The absence of ER, PR, and ERBB2 expression means that TNBC is not sensitive to endocrine therapy or molecular targeted therapy thus chemotherapy is currently the main systemic treatment.[7]

2.1.1. Critique of company's overview of current treatment pathway

The ERG found the company's description of the current treatment pathway to be consistent with NICE clinical guideline 81 (CG81).[8] The company references international consensus guidelines for advanced breast cancer (ESMO) which has a harmonising pathway.[9] The company accurately details the treatment pathway for managing mTNBC in section B.1.3.4.2 (Document B, page 15) and figure 1 (CS Document B, page 16). According to the NICE treatment pathway patients with triple negative disease (hormone receptor-negative and HER2-negative) (mTNBC) should be offered systemic chemotherapy in the following sequence:

First line: single-agent docetaxel

Second line: single-agent vinorelbine or capecitabine

Third line: single-agent capecitabine or vinorelbine (whichever was not used as second-line treatment)

Furthermore, gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.[8] NICE also recommends eribulin as an option for treating locally advanced or metastatic breast cancer in adults, only when it has progressed after at least 2 chemotherapy regimens (which may include an anthracycline or a taxane, and capecitabine).[2] The key trial (ASCENT) underpinning the current appraisal compares sacituzumab govitecan (SG) with physician's choice of vinorelbine, capecitabine, eribulin and gemcitabine.

The clinical effectiveness evidence is similar to current NICE guidance in terms of study population (CS Document B, section B.2.2, table 3, page 21) For example, the change in use of eribulin from patients who had had only 1 chemotherapy regimen to patients where the disease has progressed after at least 2 chemotherapy regimens.[2]

However, there was no indication by the company that gemcitabine was used in combination with paclitaxel in the ASCENT trial.[10] Therefore, the ERG is not certain if this is in line with NICE guidance.

The company states that that there is no established standard of care for pre-treated mTNBC. Treatment regimens are inconsistent with the current NICE clinical pathway, and treatment options are highly variable. However, the company stated that UK clinical expert feedback indicates clinicians typically use capecitabine, vinorelbine or eribulin (Document B, section B.1.3.4.3, page 17. This lack of standard care may introduce some challenges in understanding how best to assess the comparative efficacy or effectiveness of vinorelbine, capecitabine and eribulin versus SG. The ERG clinical advisor state that pre-treated mTNBC are a very challenging group to treat. In the UK, these patients will usually have had anthracyclines, taxanes and carboplatin as primary/neoadjuvant chemo (NACT) with capecitebine as adjuvant chemo in the high risk population who have not achieved a path CR with NACT, as per the CreateX study.[11]

2.1.2. Critique of the company's proposed place of the technology in the treatment pathway

The company proposed the use of SG for unresectable locally advanced and mTNBC where patients have received two prior lines of systemic therapy, of which at least one of them was given for unresectable locally advanced or metastatic disease (CS Document B, section B.1.3.5.1, page 18). The intention was for '*all patients on third-line mTNBC treatment or beyond as well as patients on second-line treatment for mTNBC who have also received at least one systemic regimen for early (operable) TNBC (i.e., as neoadjuvant or adjuvant therapy given as an adjunct to surgery) at any time prior to progression to locally advanced or mTNBC'* (clarification response, question A2.1, page 3) to receive SG. This is in line with the drug indication "*Trodelvy as monotherapy is indicated for the treatment of adult patients with unresectable or mTNBC who have received two or more prior systemic therapies, including at least one of them for advanced disease*".[12]

The company considered patients that were diagnosed with early stage TNBC before progressing to a locally advanced or metastatic disease stage and received neoadjuvant and/or adjuvant chemotherapy and surgery as potentially curative

treatment, followed by one line of systemic therapy in the metastatic setting as receiving second-line treatment (clarification question, section A2.1, page 3-4). The decision on line of therapy was informed by the stage of disease.

2.2. Critique of company's definition of decision problem

The ERG provides a comparison of the NICE final scope and CS decision problem in Table 4.

2.2.1. Population

The CS population is similar to the NICE scope "Adults with unresectable locally advanced or metastatic triple-negative breast cancer who have had at least two prior therapies, including at least one for locally advanced or metastatic disease". This is in line with the drug indication. However, the evidence submitted includes a very small number of UK patients ([redacted] from 6 centres), therefore may not be generalisable. Only 2.8% of patients enrolled in the ASCENT trial had prior systemic therapy for locally advanced TNBC . Therefore the trial evidence is may be more relevant to the use of SG in mTNBC setting.

2.2.2. Intervention

The intervention listed in the CS decision problem matches that in the NICE final scope: sacituzumab govitecan.

2.2.3. Comparators

The comparators listed in the CS decision problem are similar to the NICE final scope. However, an additional comparator was also included gemcitabine as part of TPC which is indicated for metastatic breast can only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. Gemcitabine is not used in the UK (not in treatment pathway) because of poor efficacy as a single agent in breast cancer (ERG clinical advisor).

2.2.4. Outcomes

The outcomes match the NICE scope. The primary outcome was progression free survival assessed by an independent committee. The trial evidence included additional secondary outcomes: objective response rate, clinical benefit rate, duration of response, and time to response time to progression.

Table 4: Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Population	Adults with unresectable locally advanced or metastatic triple-negative breast cancer who have had at least two prior therapies, including at least one for locally advanced or metastatic disease	Adults with unresectable locally advanced or metastatic triple-negative breast cancer who have had at least two prior therapies, including at least one for locally advanced or metastatic disease	As per scope	The trial evidence may be more relevant to the use of SG in mTNBC setting because only 2.8% of patients had prior systemic therapy for locally advanced TNBC. The target population is similar to the NICE scope. However, the evidence submitted includes a very small number of UK patients therefore generalisability is not applicable.
Intervention	Sacituzumab govitecan	Generic name: Sacituzumab govitecan Brand Name: Trodelvy	As per scope	Matches the NICE scope

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Comparator(s)	• capecitabine • vinorelbine • eribulin	• capecitabine • vinorelbine • eribulin • gemcitabine	Defining specific comparators at certain stages of the mTNBC treatment pathway is challenging, as the choice of treatment is heavily dependent on a number of individualised factors, such as prior therapies received, the patient's fitness level with regard to what they can tolerate, and an individual patient's preferences. In particular, for patients diagnosed at and treated for early-stage disease, the most effective therapies (anthracyclines, taxanes, alkylating agents, and platinum compounds) are used in the neoadjuvant setting, meaning they are not available for metastatic disease. However, after consultation with clinical experts, Gilead's view is that the use of eribulin, vinorelbine and capecitabine is an appropriate reflection of clinical practice in England for the population outlined above and are well represented in the TPC arm of the ASCENT trial. Of the three comparators, clinical expert feedback suggests that eribulin may be described as “best alternative care”. Gemcitabine was also used in a small proportion of patients in the TPC arm (15%) in the ASCENT trial. Subgroup analysis by treatment agent showed similar survival benefits as the other three agents in the TPC arm. Therefore, inclusion of gemcitabine in the TPC arm is not expected to bias outcomes of the ASCENT trial in favour of sacituzumab govitecan. UK clinical expert feedback supports that the TPC arm is a pragmatic and appropriate comparator, consisting mostly of therapies that are commonly used in England.	TPC included gemcitabine (also indicated for metastatic breast can only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate). Gemcitabine is not used in the UK (not in treatment pathway) because of poor efficacy as a single agent in breast cancer (ERG clinical advisor).

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope	ERG comment
Outcomes	• overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.	• overall survival • progression free survival • response rate • adverse effects of treatment • health-related quality of life.		The outcomes match the NICE scope and the trial evidence included additional secondary outcomes: objective response rate, clinical benefit rate, duration of response, and time to response time to progression
Economic analysis				
Subgroups	none			
Special considerations including issues related to equity or equality	none	We do not envisage any equality issues arising from the scope. However, it should be noted that the prevalence of TNBC is higher among people of African ancestry than among white people. Consequently, guidance that restricts the use of sacituzumab govitecan may disproportionately impact black people with TNBC.		

3. CLINICAL EFFECTIVENESS

3.1. Critique of the methods of review(s)

The CS includes a systematic review undertaken to “assess the comparative safety and efficacy of SG versus other therapies for mTNBC“ (CS Appendix D, page 5).

The review processes were described for searches and screening (number of reviewers) but not for full-text assessment and data extraction. Screening of potentially eligible studies was carried out by two independent reviewers. A pre-defined PICO was applied for study selection. Data extraction was not clearly described in the clinical effectiveness review (CS Appendix D). The lack of information on methodology does suggest some risk of bias however overall, the ERG considered the risk of bias to be low. The ERG full assessment of risks of bias of the CS systematic review of clinical effectiveness is in Appendix 1.

3.1.1. Searches

Summary of the company’s approach to study identification

The company’s search approached utilised searches of bibliographic databases and supplementary search methods to identify studies reporting randomised or clinical trials, single arm trials, and non-randomised studies published in English, 2000 until January 2021.

The company searched four databases, including MEDLINE and Embase. Their bibliographic search strategy was directly aligned to the decision problem, combining terms for triple negative breast cancer, 11 interventions (including the intervention and comparators in scope), and search terms for the study designs of interest. The ERG were able to re-create the searches following the company’s response to clarification questions.

Four conferences (ASCO, ESMO, ESMO Breast Cancer congress, and SABCS), and conferences indexed in Embase, were searched 2018-2021. A search of ClinicalTrials.gov was undertaken and studies included in systematic reviews published in the last two years were checked for eligible studies.

Critique of the company’s approach to study identification

The ERG considers that there are limitations in the company’s approach to study identification which could have led the company to miss relevant evidence. These limitations are:

i) aligning the search approach to the decision problem: the ERG considers that the search approach should have focused on breast cancer with the focus on the decision problem (triple negative breast cancer, specifically) made during study selection;

ii) the ERG considers that there are limitations in the bibliographic database search strategies**.** Using the Company's MEDLINE search strategy (Document B, Table 12, page 33-34) the ERG lists the following issues:

Company's MEDLINE search strategy	ERG Comments
1. exp Triple Negative Breast Neoplasms/ or (er-negative-pr-negative-her2 negative breast cancer or er-negative-pr-negative-her2 negative breast neoplasms or triple-negative breast cancer or triple-negative breast neoplasm$ or triple-negative breast cancer$ or triple-receptor-negative breast cancer$ or TNBC).ti,ab.	The highlighted terms are free-text search terms chosen by the company to search for studies reporting triple negative breast cancer in title or abstract. The company have formatted these search terms as phrases. This means that an eligible study report would have to report exactly these phrases in title or abstract to be retrieved. In addition, the company has restricted their free-text searches to title or abstract fields. Recommend best practice suggests searching on author keyword and other indexed fields. This would have improved the sensitivity of their search approach.
37. Randomized controlled trials as Topic/ or Randomized controlled trial/ or Random allocation/ or Double blind method/ or Single blind method/ or Clinical trial/ or exp Clinical Trials as Topic/ or ((clinic$ adj trial$1) or ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3))).tw. or Placebos/ or Placebo$.tw. or Randomly allocated.tw. or (allocated adj2 random).tw. or (single arm trial or singl* or single-arm).tw. or (non-random* or single group assign*).tw.	The Company have not used existing and validated search filters to limit their bibliographic searches to the study designs of interest. • The key search term when searching for randomised trials is: random* as a free text search term (where * represents truncation for random or randomly or randomised etc). This term is not present in the bibliographic search strategies. • The search strategy would miss studies that report by trial phase as opposed to method of randomisation (e.g., the Phase I/II IMMU-132-01 study (NCT01631552)). This is because 'phase 2' was not mentioned in their search syntax, so the approach relies on indexing to identify studies.[13] • Non-randomised studies are eligible for inclusion but only one search term is used to identify these studies: non-random*. Existing and validated search filters exist to identify these types of study design, and many name specific designs of interest. These were not included in the search strategies. It is very likely that non-randomised studies of interest will have been missed due to this limitation.

In summary, the ERG considers that the limitations set out above, in addition to the decision to align the search approach directly to the decision-problem, may have led to eligible studies and study data being missed through an overly restrictive search approach. The impact of this approach is likely to relate to comparator studies/data and studies/data relating to the broader breast-cancer population which the company may rely upon in their submission. The impact of this approach is likely to relate to identification of non-randomised studies and specific data (such as health related quality of life), and/or studies/data relating to the broader breast-cancer population, which the company may rely upon in their submission. As it relates to study identification, we do not consider that the deficiencies in the company's searches would have altered their ability to undertake an indirect treatment comparison

3.1.2. Inclusion criteria

The eligibility criteria for study inclusion and exclusion were defined according to population, intervention, comparators, outcomes, and study design (PICOS) framework (CS Appendix D, Table 6, page 14). The possibility of publication bias due to excluding studies in languages other than English is noted. The company provided a graphical display of the study selection process using a PRISMA study flow diagram which the ERG was able to validate following clarification questions (CS Appendix D, page 16). The number of reviewers involved in full-text assessment was not clearly reported. The ERG notes that full text assessment should be undertaken by two independent reviewers.

3.1.3. Critique of data extraction

The CS does not report the method or process of data extraction for clinical effectiveness, e.g. the number of reviewers who conducted extraction, whether extraction was checked for errors, how disagreements were managed. The ERG does not consider this systematic.

3.1.4. Quality assessment

The company's assessment of study quality of the included study, the ASCENT (IMMU-132-05) trial[10] (section B.2.5, p109 CS) is summarised in Table 5 together with the ERG's independent assessment

Appendix 2). The company's assessment of the study quality of the included study is summarised in Table 5 together with the ERG's independent assessment (

Appendix 2). The company has assessed the risk of bias according to the minimum criteria stipulated in the NICE user guide for company evidence submission.[10, 14] Quality assessment

conducted by the ERG was undertaken independently by two reviewers at study level using the RoB tool as recommended by NICE (detailed ERG assessment is available

Appendix 2).[14]

The ASCENT (IMMU-132-05) trial was assessed across the domains of randomisation, allocation concealment, blinding (participants, study personnel, and outcome assessors), the similarity of groups at baseline, sample attrition/incomplete outcome data (Intention To Treat [ITT] analysis, sensitivity analysis), and selective outcome reporting (CS Appendix D page 166 Table 39). The company does not state if the RoB assessment was performed by two independent reviewers. The company assessed the majority of domains (7 out of 8) of the ASCENT trials to be at low RoB, however the ERG downgraded the quality of evidence in comparison to the company as some ambiguous concepts or potential risks of biases. The ASCENT study was an open-label trial thus the blinding of study personnel and study participants was not possible. This may have impacted the ascertainment of patient-reported outcomes such as HRQoL, inflated the clinical benefits and affect the quality of care across the study treatment arms. Furthermore, there was a higher rate of patients not treated in the TPC group than SG group. The ERG partially agrees with some of the RoB sub-domains (

Appendix 2) assessed by the company. Overall, there are some concerns around the risk of bias of the trial.

Table 5. ERG summary assessment of ASCENT (IMMU-132-05) [10] trial quality (detailed assessment in

Appendix 2)

NICE Checklist item overall rating	CS judgement and rationale	ERG judgement and rationale
Selection bias (*randomisation, allocation concealment, group similarity*)	NR	Low
Performance bias (*same care across groups, blinding of participants, blinding of treatment delivery*)	NR	Some concern • The ASCENT study was an open-label trial because blinding of study personnel and study participants was not possible due to differences in the administration of study treatments. This may have impacted the ascertainment of patient-reported outcomes such as HRQoL and inflated the clinical benefits shown for the mean EORTC QLQ-C30 score changes in the SG arm even if the outcome assessors were independent and blinded. • Open-label design may differentially affect the quality of care across the study treatment arms
Attrition bias (*length of follow-up, groups comparability*)	NR	High A smaller percentage of patients in the SG

		group (n=9, 3.4%) compared with the TPC group (n=38, 14.5%) were randomised to study treatments but were not treated. Depending on how these observations were handled in the efficacy analyses (followed-up/not followed-up, excluded/included, imputed, censoring), this imbalance might lead to biased estimates in the efficacy endpoints (e.g., for PFS, OS, and other endpoints) due to sample attrition if the reasons for consent withdrawal or baseline prognostic factors differed across the trials arms. The ERG could not collate further information or participants' characteristics who were withdrawn from the study.
Detection bias (*length of follow-up, outcome definition, outcome methodology, blinding of investigators)*	NR	Some concern Open label trial can affect the assessment of outcomes and exaggerate the effect of intervention. The sponsor, Immunomedics, designed the trial and gathered the data. Data analysis was performed by Veristat and by authors who are employed by Immunomedics.

3.1.5. Evidence synthesis

In the CS SLR review of clinical effectiveness, the number of publications meeting the review inclusion criteria was initially reported to be 10 (Figure 1, appendix D). Of the 10, 4 trials were included in the feasibility assessment and 6 were excluded from the assessment for not being able to connect them with ASCENT study. As the indirect comparison was not feasible (Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison), these 4 trials and other remaining 'provisionally included' trials were not informative to narratively synthesize because none of them compared SG to TPC (or any relevant therapy). Table 9, appendix D presents reasons for exclusion. Consequently only the ASCENT (IMMU-132-05)[10] trial was reported narratively, including data presented in graphical and tabular form. The ERG's critique of this is given in section 2.2.

3.2. Critique of trials of the technology of interest, the company's analysis and interpretation (and any standard meta-analyses of these)

The company's submission of the comparative clinical effectiveness and safety evidence for Sacituzumab govitecan (SG) is based on a single pivotal confirmatory phase-III open-label

randomised controlled clinical trial (the ASCENT study), which is described in detail in the CS (Document B, B.2.2 page 21). The ASCENT study information was provided also in other sources such as the study protocol,[15] clinical study report IMMU-132-05 (CSR),[16] patient-reported outcome (PRO)/health-related quality of Life (HRQoL) results,[17] and peer-reviewed publications.[10]

The CS (Document B) provides summary information about the trial design, intervention, population, patient numbers (e.g., how many were eligible, randomised, allocated and dropped out), outcomes and statistical analyses. The company provided the ASCENT study CSR for use within this appraisal. Neither the company nor the ERG identified any other relevant RCT that would meet the NICE decision problem.

3.2.1. The ASCENT study: objectives, design, and outcome definitions

ASCENT (IMMU-132-05; NCT02574455) was an international, multicentre, open-label, randomised, phase III confirmatory study comparing SG with single-agent treatment of physician's choice (TPC) in patients with triple negative breast cancer (TNBC).

The primary and secondary study objectives and outcome definitions of the ASCENT study are provided in Table 1. The primary objective to assess and compare PFS between SG and TPC groups of patients was based on the sample of brain metastasis-negative (BM-ve) mTNBC patients (primary analysis population). The secondary objectives were presented for both ITT and BM-ve populations separately.

Table 1. Research objectives of ASCENT study and outcome definitions (as per the protocol).[15]

Objective	Type of endpoint (set of mTNBC population)
The primary objective statement: to compare SG and TPC for progression-free survival (PFS) by IRC assessment in the BM-ve patient population of locally advanced or mTNBC (primary analysis population).	PFS (BM-ve)
The secondary objective statement: to compare SG with TPC for the following endpoints: PFS, OS, ORR, CBR, DOR, TTR, TTP, QoL, and AEs in patient population of locally advanced or mTNBC.	PFS (ITT), OS (ITT, MB-ve), ORR (ITT, MB-ve), CBR (ITT, MB-ve), DOR (ITT, MB-ve), TTR (ITT, MB-ve), TTP (ITT, MB-ve), QoL (ITT), AEs (safety population)
Outcome definitions	
PFS (progression free survival), NICE scope, cost outcomes: The time from randomization until objective tumor progression by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 or death, whichever came first. The date of progression was date of the last observation or radiological assessment of target lesions that either showed a predefined increase (+20%) in the sum of the target lesions or the appearance of new nontarget lesions. PFS was estimated using Kaplan-Meier estimate.	
OS (overall survival) NICE scope, cost outcomes: The time from the start of study treatment to death from any cause. OS was estimated using Kaplan-Meier estimate.	

ORR (objective response rate) NICE scope outcome: The percentage of participants who had either a confirmed CR[£] or PR[β].

CBR (clinical benefit rate): The percentage of participants with either CR, PR, or stable disease (SD)[μ] with a duration of ≥6 months.

DOR (duration of response) NICE scope outcome: The number of days between the first date showing a documented response of CR or PR and the date of progression or death.

TTR (time to response) NICE scope outcome: The time from randomization to the first recorded objective response (i.e., CR or PR).

TTP (time to progression): The time from the date of randomization to the date of the first evidence of disease progression as assessed using RECIST 1.1 criteria. The date of progression was date of the last observation or radiological assessment of target lesions that either showed a predefined increase (+20%) in the sum of the target lesions or the appearance of new non-target lesions.

PRO/HRQoL (patient-reported outcome/health-related quality of life) NICE scope, cost (utility) outcomes: The EORTC QLQ-C30 consists of the following domains: global health status, 5 functional domains (physical, role, emotional, cognitive, and social functioning), and 9 symptom domains (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties). The assessments were done for 5 domains pre-determined as primary (global health status/quality of life, physical functioning, role functioning, pain, and fatigue). Each domain score ranges from 0 to 100. A higher score for global health status/QoL and functional domain represents a higher overall HRQoL (healthier level of functioning). A higher score for a symptom domain represents a higher level of symptomatology or problems.[17] The least square (LR) mean EORTC QLQ-C30 score changes (from baseline to a follow-up point) were calculated using MMRM analysis. The minimum important difference (MID) in summary scores was pre-defined as a) Responder definition (10-point threshold as a meaningful within-patient change)[18] and b) non-inferiority margin (between-group difference).[19]

- LR mean change in the EORTC QLQ-C30 score (from baseline to follow up; Day 1 of 21-day Cycles 2, 3, 4, 5, and 6)
- Proportion of subjects with a clinically meaningful HRQoL improvement or deterioration based on within-subject changes from baseline (Day 1 of 21-day Cycles 2, 3, 4, 5, and 6)
- Time to first HRQoL improvement/deterioration

All ITT subjects who had an evaluable assessment of the EORTC QLQC30 (at least one of the 15 domains/scales was non-missing at a given assessment visit) at baseline and at least one evaluable post-baseline assessment were included in the analysis.

AEs (adverse events), NICE scope outcome: The percentage of participants experiencing any TEAEs, SAEs, and TEAEs leading to discontinuation of study drug. TEAEs were defined as any AEs that begin or worsen on or after the start of study drug through 30 days after the last dose of study drug. The severity was graded based on the National Cancer Institute's Common Terminology Criteria for Adverse Events Version 4.03. An AE that met one or more of the following outcomes was classified as serious.

ITT=intention-to-treat; SG=sacituzumab govitecan; BM-ve=brain metastasis negative; IRC=independent review committee; TPC=physician's choice; PFS=progression free survival; OS=overall survival; ORR=objective response rate; CBR= clinical benefit rate; DOR=duration of response; TTR=time to onset of response; TTP= time to progression; QoL=quality of life; AEs=adverse events; TEAEs=treatment emergent adverse events; SAEs=serious adverse events; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality-ofLife Questionnaire-Core 30; CR=complete response; PR=partial response; MMRM=mixed-effect model for repeated measures; LR= least square

[£] CR: Disappearance of all target and non-target lesions; and normalization of tumour marker levels initially above upper limits of normal.

[β] PR: >30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD; and appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

[μ] SD: Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease (> 20% increase in the sum of LD of target lesions, taking as reference the smallest sum LD recorded since treatment started or appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions), taking as reference the smallest sum LD since the treatment started; and persistence of one or more nontarget lesion(s) or/and maintenance of tumour marker level above the normal limits.

The ERG considers the study objectives and overall design of the ASCENT study to be appropriate and relevant. Given the ERG evaluation, the efficacy and safety endpoints (i.e., study outcomes) were valid and appropriate to address the decision problem. The endpoints selected in the ASCENT study matched with those of the NICE scope.

The ERG believes that the company provided a detailed description and adequate definitions of endpoints of interest.[15]

The ERG however notes that the duration of treatment (time to treatment discontinuation/TTD) was modelled in the economic analysis (Document B3.3.4, Figure 36-39, pages 97-99), however no data (e.g., survival analysis, HRs, table) for this endpoint were presented in the clinical efficacy section of Document B. Upon the ERG request, the company provided KM survival curves for TTD (ITT and BM-ve populations separately) in their ERG Clarification Responses file [redacted] Further details discussed in section 3.5.5.

3.2.2. The ASCENT study: patient eligibility and methodology (randomisation, blinding, and outcome measurement)

Patients eligible for inclusion in the ASENT study had to be diagnosed with unresectable, locally advanced or mTNBC who were refractory or who had relapsed after receiving ≥2 prior standard-of-care chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease (Table 2).

Detailed description of the ASCENT study and its methodology are provided in Table 2. The patients included in the ASCENT study were randomised 1:1 to receive either SG or single-agent TPC (an active comparator), which consisted of only one of the following single-agent treatments: eribulin, capecitabine, gemcitabine, or vinorelbine (except if the patient had Grade ≥2 neuropathy).

Note that the issues addressing the risk of bias of the ASCENT trial (i.e., randomisation, blinding, missing data, dropouts) are presented in the section 3.1.4 of this report. Briefly, the randomisation and concealment of treatment allocation were performed using iterative web-based response system (IWRS). The ASCENT study was an open-label study, because blinding of study personnel and study participants was not possible due to differences in the administration of study treatments.

Table 6. The description of the ASCENT study: eligibility of patient population and the trial methodology

Study feature	ASCENT (IMMU-132-05)
Study location by country	• Multicentre: 88 sites • Belgium (5 sites), Canada (3 sites), France (10 sites), Germany (3 sites), Italy (1 site) Spain (10 sites), United Kingdom (6 sites), United States (50 sites)
Study design	• Phase III, open-label, RCT of the efficacy and safety of SG in locally advanced or mTNBC
Method of randomisation	• Patients were randomised using IWRS. • Randomisation was stratified by the number of prior treatments for advanced disease (2-3 versus >3), geographic location (North America versus rest of world) and known stable brain metastasis at baseline (yes or no).
Method of blinding	• The ASCENT study was an open-label study where blinding of study personnel and study participants was not possible due to differences in the administration of study treatments. The outcome assessors were independent (e.g., independent review committee/IRC, statisticians, medical monitors) and were unaware of the treatment type of administered for PFS and OS.
Population inclusion criteria	• Adult patients (18 years of age or older) with unresectable, locally advanced or mTNBC who were refractory or had relapsed after receiving ≥2 prior standard-of-care chemotherapies, including ≥1 prior therapy for locally advanced or metastatic disease. • Adjuvant or neoadjuvant therapy for more localised disease was considered as one of the two required regimens if progression to unresectable, locally advanced or metastatic disease occurred within 12 months of completing chemotherapy. • All patients must also have received previous taxane treatment in either the adjuvant, neoadjuvant or advanced stage. • Following a protocol amendment, only patients with known brain metastases at baseline were eligible to enrol in the trial as long as their central nervous system (CNS) disease was treated and stable for at least 4 weeks prior to randomisation. The proportion of patients with known brain metastasis at baseline was limited to 15% and this subgroup was not included in the primary efficacy analysis population.
Intervention	• 10 mg/kg SG was administered via slow IV infusion on Days 1 and 8 of a 21-day treatment cycle • Treatment was continued until disease progression, occurrence of unacceptable toxicity, study withdrawal or death, whichever came first
Comparator	One of the following single-agent treatments was selected by investigator before randomisation (TPC): • Eribulin: 1.4 mg/m^2 or 1.23 mg/m^2 was administered IV over 2-5 minutes on Days 1 and 8 of a 21-day cycle • Capecitabine: 1,000 - 1,250 mg/m^2 was administered orally twice daily for 2 weeks with a 1-week rest period over a 21-day cycle • Gemcitabine: 800 - 1,200 mg/m^2 was administered IV over 30 minutes on Days 1, 8, and 15 of a 28-day cycle • Vinorelbine: 25 mg/m^2 was administered IV over 6-10 minutes weekly • All TPC was continued until disease progression, occurrence of unacceptable toxicity, study withdrawal or death, whichever came first
Permitted concomitant medication	• Palliative and/or supportive medications at investigator's discretion • Premedication for prevention of infusion reactions with SG • Appropriate premedication for prevention and treatment of chemotherapy-induced nausea and vomiting • Low dose, stable doses of corticosteroids ≤20 mg prednisone or equivalent daily were permitted if the patient entered the study on low-dose steroids for

	treatment of brain metastasis • Topical steroids and corticosteroid inhalers
Pre-specified subgroups of analyses	• Age (<65, ≥65 years) • Race (White, Black, Asian) • Prior therapies (2-3, and >3) • Region (North America, rest of world) • Original diagnosis TNBC (yes, no) • Prior breast cancer surgery (yes, no) • Prior cancer radiotherapy • BRCA1 status (positive, negative) • BRCA1 and BRCA2 status (positive, negative) • Prior PD-L1/PD-1 use (yes, no) • Trop-2 status (percentage of membrane cells with 2+ or 3+ <85% staining, percentage of membrane cells with 2+ or 3+ staining ≥85%) • Liver metastasis at baseline (yes, no) • UGT1A1 status (*1/*1, *1/*28, *28/*28, other)
RCT=randomised controlled trial; IWRS=iterative web-based response system; SG=sacituzumab govitecan; BM-ve=brain metastasis negative; PFS=progression free survival; OS=overall survival; ORR=objective response rate; CBR= clinical benefit rate; DOR=duration of response; TTR=time to onset of response; TTP=time to progression; QoL=quality of life; AEs=adverse events; CT=computed tomography; CHF=congestive heart failure; COPD=chronic obstructive pulmonary disease; GI=gastrointestinal; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; MI=myocardial infarction; mTNBC = metastatic triple negative breast cancer; TPC=treatment of physician's choice; IV=intravenous; RECIST=Response Evaluation Criteria in Solid Tumors; BRCA=Breast Cancer gene; PD-1 = Programmed cell death protein 1; PD-L1 = Programmed death-ligand 1	

Primary and secondary outcomes for survival (PFS, OS) for this study were measured by the Independent Review Committee (IRC). The IRC evaluated tumour response by reviewing computed tomography (CT) or magnetic resonance imaging (MRI) every 6 weeks for 36 weeks and then every 9 weeks thereafter until the occurrence of progression of disease requiring discontinuation of further treatment. The disease progression and response to treatment was rates according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Other secondary outcomes (e.g., ORR, CBR, DOR, TTR, TTP) were assessed by independent review committee (IRC) and/or study investigators. The decision to discontinue a patient for progressive disease (PD) was made by the investigator (CS; Document B, page 24).

PRO/HRQoL was assessed at baseline (i.e., ≤28 days of cycle 1 day 1 [C1D1]), day 1 of each cycle, and the final study visit (i.e., four weeks after the last dose of study drug or in the event of premature study termination).[17]

The treatment dose reduction/modification rules differed across the SG and TPC arms. For example, for the first episode of neutropenic toxicity of grade 3 or more, the SG arm was allowed 25% dose reduction and received granulocyte colony-stimulating factor (G-CSF), whereas for the same episode the treatment in the TPC arm was discontinued and no G-CSF was administered (Bardia 2021, Figure S8).[10]

In general, the ASCENT study population eligibility criteria matched those listed in the NICE scope's decision problem.

The application of differential dose reduction/modification rules across the SG and TPC arms for high grade neutropenic toxicity may have favoured the SG arm if the proportion of patients who experienced this toxicity was greater in the SG vs. TPC arm.

3.2.3. The ASCENT study: statistical analysis of the study results

In order to minimise the type-I error (significance level α=0.05), a hierarchical testing strategy was employed for testing the endpoints of IRC assessed PFS and OS, where a given hypothesis was only declared statistically significant if all previous hypotheses in the hierarchy were also statistically significant. This hierarchy (from the highest to lower) was as follows: PFS (BM-ve), OS (BM-ve), PFS (ITT), and OS (ITT). In other words, ITT population for PFS analyses was used only after this endpoint was tested in the primary analysis population of patients without brain metastases (CS Document B, Figure 6, page 38).

The analyses of PFS and OS for comparison between SG and the TPC group was performed using log-rank tests stratified by a randomization factors. Estimate of hazard ratio (HR) and its 95% confidence interval (CI) was based on stratified Cox proportional-hazards model with group as the only covariate, stratified by the same stratification factors employed in the randomization. The survival functions were plotted over time using Kaplan-Meier (KM) curves; median PFS and its associated 95% CIs were determined by the Brookmeyer and Crowley method with log-log transformation. Based on KM estimates, PFS rates were determined at 6 months, 9 months, and 12 months. The corresponding OS rates were determined at 12 months, 18 months and 24 months of follow-up.

The TTP was analysed using the survival analysis approach described above.

Five sensitivity analyses were conducted for PFS in the BM-ve and ITT Populations using different censoring rules (CS CSR pages 46-49).[16] These analyses deal with different scenarios in terms of progressive disease and attended assessments. The results of the primary analysis were insensitive to the various censoring rules used in the sensitivity analyses. One point to note is that in Table 13 of the CSR (pages 48-49), the censoring rule for ‘Continued scheduled response assessments until objective progressive disease or death’, row ‘Progressive disease at scheduled assessment, or prior to missing 2 scheduled successive assessments’ was missing.

A hazard ratio (HR) of 0.667, corresponding to a 50% improvement in PFS, was considered a clinically meaningful difference between the study treatment groups. A total of 488 patients were anticipated to be enrolled in order to detect such difference with 95% statistical power. The population of patients with brain metastases was limited to 15% (n=74) of the study

population. The ASCENT study had a 95% power to detect a statistically significant improvement in PFS (two-sided type-I error; significance level α=0.05) if data were analysed after 315 PFS events by IRC assessment (primary efficacy endpoint). The study had approximately 90% power to detect an improvement in OS (HR=0.70) if 238 deaths had occurred at the time of the interim analysis. The ERG confirmed this sample size requirement by using the 'power' command in StataSE 17.

At the time of final analysis (data cut-off 11 March 2020), 316 PFS events (disease progression or death) and 340 OS events (i.e., deaths) had occurred in the primary analysis population (CS CSR page 43).[16]

In general, the company performed adequate statistical analyses to calculate the study power, assess the study clinical endpoints, and conduct sensitivity analyses (using different censoring rules). The PFS and OS data were mature (i.e., KM curves for both SG and TPC arms crossed the median time to survival point) at the time of final analysis (11 March 2020). Given the KM curves for PFS and OS, the proportionality assumption of the survival analysis was not violated. The MMRM analysis of continuous HRQoL data (mean EORTC QLQ-C30 score changes from baseline) was appropriate.

3.2.4. The ASCENT study: analysed populations and study sample disposition

A total of 730 patients enrolled in the ASCENT study between November 2017 and September 2019 across 88 sites. Of the 730 patients screened (Table 7), 529 eligible patients (ITT population) were randomised to receive either SG (n=267) or TPC (n=262). Of all 529 patients randomised, 468 patients without brain metastases (BM-ve population) received (SG n=235) or TPC (n=233). In the ITT population (n=529 patients), 9 (3.4%) patients in SG and 38 (14.5%) in TPC arm did not receive the assigned treatment(s) due to consent withdrawal. The untreated patients were excluded from the safety population analysis (total n=482, SG n=258 vs. TPC n=224).

Table 7. Sets of analysed populations

Analysis type	Sample size	Population set
Screened population	Total n=730	All patients who have signed an informed consent and participated in screening procedures at the investigative site to assess eligibility.
Randomized population	Total n=529 SG: n=267 TPC: n=262	All patients who were randomised to receive treatments (including 61 patients with brain metastasis at baseline).
ITT Population	Total n=529 SG: n=267 TPC: n=262	All patients who were randomised and analyzed based on randomised treatment assignment (including 61 patients with brain metastasis at baseline).
BM-ve Population (primary analysis)	Total n=468 SG: n=235	All patients randomised without brain metastasis.

	TPC: n=233	
Safety Population	Total n=482 SG: n=258 TPC: n=224	All patients randomised who received at least 1 dose of SG or TPC. Patients who did not receive the treatment due to consent withdrawal (SG: n=9 [3.4%] vs. TPC: n=38 [14.5%]) were excluded from the safety population.
ITT=intention-to-treat; TPC= treatment of physician's choice; SG=sacituzumab govitecan; BM-ve=brain metastasis negative		

Details on patient disposition in the ASCENT study are presented in Table 8 (for primary analysis BM-ve population, n=468 patients). The CS CSR provides further details on the BM-ve population study sample disposition (Table 17, page 58).[16]

Table 8. Study sample disposition (primary analysis, BM-ve population)

	SG n (%)	TPC n (%)	Total
Treatment status			
On study treatment	15 (6.4)	0	15 (3.2)
Discontinued study treatment	213 (90.6)	201 (86.3)	414 (88.5)
Not treated	7 (3.0)	32 (13.7)	39 (8.3)
Reasons for study treatment discontinuation			
Progressive disease	199 (84.7)	166 (71.2)	365 (78.0)
Adverse event	6 (2.6)	7 (3.0)	13 (2.8)
Consent withdrawal	4 (1.7)	17 (7.3)	21 (4.5)
Physician's decision	3 (1.3)	4 (1.7)	7 (1.5)
Unacceptable toxicity	0	1 (0.4)	1 (0.2)
Lost to follow-up	0	0	0
Study withdrawals			
Patients who withdrew from study	161 (68.5)	203 (87.1)	364 (77.8)
Reasons for study withdrawals			
Death	151 (64.3)	177 (76.0)	328 (70.1)
Consent withdrawal	7 (3.0)	23 (9.9)	30 (6.4)
Lost to follow-up	3 (1.3)	3 (1.3)	6 (1.3)
Survival status			
Dead	155 (66.0)	185 (79.4)	340 (72.6)
Alive	69 (29.4)	33 (14.2)	87 (18.6)
Lost to follow-up	11 (4.7)	15 (6.4)	26 (5.6)

Briefly, at the study data lock point (11 March, 2020) there were 15 patients still receiving the treatment and all of them were in SG arm. Most frequent reason for treatment discontinuation was the occurrence of disease progression (78.0%) and it was more frequent in SG (84.7%) vs. TPC (71.2%) group of patients. Other reasons for treatment discontinuation (adverse events, unacceptable toxicity, consent withdrawal, lost to follow-up) did not markedly differ between the two study groups. Most frequent reason for patients leaving study was death (72.6%) which was more frequent in TPC group (n=177, 76.0%) vs. SG group (n=151, 64.3%). A higher percentage of patients in TPC group vs. SG group died in survival follow-up (79.4% vs. 66.0%, respectively). In the ITT population, the between group difference in death during the follow-up was similar, i.e., the corresponding numbers of

patients who died in the TPC and SG treatment groups were 206 (78.6%) vs. 179 (67.0%), respectively (The CS CSR, page 59).[16]

The proportions of patients lost to follow-up did not differ between the two study groups.

The frequency of protocol violation was slightly greater in patients treated with TPC compared to SG-treated patients (39.7% vs. 34.5%). Of these, the most frequent important protocol deviation in the SG and TPC groups was a violation of the procedures for study conduct (SG: 20.6% vs. TPC: 19.5%) (CSR: page 60 and CSR Post-Text Table: Table 14.1.2, page 30).[16, 20]

The ERG agrees with the company's definitions and analyses for the primary (TNBC patients without brain metastasis at baseline), ITT (all TNBC patients randomised), and safety population (received at least one dose of study drug*).*

The company provides data on study sample disposition (e.g., treatment discontinuations, study withdrawals, AE/drug toxicity, losses to follow-up (CSR Table 17, page 58) for the primary analysis population (BM-ve) only. No similar data are provided the for ITT population. This would allow the ERG to assess if the disposition characteristics between the two populations markedly differed. Although the company states that there were no differences in between ITT and BM-ve populations in terms of survival follow-up status (CSR, page 59)*.*[16]

According to the study sample disposition data, most frequent reason for treatment discontinuation was the occurrence of disease progression and it was more frequent in SG (84.7%) vs. TPC (71.2%) group of patients. This observation contradicts the PFS data which indicates the opposite that the risk of disease progression or death was significantly reduced in the SG vs. TPC arm (HR=0.41, 95% CI: 0.32, 0.51).[16] In the ERG Clarification Response file, the company stated that the imbalance in disease progression was due to more patients being censored at randomisation in the TPC vs. SG arm and not contributing to the event count (Section C4.3, page 31). Indeed, as the ERG noted a smaller percentage of patients in the SG group (n=9, 3.4%) compared with the TPC group (n=38, 14.5%) randomised to study treatments were not treated due to consent withdrawal (Document B Figure 4, page 32). The ERG is uncertain how the sample of untreated patients in both study arms were handled in the efficacy analyses and how they were censored. If they were simply excluded from the efficacy analyses (for PFS, OS, clinical response), the ITT sample of population would be violated, thereby leading to selection bias due to differential sample attrition, especially if these reasons for consent withdrawal differed (i.e., were non-random) across the study

arms. The ERG is unclear whether or not these untreated patients were followed-up (for progression, death) and/or analysed, what were the censoring rules, and if these rules differed across the SG and TPC arms. The company did not provide a sensitivity analysis for PFS/OS (and other efficacy endpoints) showing the influence of inclusion/exclusion from the analyses and different censoring scenarios applied to the data for untreated patients. Likewise, the baseline patient characteristics of the untreated sample were not provided, as this information would aid the ERG team in gauging the magnitude and direction of bias in the effect estimates of PFS, OS, and other endpoints of interest. Also, the company did not report if any imputation techniques were used to keep the untreated patients analysed in the ITT and BM-ve sets of population analyses.

Several other reasons for treatment discontinuation such as death, treatment delay, adverse events, physician's decision, lost to follow-up, and unacceptable toxicity did not differ across the SG and TPC study arms. Missing values for the survival status (dead/alive) were low in number and were balanced between SG and TPC arm (4.7% vs. 6.4%).

Because of missing values for EORTC QLQ-C30 score at a follow-up, there was attrition in the ITT sample in the SG arm (88.3%; 236/267) and TPC arm (69.8%; 183/262), and magnitude of this attrition was greater in the TPC arm vs. SG arm (30.2% vs. 11.7%). As the company did not provide the reasons for this missing information, it is difficult to judge whether or not patients with missing data were systematically different across the SG and TPC arms for HRQoL. The differential sample attrition could lead to biased treatment effect estimates for HRQoL which bears direct implications on the cost-effectiveness analysis (section 4.9.7). In the absence of reasons for such missing data, it is not possible to estimate the magnitude and direction of bias in the effect estimates.

3.2.5. The ASCENT study: baseline patient characteristics

The summary of baseline patient characteristics is presented in Table 9. Patients had a median age of 54 years (SD=11.7) and the majority were White (79%). Most patients had an original diagnosis of TNBC (70.3%), did not have either a BRCA1 or BRCA2 mutation (56.0%), and had normal renal and hepatic function (creatinine clearance: 110.5 mL/min). Overall, 70.5% of patients had received 2-3 prior chemotherapies and 29.5% had received >3 prior chemotherapies. Median number of prior systemic regimens was 4 in both the SG and TPC groups. The population from the trial seem to be heavily pre-treated triple negative, the ERG advisor agree that this is reprehensive of UK practice.

Table 9. Baseline characteristics of patients in the ASCENT study (ITT population)

Characteristics	SG (N=267)	TPC (N=262)
Mean (SD) age [years]	54.0 (11.3)	54.0 (11.7)
Race [n (%)]		
White	215 (80.5)	203 (77.5)
Black	28 (10.5)	34 (13.0)
Asian	13 (4.9)	9 (3.4)
Other	11 (4.1)	16 (6.1)
Mean (SD) BMI [kg/m^2]	26.82 (6.5)	26.74 (6.2)
Number of prior chemotherapies [n (%)]		
2-3	184 (68.9)	181 (69.1)
>3	83 (31.1)	81 (30.9)
Presence of known brain metastases at study entry for randomisation stratification [n (%)]		
Yes	32 (12.0)	29 (11.1)
No	235 (88.0)	233 (88.9)
Treatment of physician choice [n (%)]		
Eribulin	0	139 (53.1)
Capecitabine	0	33 (12.6)
Gemcitabine	0	38 (14.5)
Vinorelbine	0	52 (19.8)
Frequent (>20% in either group) tumour locations based on IRC [n (%)]		
Liver	107 (40.1)	114 (43.5)
Lung	131 (49.1)	115 (43.9)
Mediastinal lymph node	61 (22.8)	68 (26.0)
Chest wall	51 (19.1)	68 (26.0)
Axillary lymph node	59 (22.1)	78 (29.8)
Bone	62 (23.2)	63 (24.0)
Original diagnosis TNBC [n (%)]		
Yes	192 (71.9)	180 (68.7)
No	75 (28.1)	82 (31.3)
Mean (SD) time from diagnosis of stage 4 to study entry [months]	21.74 (21.2)	22.35 (20.3)
BRCA1/BRCA2 Mutational Status [n (%)]		
Negative	150 (56.2)	146 (55.7)
Positive	20 (7.5)	23 (8.8)
Screening ECOG performance status [n (%)]		
0: Normal Activity	121 (45.3)	108 (41.2)
1: Symptoms but Ambulatory	146 (54.7)	154 (58.8)
Mean (SD) number of prior systemic therapies	4.5 (2.0)	4.6 (2.1)
Frequent prior systemic therapies [n (%)]		
Cyclophosphamide	221 (82.8)	216 (82.4)
Paclitaxel	204 (76.4)	210 (80.2)
Carboplatin	164 (61.4)	179 (68.3)
Capecitabine	171 (64.0)	183 (69.8)
Doxorubicin	142 (53.2)	141 (53.8)
Gemcitabine	85 (31.8)	106 (40.5)

Docetaxel	101 (37.8)	83 (31.7)
Eribulin	88 (33.0)	85 (32.4)
SD=standard deviation; BMI = body mass index; BRCA = breast cancer gene; ECOG = Eastern Collective Oncology Group; ITT = intention-to-treat; IRC = Independent Review Committee; SG = Sacituzumab govitecan; TPC = treatment of physician's choice		

The most frequent prior systemic therapies in the SG and TPC groups were cyclophosphamide (82.6%), paclitaxel (78.3%), carboplatin (64.8%) and capecitabine (66.9%).

In general, the majority of baseline demographic and clinical characteristics of the participants randomised in the trial were comparable across the SG and TPC treatment groups. There were more patients with tumour location in mediastinal lymph node (26.0% vs. 22.8%) and axillary lymph node (29.8% vs. 22.1%) in the TPC compared to SG arm, respectively. Previous research has shown that patients with metastatic breast cancer located in lymph nodes had poorer prognosis in survival.[21-23] If this is the case in the ASCENT study, then the true clinically beneficial treatment effects of SG compared to TPC may have been inflated at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.

Following a protocol amendment, only patients with known brain metastases at baseline required a brain MRI at screening and were eligible to enrol in the trial as long as their central nervous system (CNS) disease was treated and stable for at least 4 weeks prior to randomisation (Document B, pages 25-26). It is not clear if all patients classified by the company as 'BM-ve' (primary population analysis) were truly free of BM. The ERG deems this issue problematic because this characteristic (presence/absence of BM) is a strong prognostic factor that has the potential to confound the treatment efficacy estimates if imbalanced at baseline between the study arms or unless controlled at the randomisation or analysis stage. The company stated in the ERG Clarification Response that "Patients enrolled in ASCENT were not routinely examined for BM. Only patients with known BM at screening were required to have brain MRI to confirm that the existing central nervous system (CNS) disease was stable" and "Patients who were defined as BM negative encompassed all patients who did not have a diagnosis of BM prior to enrolment. These patients were not examined for the presence of BM at screening. Therefore, it is likely that some patients in the BM negative subpopulation had asymptomatic, undetected BM." However, the ERG clinical advisor stated that BM is not screened for prior to the initiation of standard treatment outside of a research trial. A brain MRI would only be performed based on concerning symptoms.

3.2.6. The ASCENT study: efficacy and safety of sacituzumab govitecan, including subgroup analysis

Informed by the recommendation of the Data Safety Monitoring Committee, the ASCENT study was stopped early (in March 2020) because of compelling evidence of efficacy demonstrated by SG over TPC (CS Document B, page 43). The final data analysis was initiated.[10]

Overall findings for efficacy endpoints

At data lock point (11 March, 2020), in the ITT population, the median study follow-up was 10.55 months (SG arm) vs. 6.28 months (TPC arm). This is usually observed in oncology trials because higher survival in the treatment arm. During the study follow-up, 385 deaths occurred: 179 (67.0%) and 206 (78.6%) in the SG and TPC groups, respectively.

The summary of efficacy results from the ASCENT study is presented in Table 10. The median time to disease progression or death (PFS) was significantly longer in patients treated with SG vs. TPC in both ITT (4.8 months vs. 1.7 months) and primary (5.6 months vs. 1.7 months) population analyses, indicating significantly reduced risk of disease progression or death in the SG vs. TPC group (57% reduction in ITT and 59% reduction in primary analysis population).

Similarly, the median time to death (OS) was significantly longer with SG compared with TPC treatment in the ITT (11.8 months vs. 6.9 months) as well as the primary analysis population (12.1 months vs. 6.7 months), which was associated with a significantly reduced risk of death in patients treated with SG vs. TPC (50% reduction in ITT and 52% reduction in primary analysis population).

Patients treated with SG achieved a significantly greater rate of objective response (ORR, either complete or partial) compared to those treated with TPC in the ITT (OR=10.99, 95% CI: 5.65, 21.35) and primary analysis population (OR=10.85, 95% CI: 5.59, 21.09). Similar improvement was observed with respect to clinical benefit rate (CBR), which was significantly greater in the SG vs. TPC treatment arm for the ITT (OR=8.06, 95% CI: 4.83, 13.45) and primary analysis population (OR=8.54, 95% CI: 5.05, 14.43).

The median time (in months) to disease progression was significantly longer with SG vs. TPC in the ITT ([redacted]) and primary analysis population ([redacted]).

Only patients achieving either a CR or PR (ITT population: SG n=83 vs. TPC n=11) were included in the calculation for DOR and TTR. Given the small sample and wide variability in estimates, the findings suggested a prolonged DOR in the SG vs. TPC (6.3 vs .3.6), however, the corresponding HR estimates did not reach the pre-specified level of statistical significance (HR=0.39, 95% CI: 0.14, 1.06, p=0.057). For patients with a confirmed/partial response, the median time (in months) to first response (TTR) was similar between the SG and TPC groups (1.54 vs. 1.45) in both the ITT and primary analysis population. No HR and 95% CIs were reported.

Table 10. Summary of efficacy endpoints for SG vs. TPC in the ASCENT study

Endpoint		**ITT population**		**Primary analysis (BM-ve patients) population**	
		SG	**TPC**	**SG**	**TPC**
PFS£	n	267	262	235	233
	Median months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	5.6 (4.3, 6.3)	1.7 (1.5, 2.6)
	HR (95% CI)	0.43 (0.34, 0.54)		0.41 (0.32, 0.51)	
OS	n	267	262	235	233
	Median months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)	12.1 (10.7, 14.0)	6.7 (5.8, 7.7)
	HR (95% CI)	0.50 (0.41, 0.62)		0.47 (0.38, 0.59)	
ORR£ [CR + PR]	n	267	262	230	230
	% ORR (95% CI)	31.1 (25.6, 37.0)	4.2 (2.1, 7.4)	34.9 (28.8, 41.4)	4.7 (2.4, 8.3)
	OR (95% CI)	10.99 (5.65, 21.35)		10.85 (5.59, 21.09)	
CBR£ [CR + PR + stable disease for ≥6 months]	n	261	257	235	233
	% CBR (95% CI)	40.4 (34.5, 46.6)	8.0 (5.0, 12.0)	44.7 (38.2, 51.3)	8.6 (5.3, 12.9)
	OR (95% CI)	8.06 (4.83, 13.45)		8.54 (5.05, 14.43)	
DOR£ [CR + PR]	n	83	11	82	11
	Median months (95% CI)	6.3 (5.5, 9.0)	3.6 (2.8, NR)	6.3 (5.5, 9.0)	3.6 (2.8, NR)
	HR (95% CI)	0.39 (0.14, 1.06)		0.39 (0.14, 1.06)	
TTR£ [CR + PR]	n	83	11	82	11
	Median months (95% CI)	1.54 (NR)	1.45 (NR)	1.54 (NR)	1.45 (NR)
	HR (95% CI)	NR (NR)	NR (NR)	NR (NR)	NR (NR)
TTP£	n	[redacted]			
	Median months (95% CI)				
	HR (95% CI)				

NR=not reported; ITT=intention-to-treat; SG=sacituzumab govitecan; BM-ve=brain metastasis negative; IRC=independent review committee; TPC=physician's choice; PFS=progression free survival; OS=overall survival; ORR=objective response rate; CBR= clinical benefit rate; DOR=duration of response; TTR=time to response; TTP= time to progression; 95% CI=95 percent confidence interval; HR=hazard rate ratio; OR=odds ratio; CR=complete response; PR=partial response

£ Independent review committee (IRC) assessment

There were statistically significant and clinically meaningful improvements from baseline in health related quality of life (HRQoL) for patients treated with SG vs. TPC across all primary EORTC QLQ-C30 score domains, except role functioning where the improvement with SG vs. TPC was still statistically significant ($p<0.05$), but slightly below the clinically meaningful threshold (5.59 vs. 6.00) (Table 11).

Table 11. Least squares (LS) mean changes from baseline in EORTC QLQ-C30 scores (ITT population)£

Primary domain	n=236)	(n=183)		

CI = confidence interval; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer - Quality of life Questionnaire Core 30; ITT=intent-to-treat; QoL = quality of life; SG=sacituzumab govitecan; TPC=treatment of physician's choice; MID=minimum important difference

£ LS mean changes calculated using Mixed-effect Model for Repeated Measures (MMRM)

Among the secondary domains of EORTC QLQ-C30 score, patients treated with SG compared with those in TPC group experienced statistically significant and clinically meaningful improvements from baseline in mean difference (MD) across emotional functioning (MD=3.89, 95% CI: 0.56, 7.22), dyspnoea (MD=-7.74, 95% CI: -12.13, -3.35), and insomnia (MD=-5.03, 95% CI: -9.89, -0.16). Across other secondary domains (e.g., cognitive functioning, social functioning, and appetite loss), SG demonstrated non-inferiority to TPC with the exception of nausea/vomiting and diarrhoea (the mean score was worse in SG vs. TPC) (Document B, Table 10, page 50-51).

Based on within-subject changes from baseline for the primary domains of EORTC QLQ-C30 score (Day 1 of 21-day Cycles 2, 3, 4, 5, and 6), the proportion of patients with meaningful improvement tended to be higher in the SG arm vs. TPC arm for global health status (OR=2.61, 95% CI: 1.29, 5.26) and fatigue (OR=1.95, 95% CI: 1.02, 3.73). The proportion of patients with meaningful worsening in physical functioning was slightly lower in the SG arm vs. TPC arm (OR=0.37, 95% CI: 0.18, 0.73).

There was no statistically significant difference between treatment arms in the proportion of patients with meaningful improvement or deterioration across visits in role functioning (OR= 0.57, 95% CI: 0.32, 1.00). The proportion of patients with meaningful improvement in fatigue was slightly higher in the SG arm vs the TPC arm across visits (OR=1.95, 95% CI: 1.02, 3.73). The proportion of patients with meaningful improvement in pain was higher in the SG arm vs the TPC arm across visits (OR=2.53, 95% CI: 1.52, 4.21).[17]

[redacted] (Document B, Figure 13, page 53).

[redacted]

Sensitivity analysis

The sensitivity analyses conducted in different populations (ITT, BM-ve) confirmed the robustness and consistency of results for PFS, OS, ORR, and CBR.

Median PFS (assessed either by IRC or investigator) was significantly ($p<0.0001$) longer in the SG group compared with the TPC group in each of the sensitivity analyses for the BM-ve, ITT, and Safety Population. The corresponding HRs were also consistent in indicating significantly reduced risk of disease progression or death in the SG- vs. TPC-treated patients.[16, 20]

Similarly, robust and consistent results were demonstrated for the median of OS in both the BM-ve and ITT populations, indicating significantly longer OS (i.e., reduced hazard for death) in the SG vs. TPC arm.[16, 20]

The analyses for ORR and CBR (assessed either by IRC or investigator) yielded consistent results across ITT vs. BM-ve populations, indicating higher ORR and CBR for patients in the SG vs. TPC study arm.[16, 20]

Subgroup analysis

The NICE scope did not specify any subgroup analysis. However, the company reports subgroup analysis that were pre-specified. The subgroup analysis suggests the robustness of the beneficial effect of SG.

The clinical benefits of the SG treatment compared to TPC as demonstrated by PFS and OS in the ASCENT study were consistent across the pre-specified subgroups of interest in patients with TNBC (Table 12). The interpretation of findings is complicated for some subgroups with small samples (e.g., BRCA1-positives, BM-positives, prior breast cancer surgery).

The company's subgroup analysis demonstrated consistent improvements in PFS/OS with SG treatment relative to TPC across all the key pre-planned subgroups investigated within the ITT population (Document B, Table 11, page 54). However, the ERG notes that in the subgroup of patients with brain metastasis in who the magnitude of effect of SG was notably smaller (or was compatible to 'no effect') compared to the effects of SG observed in ITT and BM-ve populations as well as other subgroups of patients. Specifically, the HRs (95% CIs) for PFS and OS in patients with brain metastasis were 0.68 (0.38, 1.20) and 0.95 (0.52, 1.72), respectively. Although the ERG recognise the limitation of these data as inconclusive due to the small sample, the magnitude of clinical effect of SG on survival in patients with brain metastasis does not conform to the general pattern observed across all the remaining subgroup effects in suggesting either 'no significant effect' or notably smaller magnitude of survival benefits of SG compared to TPC.

Table 12. Subgroup analysis: results for key pre-specified subgroups in the ASCENT study (ITT population)

Subgroup (ITT population)	SG vs. TPC		
	n	PFS, HR (95% CI)	OS, HR (95% CI)
Age group			
<65			
>65			
Race			
White			
Black			
Asian			
Prior systemic therapies β			
2-3			
>3			
Brain metastases			
Yes			
No			
Region			
North America			
Rest of World			
Prior breast cancer surgery			
Yes			
No			
Original diagnosis TNBC			
Yes			
No			

Prior cancer radiotherapy Yes No	[redacted]	[redacted]	[redacted]
BRCA1 status Positive Negative	[redacted]	[redacted]	[redacted]
BRCA1 + *BRCA2* status Positive Negative	[redacted]	[redacted]	[redacted]
Prior PD-L1/PD-1 use Yes No	[redacted]	[redacted]	[redacted]
Trop-2 status: I2+I3 <85% I2+I3 ≥85%	[redacted]	[redacted]	[redacted]
Liver metastases Yes No	[redacted]	[redacted]	[redacted]

CI: confidence interval; HR: hazard ratio; ITT = intent-to-treat; OS = overall survival; PFS = progression-free survival; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice

[β] In metastatic or locally advanced setting

In the primary analysis population (BM-ve population), treatment benefits with SG vs. TPC (i.e., median PFS and OS) were demonstrated regardless of the type of chemotherapy treatment used in the TPC group (eribulin, vinorelbine, capecitabine or gemcitabine). None of the comparators exhibited any outlying outcomes to potentially confound and bias the effect of TPC (Document B, Figures 14 and 15, page 56).

Safety endpoints – adverse events

The company reported adverse events for the safety population of the ASCENT study, which was defined as all patients who received at least one dose of study drug in each study arm after randomisation (total n=482; SG: n=258 vs. TPC: n=224). The safety population of the TPC group included patients who received eribulin (n=122), capecitabine (n=22), gemcitabine (n=31) and vinorelbine (n=43). Median treatment duration was longer in the SG group (4.4 months) than TPC group (up to 1.6 months).

Table 13. Summary of treatment emergent adverse events in the ASCENT study (safety population n=482 patients)

Adverse event	SG (n=258)	TPC (n=224)
Any TEAE, n (%)	257 (99.6)	219 (97.8)
Treatment-related TEAE, n (%)	252 (97.7)	192 (85.7)
Serious TEAE, n (%)	69 (26.7)	63 (28.1)
TEAEs leading to dose reduction, n (%)	56 (21.7)	59 (26.3)
TEAEs leading to drug interruption, n (%)	162 (62.8)	87 (38.8)
TEAEs leading to drug discontinuation, n (%)	12 (4.7)	12 (5.4)
Grade 3 TEAE, n (%)	132 (51.2)	100 (44.6)
Grade 4 TEAE, n (%)	52 (20.2)	43 (19.2)

TEAEs leading to death, n (%)	1 (0.4)	3 (1.3)
TEAEs=treatment emergent adverse events		

Most patients treated with SG or TPC had at least one TEAE after the start of treatment (99.6% and 97.8%, respectively). Treatment-related TEAEs were more common in the SG group versus TPC (97.7% versus 85.7%). More patients in the SG vs. TPC group experienced TEAEs leading to drug interruption (62.8% vs. 38.8%) and TEAEs with grade 3 (51.2% vs. 44.6%). TEAEs leading to dose reduction were more frequent in the TPC (26.3%) vs. SG arm (21.7%). There was no between-group difference in the occurrence of serious TEAEs (26.7% vs. 28.1%), TEAEs with grade 4 (20.2% vs. 19.2%), and TEAEs leading to drug discontinuation (4.7% vs. 5.4%) or TEAEs leading to death (0.4% vs. 1.3%) (Table 9).

[redacted]

[redacted]Decreased neutrophil count (grade 4 TEAE) was more frequent in the SG vs. TPC group (8.5% vs. 4.5%). The frequency of occurrence of other grade 4 TEAEs (neutropenia, nausea, and vomiting) was rather low and did not differ between the two study treatment groups.

Table 14. Most common (≥25%) specific treatment emergent adverse events by preferred term in the ASCENT study (safety population n=482 patients)

Adverse event	SG (n=258)			TPC (n=224)		
	Any grade	grade 3	grade 4	Any grade	grade 3	grade 4
Diarrhoea	[redacted]					
Nausea						
Fatigue						
Alopecia						
Neutropenia						
Anaemia						
Constipation						
Vomiting						
Decreased appetite						
Neutrophil count decreased						

SG = sacituzumab govitecan; TEAE treatment-emergent adverse event; TPC = treatment of physician's choice

The ERG notes that the ASCENT study demonstrated clinical benefits of SG compared to TPC (single-agent chemotherapy) across multiple efficacy endpoints in heavily pre-treated patients with TNBC. Both PFS and OS assessed by IRC were significantly longer with SG than TPC in both BM-ve and ITT populations. The SG treatment seemed to have similar effects in improving PFS and OS compared to TPC. It is not clear if patients received any treatment post-progression (either in the SG or TPC arm), as this would reduce the correlation between PFS and OS by diluting the SG effect on OS.[24, 25]

Findings for the secondary outcomes ORR and CBR assessed by IRC were consistent with those for PFS and OS in indicating significantly improved response rates and longer DOR in the SG arm compared with TPC arm in the BM-ve and ITT Populations. The sensitivity analyses conducted in different populations (ITT, primary, and safety) confirmed the robustness and consistency of results for PFS, OS, ORR, and CBR.

The ERG considers the company's interpretation of outcome data on effectiveness and safety to be appropriate.

The company stated that patients in the TPC arm whose disease progressed were not crossed over to SG treatment. As there is a good agreement between PFS and OS in terms of the magnitude of clinical benefit conferred by SG vs. TPC, it is less likely that OS was confounded by post-progression treatments.

The caution should be exercised as the ASCENT trial was stopped early for showing benefits of the SG treatment. Evidence show that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment.[26]

The efficacy estimates (e.g., for PFS, OS, and other endpoints) may have been biased because the proportion of randomised but untreated patients was notably higher in TPC (14.5%) vs. SG (3.4%) treatment group. There is uncertainty as to how the data on the sample of untreated patients was handled in the analyses efficacy endpoints. The ERG is not clear if this sample was followed-up for the endpoints (PFS, OS), was included/excluded from the efficacy analyses, any imputation performed, or if censoring was done and whether it differed across the study arms. A sensitivity analysis of the impact of these factors on the endpoints of interest or baseline patient characteristics would be informative for the ERG to gauge the possible magnitude and direction of bias in the effect estimates of interest.

There were more patients tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.

The company-selected safety outcomes were valid and appropriate to address the decision problem. In general, drug-related toxicity was more frequent in the SG vs. TPC arm. Grade 3 TEAEs such as neutropenia, diarrhoea, and anaemia occurred more frequently in the SG arm than in TPC arm. The higher rate of adverse events in the SG arm could be partially or totally due to the longer median treatment duration in the SG (4.4 months) and TPC arm (range: 1.0 to 1.6 months). Upon ERG request, the company provided the safety data on exposure-adjusted incidence rates of adverse events (# of persons with event / # of person-years exposed) in the ERG Clarification Response file (Section A4, Table 4, page 11).

In the ASCENT study, the median total follow-up from randomisation was 8.38 (range: 0-24) months (SG arm: 10.55 months vs. TPC arm: 6.28 months). Therefore, there is uncertainty regarding a longer-term efficacy and safety of SG treatment in patients with locally advanced or mTNBC with ≥2 prior therapies.

The extent of generalizability of the ASCENT study findings to the UK clinical setting is limited as the number and types of prior therapies that patients received in the ASCENT trial differ across the participant countries and there were only 6 UK sites ([redacted]) represented in this trial. Moreover, the TPC arm may not closely represent the chemotherapy options in the UK available to patients with locally advanced or mTNBC with ≥2 prior therapies.

3.3. Critique of trials identified and included in the indirect comparison and/or multiple treatment comparison

As the company did not identify any other RCTs like ASCENT study, comparing SG with TPC in patients with locally advanced or mTNBC with ≥2 prior therapies, no pairwise conventional meta-analysis was conducted. Likewise, the company did not identify any RCTs comparing head-to-head SG with individual relevant active comparator treatments.

In the absence of head-to-head RCTs, the company attempted to undertake a network meta-analysis (NMA) to assess the relative clinical effectiveness and safety of SG compared to the active relevant comparators (i.e., capecitabine, vinorelbine, eribulin, or gemcitabine) specified in the final scope of the NICE and the decision problem statement of the company's submission (Document B, Table 1, page 9-10).

The company conducted a feasibility assessment for conducting an NMA by considering the network connectivity (through a common comparator) and the distribution of baseline characteristics (i.e., treatment effect modifiers) of 4 RCTs of patients with locally advanced or mTNBC with ≥2 prior therapies that evaluated efficacy and safety of relevant comparator treatments. The company identified 4 RCTs through the systematic literature review (SLR) searches. The methodology of searches and screening procedures conducted for the SLR are described section 2.1. The four RCTs considered in the NMA's feasibility assessment are ASCENT,[10] EMBRACE,[27] EMBRACA,[28] and KEYNOTE-119,[29] which are listed in CS Appendix D for Document B (CS Table 10, page 26). The treatments of interest evaluated in these trials of locally advanced TNBC and mTNBC (except ASCENT study) included eribulin (EMBRACE study), talazoparib (EMBRACA study), and pembrolizumab (KEYNOTE-119). In all four RCTs, there was a common comparator arm TPC, which could be used as an anchor in the NMA (Table 15).

Table 15. Randomised controlled trials and their characteristics considered for the feasibility assessment of network meta-analysis

ASCENT study [10]	KEYNOTE-119 study [29]	EMBRACA study [28]	EMBRACE study [27]
Study design			
Phase-3 open label RCT	Phase-3 open label RCT	Phase-3 open label RCT	Phase-3 open label RCT
Study population (main diagnosis of trial eligibility)			
TNBC	TNBC	HER2-negative locally advanced or mBC and a deleterious gBRCA1/2 mutation	heavily pretreated patients with locally recurrent or mBC
Prior therapy criteria			
≥2 prior therapies for TNBC (up to 1 could be adjuvant or neoadjuvant therapy); previous treatment with a taxane	1-2 previous systemic treatments for mBC; previous treatment with an anthracycline or a taxane in the neoadjuvant, adjuvant, or metastatic setting	≤3 previous cytotoxic regimens for advanced disease and previous treatment with a taxane, an anthracycline, or both, unless contraindicated	2-5 previous chemotherapy regimens, including an anthracycline and a taxane, and ≥2 regimens
Intervention vs. comparator			
SG vs. TPC	Pembrolizumab vs. TPC	Talazoparib vs. TPC	Eribulin vs. TPC
TNBC and ≥2 prior therapies (total sample vs. subgroup) n (%)			
Total	Subgroup (line of treatment: 2 prior treatments) Pembrolizumab 124	Subgroup (TNBC, line of treatment: 2-3 prior treatments) Talazoparib:130 (45.3%)	Subgroup (TNBC) 19% (144 patients);

	(40.0%) vs. TPC 123 (40.0%)	vs. TPC 60 (41.7%)	distribution by study arm: NR
Patient baseline characteristics for TNBC and ≥2 prior therapies[£]			
Yes	NR	NR	NR
Study endpoints			
PFS, OS	PFS, OS	PFS, OS	OS, PFS
TPC arm (distribution of each chemotherapy agent use) n (%)			
Total trial ITT sample (TNBC) Capecitabine 33 (12.6%) Eribulin 139 (53.1%) Gemcitabine 38 (14.5%) Vinorelbine 52 (19.8%)	NR	Total trial sample (ITT; HER-2 negative): Capecitabine 55 (43.6%) Eribulin 50 (39.7%) Gemcitabine12 (9.5%) Vinorelbine 9 (7.1%) TNBC subgroup data: NR	Total trial sample (ITT): Capecitabine 44 (18.4%) Gemcitabine 46 (19.3%) Vinorelbine 61 (25.6%) Taxanes 38 (16.0%) Anthracyclines 24 (10.0%) Other chemotherapies 25 (10.0%) TNBC subgroup data: NR
NR=not reported; mBC=metastatic breast cancer; ITT = intention-to-treat; mTNBC= metastatic triple-negative breast cancer; RCT = randomized controlled trial; SG = sacituzumab govitecan; TNBC = triple-negative breast cancer; TPC = treatment of physician's choice; OS=overall survival; PFS=progression-free survival			

[£] Availability of patient baseline characteristics for the relevant population of interest reported in the primary study publication (TNBC and ≥2 prior therapies)

The company found the conduct of the NMA to be infeasible despite the fact that the 4 RCTs could be connected with a common comparator of TPC. The following issues preventing the feasibility of NMA were identified (Table 15):

- Differences in patient inclusion criteria (type of breast cancer and line of prior therapy) across ASCENT study vs. EMBRACE, EMBRACA and KEYNOTE-119 studies.

- In three RCTs (EMBRACE, EMBRACA and KEYNOTE-119 studies), patients with TNBC ≥2 prior therapies were represented as subgroups for which neither baseline characteristics nor the endpoints (OS, PFS) were reported separately.

- The distribution of individual chemotherapies across the TPC arms of the three RCTs was not reported (EMBRACE, EMBRACA and KEYNOTE-119 studies). Apart from ASCEND study, only two trials (EMBRACE and EMBRACA) reported the distribution of individual chemotherapies across the TPC arms, but only for ITT samples, which did not represent patients with TNBC ≥2 prior therapies. There were marked differences in the distribution of individual chemotherapies used in the TPC arms across the ASCEND, EMBRACE, and EMBRACA studies (Table 11).

In the absence of an NMA, alternate statistical approaches for indirect treatment comparisons including population-adjusted indirect comparison (PAIC) were considered. However, PAIC approaches were not feasible since patients with TNBC ≥2 prior therapies were represented as a subgroup across all the comparator trials (EMBRACE, EMBRACA and KEYNOTE-119 studies) for which neither baseline characteristics nor the endpoints were reported separately.

The feasibility of NMA was assessed and due to the absence of necessary evidence (population of interest in three trials was represented as a subgroup for who no baseline patient characteristics were reported) and violations in transitivity-consistency assumptions (for the TPC arms either no subgroup data was available or their ITT samples had differential distribution of effect modifiers), the conduct of NMA was not possible. Likewise, PAIC analysis was not feasible since the population of interest in comparator trials was represented as a subgroup for which no baseline characteristics or endpoints were reported.

The ERG considers the company's overall approach for assessing the feasibility of NMA/PAIC to be appropriate, as it follows the existing recommendations.[30-35]

3.4. Critique of the indirect comparison and/or multiple treatment comparison

The company did not perform indirect comparison and/or multiple comparison analyses (including population-adjusted indirect comparison PAIC) due to infeasibility in light of the absence of relevant evidence and/or violation of transitivity-consistency assumption. See Section 2.3 for further details.

3.5. Additional work on clinical effectiveness undertaken by the ERG

3.5.1. Health related quality of life

The ERG notes the following point:

- Heavy sample attrition in the EORTC QLQ-C30 data analysis is present.

Much uncertainty (wide 95% CIs) in the EORTC QLQ-C30 mean change estimates beyond Cycle 6.

- Great discrepancy in the results for the unadjusted vs. adjusted EORTC QLQ-C30 data analysis. Unadjusted analysis does not support the superiority of SG over TPC, whereas the adjusted analysis supports that SG outperformed TPC.
- The criteria to determine the minimum important difference (threshold) in the mean EORTC QLQ-C30 score change was less conservative in the adjusted analysis (threshold of between-group mean difference: 4-6 points according to Cocks et al. 2011) than in the OR analysis (% patients with ≥10 point improvement or worsening in each treatment group according to Osoba et al. 1998). Moreover, the Cocks et al. 2011 between-group threshold criteria were expert-based, whereas those in the Osoba et al. 1998 were patient-based. The two analyses given these differences would yield inconsistent evaluations and interpretations of treatment efficacy.
- Some of the ORs provided by the company exaggerate the magnitude of clinical benefit of SG (measured with EORTC QLQ-C30 score).

Unadjusted analysis: observed mean changes from baseline in EORTC QLQ-C30 (5 primary domains)

HRQoL measurements (5 primary domains: global health status, physical functioning, role functioning, fatigue, and pain) are based on the safety population (untreated 9 and 38 patients in SG and TPC arms are excluded): SG n=258 vs. TPC n=224 (CSR-Tables file: Table 14.2.6.1). Additionally, there were missing values for post-baseline visits missing (about 63 patients), leaving the baseline sample of SG n=236 vs. TPC n=183 for which QoL measurements were available. (CSR-Tables file: Table 14.2.6.1; PRO analysis file, figures on page 17-21)

There is further sample attrition probably due to disease progression/death or censoring for any given reason from Cycle 1 (SG n=236 vs. TPC n=183) onwards about up to Cycle 15 after which the TPC arm dwindles out to zero patients. So the between-arm comparison of the mean EORTC QLQ-C30 score change from baseline could not be done beyond Cycle 15 (there were 33 treatment Cycles along the trial).

The SG group tended to have a slightly greater mean EORTC QLQ-C30 score (5 main domains) improvement than TPC group, however the mean change values for both arms tended to converge at Cycle 6 visit and beyond up to Cycle 10 visit. (PRO analysis file, figures on page 17-21).

Adjusted analysis: MMRM LS mean changes from baseline in EORTC QLQ-C30 (5 primary domains)

For this analysis, the company used EORTC QLQ-C30 on-treatment data collected up to Cycle 6 (where sample was ≥25 in both arms). The ERG notes that due to small sample size in the TPC, no EORTC QLQ-C30 measurements were analysed beyond Cycle 6. The company averaged the mean changes across Cycles 2 and 6. (Document B, Table 7; PRO analysis file, figures on page 25-29).

The ERG is uncertain what effective sample size was used for the adjusted analysis (MMRM LS mean changes). The company reports only the baseline sample size (at Cycle 1: SG n=236 vs. TPC n=183) used for the unadjusted analysis (see above 'Observed mean changes from baseline in EORTC QLQ-C30'). The ERG believes that the adjusted analysis of MMRM LS mean change would be based on a smaller

baseline sample (Cycle 1) and consequent samples (Cycles 2-6) than the corresponding samples in unadjusted analysis simply due to missing covariate data.

Odds ratio (OR) analysis – the proportion of patients with clinically meaningful change (improvement or worsening) in EORTC QLQ-C30 (5 primary domains)

This analysis is based on the same baseline (at Cycle 1) sample as the unadjusted analysis (SG n=236 vs. TPC n=183). The mean EORTC QLQ-C30 score changes were analysed across Cycle 2 (SG n=216 vs. TPC n=157), Cycle 3 (SG n=189 vs. TPC n=94), Cycle 4 (SG n=178 vs. TPC n=71), Cycle 5 (SG n=145 vs. TPC n=48), and Cycle 6 (SG n=143 vs. TPC n=36). (PRO analysis file, figures on page 31-35)

The ERG re-analysed statistically significant SG vs. TPC differences (OR, 95% CI) with meaningful change from baseline in EORTC QLQ-C30 score (% patients with ≥10 point improvement or worsening from baseline).(PRO analysis file, figures on page 31-35).

The results presented in Table 16, indicate that the company-based ORs for the proportion of patients with ≥10 point meaningful improvement for global health status and fatigue domains at Cycle 3 exaggerated the magnitude of benefit of the SG compared to TPC. In fact, neither of the ORs calculated by the ERG was statistically significant. The magnitude of benefit for pain domain score at Cycle 2 was also overestimated (but not the statistical significance) by the company.

In contrast, the company-based ORs for the proportion of patients with ≥10 point meaningful worsening for physical functioning, role functioning, and pain domain scores were in agreement with the ERG-based OR estimates, indicating a lower proportion of patients in the SG compared to TPC arm who deteriorated in QoL.

Table 16. Statistically significant ORs (95% CIs) for the proportion of patients with the meaningful change in EORTC QLQ-C30 score (% patients with ≥10 point improvement or worsening from baseline)

% of subjects experiencing clinically meaningful change in EORTC QLQ-C30 score	(%) reported in the company submission (PRO analysis file, Figures on page 31-35)		The company reported OR (95% CI)	ERG calculated OR (95% CI)
	SG arm	TPC arm		
Proportion of patients with ≥10 point meaningful improvement				
Global health status/QoL domain score at Cycle 3				

Patients with ≥10 point improvement	59 (31.7%)	19 (20.7%)	2.61 (1.29, 5.26)	1.78 (0.98, 3.22)
Patients without ≥10 point improvement	127	73		
Total	186	92		
Fatigue domain score at Cycle 3				
Patients with ≥10 point improvement	64 (34%)	23 (24.5%)	1.95 (1.02, 3.73)	1.59 (0.91, 2.78)
Patients without ≥10 point improvement	124	71		
Total	188	94		
Pain domain score at Cycle 2				
Patients with ≥10 point improvement	90 (41.1%)	41 (25.9%)	2.53 (1.52, 4.21)	1.99 (1.27, 3.11)
Patients without ≥10 point improvement	129	117		
Total	219	158		
Proportion of patients with ≥10 point meaningful worsening				
Physical functioning score at Cycle 4				
Patients with ≥10 point worsening	25 (14%)	21 (29.6%)	0.37 (0.18, 0.73)	0.38 (0.20, 0.75)
Patients without ≥10 point worsening	153	50		
Total	178	71		
Role functioning at Cycle 3				
Patients with ≥10 point worsening	50 (26.5%)	35 (37.2%)	0.57 (0.32, 1.00)	0.60 (0.35, 1.03)
Patients without ≥10 point worsening	139	59		
Total	189	94		
Pain domain score at Cycle 2				
Patients with ≥10 point	42 (19.2%)	52 (32.9%)	0.43 (0.26, 0.70)	0.48 (0.30, 0.77)

worsening				
Patients without ≥10 point worsening	177	106		
Total	219	158		
OR=odds ratio; 95% CI=95 percent confidence interval; SG = sacituzumab govitecan; TPC = treatment of physician's choice; EORTC QLQ-C30=European Organisation for Research and Treatment of Cancer Quality-of Life Questionnaire-Core 30				

3.5.2. ERG's approach to modelling PFS, OS, and TTD

This section describes the ERG's approach to modelling PFS, OS, and TTD. The ERG requested the company to provide the individual Kaplan-Meier data to accurately construct curves, and allow a more reliable comparison between the models chosen by the company and those chosen by the ERG. However, the company did not provide the data. The ERG digitised figure 7 (PFS), figure 8 (OS), and figures 36 and 37 (TTD). The ERG followed the methods described by Guyot *et al* the IPD could be reconstructed from the digitised figures, which would then be used to model the various parametric curves.[36]

A summary of the results of the ERG's approach to curve fitting is shown below in Table 17.

Table 17. Summary of curve fitting for the ERG and the company

		Best fitting model		
Outcome	**Group**	**Company**	**ERG**	**Scenario**
PFS	SG	Log-normal	Log-normal	Log-logistic
	TPC	Log-logistic	Generalised-gamma	None
OS	SG	Log-logistic	Log-logistic	None
	TPC	Log-logistic	Log-logistic	Log-normal
TTD	SG	Exponential	Log-normal	None
	TPC	Exponential	Exponential	None
OS = overall survival; PFS = progression-free survival, SG = Sacituzumab govetican; TPC = treatment of physician's choice; TTD = time to treatment discontinuation				

3.5.3. Progression-free survival

The ERG fitted the six parametric curves to the SG and TPC groups separately (independent fit), and then together (joint fit). According to statistical fit via information criteria (Table 18), the log-logistic performed best fit for the SG group,

and generalised-gamma was the best fit model for the TPC group, compared to the company's preferred models which was log-normal for the SG group and log-logistic for the TPC group. When modelling the whole sample, the log-logistic was the best fit.

Table 18. Comparison of model fit between company (blue) and ERG (green)

	SG			TPC			SG and TPC		
	AIC	BIC	AIC + BIC	AIC	BIC	AIC + BIC	AIC	BIC	AIC + BIC
Exponential	1137.49	1141.08	2278.57	748.14	751.71	1499.86	1885.636	1894.178	3779.81
Weibull	1134.54	1141.71	2276.25	746.09	753.23	1499.32	1878.674	1891.487	3770.16
Log-normal	1123.93	1131.10	2255.03	658.68	665.81	1324.49	1794.645	1807.458	3602.10
Log-logistic	1118.27	1125.44	2243.71	644.81	651.95	1296.77	1777.112	1789.925	3567.04
Gompertz	1139.45	1146.62	2286.07	734.96	742.09	1477.05	1881.21	1894.023	3775.23
Gen Gamma	1122.57	1133.33	2255.91	613.31	624.02	1237.33	1796.149	1813.233	3609.38

To support the comparison between preferred model choices, the ERG used the evidence from figure 3 of Deluche *et al,*[37] and from the ASCENT trial, which are presented in Table 19.

For the SG group, the ERG agree that the PFS extrapolations are closer to the company's preferred model of log-normal than the log-logistic. Therefore, the ERG believes that, for the SG group, the log-logistic model should be used as a scenario analysis.

For the TPC group, the only evidence was from ASCENT at 6 and 12 months. At 6 months, the log-logistic is a better fit, but at 12 months, the generalised gamma was a better fit. Therefore the ERG preference for the base model (informed by the information criterions) is the generalised gamma model for TPC.

Table 19. PFS extrapolations

Months		**6**	**12**	**20**	**40**	**60**	**80**	**100**	**120**
Deluche 2020 ASCENT SG		[redacted]	[redacted]	8.86%	2.52%	1.22%	0.68%	0.18%	0.00%
SG, company	**Log-normal**	40.70%	19.10%	8.90%	2.30%	0.90%	0.40%	0.20%	0.10%
SG, ERG	**Log-logistic**	39.70%	17.50%	8.50%	2.90%	1.50%	1.00%	0.70%	0.50%
ASCENT TPC		[redacted]	[redacted]						
TPC, company	**Log-logistic**	10.50%	0.23%	0.70%	0.14%	0.05%	0.03%	0.02%	0.01%
TPC, ERG	**Gen Gamma**	17.20%	6.98%	3.53%	1.39%	0.81%	0.55%	0.40%	0.32%
Both groups, ERG	**Log-logistic**	37.54%	14.10%	5.93%	1.69%	0.80%	0.47%	0.31%	0.22%
		16.44%	5.10%	2.02%	0.56%	0.26%	0.15%	0.10%	0.07%

Figure 1 and Figure 2 show the overlap of the parametric curves by the Kaplan-Meier plot for PFS for the SG and TPC groups, respectively. These can be used to visually assess model fit in relation to the KM plot.

Figure 1. Parametric curve fit to PFS for the SG group

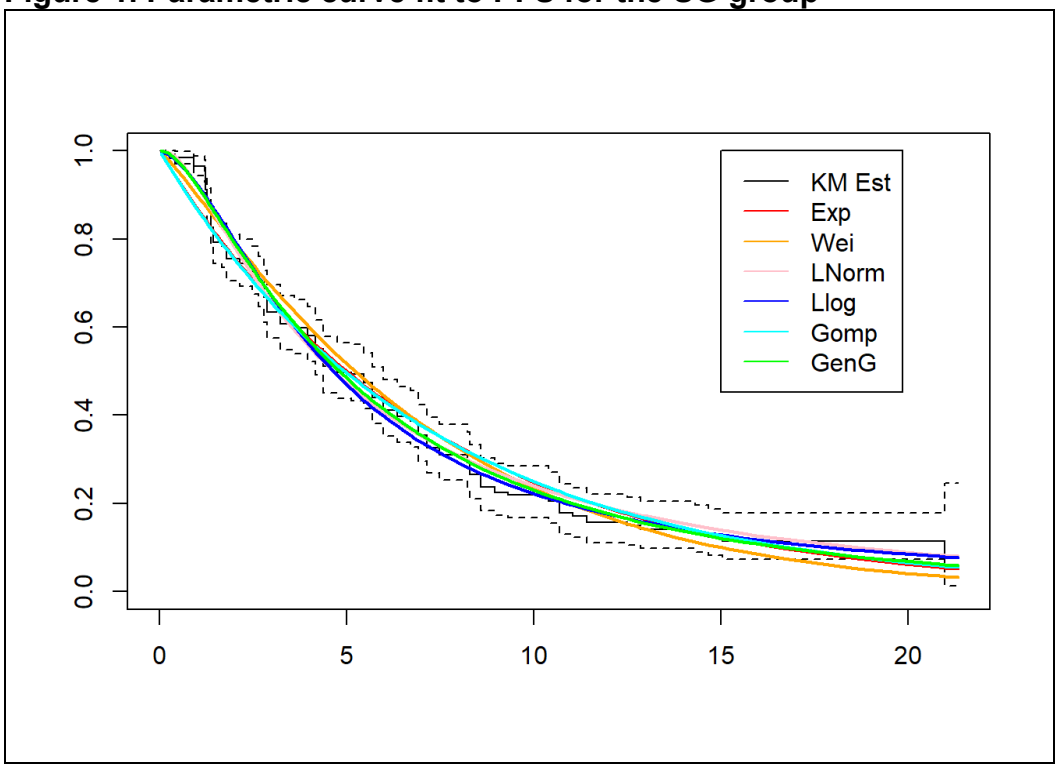
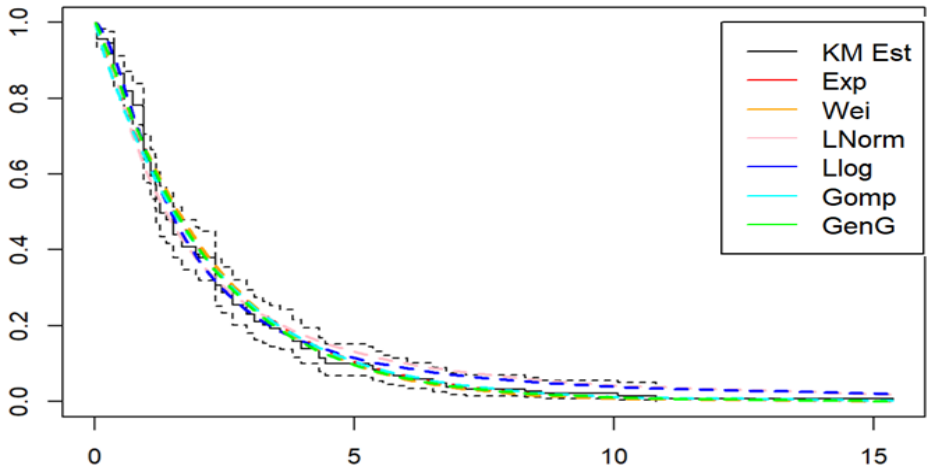


Figure 2. Parametric curve fit to PFS for the TPC group



3.5.4. Overall survival

The same methods were used to fit parametric models for OS. According to AIC and BIC (Table 20), the best model for the SG group alone was the Weibull model, for the TPC it was the log-normal model. For modelling the overall sample, the log-logistic model was the best-fit. The log-logistic model was a better joint fit statistically (digitised data) in terms of AIC and BIC.

Table 20. Comparison of model fit between company (blue) and ERG (green)

	SG			TPC			SG and TPC		
	AIC	BIC	AIC + BIC	AIC	BIC	AIC + BIC	AIC	BIC	AIC + BIC
Exponential	1322.947	1326.534	2649.481	1300.521	1304.089	2604.61	2623.468	2632.01	5255.478
Weibull	1293.592	1300.797	2594.389	1271.918	1279.055	2550.973	2564.057	2576.87	5140.927
Log-normal	1304.994	1312.168	2617.162	1250.092	1257.229	2507.321	2556.593	2569.406	5125.999
Log-logistic	1295.938	1303.112	2599.05	1253.349	1260.485	2513.834	2548.152	2560.965	5109.117
Gompertz	1302.797	1309.971	2612.768	1293.6	1300.737	2594.337	2595.892	2608.705	5204.597
Gen Gamma	1295.26	1306.022	2601.282	1252.019	1262.724	2514.743	2551.35	2568.434	5119.784

As with PFS, the ERG compared to extrapolation estimates for the best-fitting models with Deluche 2020 and data from ASCENT for OS, presented in Table 21.[37] The joint log-logistic model, which modelled SG and TPC together, fits the best with respect to extrapolation estimates. When separately considered, the Weibull and log-normal curves have the best fit.

Table 21. OS extrapolations

Months		6	12	18	20	40	80	100	120
Deluche 2020					32.77%	10.12%	1.45%	0.51%	0.07%
ASCENT SG		[redacted]	[redacted]	[redacted]					
SG, ERG	**Weibull**	79.10%	51.80%	30.00%	24.50%	1.95%	0.00%	0.00%	0.00%
ASCENT TPC		[redacted]	[redacted]	[redacted]					
SG, ERG	**Log-normal**	56.30%	25.40%	12.60%	10.20%	1.83%	0.18%	0.07%	0.03%
ERG and company	**Log-logistic**	79.43%	49.75%	30.87%	26.64%	8.52%	2.33%	1.52%	1.07%
		56.81%	25.23%	13.21%	11.01%	3.08%	0.81%	0.52%	0.37%

However, when fitting the Weibull model to SG and log-normal or log-logistic curves to TPC, the extrapolations cross at around 37-38 months.

Figure 3. Parametric curve fit of OS for the SG group

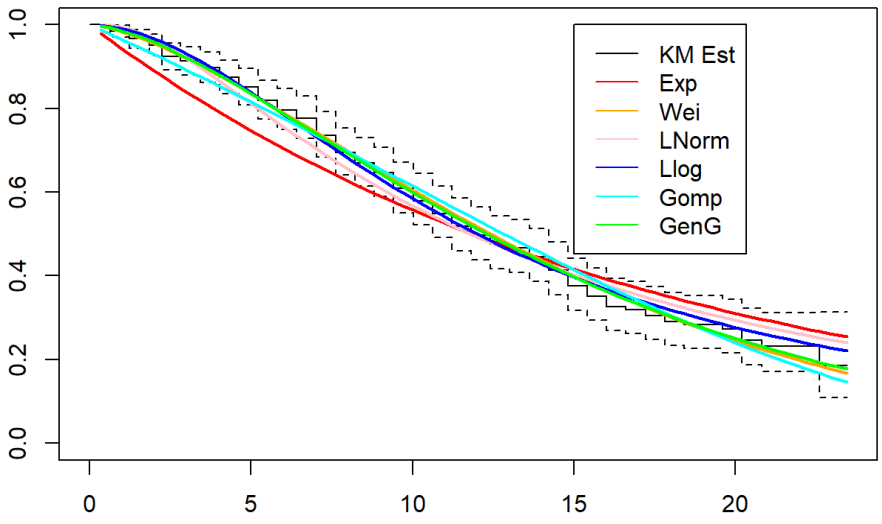
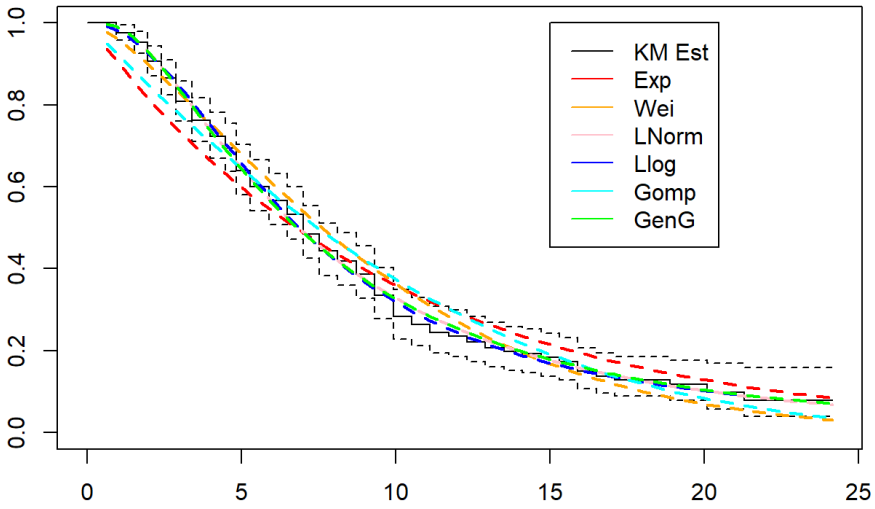


Figure 4. Parametric curve fit of OS for the TPC group



3.5.5. Time To Treatment Discontinuation

Parametric models were fit to the digitised Kaplan-Meier curves for treatment discontinuation (TTD). In terms of AIC and BIC (Table 22), the best fitting model was the log-normal for the SG group, exponential model for TPC, and generalised-gamma for the overall sample. This was consistent with the company for the TPC group, but not for the SG group, where the company preferred the exponential model.

Table 22. Comparison of model fit between company (blue) and ERG (green)

	SG			TPC			SG and TPC		
	AIC	BIC	AIC + BIC	AIC	BIC	AIC + BIC	AIC	BIC	AIC + BIC
Exponential	1328.85	1332.41	2661.26	756.35	759.76	1516.11	2085.204	2093.559	4178.763
Weibull	1324.92	1332.03	2656.95	756.51	763.34	1519.85	2080.069	2092.603	4172.672
Log-normal	1312.32	1319.43	2631.75	784.95	791.78	1576.73	2098.558	2111.092	4209.65
Log-logistic	1316.51	1323.62	2640.13	760.54	767.37	1527.91	2075.08	2087.613	4162.693
Gompertz	1330.82	1337.93	2668.75	758.29	765.12	1523.41	2087.201	2099.735	4186.936
Gen Gamma	1312.95	1323.61	2636.55	755.72	765.96	1521.68	2069.572	2086.284	4155.856

There were no real-world TTD data to compare with the company's assumptions.

Figure 5. Parametric curve fit of TTD for the SG group

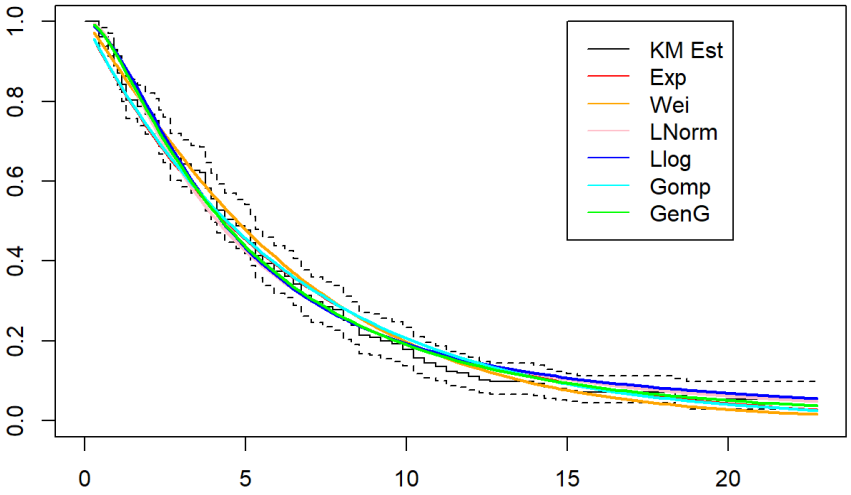
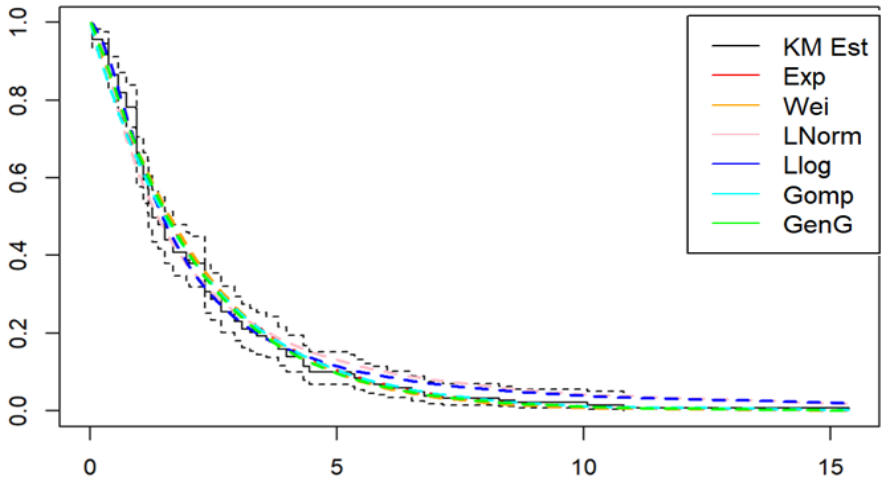


Figure 6. Parametric curve fit of TTD for the TPC group



3.6. Conclusions of the clinical effectiveness section

In general, the company's submitted evidence reflects the decision problem defined in the final scope. The population included 2.8% of patients had prior systemic therapy for locally advanced TNBC, the trial evidence may be more relevant to the use of SG in mTNBC setting. TPC included gemcitabine (not specified in the NICE scope) which is indicated for metastatic breast can only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. Trial evidence included additional secondary outcomes that were not listed in the scope: objective response rate, clinical benefit rate, duration of response, and time to response time to progression.

The company's submission of the comparative clinical effectiveness and safety evidence for SG is based on a single pivotal confirmatory phase-III open-label randomised controlled clinical trial (the ASCENT study) comparing SG to TPC in patients with locally advanced or mTNBC with ≥2 prior therapies. The company did not identify other RCTs comparing head-to head SG with TPC or any relevant individual active comparator treatment. Understandably, no pairwise conventional meta-analysis was conducted. The company could not perform indirect comparison and/or multiple comparison analyses (including population-adjusted indirect comparison) due to infeasibility of such analyses in light of the absence of relevant evidence (lack of subgroup data on baseline patient characteristics and outcomes for endpoints in comparator trials) and/or violation of transitivity-consistency assumption.

In general, the design and methodology of the ASCENT study were adequate to address the decision problem. The ASCENT study demonstrated clinical benefits of SG compared to TPC across multiple efficacy endpoints in pre-treated patients with TNBC. Both PFS and OS assessed by IRC were significantly longer with SG than TPC in both BM-ve and ITT populations. Findings for the secondary outcomes ORR and CBR assessed by IRC were consistent with those for PFS and OS in indicating significantly improved response rates and longer DOR in the SG arm compared with TPC arm in the BM-ve and ITT Populations.

The company's subgroup analysis demonstrated consistent improvements in PFS/OS with SG treatment relative to TPC across the majority of subgroups within the ITT population.

Drug-related toxicity was more frequent in the SG vs. TPC arm. Grade 3 TEAEs (neutropenia, diarrhoea, and anaemia) occurred more frequently in the SG arm than in TPC arm. In order to optimize the risk benefit profile of the SG treatment, adequate and effective pharmacovigilance and risk mitigation measures should be in place.

3.6.1. Limitations and uncertainties

- Evidence base for clinical effectiveness and safety of SG relative to other relevant comparators used for the treatment of patients with locally advanced or mTNBC with ≥2 prior therapies is limited to one RCT where the population of interest is represented as ITT (ASCENT study).

- The absence of pairwise conventional meta-analysis (relevant data available only from one RCT – ASCENT study) and infeasibility of indirect comparison and/or multiple comparison analyses (including PAIC approach) due to the absence of relevant evidence and/or violation of transitivity-consistency assumption.

- The extent of generalizability of the ASCENT study findings to the UK clinical setting may be limited given that there were only 6 UK sites ([redacted]) represented in this trial. The number and types of prior therapies that patients received varies across the countries that participated in the trial.

- Lack of longer-term data on efficacy and safety of SG treatment in patients with locally advanced or mTNBC with ≥2 prior therapies. In the ASCENT study, the median total follow-up from randomisation was 8.38 (range: 0-24) months (SG arm: 10.55 months vs. TPC arm: 6.28 months).

- The TPC arm may not closely represent the chemotherapy options available to patients with locally advanced or mTNBC with ≥2 prior therapies in the UK since the ASCENT study was a multicenter trial that was conducted in multiple different countries.

- There is uncertainty if the primary analysis population (BM negative patients) was truly free of BM (only those patients with 'known BM' were MRI-ed and excluded from the primary analysis). The presence of BM is a strong predictor for disease progression and poorer prognosis (as shown in the subgroup analysis of the ASCENT study and previous research findings) and its imbalanced distribution between the SG and TPC study arms could bias the SG treatment effect estimates for PFS and OS.

- The ASCENT study was an open-label investigation. Due to differences in the treatment administration, blinding of study personnel and participants was not feasible. This may have impacted the ascertainment of patient-reported outcomes such as HRQoL and inflated the clinical benefits shown for the mean EORTC QLQ-

C30 score changes in the SG arm even if the outcome assessors were independent and blinded.

- There was a differential attrition of ITT sample due to missing values for EORTC QLQ-C30 score at a follow-up in the SG arm (11.7%) and TPC arm (30.2%). As the company did not provide the reasons for this missing information, it is difficult to judge whether or not the patients with missing data were systematically different across the SG and TPC arms in their HRQoL. The differential sample attrition might have led to biased treatment effect estimates for HRQoL particularly with respect to the estimation of a treatment effect on the quality of life scale.. In the absence of reasons for such missing data, it is not possible to estimate the magnitude and direction of bias in the effect estimates.

- The proportion of randomised but untreated patients (who withdrew their consent after randomisation) was notably higher in TPC (14.5%) vs. SG (3.4%) treatment group. This may have resulted in more censoring in the TPC vs. SG arm contrary to the PFS/OS results (i.e., with more disease progression observed in the SG vs. TPC arm). The ERG is uncertain how the untreated patients were handled in the efficacy analyses. Their exclusion from the efficacy analyses would likely distort (i.e., bias due to non-random sample attrition) the ITT/MB-ve population comparisons if the reasons for consent withdrawal differed across the study arms. The ERG is unclear whether or not the untreated patients were followed-up (for progression, death) and/or analysed, what were the censoring rules, and if these rules differed across the SG and TPC arms. The company did not provide a sensitivity analysis showing the influence of untreated patients' data exclusion/inclusion from ITT/BM-ve (with or without value imputation), and different censoring scenarios on the estimates of PFS/OS (and other efficacy endpoints). Likewise, the baseline patient characteristics of the untreated sample were not provided, as this information would aid the ERG team in gauging the magnitude and direction of bias in the effect estimates of PFS, OS, and other endpoints of interest.

- There were more patients tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.

- High grade neutropenia was more frequent in the SG vs. TPC arm. Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the TPC arm the treatment was discontinued and no G-CSF was administered.

- The caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment

- The company provided joint-fit curves from the SG and TPC for OS outcome. Although the company justified this approach, this does not necessarily provide a better fit than models stratified by treatment group. Stratified models may yield to a better fit.

- For PFS, the generalised gamma model has a better statistical fit from digitised Kaplan-Meier data than the log-logistic. The generalised gamma model provided more reliable extrapolation percentages at 12 months.

- For TTD outcome in the SG group, the ERG analysis showed that the exponential model was the 5th best fit model while the company had this as best fit.

4. COST EFFECTIVENESS

4.1. ERG comment on company's review of cost-effectiveness evidence

- *Search strategy*

The company report two systematic searches to cover their approach to identifying economic models and costs/resource use data (Appendix G and I). Since both reviews draw upon identical searches, we report and critique both here.

4.1.1. Summary of the company's approach to study identification

The company's search approach utilised searches of bibliographic databases and supplementary search methods to identify economic analyses/models and costs/resource use data published in English, 2010 to July 2021.

The company searched six databases, including MEDLINE and Embase. Their search strategy took the following form: ((terms for triple negative breast cancer OR disease stage) AND (terms for costs OR resource use OR disease burden) AND (terms for longitudinal/observational studies OR cost analyses)). The ERG were able to re-create the searches following the company's response to clarification questions.

The company searched conference abstracts via Embase.com and handsearched SABCS 2020 Annual Meeting, ASCO 2021, and ESMO Breast Cancer 2021. Health Technology Assessments of 'recent market entrants', which reported cost-effectiveness data, and were available via NICE, Scottish Medicines Consortium, Canadian Agency for Drugs and Technologies in Health, and the Pharmaceutical Benefits Advisory Committee, were also searched for the review of economic models.

4.1.2. Critique of the company's approach to study identification

The ERG considers that there are limitations in the company's approach to study identification. Namely:

i) aligning the search approach to the decision problem: the ERG consider that the search approach should have focused on breast cancer with the focus on the decision problem (triple negative breast cancer, specifically) made during study selection. This would also have ensured a systematic approach to identifying relevant data generally and in the broader breast cancer population for the modelling specifically.

ii) the ERG considers that there are limitations in the structure of the bibliographic database search strategies: The company have limited their bibliographic searches to observational studies or studies reporting economic models. Limiting searches for cost-effectiveness data to a specific design or publication type is not recommended best practice.[38] The ERG are concerned that the company may have missed studies or data using other designs or methods.

4.2. Health-related quality of life

4.2.1. Summary of the company's approach to study identification

The company's search approach utilised searches of bibliographic databases and supplementary search methods to identify economic analyses/models published in English since 2010 to July 2021.

The company searched five databases, including MEDLINE and Embase. Their search strategy took the following form: ((terms for triple negative breast cancer OR disease stage) AND (terms for health-related quality of life) AND (terms for longitudinal/observational studies OR cost analyses)). The ERG were able to re-create the searches following the company's response to clarification questions.

The company searched conference abstracts via Embase.com and handsearched SABCS 2020 Annual Meeting, ASCO 2021, and ESMO Breast Cancer 2021. Studies

reporting utility data identified by the company's cost-effectiveness search were eligible for inclusion in this review.

4.2.2. Critique of the company's approach to study identification

The ERG considers that there are limitations in the company's approach to study identification. Namely:

i) aligning the search approach to the decision problem: the ERG consider that the search approach should have focused on breast cancer with the focus on triple negative breast cancer made during study selection. The company will have missed studies which report natural history, and it is unclear how they identified utility data from patients in the broader breast cancer disease state, or through disease progression.

ii) **the ERG considers that there are limitations in the scope and the structure of the bibliographic database search strategies:** The company have not used any existing or validated search filters to identify data for this review. The design of their search strategies is generally poor, since it focuses on a limited number of general terms for health-related quality of life and only two specific instruments (SF-36/ EQ5D).

The company have limited their bibliographic searches to observational studies or studies reporting economic models. This approach has the potential to limit the identification of eligible data from other study designs and it is inconsistent with recommended best practice.

iii) Searches do not exhaust a literature review.
Importantly, the ERG considers that literature review conducted by the company is limited to conducting searches, tabulating results from papers included, but the entire critical appraisal work, contextualisation and interpretation of findings from the existing literature is not conducted.

This has important implications on the discussion of utility values incorporated in the model, obtained from the ASCENT study, which not contextualised nor appraised in the context of other potential sources of utility values.
It also has important implications on the discussion of model characteristics, which are not compared to any of the pre-existing work.
Often, modelling choices can be justified referring to previous work, however precedence is only acceptable when contextualised and the conditions of choices made in preceding work are assessed for relevance for the current appraisal. Current modelling choices should be justified based on their merit, and precedence can only be used to strengthen the case, identifying situations when similar choices have been made given similar premises.
Likewise, the company did not present a review of utility scores used in prior publications. This is particularly important in the context of this appraisal which appears the first to claim a treatment effect on utility scores during treatment with the drug being assessed, SG (Section 4.9.7).

4.3. Company cost-effectiveness results

The company's cost-effectiveness case was developed using a partitioned survival model including time to treatment discontinuation, progression free survival and overall survival. The model compared SG and TCP

The model was used to calculate costs and QALYs for SG and TCP. Costs included drug acquisition, drug administration and monitoring costs, the cost of concomitant medications and adverse events costs, and cost of therapies given after progression.

Utility scores were calculated from the ASCENT study and applied to pre-progression (on treatment) and post progression states. Utility scores were higher for SG for equal model state, for both states, [redacted] (SG) and [redacted] (TPC) for the period on treatment and [redacted] (SG) and [redacted] (TPC) post-progression.

Over a timeframe of 10 years, SG resulted in higher total cost of care [redacted] SG vs [redacted] TPC) and higher QALYs ([redacted]), compared with TPC, with incremental QALYs of [redacted], equivalent to an improvement in survival of [redacted] months in full health compared with TPC. The resulting ICER was £49,651.

4.4. NICE reference case checklist

Table 23: NICE reference case checklist

Element of health technology assessment	Reference case	ERG comment on company's submission
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers	The model includes direct costs of care for people treated with each comparator: treatment acquisition costs, administration, monitoring and other healthcare costs, cost of concomitant treatment and costs of treatments subsequent to first progression (post-progression costs)
Perspective on costs	NHS and PSS	NHS and PSS unit costs have been used. Drug costs however are estimated using wastage, which assumes a hospital perspective for resource use in the case of drugs part of this appraisal.
Type of economic evaluation	Cost–utility analysis with fully incremental analysis	Cost-utility analysis and full incremental analysis, in addition to cost-effectiveness (cost per life years gained)
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared	The model uses a 10 years' time horizon, which appears appropriate for the patient population and the condition
Synthesis of evidence on health effects	Based on a systematic review	The model uses data from one clinical trial conducted on the population of the scope. No additional synthesis of evidence has been conducted.
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of health-related quality of life in adults.	The model used QALYs, obtained from utility values generated in the ASCENT trial.[10] Utility values were obtained from the EORTC QLQ-C30 questionnaire administered to patient in the ASCENT trial. EORTC QLQ-30 were converted to EQ-5D-3L utility scores using a published algorithm.[39] Generally speaking, the mapping seems appropriate although the EORTC QLQ-30 values used in the mapping may be affected by substantial and differential attrition between study arms in the ASCENT study (Section 3.5.1).

Element of health technology assessment	Reference case	ERG comment on company's submission
Source of data for measurement of health-related quality of life	Reported directly by patients and/or carers	As above
Source of preference data for valuation of changes in health-related quality of life	Representative sample of the UK population	The company used a mapping algorithm (Longworth et al)[40] to convert EORTC QLQ C30 into EQ-5D-3L utility values. The population sample used to elicit EORTC QLQ30 values was international; the conversion algorithm uses data from the UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	No equity considerations apply
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS	NHS and PSS unit costs and resource use are obtained from relevant UK sources and calculated consistently with the reference case, with the exception of drug costs. Resource use is obtained from the ASCENT trial and where relevant, clinical advice.
Discounting	The same annual rate for both costs and health effects (currently 3.5%)	Both costs and QALYs were discounted at 3.5%
PSS: personal social services; QALYs: quality-adjusted life years; EQ-5D: standardised instrument for use as a measure of health outcome.		

4.5. Model structure

The company's model is a partitioned survival model, a typical structure for cancer models, including an on-treatment state, a pre-progression state, a progressed state and a dead state for both comparators. This model structure has been used in prior TNBC appraisals and appears appropriate.

The model uses a one-week cycle which generates underestimation of therapy costs when drug costs are calculated by cycle (see Section **Error! Reference source not found.**). This aspect is easily resolved; the ERG has modified costing calculations to provide correct estimates.

The time-on-treatment survival parametric curve is used to calculate the cost of therapy for SG and TPC; however, the cost of subsequent therapies is included as a

one-off cost, independent from modelled time spent in post-progression and before death. Whilst this structural approximation is an acceptable compromise between complexity of model structure and impact of subsequent costs, caution should be used when assessing the cost-effectiveness of SG over a time-horizon shorter than lifetime, and particularly, for very short time horizons such as 1-2 years. This is because some post-progression costs are added for a small number of people that progress some time near the timeframe cut-off, whilst in fact, a fraction of post-progression costs would occur after the cut-off. When using a short time horizon in the model, therefore, fixed costs are likely to be overestimated because of costs that extend beyond the chosen timeframe.

4.6. Population

The model population is locally advanced or metastatic triple negative breast cancer, representing the population in the ASCENT trial. The cost-effectiveness analysis uses data for all women who took part in the trial, including those who received (post-metastatic diagnosis-) first line eribulin. The economic analysis therefore suffers from the overall lack of representativeness for the UK as described in the clinical Section of this report section 3.2.

4.7. Interventions and comparators

The model includes two groups:

- Sacituzumab Govetican (SG)

- Treatment of physician's choice (TPC) The justification for using a comparator arm made up by multiple treatments is assessed in Section 3.2.

4.8. Perspective, time horizon and discounting

The model uses the NHS-PSS perspective, including all costs relevant for the NHS accrued in conjunction with either comparator. Nevertheless, some aspects of costing appear informed by a hospital perspective. These have been discussed where pertinent in the costing section.

Given the short life-expectancy for the TNBC population (<1 year) the model uses a 10-years' time-horizon in the base case which effectively represents lifetime.

4.9. Treatment effectiveness and extrapolation

4.9.1. Progression-free survival curves (PFS)

PFS data in ASCENT ITT population were mature (patients alive at 12 months: SG = 17.2%, TPC = 6.0%), with

[redacted]

[redacted]. The company fitted curves and applied diagnostic plots to see if the two treatment curves can be fitted together or separately.

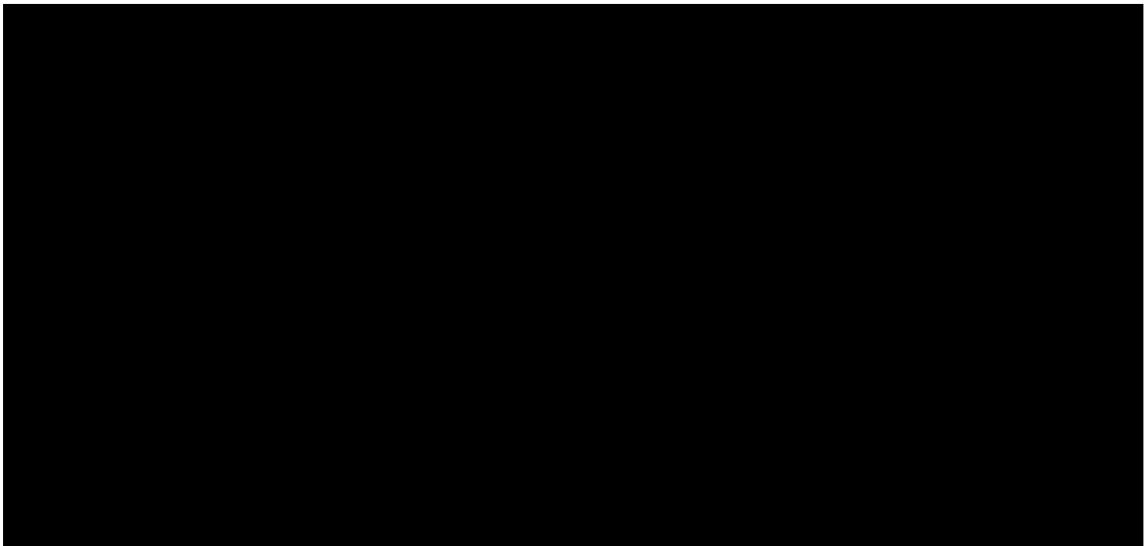
The Q-Q plot (Document B, Figure 20 page 84) compared two probability distributions by plotting their respective quantiles against each other (SG quantiles on the x-axis, TPC quantiles on the y-axis). If distributions were similar, the points of the Q-Q plot will approximately lie on the line y=x. This can be used to check the assumption of accelerated failure time (AFT) models, which is an alternative to a proportional hazards (PH) model, and assumes that the effect of a covariate is to accelerate or decelerate the life course of a disease by some constant. The plots on Figure 20 (document B, page 84) shows a light deviation, with the points waving more than being straight, suggesting a possible violation of AFT assumptions.

Figures 21, 22 and 23 (document B, page 84 – 85) test the PH assumption. Figure 21 was a plot of the Cox-Snell residuals, where a deviation from the line y=x suggests a violation of the PH assumption. In this plot, Cox-Snell residuals>2.5 deviated from the y=x line, suggesting a violation of the PH assumption. Figure 22 was a plot of the Schoenfeld residuals, where a non-random pattern against time is evidence of PH assumption violation. Figure 22 showed some semblance of pattern, however p=0.2649, thus there was evidence of PH assumption violation. Finally, figure 23 was a log-log plot, where the PH assumption is met if the log-log KM survival estimates against log-time curves are reasonably parallel where in this case they were not. The parametric survival curves for PFS in the ASCENT ITT population are presented in **Error! Reference source not found.**, and **Error! Reference source not found.** corresponding information criteria are presented in Table 24.

Figure 7. ASCENT ITT population SG PFS KM and parameterised curves (figure 24 of the CS)

Figure 8. ASCENT ITT population TPC PFS KM and parameterised curves (figure 25 of the CS)

Figure 9. ASCENT ITT population TPC PFS KM and parameterised curves (figure 23 of the CS)



The curves with the lowest AIC, BIC and AIC+BIC are highlighted in bold, which are the log-normal for the SG group, and log-logistic for the TPC group. The company used these curves, respectively.

Figure 10. ASCENT ITT population SG PFS KM and parameterised curves (figure 24 of the CS)

Figure 11. ASCENT ITT population TPC PFS KM and parameterised curves (figure 25 of the CS)

Table 24. Company ASCENT ITT PFS parameterised curves information criteria

Group	Distribution	WEI	LOGN	LOGL	EXPO	GGAM	GOMP
SG	AIC	1126.2	**1103.5**	1106.4	1129.2	1105.5	1131.0
	BIC	1133.4	**1110.6**	1113.5	1132.8	1116.1	1138.2
	Sum	2259.6	**2214.1**	2219.9	2262.0	2221.6	2269.2
TPC	AIC	720.0	682.4	**670.1**	738.7	684.4	740.5
	BIC	727.0	689.5	**677.2**	742.2	695.0	747.5
	Sum	1447.0	1371.9	**1347.3**	1480.9	1379.4	1488.0

Company's preferred model shown in **bold**

AIC = Akaike's information criterion; BIC = Bayesian information criteria; EXPO = exponential; GGAM = generalised gamma; GOMP = Gompertz; LOGL = log-logistic; LOGN = log-normal; SG = Sacituzumab govetican; TPC = treatment of physician's choice; WEI = Weibull

It is worth noting that the lognormal, log-logistic and generalised gamma have very similar values for parametric statistical fit, therefore the choice of distribution should be taking into account the plausibility of long-term projections for all these curves.

Figures 26 and 27 in the CS (document B, page 88) present long-term projections for PFS (up to 60 months) of the fitted parametric curves for SG and TPC, respectively. The company followed a visual assessment of the curves because of 1) the maturity of the data, 2) the similarity of extrapolations across distributions. These were presented in table 22 of the CS (document B, page 89) for the SG and table 23 for the TPC (document B, 89).

The similarity of the projections made using the log-normal, log-logistic and the generalised gamma distributions is also clarified in table 22 of the CS (document B, page 89) for SG and table 23 for TPC (document B, 89), which provide median and mean PFS (in months). These fall in a range of 4.59 and 4.62 months for SG (ASCENT: median 4.8 months) and 2.14-2.22 months for TPC (ASCENT: median 1.7 months).

The company preferred choice of curves therefore (SG: log-normal; TPC: log-logistic) seem acceptable. In addition, the ERG tested alternative scenarios using the combinations of the three distributions (Table 25, and Table 26).

Table 25: PFS in the ITT population: predictions by distribution in the SG treatment arm

Distribution	Median (months)	Mean (months)	1-Year PFS	2-Year PFS	3-Year PFS	5-Year PFS	10-Year PFS
KM (ASCENT) [10]	4.8						
Log-normal	**4.62**	**7.68**	**17.94%**	**5.66%**	**2.42%**	**0.68%**	**0.09%**
Log-logistic	4.59	8.16	17.08%	6.18%	3.27%	1.44%	0.46%
Generalized gamma	4.60	7.68	18.06%	5.83%	2.56%	0.76%	0.11%
Non-relevant distributions							
Weibull	5.20	6.80	16.56%	1.90%	0.19%	<0.01%	<0.01%
Exponential	4.95	7.08	18.64%	3.47%	0.65%	0.02%	<0.01%
Gompertz	4.88	7.33	19.01%	4.17%	1.04%	0.09%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; SG = sacituzumab govetican

Table 26: PFS in the ITT population: predictions by distribution in the TPC treatment arm

Distribution	Median (months)	Mean (months)	1-Year PFS	2-Year PFS	3-Year PFS	5-Year PFS	10-Year PFS
KM (ASCENT) [10]	1.7						
Log-normal	2.22	3.00	1.72%	0.14%	0.02%	<0.01%	<0.01%
Log-logistic	**2.14**	**2.85**	**1.81%**	**0.37%**	**0.14%**	**<0.01%**	**<0.01%**
Generalized gamma	2.22	3.00	1.71%	0.14%	0.02%	<0.01%	<0.01%
Non-relevant distributions							
Weibull	2.46	2.99	0.41%	<0.01%	<0.01%	<0.01%	<0.01%
Exponential	2.20	3.14	2.27%	0.05%	<0.01%	<0.01%	<0.01%
Gompertz	2.24	3.15	1.78%	0.01%	<0.01%	<0.01%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; PFS = progression-free survival; TPC = treatment of physician's choice

4.9.2. Overall survival curves

OS data in ASCENT ITT population were mature (median OS: SG = 11.8 months, TPC = 6.9 months), with [redacted].

The company fitted curves and applied diagnostic plots (similar methodology to PFS, section 2.5.1).

The Q-Q plot was presented in figure 28 in the CS (document B, page 90). The plots were slightly wavy but adhered to the y=x line, suggesting that the AFT assumption

holds for OS. The company concluded that SG and TPC should be modelled using a joint model under the AFT assumption; nevertheless, whilst these arguments are a justification for the AFT assumption, the specific rationale why joint models should also be pursued is not given. The company also assessed whether the proportional hazard (PH) assumption could be violated, using a similar approach to that used for PFS. The company concluded that the assumption of PH may have been violated.

The parametric curves for OS in the ASCENT ITT population were therefore only estimated for the joint models, and are presented in Figure 12 and Figure 13, with corresponding information criteria are presented in **Table 27**. The curves with the lowest AIC, BIC and AIC+BIC are highlighted in bold, which is the log-logistic curve that was chosen by the company. The curves with the lowest AIC, BIC and AIC+BIC are highlighted in bold, which is the log-logistic curve that was chosen by the company.

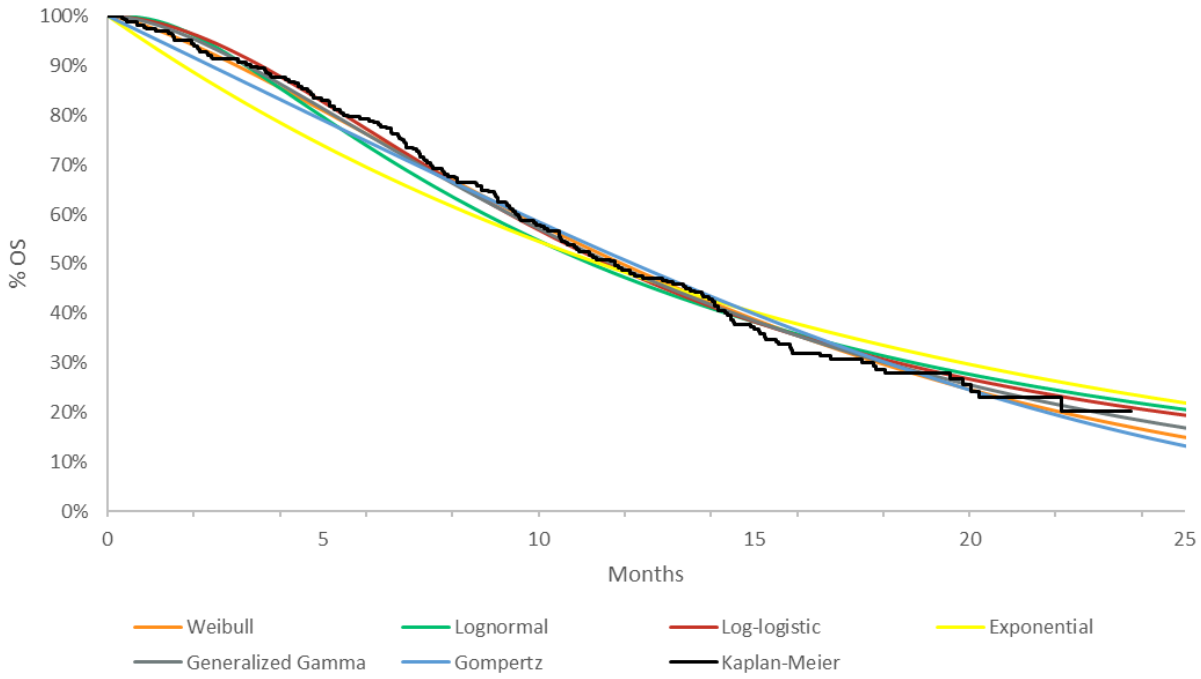


Figure 12. ASCENT ITT population SG OS KM and parameterised curves (figure 32 of the CS)

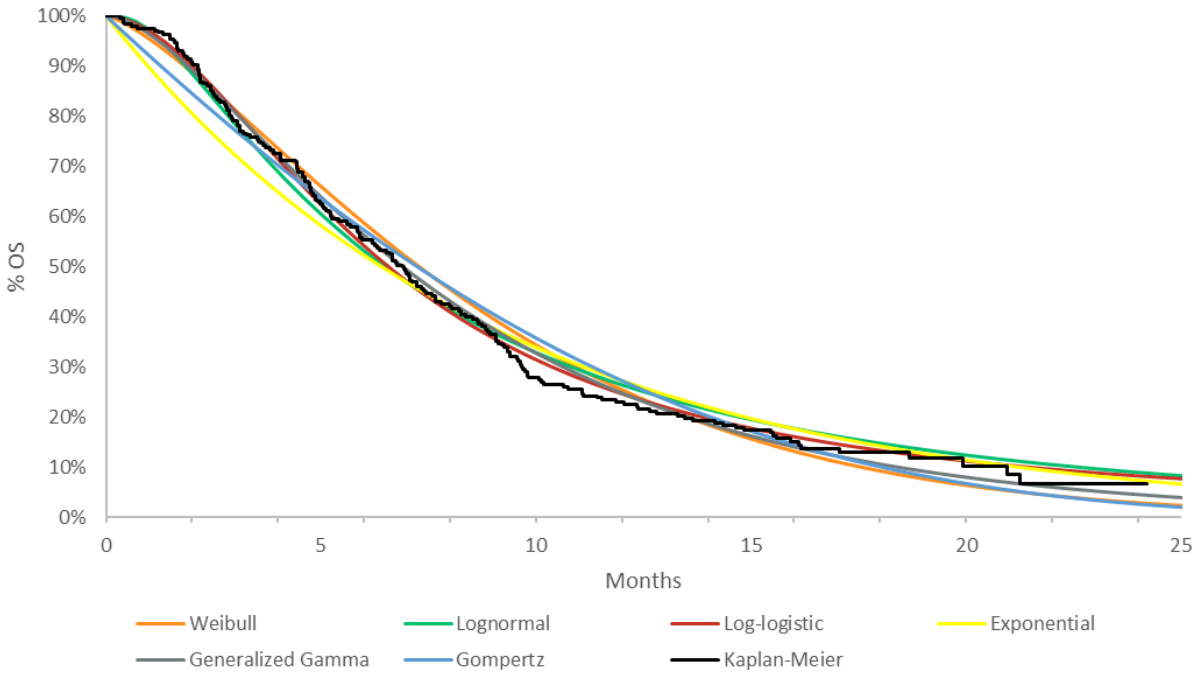


Figure 13. ASCENT ITT population TPC OS KM and parameterised curves (figure 33 of the CS)

Table 27. Company ASCENT ITT OS parameterised curves information criteria

Distribution	WEI	LOGN	LOGL	EXPO	GGAM	GOMP
AIC	2649.7	2662.3	**2642.8**	2694.1	2644.8	2672.6
BIC	2662.4	2675.1	**2655.6**	2702.6	2661.8	2685.4
Sum	5312.1	5337.4	**5298.4**	5396.7	5306.6	5358.0

Company's preferred model shown in **bold**

Abbreviations: AIC = Akaike's information criterion; BIC = Bayesian information criteria; EXPO = exponential; GGAM = generalised gamma; GOMP = Gompertz; LOGL = log-logistic; LOGN = log-normal; WEI = Weibull

The company selected the log-logistic based on 1) the information criteria, 2) visual inspection of the curves. Overall, the company opted for the log-logistic model on grounds of best statistical fit. When visually comparing the fitted models to the observed KM data from ASCENT CSR for the SG group, the log-logistic model shows a reasonably close fit. However, the company's approach seems rather crude and fails to strike a balance between criteria that should be used to assess fit on the whole.

With regards exclusively to statistical fit, the log-normal, exponential and Gompertz distributions show a poor fit. Nevertheless, these conclusions depend on the presentation of statistical fit parameters for the joint model only. The company omitted statistical fit data for the 'stratified' models for OS entirely. In fact, alternative distributions, fitting the KM data equally well in terms of AIC and BIC (Weibull, generalised gamma), fit the ASCENT KM data better (generalised gamma, Weibull for SG) than the log-logistic.

For TPC, although excluded as potential distribution on grounds of (joint model) statistical fit, the log-normal distribution appears a reasonable approximation based on both ASCENT rates and the visual KM curve.

For SG, the Weibull appears to have a weak visual fit; this conclusion however appears to be the consequence of restricting the model choice to the joint model, under which Weibull is not the best alternative overall because it does not seem the best fit for TPC, whilst in fact, it does fit the KM well, or even, best overall, for SG.

Using visual fit criteria, the ERG therefore identified two potential sets of distributions for SG and TPC that should be assessed for best fit overall. The selected distributions are

- SG: log-logistic (company preferred), generalised gamma, Weibull;
- TPC: log-logistic (company preferred), lognormal, generalised gamma

Table 28 shows the calculated proportions of patients surviving at specific time points in the model, given each parametric distribution. The company preferred distribution has a lower median time to death (11.6 months), compared with the generalised gamma, but the highest mean time to death (18.24 months) compared with both the generalised gamma and the Weibull. The mean, and not the median, has a direct impact on cost-effectiveness estimates. The log-logistic has a marginally lower proportion of survivors at 1 year (48.42% vs 48.93% and 49.75%) but substantially higher rates of survival are modelled in the longer term: the risk of surviving with SG using the log-logistic, is 12% higher than with the generalised gamma and 24% higher than with the Weibull at 2 years, 60% and 146% higher than with the GG and Weibull at 3 years and separates further over the longer term.

Table 28: OS in the ITT population: predictions by distribution in the SG treatment arm (excluding log-normal, exponential and Gompertz distributions)

Distribution	Median (months)	Mean (months)	1-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
KM (ASCENT) [10]	11.8						
Log-logistic	**11.60**	**18.24**	**48.42%**	**20.63%**	**10.93%**	**4.55%**	**1.30%**
Generalized gamma	11.72	15.01	48.93%	18.40%	6.82%	0.99%	0.01%
Weibull	11.94	14.24	49.75%	16.65%	4.45%	0.20%	<0.01%
Crude risk difference (%) between log-logistic and:							
Generalized gamma	-1%	22%	-1%	12%	60%	360%	12900%
Weibull	-3%	28%	-3%	24%	146%	2175%	12900%

ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; SG = sacituzumab govetican

For the TPC group, the generalised gamma has the same median survival month as the observed ASCENT data. The log-logistic gives the highest mean survival of 10.34 months and the highest survival over the longer term. The log-normal gives the highest survival rates for TPC in the short term and fits similarly to the log-logistic in the longer term. Both distributions give higher estimates of survival compared with the generalised gamma.

Table 29: OS in the ITT population: predictions by distribution in the TPC treatment arm (excluding exponential, Gompertz and Weibull)

Distribution	Median (months)	Mean (months)	1-Year OS	2-Year OS	3-Year OS	5-Year OS	10-Year OS
KM (ASCENT) [10]	6.9						
Log-normal	6.49	10.19	26.51%	9.07%	4.00%	1.15%	0.14%
Log-logistic	**6.57**	**10.34**	**24.69%**	**8.32%**	**4.11%**	**1.64%**	**0.46%**
Generalized gamma	6.9	8.84	24.82%	4.62%	0.90%	0.04%	<0.01%

ITT = intention-to-treat; KM = Kaplan-Meier; OS = overall survival; TPC = treatment of physician's choice

Figure 14, Figure 15, Figure 16, Figure 17, and

Figure 18**Figure 17. Parametric fitted OS, Weibull joint model, and ASCENT Kaplan-Maier, SG and TPC**

Figure 18 below illustrate the differences between the log-logistic, generalised gamma, Weibull, and log-normal distributions (modelled as joint curves for SG and TPC).

Compared with the generalised gamma, the log-logistic overfits the SG data up to 4 months and over the longer term from 14 months onwards. The Weibull appears to be the best visual fit to the SG KM overall, but it fails to rank as best model overall because of poorer fit to the TPC KM.

With regards to the KM fit, the log-logistic distribution is the most optimistic of alternatives compared with the generalised gamma and with the Weibull.

Although the lognormal does not show the best statistical fit, and it probably fits the SG data less well overall, it does seem to fit the TPC data reasonably well, particularly in the first 10 months of the ASCENT trial.

It is perhaps useful to underline that, although the use of parametric distributions is typically justified for extrapolation purposes when trial data are immature (i.e. long term outcomes can only be estimated), the incorporation of these curves in a cost-effectiveness model also does have a large impact in the early periods modelled. Therefore, in this model, overfitting or underfitting the KM curves in the first six months in the model may have an impact equally important as the longer-term extrapolation.

Figure 14. Parametric fitted OS, log-logistic joint model, and ASCENT Kaplan-Maier, SG and TPC

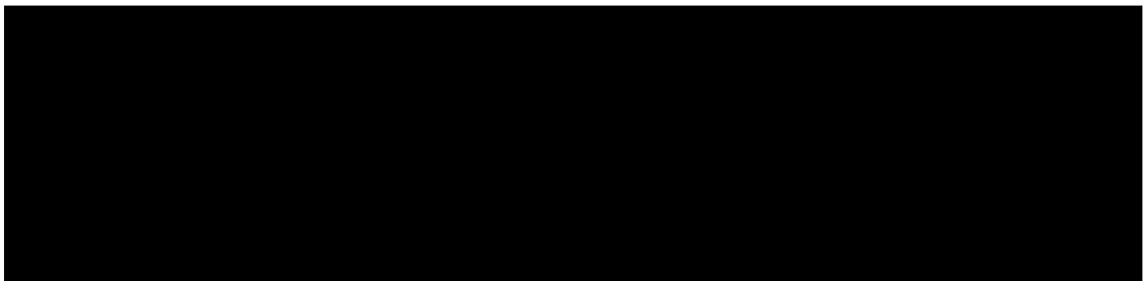


Figure 15. Parametric fitted OS, generalised gamma joint model, and ASCENT Kaplan-Maier, SG and TPC

Figure 16. Parametric fitted OS, log-logistic and generalised gamma comparison, SG and TPC

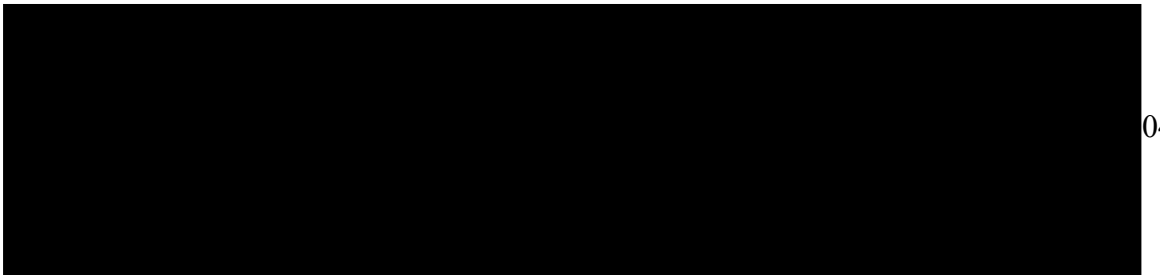
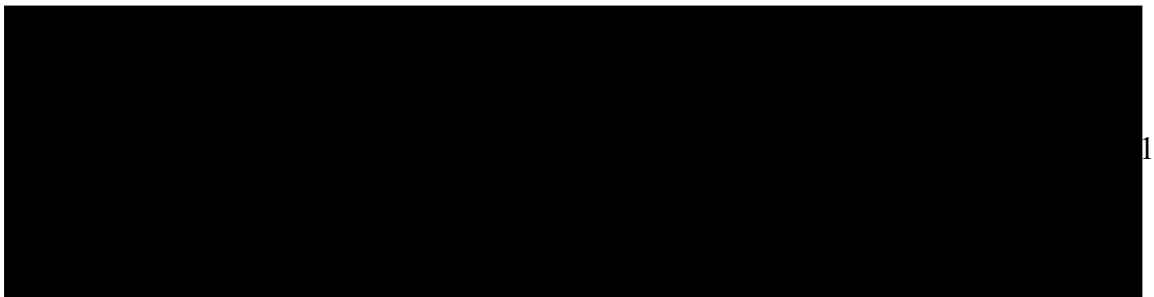


Figure 17. Parametric fitted OS, Weibull joint model, and ASCENT Kaplan-Maier, SG and TPC

Figure 18. Parametric fitted OS, log-normal joint model, and ASCENT Kaplan-Maier, SG and TPC



4.9.3. Validation with external data

The company did not extensively address validation with respect to external data, other than a mention that the fit of the chosen distribution (log-logistic) is consistent with real world data identified in two other sources in addition to the ASCENT trial data: Deluche et al , and Chue et al.[16, 37, 41]

- Chue et al was a case report of survival for a woman with TBNC, who lived for over 15 years. Although the company does not state what the relevance of this case report is with respect to validation of model extrapolation, case studies are generally not suitable to assess curve fit. Such case report is clearly focussing on exceptional survival and therefore does not provide info to validate extrapolation valid for a population.
- The Deluche et al paper was a study based on real-world data from 22,000 French women with metastatic breast cancer, and included a subgroup of 2963 women who had a diagnosis of triple-negative (HR-/HER-) breast cancer, the only relevant subgroup for the purpose of this assessment. The TNBC cohort includes women with similar age and gender as the ASCENT study; the comparability in disease severity is unclear as the cohort includes 15% of women with brain metastases, and 33% of are of 0-1 performance status, although the paper does not declare which performance status score it used and the score is missing for a large majority (58%) of the sample.

The company's view is that this study is not a good support for validating modelled survival. The ERG agrees, as the relevant subgroup in this study included women newly diagnosed with TMBC who started (first line) chemotherapy between 2006 and 2016. As such, this population is not a relevant population for this assessment.

The Deluche data would be useful to validate TPC only. The study provides median PFS and OS data from treatment initiation, 4.8 months and 14.8 months respectively. Assuming that women would become eligible for second (after metastatic diagnosis) line therapy as soon as progression occurs, then the approximate survival for this population after first progression is 10 after which a second progression should occur before women become eligible for SG. Therefore, the study may be useful in so far it provides the upper bound for median survival in this this population (Figure 14) . However, the study does not provide data on time alive after second progression; because log-logistic and generalised gamma curves give similar rates at 10 months and in general, fall below the Deluche estimates, it is unlikely that this study may provide a robust basis for extrapolation validation.

4.9.4. Waning treatment effect

The cost-effectiveness analysis did not take into account potential treatment waning effects. Considering the maturity of the data, the ERG agrees with this assumption, as the potential effect of waning on the cost-effectiveness ratio is probably undiscernible.

4.9.5. OS extrapolations, summary

In the absence of a strong statistical rationale and visual fit that shows that the log-logistic distribution is the best fit to data, and in the absence of a comparison to external data, the choice of log-logistic appears selective, on grounds that it provides the most optimistic scenario for clinical efficacy. Notwithstanding that the discussion is constrained by the availability of curves from joint models only, the ERG has elected to assess scenarios with both joint distributions and different distributions by arm. This is because the ERG believes that a stratified fit would be preferable to a joint fit for OS, although this conclusion is reached in the absence of appropriately estimated extrapolations and may not hold once the appropriate curves are incorporated in the model. The stratified analyses presented here should be considered indicative, because they rely on single distributions from the joint

modelled distribution. The appropriate analysis requires that the company incorporates stratified models for OS in the cost-effectiveness model to provide the Committee with reliable estimates of the ICER.

For scenarios with joint models, the ERG prefers the generalised gamma distribution because it has very similar statistical fit to the ASCENT data overall, compared with the log-logistic, but it has better visual fit overall, it does not overestimate the proportion of women alive in the longer term and has a better fit in the short term (<12 months) than the log-logistic.

As an approximation of the possible model outcomes when stratified fit is considered, the Weibull appears the best fitting distribution for SG and the generalised gamma for TPC.

4.9.6. Treatment duration curves

Time to treatment discontinuation was modelled despite a high positive correlation between TTD and efficacy as noted by the company. The company presented a comparison of PFS and TTD KM plots for SG (document B, figure 36 page 97) and TPC (document B, figure 37 page 98) which show that the curves are correlated.

Fitted curves are shown in Figure 19 and Figure 20. The information criteria are presented in Table 30.

Figure 19. ASCENT ITT population SG TTD KM and parameterised curves (figure 38 of the CS)

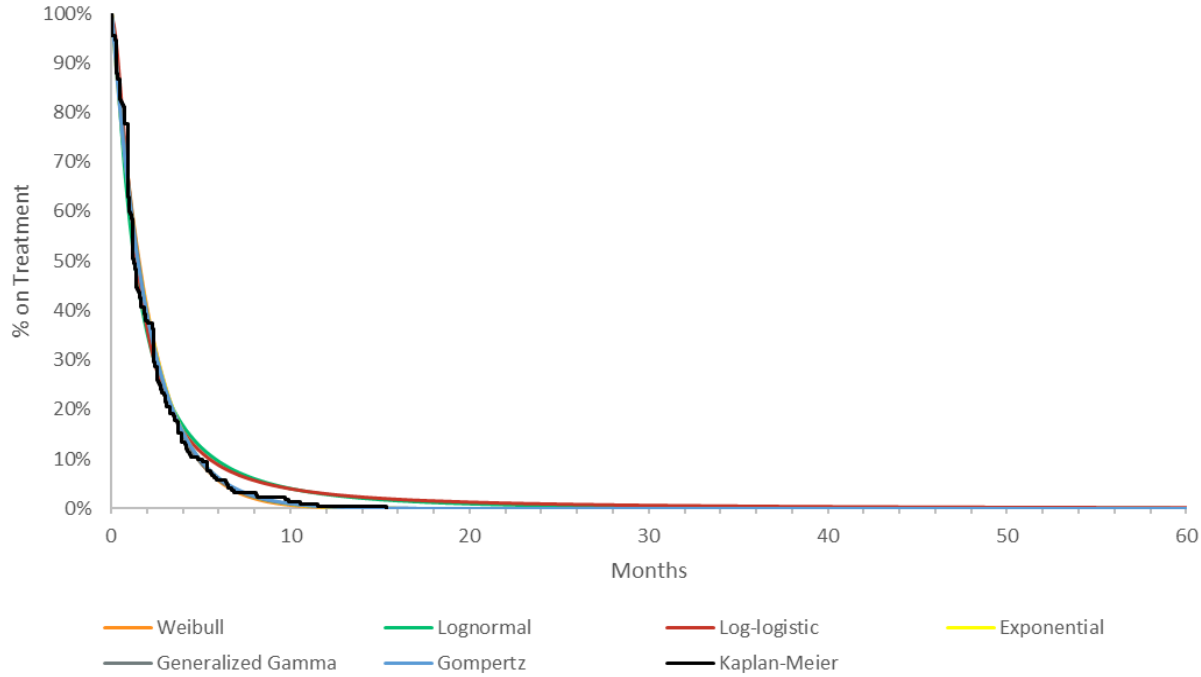


Figure 20. ASCENT ITT population TPC TTD KM and parameterised curves (figure 39 of the CS)

Table 30. For the TPC group, the exponential model has the best statistical fit (AIC, BIC, and AIC+BIC). For SG group, Weibull, exponential and Gompertz models fit well, with the exponential having the best statistical fit (AIC+BIC). The Weibull, exponential and generalised gamma, in addition, appear to overlap. The exponential model was chosen by the company and this selection seems appropriate.

However, given that the company argued for a stratified model, it is unclear why the best fitting curves selected are the same and specifically, exponential, which would signal that the joint model may be a better fit.

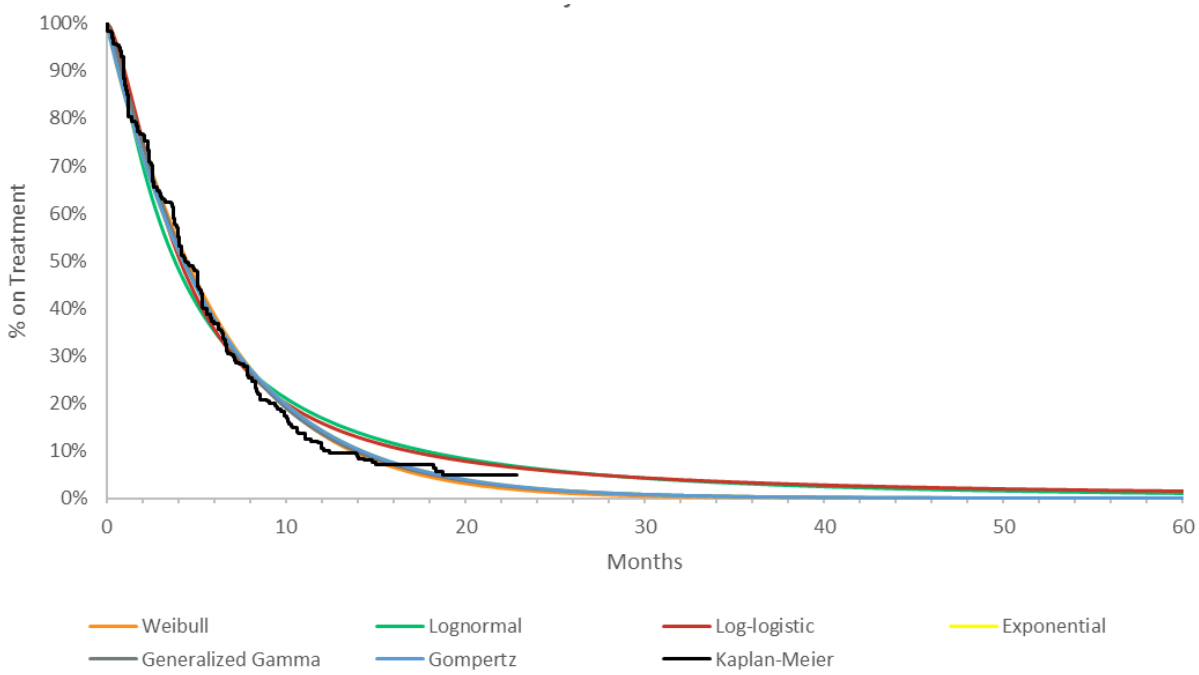


Figure 19. ASCENT ITT population SG TTD KM and parameterised curves (figure 38 of the CS)

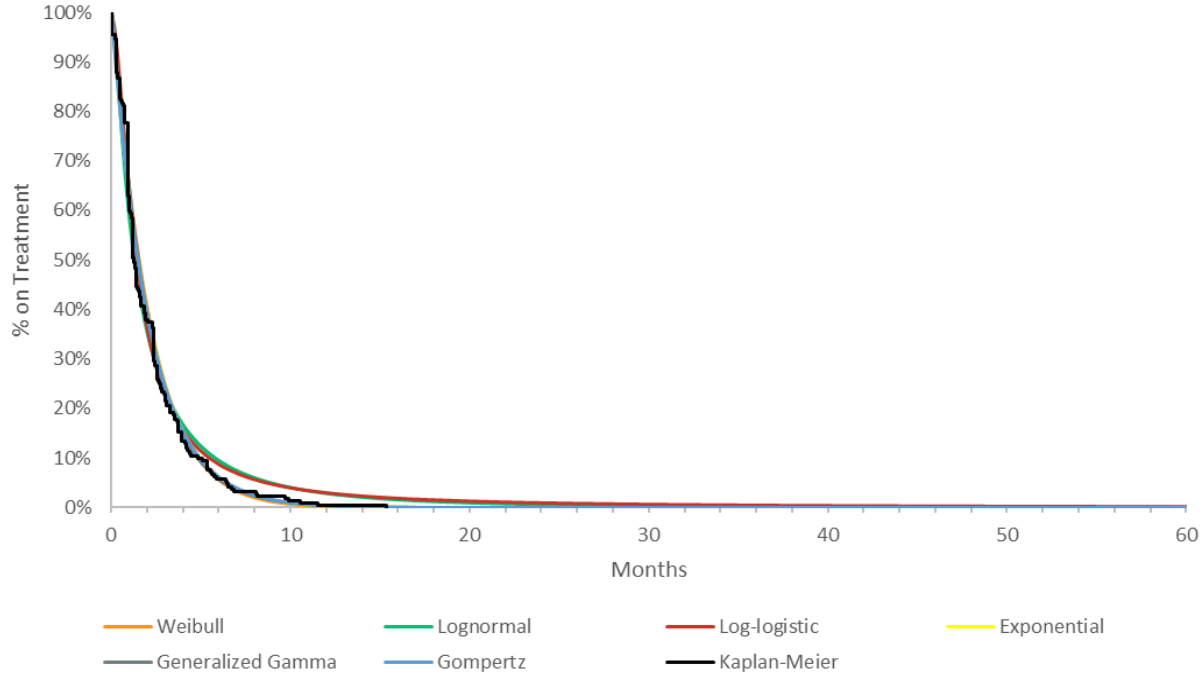


Figure 20. ASCENT ITT population TPC TTD KM and parameterised curves (figure 39 of the CS)

Table 30. Company ASCENT ITT TTD parameterised curves information criteria

Group	Distribution	WEI	LOGN	LOGL	EXPO	GGAM	GOMP
SG	Mean time on treatment	6.07	7.46	7.81	6.12	6.12	6.19
	AIC	1361.4	1390.8	1368.1	**1361.4**	1361.8	1363.4
	BIC	1368.5	1397.9	1375.2	1364.9	1372.4	1363.4
	Sum	2729.9	2788.7	2743.3	**2726.3**	2734.2	2726.8
TPC	Mean time on treatment	2.12	2.44	2.55	2.11	2.11	2.17
	AIC	790.6	823	803	**789.3**	790.9	791.2
	BIC	797.4	829.7	809.7	**792.7**	801.1	797.9
	Sum	1588	1652.7	1612.7	**1582**	1592	1589.1

Company's preferred model shown in **bold**

Abbreviations: AIC = Akaike's information criterion; BIC = Bayesian information criteria; EXPO = exponential; GGAM = generalised gamma; GOMP = Gompertz; LOGL = log-logistic; LOGN = log-normal; SG = Sacituzumab govetican; TPC = treatment of physician's choice; WEI = Weibull

4.9.7. Health related quality of life

4.9.7.1. Mapping of utilities

The model uses utility scores derived from a mapping analysis applied to EORTC QLQ-C30 scores generated from the ASCENT clinical trial. EORTC QLQ-C30 measurements obtained from the trial were mapped onto the EQ-5D-3L using the Longworth mapping algorithm.[40] No direct measurement of EQ5D data occurred in the ASCENT trial.

EORTC QLQ-C30 questionnaires were completed by all patients at baseline, on day 1 of each therapy cycle (until disease progression warranting discontinuation or unacceptable toxicity), i.e. every 3 weeks whilst on treatment, and at the final study visit (four weeks after the last dose of study drug or in event of premature study termination (CS, Document B, page 101). The last study visit was conducted within 4 weeks from end of treatment; therefore, the last measurement represents a reading obtained at the time when patients were just entering the post-treatment phase in the trial.

4.9.7.2. Summary of utility data

The company submission provides a graph (document B, figure 40, page 104) of utility values and CIs at each cycle (as per collection time points in the trial).

At baseline, mean utility was [redacted] The mean overall utility at baseline was [redacted] showing that there is no statistically significant difference in the distribution of utility values at baseline between treatments.

Utilities applied in the model are illustrated in Table 31 below (document B, table 30, page 106).

Essentially, the company Submission makes three claims about the value of utilities with SG:

3. The ASCENT trial shows that utility on treatment with SG is consistently higher than at baseline;

4. And that, all other things being equal, SG confers higher utility than TPC when patients are in the pre-progression state

5. The improvement with utility with SG during the treatment period carries over to the post-progression period undiminished, for the remainder lifetime for these patients.

The company submission (document B, page 106) states that with SG, patients achieve higher, durable response rates with SG vs. TPC driving better symptom control (e.g., pain).

These two claims translate into the model as higher utility applied in the pre-progression state with SG compared with TPC, by a factor of 0.084, in addition to a longer period spent in pre-progression, and a higher utility value with SG, by the same factor as in pre-progression, also applied in the post-progression state.

Table 31. Utility model including treatment arm and progression status as predictors

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]

CI: confidence interval; SE: standard error; SG: sacituzumab govetican; TPC: treatment of physician's choice

The submission does provide a summary of utility data from the literature, however there are no considerations regarding the comparability of data from ASCENT to other sources, nor a discussion of which utility data are the most robust. Table 32 below reports utility data used in other cost-effectiveness analyses in TNBC.

Table 32. Utility values in published studies (Document B, table 29, page 103)

Study	PFS	PD	Comment
TA423[2]	• Eribulin: 0.705 • TPC: 0.701	• 0.679 • 0.59 (revised estimate, in line with committee assumptions)	Utilities were obtained by mapping EORTC QLQ-C30 into EQ-5D using the Crott algorithm.[42] The committee commented that small decrease between stable disease and PD that was not plausible and noted that the Crott algorithm had been developed using data from people with locally advanced but not metastatic breast cancer, and who had good baseline health status.
TA639[1]	• Both treatment arms: 0.726 • Atezolizumab: 0.741 • TPC: 0.710	• 0.653	Utilities were derived by mapping EQ-5D-5L scores collected from the trial to the EQ-5D-3L using the Van Hout algorithm. Treatment was not a significant factor in the prediction of utility. A consistent utility value for PFS and PD was used across treatment arms in the base case analyses.
Lloyd, 2006[43]	• Baseline SD: 0.715	• 0.496	The ERG recommend using PD value from this study for eribulin in 3L NICE assessment (TA423).[2]

4.9.8. Resources and costs

The model calculates the costs of therapy with SG and TPC using a mixture of trial data and published sources. For both therapies, the following costs are modelled:

a) Drug acquisition costs, administration costs and cost of pharmacological concomitant therapies

b) Adverse events costs associated with treatment

c) Pre- and post-progression disease management costs, including monitoring costs

d) Costs of subsequent therapies, used after first progression

4.9.8.1. Drug acquisition costs

SG is administered as IV infusion on days 1 and 8 of a 3-weeks therapy cycle.

In the base case, the company assumes that the cost of SG is a weighted average of a waste-free cost and a cost with wastage, in the proportion of 50% each (with sensitivity analyses using 0% and 100%) on grounds that in clinical practice efforts are made to minimise waste, as well as using the argument of precedence in TA523 (also referenced in TA704).[44, 45]

The waste-free cost used in the base-case is calculated based on the label dose of at 10mg/kg, and the average weight for people in the ASCENT trial, restricted to the ex-US subgroup. This weight was [redacted] on average. One SG vial, containing 18ml, at a potency of 10mg/ml, costs £793 at list price [redacted]. The average patient requires [redacted] (assuming no wastage).

The cost of therapy with wastage is obtained from the weight distribution of ex-US patients in ASCENT, reported in Table 33.

Table 33. Weight distribution from ASCENT, Ex-US patients only (b)

Weight (Kg) (a)	Weight distribution (b)	Dose required for weight (c)	Vials		
[redacted]	[redacted]	[redacted]	1	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	2	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	3	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	4	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	5	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	6	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	7	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	8	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	9	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	10	[redacted]	[redacted]
					[redacted]

A non-parametric weight distribution was used for SG, taken directly from ASCENT. In the calculation of the cost of therapy using the weight distribution, an RDI of 94.2% is used as well, to represent the impact of dose reductions and adjustments.

To summarise, the cost of SG applied in the model is [redacted], the weighted average (in a proportion of 50% - 50%) of the cost with wastage [redacted], Table 33) and without wastage [redacted]).). Unlike for SG, the cost of TPC was calculated based on

a parametric (normal) distribution for BSA, obtained from the ASCENT trial considering only ex-US patients.

Drug	Dosing Regimen
Eribulin	Administered as an IV injection over 2 to 5 minutes at a dose of 1.4 mg/m^2 at North American sites and 1.23 mg/m^2 at European sites [1.23 mg/m^2 used in the model] on Days 1 and 8 of a 21-day cycle.
Vinorelbine	25 mg/m^2 was administered as a weekly IV injection over 6 to 10 minutes
Gemcitabine	1200 mg/m^2 was administered as an IV injection over 30 minutes on Days 1, 8 and 15 of a 28-day cycle
Capecitabine	1,250 mg/m^2 was orally administered in a 21-day cycle, twice daily for 2 weeks followed by 1-week rest period

4.9.8.2. Relative dose intensity (RDI) for SG

The value of 94.2% for the relative dose intensity (RDI) was applied in the model. The company submission does not report where this value was taken from nor how it was calculated or what was included. It is assumed that the RDI was taken directly from the ASCENT CSR, using the RDI calculated for drug exposure for safety and PK analysis (CSR, Section 9.7.11.1, page 50).

The ASCENT CSR definition for RDI is as follows:

- The RDI included patients who had a dose reduction and patients who had an infusion terminated prematurely;
- The delivered dosage was calculated as the delivered dose by body weight;
- Cumulative dosage was calculated as the sum of all doses delivered for all infusions;
- Total assigned doses were the number of doses that the patient was scheduled to receive, including skipped doses;
- RDI was the cumulative dosage (total volume administered) divided by the total assigned doses.

4.9.8.3. Drug acquisition costs applied in the model

The ERG amended a minor error in the cost calculation for vinorelbine (5, 10mg vials counted twice instead than 4 vials and 5 vials) which marginally changed the cost applied (Appendix 3).

The ERG also considered that the cost of capecitabine was incorrectly applied in the model as the cost of a fixed dose (1250mg), contrarily to indications reported in the capecitabine SMPC where the posology of capecitabine for the breast cancer indication is BSA-based.[46] Because capecitabine is only available in two strengths (150mg and 500mg), the dose per BSA is approximated, as detailed in the SMPC and Table 34 below. The ERG has modified model costing to apply the cost of capecitabine in line with SMCP dosing. It is worth noting that the dosing implies laborious costing, for very little difference in the overall model costing for TPC given the small proportion of women receiving this drug in the TPC comparator.

Table 34: BSA dosing, capecitabine (breast cancer indication)

Max BSA for dose	% Women in ASCENT, by max BSA	Dose required for BSA value	Required number of 150mg pills	Required number of 500mg pills	Duration 150mg pack (days)	Duration 500mg pack (days)	Resulting dose (capecitabine dose, mg, BID)
1.26	0.86%	1500	0	3	0	20	3000
1.38	2.73%	1650	1	3	30	20	3300
1.52	9.49%	1800	2	3	15	20	3600
1.66	19.74%	2000	0	4	0	15	4000
1.78	22.59%	2150	1	4	30	15	4300
1.92	23.80%	2300	2	4	15	15	4600
2.06	13.99%	2500	0	5	0	12	5000
2.18	4.88%	2650	1	5	30	12	5300
>2.18	1.91%	2800	2	5	15	12	5600

4.9.8.4. Post-progression therapies costs

The cost-effectiveness included the cost of post-progression therapies applied as a one-off cost at each cycle, based on the proportion of people who transitioned to the post-progression state at each model cycle. The company submission refers to this as ‘micro-costing’.

It was assumed that 70.5% and 66.4% of patients in the SG and TPC arms respectively received subsequent treatment. Table 35 summarises the type of

drugs, percent of the cohort assumed to receive each drug and duration of therapy courses, for both SG and TPC.

Table 35.Subsequent therapies applied in the model

Treatment	SG		TPC	
	% of cohort	Duration, weeks	% of cohort	Duration, weeks
Eribulin	66.00%	10.7	46.90%	12.9
Paclitaxel	0.70%	13.1	8.40%	17.8
Carboplatin	7.90%	9.9	5.30%	11.7
Gemcitabine				
Capecitabine	8.60%	11.4	14.00%	16.0
Epirubicin	8.20%	14.0	9.90%	12.0
Vinorelbine	8.60%	6.6	15.50%	10.1
Cyclophosphamide				
Total	100%		100%	

Based on clinical advice received, the company used the cost of epirubicin, and distribution and treatment duration based on observed doxorubicin use in ASCENT; Single-agent gemcitabine and cyclophosphamide were also set to zero.
Overall, the costs applied to subsequent therapies were £4,075.94 in the SG arm and £3,566.55 in the TPC arm.

4.9.8.5. Disease management, monitoring and AEs costs

The cost-effectiveness analysis also included costs of medical management, disease monitoring and terminal care. These costs are assigned as per cycle costs, and are made up by the cost of one oncologist visit, one GP visit and one clinical nurse specialist for both pre-and post-progression, in addition to 0.5 visit of a community nurse pre-progression and 0.68 post-progression (Table 36).

Table 36.Disease management frequency by heath state and unit cost

	Unit cost	Frequency per month (PFS)	Frequency per month (PD)
Oncologist visit	£200.20	1	1
GP visit (surgery)	£39.23	1	1
Clinical nurse specialist	£99.30	1	1
Community nurse	£43.46	0.5	0.68
Source	National Schedule of NHS Costs[47]; PSSRU: Unit Costs of Health and Social Care 2020[48]	NICE TA639[1]; NICE TA423[2]	

GP: general practitioner; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PD: progressed disease; PFS: progression-free survival; PSSRU: Personal Social Services Research Unit

Monitoring costs were costs (Table 37) associated with each comparator (as per respective monitoring requirements per label). Monitoring costs were applied per cycle.

Table 37: Monitoring frequency and unit costs

	CT scan	Full blood count	Liver function	Renal function	ECG	Source
Unit Cost	£120.55	£2.53	£9.60	£12.00	£61.80	National Schedule of NHS Costs 2019/2020[47]
Frequency per month - PFS						
SG	0.33	2.67	-	-	-	TRODELVY® SmPC[12]
TPC	0.33	2.67	0.33	0.33	0.33	Xeloda SmPC[49]; Halaven SmPC[50]; Gemcitabine SmPC[51]; Vinorelbine SmPC[52]
Frequency per month - PD						
All Treatments	0.33	2	0.33	0.33	0.33	Assumption

5. EVIDENCE REVIEW GROUP'S ADDITIONAL ANALYSES

5.1. Health-related quality of life measurement

The ERG disagrees with the arguments put forward in respect to utility values incorporated in the model.

The first argument is that the ASCENT trial utility data show that both SG and TPC may confer an improvement in utility as long as patients remain on treatment, however, according to the measurement taken at end of treatment (i.e. after the last treatment cycle before progression), the average overall utility scores for all patients is:

1. lower than at baseline for both SG and TPC;
2. numerically better with SG than with TPC, indicating a potentially slower decline with SG; and
3. when considering *mean change from baseline* for each patient *on-treatment*, rather than the crude score difference (as a more appropriate statistical analysis of utility data) between patients at any point in time, utility may not be different by treatment arm, considering that the mean utility at baseline was also numerically higher with SG

The second argument is that the evidence that improved utility with SG carries over undiminished after progression is not supported by any data. Finally, the methods used to calculate the potential advantage with SG compared with TPC during treatment are not transparently presented and cannot be verified.

5.2. Validation of treatment effect on utility applied in the model

The description of the methods used to analyse utility data was very basic and does not provide statistical details, therefore the analysis cannot be verified. The company states that an overall improvement in utility of 0.084 was obtained from a multivariate regression model, using mixed-effects linear regression with a random intercept for each patient to account for the clustering of multiple observations. The utility models investigated the potential effect on EQ-5D utilities of treatment arm and progression status (PD vs. PF), one at a time (univariate models) and in

combinations (multivariate' models) (Document B, page 104). The multivariate model includes treatment and pre-progression vs post-progression only, but no other predictor or stratifier. Univariate and multivariate models provide very close estimates for the effect of treatment and pre-post progression.

The description of the methods used to obtain such SG-treatment-specific improvement in utilities is extremely basic.

- The company provides no descriptive analyses of the utility data obtained from the ASCENT trial. As described in the clinical section, the EORTC QLQ trial data [3.2] were strongly affected by attrition (in excess of 30% of the initial sample in TPC but far lower in SG) with unexplained consequence. The company does not explore how attrition has affected the comparability of the two treatment arms in ASCENT and specifically, whether patient characteristics, prognostic factors or other treatment effect modifiers may have become unbalanced. In this case, the difference seen in utility values between SG and TPC may be in fact due not to treatment but to imbalances in important determinants of benefit between the SG and TPC groups.

- Regardless of attrition, another utility values may have become unbalanced because of reasons related with study procedures, that may or may not overlap with those for attrition. Utility values were included in the regression analysis if at least two measurements were collected during the trial, i.e. the analysis included only people who had at least two treatment cycles. Given that the first progression assessment occurred at 6 weeks, only a few patients would have received less than 2 cycles, therefore the number of patients excluded should be low. A relatively large number of women in TCP did not receive treatment, for reasons that are also not explained.

- Given that the two groups (SG, TCP) appear to have different mean utility at baseline, it is important to know whether different utility at baseline is the result of imbalances in baseline characteristics, due to attrition or other reasons, and specifically, whether adjusted analyses of utility values are warranted.

- The company provides no description of the functional specification for the model chosen; no information is given with regards to analyses on the data to ascertain the best model specification for trial utility data and model fit. It was assumed, in the absence of evidence to the contrary, that such assessments were not conducted.

- No information is provided on model predictors used to compare SG to TPC other than a description of separate OLS regressions (one regression with treatment as covariate, regardless of progression status, and one regression with progression status, PF vs PD regardless of treatment) vs a multiple regression model with a treatment term and a progression term;

    - Trial randomisation was stratified for US vs ex-US geography. It is unclear whether utilities were also adjusted for these proportions, as should be for any analyses when a trial uses randomisation strata

    - The ASCENT CSR clearly states that utility values were collected until patients were discontinued from treatment, it is unclear what data were used to estimate post-progression utilities and a treatment effect for SG. The ERGs interpretation is that utilities collected at the end of treatment visit were assumed to represent utilities post-progression for the entire lifetime of the model.

ERGs interpretation is that utilities collected at the end of treatment visit were assumed to represent utilities post-progression for the entire lifetime of the model.

5.3. Interpretation of utility data

It is difficult to estimate how attrition that occurred in the collection of the EORTC QLQ scores, and how this specifically affected utility estimates, in the absence of an assessment of missingness patterns or an acknowledgement that this factor may introduce a potentially large bias in the estimation of QLQ scores and utilities alike.

The company did not provide the number of utility data points available at each visit. Using sparse data, the ERG estimated that EORTC QLQ estimates may be missing for up to 30% of the TPC group, whilst for the SG group, this proportion is likely to be much lower, at around 10%.

From the summary of PRO data from ASCENT presented as supporting document to this submission,[17] EORTC-QLQ-C30 data were available at baseline for the largest majority of the ASCENT participants (SG: n=255, TPC, n=245), however at cycle 2, the numbers for TPC were substantially reduced, n=163. It is unclear how progression has impacted this number. However, according to the definition of data collected, a data point should also be available at the end of treatment. Overall, the denominators for end of treatment were n=172 for SG and n=152 for TPC.

Using estimated numbers at risk for TTD, provided as part of the clarification questions (Table 5, page 18) and data on cases with data for EORTC-QLQ-C30 (Table 14.2.6.1 Summary of EORTC-QLQ-C30 Scores by Visit Safety Population, taken from post-text Tables, ASCENT CSR) the ERG reconstructed a possible pattern of attrition, and noted that missingness seems much larger for TPC arm, and affected the data collection particularly in the early therapy cycles in ASCENT (Figure 21 below). To note, the % calculated in Figure 21 are with respect to people still on treatment (net of progression rates) and not to the ITT numbers.

Figure 21 Proportion of cases with EORTC-QLQ0C30 data over number at risk (TTD), ASCENT.

EORTC-QLQ-C30 scores were converted to EQ05D utilities using the Longworth algorithm.[40] [redacted] (document B, figure 40, page 104) provides indications around the change in utility at the end of each therapeutic cycle, when utility data were assessed for all patients remaining on treatment. The ERG calculated the possible numbers at risk, not provided in the company submission, from the proportion of people who had not progressed at each treatment cycle and that were still receiving treatment and therefore eligible to have an EORTC QLQ data point. These possible numbers at risk are derived from the economic model, using the probability of remaining in pre-progression at the corresponding therapy cycle.

The graph was used in the submission to argue that utility with SG is 'consistently higher than baseline' during follow-up. The comparison with the baseline average, however, is misleading, because at each utility assessment, people who remain on treatment are a (selected) subset of people who contributed values at baseline. In other words, the baseline values for people with values at, e.g., cycle 5, is not represented in the graph. It is not possible to conclude whether baseline values for people whose values are assessed at each cycle, was lower or higher than at each assessment.

Conversely, the last bars to the right, representing average utility at end of the last treatment cycle for patients in the study who had data[1], are, at least in principle and not accounting for missingness, directly comparable with the average utility at baseline for the same group of people. The comparison shows that utility scores for all people on treatment, including values for all people the progressed or not, on average, declined between first and last measurement from [redacted] C, with an overall decline of [redacted] ([redacted] 22). It is necessary however to caveat this argument with the possible high number of missing values.

[redacted] 22 [redacted]

[1] From the ASCENT CSR, "Patients were treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal, or death, whichever came first.
All patients who discontinued treatment underwent an end-of-study evaluation within 4 weeks" (page 20)

The graph also shows that, at each assessment visit, average utilities for people that remain on treatment remain constant. For people that stay in pre-progression for longest, average utilities increase slightly. This is not unexpected, resulting from likely selection of patients that respond for longer being those that retain good quality of life. Both trends are common for SG and TPC. However, a comparison remains difficult because the TPC group, has, on average, lower utilities at baseline, and it is possible that apparently higher crude average utilities with SG may in fact be compounded with higher utility at baseline.

The ERG recalculated a crude, weighted average of the mean difference between utility scores with SG and TPC, using numbers at risk obtained from the time to treatment discontinuation proportions from the model as estimated in the company's base case (scaled up to the number of people allocated to each treatment group in the trial), and using the values of the overall sample at baseline ( ) as reference for both TPC and to rescale the values of SG to a common base (see model for details).[53] The weighted average obtained is for TPC and for SG, implying a difference of between treatments. This value is presented in the company submission (0.084).

The ERG preference would be to have an appropriately developed regression model for utilities that would adjust for attrition and potential selection biases by means of an appropriate exploration of clinical prognostic factors and treatment modifiers.

This would also include the full exploration of the robustness of the evidence around treatment effect on the utility scale for SG.

In the absence of this model, the ERG's preferred approach would be to use the average utility for SG during treatment (0.710, as per original value proposed by the company and also equal to the value for TPC used in TA639), assume no treatment effect relative to TPC (utility of TPC on treatment=utility of SG on treatment) and equal utility for both drugs post-progression (0. 653) also taken from TA639.[1]

5.4. Model unit costs and cost estimation

5.4.1. Drug acquisition cost, SG and TPC

Initially, the company applied costs using a half cycle correction in the model. In general, this is not appropriate because the half cycle decreases the number of people who receive a drug dose at the start of the model. This proportion should be 100% in any model. In this particular model, the company correctly assigned 100% doses at the start of the model, but because of the half cycle correction, a second dose was added in the model at the first half cycle, effectively at day 3.5. This implies that the first 7 days cycle in the model implied 2 doses of therapy. The half-cycle correction was excluded from the costs (improving the ICER) although ultimately, the removal of costing by cycle made the half cycle correction not important.

The duration of the model cycle is one week, whilst the duration of therapy cycles for any of the drugs considered in the model extends over more than one model cycle (**Error! Reference source not found.** Table 38 below). Drug costs in the model are calculated based on therapeutic cycle (i.e., for SG, the cost of one cycle is the cost of two IV sessions at the appropriate dose as per patient population etc..); the cost of the therapeutic cycle is then split by 3 (4, for capecitabine) and applied as a cycle cost in the model (for example, see Table 38)

Table 38. Study drugs, administration schedule

Drug	Therapy cycle	Costs by cycle
SG	21 days	Days 1 and 8 Cycle cost: 1,2 every 3
Eribulin	21 days	Days 1 and 8 Cycle cost: 1,2 every 3

Vinorelbine	7 days	Day 1 (one weekly infusion)
Gemcitabine	28 days	Days 1, 8 and 15 Cycle 1,2,3 every 4
Capecitabine	21 days	Week 1,2 Cycle cost: 1,2 every 3

A very simple example (Table 39) will clarify why this approach is incorrect and leads to a systematic underestimation of drug costs in the model. If we consider the total cost of treating 100 patients with a drug at a cost of £300 per dose: the total cost is £300x100 = £30,000. Assuming that this drug is delivered as one dose every 3 weeks, and that patients die at a rate of 10% per week, the computation of the cost of the drug, using a weekly cycle and applying a third of the cost (£100) to each cycle will be £27,100, which clearly differs from the real cost, £30,000 substantially underestimating the total cost of therapy.

Table 39. Calculation of drug costs based on split costs per therapy cycle

Cycle	On treatment	Dead	Cost per cycle
1	100	0	£10,000
2	90	10	£9,000
3	81	19	£8,100
Total			£27,100

The underestimation is systematic, for all drugs, and accrues throughout the model, beyond the first 3 cycles used in this example. The reason for the underestimation is that the costs are not accrued by people who leave the treatment state over time, because of death or progression or transition. A similar bias accrues for all costs that are applied in conjunction with the treatment (for example, administration costs).

Cycle costs were applied to the model supporting the cost-effectiveness analysis in this submission. The ERG amended the costs applied in the model to take into account the correct state occupancy at each infusion and the time gaps between an infusion and another. For SG, the entire cost of one infusion was applied to week 1 and 2 of every 3 weeks period in the model; the same approach was applied to administration costs. For TPC, the cost of eribulin and capecitabine were applied for 2 weeks every 3 weeks and the cost of gemcitabine was applied for week 1,2,3, out of 4 weeks. The cost of vinorelbine was applied as a cycle cost (1 infusion per week).

Although concomitant drug costs represent a very small fraction of therapy costs, these costs were also applied (to both comparators) based on the method used for infusions, for all drugs delivered with infusions (i.e., antiemetics and antinauseants) and as cycle cost for the entire alive cohort, for drugs taken continuously (i.e., corticosteroids, antihistamines etc..).

5.4.2. Weight / BSA based drug acquisition cost, SG and TPC

The model used the weight distribution from ASCENT, limited to the ex-US patient group to calculate the weight-based costs of SG. This choice is, in theory, appropriate, as long as the weight distribution is used for all model comparators. At the same time, the model used a parametric distribution calculated from mean and standard deviation of weight from the ASCENT trial for TPC. Because the non-parametric distribution had a lower average than the mean weight for the same group of women, the drug cost so calculated [redacted] introduced a bias in the model in favour of SG.

In addition, the model uses hard-coded values and therefore the SG weight distribution does not adjust when other parameters are changed.

For these reasons, the ERG replaced the ASCENT non parametric ex-US distribution for SG with a normal parametric distribution for weight, in common for SG and TPC, using the model average weight and SD [redacted] ([redacted] 23).

[redacted] 23

[redacted]

5.4.3. RDI, SG

There are three elements to RDI:

1. Skipped doses
2. Infusions terminated prematurely
3. Doses assigned as a proportion of doses as described in the label.

From a viewpoint of clinical 'exposure', all three are part of the RDI because they make up the total quantity of drug that the patient has been exposed to.
However, the 'exposure' RDI is not a valid measure of the RDI required for costing, and specifically, it is an overestimation of the reduction in costs of therapy related with dose adjustments, because infusions terminated prematurely and at reduced doses do not necessarily have implications in terms of reduced number of vials to deliver the therapy:

1. In the case of an infusion terminated prematurely, the amount of drug prepared but not delivered is a cost, in the form of wastage: wastage is not included in the PK definition of RDI;
2. Infusions at reduced doses with respect to the label dose (10mg/km) should be subtracted from the cost only if the dose reduction corresponds to a change in the number or type of vials required for that infusion
3. Skipped or delayed doses are generally not a cost, therefore should be subtracted from total cost.

The company uses the 'exposure' RDI inappropriately to decrease the cost of therapy. As part of regulatory requirements for conducting a clinical trial, data collection is mandated for dates and doses delivered for the investigational drug, by session, for all patients in the trial. A correct RDI pertinent for costing can be easily calculated from such datasets.
In the absence of evidence of a correctly calculated RD, the RDI applied in the model should be 100%.
The corresponding drug costs with 100% RDI are, respectively, [redacted] (no wastage) and [redacted] (with wastage) resulting in a cost applied in the model of [redacted] (Table 40). Because the weight distribution from ASCENT is hard-coded in the model, and takes into account the original RDI (i.e. with a reduced RDI, the distribution is coded for higher weight brackets), a change in the RDI costs is not

propagated through. The ERG removed this constraint using the normal parametric distribution for weight.

Table 40. Study drugs, unit costs and cost per dose, without wastage and assuming 50% wastage

Treatment	Dose/Vial Concentration	Pack Size/Vial Volume	Cost per Pack/Vial	Cost per Dose (no wastage)	Cost per Dose (50% wastage)	Administration route	Source
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	
Eribulin	0.44 mg/ml	2 ml 3ml	£361.00 £541.50	£883.95	£1,057.54	IV	MIMS[54]
Vinorelbine	10 mg/ml	1 ml 5ml	£5.25 £15.77	£13.81	£17.57	IV	eMIT[55]
Gemcitabine	100 mg/ml	10 ml 20ml	£10.20 £20.66	£21.44	£27.13	IV	
Capecitabine	150 mg 500mg	60 120	£4.28 £25.02	£0.91	£0.91	Oral	

5.4.4. Drug wastage

Although it is customary to use vial sharing in clinical practice, this practice should not be used to decrease the cost of therapy.

The UK Pharmaceutical Services Committee (PSNC) states that, as per the Pharmaceutical Services Regulations, when a prescription is filled in, only the original pack should be supplied (or a multiple).[56] All drugs classified as dispensed via 'special containers' should be supplied as full pack. For reimbursement, the special container rules are automatically applied, implying that reimbursement will be set at nearest pack or combination of packs necessary to fulfil the dose. For this reason, even if vials may be shared at the point of delivery, the NHS reimbursement is always set at the nearest full pack for a dose that requires the use of a fraction of the pack (or combinations or multiple packs). The assumption of vial sharing in fact is from the hospital perspective, as the hospital may support lower costs to deliver a dose than the full pack, but not the NHS perspective as the NHS will always reimburse the full pack.

For this reason, the ERG set wastage to 100% (Table 41) as any amount wasted does not translate into a reduction in the acquisition cost to the NHS.

Table 41. Study drugs, cost per dose, without wastage and assuming 50% or 100% wastage

Treatment	Model Cost per Dose (no wastage)	Model Cost per Dose (100% wastage)	Model Cost per Dose (50% wastage)	Cost per Treatment Cycle (100% wastage)	Cost per Model Cycle (100% wastage)	Cost per Treatment Cycle (50% wastage)	Cost per Model Cycle (50% wastage)
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eribulin	£883.95	£1,057.54	£970.75	£2,115.07	£705.02	£1,941.49	£647.16
Vinorelbine	£13.81	£17.57	£15.69	£17.57	£17.57	£15.69	£15.69
Gemcitabine	£21.44	£27.13	£24.29	£81.40	£20.35	£72.86	£18.22
Capecitabine	£0.91	£0.91	£0.91	£25.57	£8.52	£25.57	£8.52

5.4.5. Post-progression therapies costs

The model used hard-coded values for post-progression therapies. This was amended, to be able to vary the proportions assumed for the various therapies.

With regards to the method used to incorporate subsequent therapies, whilst in principle the 'micro-costing' method may not be appropriate because it inflates post-progression costs (because it assumes that anyone receiving post-progression costs will stay alive for a set time), it is likely that on average, the calculation bias will be small, given the very short time that these patients spend in post-progression before death.

However, the essential condition for the acceptability of this method is that the average costs applied are pertinent with respect to survival in the model population. The ERG believe that the post-progression costs applied in the model are not consistent with the time left in the model before death.

- The duration of post-progression treatment applied to SG (10.6 weeks on average) was generally shorter than that applied to TPC (13.2 weeks on average). This is implausible, because not only do patients with SG, on average, live longer in the post-progression state, but also, the duration used for TPC subsumes that people in this arm are treated to the very end of life, whilst in SG, therapies are interrupted well before time of death.

From the clinical efficacy section (Table 9: Summary of efficacy results for ASCENT in ITT population (IMMU-132-05), page 43), people treated with SG reported a median PFS of 5.6 months and OS of 12.1 months, with 6.5 months between progression and death, whilst people on TPC had a median PFS of 1.7 and median survival of 6.7 months, with 5 months between progression and death. The model

already takes into account near-death costs and it is plausible to assume that patients would receive no therapy for the few weeks before death.

Assuming 3 weeks therapy-free, the total number of weeks left after progression when patients could receive therapy is 25.2 for SG and 18.7 for TPC.

The model therefore assumes that paclitaxel and capecitabine costs are accrued by approximately 16% of the TPC cohort at 5.7 months. At this time, the number of people alive in the TPC arm of the model is approximately 49%; therefore, subsequent therapies are assumed to be given to 30% of people still alive at median OS.

In contrast, in the SG arm of the model, the proportion still on treatment (at the time of longest therapy, 14 weeks after PFS, i.e. at 42 weeks) is 9%, whilst at this time the population alive is 58%, translating in a proportion of people of 15% still in treatment. At median OS (12 months) no one in the SG cohort receives subsequent therapies.

Therefore, the ERG recalculated subsequent therapy costs assuming that subsequent therapies are given for half the time post-progression and before death, for both arms. This translates in post-progression costs applied for 12.5 weeks in SG and 9.5 weeks in TPC.

The company submission states that ‘eribulin use was expected to be lower after TPC than SG, given that patients receiving prior eribulin were not likely to be rechallenged with eribulin in a subsequent line of therapy’ (document B, page 112). The ERG agrees in principle; however, it is important to note that this principle applies to any treatment line where patients may have received eribulin.

From the CSR [Table 14.1.6.1], a proportion of 32.4% of people who were allocated to TPC in the trial had received eribulin in prior treatments. In the ASCENT clinical trial, participants were assigned to one of the possible TPC study treatments before randomisation, based on clinical appropriateness; this was the treatment they would receive if, later randomised to TPC. It is plausible to think that people who had prior exposure to eribulin would be assigned to vinorelbine, gemcitabine or capecitabine, therefore the overall proportion of people exposed to eribulin in ASCENT is 85.5% (32.4% prior to the trial and 53.1% in the trial), approximately 15% of the cohort is

eribulin-naïve, which makes the value of 46.9% for post-progression therapies in TCP not plausible.

On the contrary, the proportion of people in SG assumed to receive eribulin post-progression is 66%, also the proportion of people who did not receive eribulin prior to the trial and therefore plausible.

The preferred distribution of subsequent drugs, by drug type, applied in the model, is illustrated in Table 42

Table 42. ERG preferred distribution of subsequent therapies

	Company base case				ERG preferred distribution			
Treatment	**SG**		**TPC**		**SG**		**TPC**	
	% of cohort	**Duration, weeks**	**% of cohort**	**Duration, weeks**	**% of cohort**	**Duration, weeks**	**% of cohort**	**Duration, weeks**
Eribulin	66.00%	10.7	46.90%	12.9	66.00%	12.5	14.00%	9.5
Paclitaxel	0.70%	13.1	8.40%	17.8	0.70%	12.5	0.7%	9.5
Carboplatin	7.90%	9.9	5.30%	11.7	7.90%	12.5	7.90%	9.5
Gemcitabine								
Capecitabine	8.60%	11.4	14.00%	16.0	8.60%	12.5	26.8%	9.5
Epirubicin	8.20%	14.0	9.90%	12.0	8.20%	12.5	22.6%	9.5
Vinorelbine	8.60%	6.6	15.50%	10.1	8.60%	12.5	28%	9.5
Cyclophosphamide								
Total	100%		100%		100%		100%	

5.5. ERG's preferred assumptions

The ERG's preferred key assumptions are listed here below. The preferred parametric distributions used for extrapolations are the Weibull distribution for SG, which provides the best fit, and the generalised gamma for TPC.

In the absence of robust demonstration that SG is associated with an independent treatment effect on utility scores, the same utility values should be used during treatment with SG or TPC, consistently with prior appraisals (TA639) where no treatment effect was demonstrated on the utility scale.[1]

Post-progression utilities should be the same for SG and TPC, ss these data were not collected in the ASCENT trial. Post-progression utilities should be the same as those used in TA639.[1]

Post-progression therapies should be applied for half the period after progression, based on time left to live for each comparator. The proportion of eribulin in TPC should be equal to 14% (similar to data from ASCENT and equal to the maximum proportion of women that would be eribulin-naïve at the point of progression in the ASCENT trial.

Therapy costs should be applied in the model at 'transitions' instead than by state; the cost of capecitabine should be calculated by BSA.

In the absence of a correctly quantified RDI, the RDI has been reset to 100%.

The relevant RDI, with all cost components accounted for, should be recalculated and RDI calculation methods should be provided and thoroughly described.

Because all drugs used in theis cost-effectiveness analysis are reimbursed as full packs, wastage should not be used to reduce acquisition costs in the analysis. The ERG prefers wastage to be set at 100% to this effect.

To calculate the acquisition cost of SG and TPC, the ERG preferred weight distribution is equal for SG and TPC and is a parametric normal distribution with mean weight and SD taken from (ex-US) women's data from ASCENT.

Table 43. ERG's revised ICERs, QC and corrections

Preferred assumption	Section in ERG report	Cumulative ICER £/QALY
Company base case		£49,651
Correction of error in Vinorelbine cost calculation	5.4.1	£49,673
No half cycle correction for drug acquisition cost, administration cost and concomitant drugs cost	5.4.1	£49,202
Costing using correct treatment cycles incorporation	5.4.1	£50,053

Table 44. ERG's preferred model assumptions

Scenario	Incremental cost	Incremental QALYs	ICER
Company's revised base case	[redacted]	[redacted]	£50,070
RDI set to 100%, both SG and TPC			£50,883
Patients weight distribution equal for SG and TPC, based on normal distribution	[redacted]	[redacted]	£51,878
Drug wastage set to full wastage	[redacted]	[redacted]	£54,118
Cost of subsequent therapies, eribulin assumed for eribulin naïve patients for both comparators	[redacted]	[redacted]	£59,125
Utility values, no utility difference for post-progression therapies (SG and TPC equal utility)	[redacted]	[redacted]	£66,334
Utility values, no SG treatment effect on utility during treatment	[redacted]	[redacted]	£70,021
OS distributions, using joint generalised gamma	[redacted]	[redacted]	£79,131
OS distributions, using Weibull (SG) and generalised gamma (TPC)	[redacted]	[redacted]	£88,546
ERG's preferred base case	[redacted]	[redacted]	£88,546

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Appendix 1. ERG assessment of risks of bias of the CS systematic review

ROBIS domain, and signalling questions	**ERG's assessment of whether criteria met, with comments**
1: Study eligibility criteria	
1.1 Did the review adhere to pre-defined objectives and eligibility criteria?	**Probably yes.** Eligibility criteria are defined in table 6, appendix D. Inclusion and exclusion criteria were applied to the search strategy. Literature searches were initially run

	20 January 2021 and updated 7 July 2021.
1.2 Were the eligibility criteria appropriate for the review question?	**Yes**. The objective of the submission was to evaluate SG with TPC for progression-free survival (PFS) in patients with locally advanced TNBC or mTNBC with ≤2 prior therapies, including ≤1 prior therapy at an earlier disease stage. All areas were covered within the criteria reported.
1.3 Were eligibility criteria unambiguous?	**Yes.** All eligibility criteria clear in table 6, appendix D.
1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate?	**Yes.** Restrictions were applied to the population, interventions, comparators, study design and publication type. The ERG deemed All restrictions appropriate.
1.5 Were any restrictions in eligibility criteria based on sources of information appropriate?	**Probably yes.** The search spanned the past 21 years excluding articles published before 2000 (section D1.1.1., appendix D). Information regarding the publication status and format is provided in table 6, appendix 5. Studies were excluded for not reporting on intervention, comparator and outcomes of interest. Studies presented in Non-English language were excluded. Observational studies were excluded however were to be examined by a separate targeted literature review.
Domain 1 risk of bias	**Low**
2: Identification and selection of studies	
2.1 Did the search include an appropriate range of databases/ electronic sources for published and unpublished reports?	**Yes**. Searches were conducted in an appropriate set of bibliographic databases (MEDLINE, MEDLINE In-Process, EMBASE, CDSR, Cochrane Library).
2.2 Were methods additional to database searching used to identify relevant reports?	**Yes**. Supplementary searches of conferences (published in 2018 and onwards) and a clinical trial register were conducted as well as hand searching referencing lists of systematic literature reviews.
2.3 Were the terms and structure of the search strategy likely to retrieve as many eligible studies as possible?	**Probably yes**. Detailed search strategy provided (CS Appendix D, Tables 1 – 3). Suitable terms for the condition, treatment and study types were included and combined appropriately. Terms for NICE comparators plus thirteen additional treatments were included.
2.4 Were restrictions based on date, publication format, or language appropriate?	**Yes**. Company restricted the search retrospectively to 2000 onwards. Language was restricted to English. The restrictions applied to publication format were appropriate.

2.5 Were efforts made to minimise errors in selection of studies?	**Probably yes.** Appropriate study selection by two independent reviewers, with discrepancies resolved by a third reviewer. No information was provided on reviewers screening titles and abstracts, and data extraction for clinical studies. However, methods for cost effectiveness and HRQoL studies titles and abstracts were screened by one reviewer with a second reviewer screening approximately 20% of the identified studies in parallel, referring any disputes to a third reviewer. Full texts were then screened by one reviewer with rejected studies reviewed by a second reviewer and discrepancies were resolved by a third reviewer. Thus, it may be that the same methods were used for clinical effectiveness studies but not described. The PICO and reasons for exclusion are clearly presented (Table 17 and Figure 3, appendix D).
Domain 2 risk of bias	**Low**
3: Data collection and study appraisal	
3.1 Were efforts made to minimise error in data collection?	**Partially**. No information was provided about data extraction for clinical-effectiveness studies. Data extraction for cost-effectiveness studies and HRQoL studies were undertaken by one reviewer which was independently validated by a second reviewer. It may be that the same methods were used for clinical effectiveness studies but not described.
3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?	**Probably no**. Extensive information about the ASCENT trial is presented in the CS (Pages 21-67 and appendix D). No further information is provided regarding the remaining studies included in the SLR. Details were provided on four studies included in feasibility analysis in table 10 (appendix D).
3.3 Were all relevant study results collected for use in the synthesis?	**Probably no**. Ten studies were included for the SLR (figure 1, appendix D). Extensive information about the ASCENT trial is presented in the CS (Pages 21-67 and appendix D). No further information is provided regarding the remaining 9 included studies named in table 7 (appendix D). Details were provided on four studies included in feasibility analysis in table 10 (appendix D).
3.4 Was risk of bias (or methodological quality) formally	**Partially**. The company have assessed risk of bias in the one included trial, ASCENT (IMMU-132-05) according to

assessed using appropriate criteria?	latest NICE guidance which recommends the Cochrane risk of bias tool as the preferred checklist[10] (section B.2.5, p109 CS). However, some domains from the checklist were not reported including subsections for performance bias, attrition bias and detection bias. In addition, signalling questions (rather than domains) were rated for risk of bias. No other studies were assessed for risk of bias.
3.5 Were efforts made to minimise error in risk of bias assessment?	**Probably No.** The company does not state if the risk of bias assessment was performed by two independent reviewers.
Domain 3 risk of bias	**Some risk of bias**
4: Synthesis and findings	
4.1 Did the synthesis include all studies that it should?	**Yes.** The search queries are suggestive of a very sensitive search which would mean a very low probability that potentially relevant studies were missed.
4.2 Were all predefined analyses followed or departures explained?	**Yes.** Section B.2.8 Document B
4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?	**Yes.** Following a systematic literature review four trials met the inclusion criteria. However, NMA was not feasible due to heterogeneity in the distribution of chemotherapies used in the TPC arms which could not be combined into a single node to connect to the network. Thus, a narrative synthesis was appropriately conducted.
4.4 Was between-studies variation (heterogeneity) minimal or addressed in the synthesis?	**Yes.** Variation between studies was discussed in the considerations of statistical synthesis such as NMA and PAIC. Heterogeneity led to narrative synthesis being conducted.
4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?	Not applicable due to narrative synthesis.
Domain 4 risk of bias	**Low**
Overall risk of bias in the review	

Appendix 2. ERG quality assessment of ASCENT (IMMU-132-05)[10]

NICE checklist item	*CS judgment and rationale*	*ERG judgment and rationale*
Selection bias		
Was randomization carried out appropriately?	Yes- low RoB Yes, patients were randomised using IWRS. Randomisation was stratified by the number of prior treatments for advanced	Yes- low RoB Yes, patients were randomly assigned in a 1:1 ratio by interactive web-based response system (IWRS) to receive sacituzumab govitecan or treatment of physician's choice (TPC). Patients

	disease, geographic location, and known brain metastases at baseline.	were stratified at randomization according to the 1) number of previous treatments (2 to 3 vs. >3), 2) presence of known brain metastases at study entry (yes vs. no), and 3) North America vs. rest of the world. Metastatic disease was documented by computed tomography (CT) or magnetic resonance imaging (MRI) per RECIST 1.1. Screening for brain metastasis was not mandatory.[10] The ERG finds this allocation sequence appropriate and of low bias.
Was the concealment of treatment allocation adequate?	Yes- low RoB, as the blinded IRC assessed the primary PFS endpoint ASCENT was open label. Blinding of site personnel was not possible due to differences in treatment administration; however, potential bias was minimised by blinding the IRC, Sponsor's and contract research organisation's statisticians, and all medical monitors.	Yes- low RoB Patients were randomised using IWRS.
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes- low RoB There were no differences between the groups in demographics, stratification factors or disease characteristics at baseline.	Yes- low RoB There were no differences between the groups in demographics, stratification factors or disease characteristics at baseline for patients without brain metastases.
Overall rating of selection bias	NR	Low
Performance bias		
The comparison groups received the same care apart from the intervention(s) studied	NR	Yes – Low RoB Both groups were monitored for adverse events (Table 3, [10]). CT/MRI scans were obtained at baseline, every 6 weeks for 36 weeks, and then every 9 weeks until disease progression.
Participants receiving care were kept 'blind' to treatment allocation	NR	No - High RoB ASCENT was an open label study thus patients are aware of the treatment they were given.
Individuals administering care were kept 'blind' to treatment allocation	Low RoB No, ASCENT was open label, and only outcome assessors were blinded.	No ASCENT was an open label study
Overall rating of performance bias	NR	Some concern
Attrition bias		

All groups were followed up for an equal length of time (or analysis was adjusted to allow for differences in length of follow-up)	NR	Yes – Low RoB Data cut off was March 11, 2020 for patients randomised. The overall median follow-up was 17.7 months (22.87 months for SG and 15.34 months for TPC).
The groups were comparable for treatment completion (that is, there were no important or systematic differences between groups in terms of those who did not complete treatment)	High RoB A larger percentage of patients in the TPC group compared with the SG group were randomised but not treated (14.5% and 3.4%, respectively). Communication with the study sites suggest that some patients in the TPC group elected not to participate in the study upon not being randomised to the SG group.	No – High RoB A smaller percentage of patients in the SG group, compared with the TPC group, were randomised but not treated (3.4% and 14.5%, respectively).
The groups were comparable with respect to the availability of outcome data (that is, there were no important or systematic differences between groups in terms of those for whom outcome data were not available).	NR	Yes – High RoB Outcome data differed between groups for QLQ-30.
Overall rating attrition bias	NR	High RoB
Detection bias		
The study had an appropriate length of follow-up	NR	Yes- low RoB The study ran from November 7, 2017 to March 11, 2020 (2 years, 4 months and 4 days).[10, 15] In patients without brain metastases the median follow-up time from patients' randomization date was 17.7 months (range, 5.8 to 28.1). Only the PFS follow-up time is stated for the full population (4.8 months (95% CI, 4.1 to 5.8)) [10].
The study used a precise definition of outcome	NR	Yes- low RoB The outcomes of interest were defined.
A valid and reliable method was used to determine the outcome	NR	Yes- low RoB Tumour response was assessed by computed tomography (CT) or magnetic resonance imaging (MRI). All available CT or MRI scans were reviewed using modified Response Evaluation Criteria in Solid Tumors (RECIST)

		version 1.1 to assess disease progression and response to treatment. The decision to discontinue a patient for progressive disease (PD) was made by the investigator. Patients were treated until progression requiring discontinuation of further treatment, unacceptable toxicity, study withdrawal or death, whichever came first. In the ASCENT clinical trial, EORTC QLQ-C30 questionnaires were completed by all patients. Preference-based measures such as the EQ-5D were not administered in the ASCENT study. In accordance with NICE guidance, which recommends EQ-5D as a preferred elicitation tool, mapping from the EORTC QLQ-C30 to EQ-5D was performed, using the Longworth mapping algorithm, to estimate utilities for patients enrolled in the ASCENT clinical trial.
Investigators were kept 'blind' to participants' exposure to the intervention	Low, as the blinded IRC assessed the primary PFS endpoint No, ASCENT was open label, and only outcome assessors were blinded.	Some concern ASCENT was an open label study thus both health providers were aware of the drug or treatment being given. The primary outcome (PFS) was measured by blinded Independent Review Committee (IRC).[10, 15] The ERG agree with the company's rating of the 'concealment of treatment allocation' domain as 'low RoB' for progression-free survival (PFS). High RoB is present for patient reported outcomes (PRO). Being unblinded to their treatment patients are likely to be biased in reporting their outcomes in relation to their allocated treatment.
Investigators were kept 'blind' to other important confounding and prognostic factors	NR	No ASCENT was an open label study.[10, 15]
Overall rating detection bias	NR	Some concern Open label trial. The sponsor, Immunomedics, designed the trial and gathered the data. Data analysis was performed by Veristat and by authors who are employed by Immunomedics.
Questions listed on the company submission, recommended by NICE		
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Yes- low RoB "All pre-specified outcomes reported"	Yes- high RoB The ERG found listed primary, secondary, and exploratory objectives and outcomes reported. However, TTD was measured but not reported. The data was provided by the company on request

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Low RoB Low, as the primary endpoint was also assessed in the ITT population with supportive results. All patients who were randomised, including 61 patients with brain metastasis at baseline were included in the ITT population. This population was used for efficacy analyses after the primary endpoint was tested in the primary analysis population.	Yes - Low RoB ITT analysis was conducted. All patients who were randomized (including 61 patients with brain metastasis at baseline), with patients analyzed based on randomized treatment assignment. This population was used for efficacy analyses after the primary endpoint was tested in the primary analysis population of patients without brain metastases' (CSR table 12).

Appendix 3. Model QC, redundancy and error corrections

The ERG did not conduct a formal QC of the model as this is out of scope. Nevertheless, some errors were found in the model and amended (as per costing tables below, sheet Drug Cost Calcs, cell I82). This was an error in the calculation of the TPC costs and is now resolved.

Furthermore, the company added a Section (3.9) to Document B detailing some actions intending to technically validate the model file. The ERG found inconsistencies and redundancy in the model that could generate potential errors.

The model is a reduced version of a larger model with several comparators, parameters for which have not been taken out of the model altogether but remain as errors.

The model has VBA code to hide and unhide rows and columns which cause sheets in the file to expand or collapse automatically every time the file is saved. We have cleared some of this redundancy but the potential remains for unpredictable errors resulting from it.
Some of the parameters are incorporated in the model as 'lists' making it not possible to test alternatives to the original values. Where necessary, the ERG has removed lists and connected single parameters to the relevant cells.

The model, finally, includes several options that are a residual of previous drop-down functions. It is unclear which options are supposed to be used in the Appraisal and which are not.
The ERG has reinstated some of these functions as required but it is unclear whether the model contains potential bugs resulting from non-used content.

	Dose	Package size 1	Package size 2	Price 1	Price 2			
Vinorelbine	25 mg/m2	10 mg	50 mg	£5.25	£15.77			
# Vials min unit	Max BSA for dose	Cumulative	Per dose	Dose required for BSA value	Total cost for BSA value	# Dose 1	# Dose 2	Resulting dose
-								
1	0.40	0.00%	0.00%	10	£5.25	1	0	10
2	0.80	0.00%	0.00%	20	£10.51	2	0	20
3	1.20	0.38%	0.38%	30	£15.76	3	0	30
4	2.00	88.52%	88.14%	50	£26.27	5	0	50
5	2.00	88.52%	0.00%	50	£15.77	0	1	50
6	2.40	99.91%	11.40%	60	£21.02	1	1	60
7	2.80	100.00%	0.09%	70	£26.28	2	1	70
8	3.20	100.00%	0.00%	80	£31.53	3	1	80
9	3.60	100.00%	0.00%	90	£36.79	4	1	90
				Per Dose Cost (vial sharing not allowed/include	£25.63			

	Dose	Package size 1	Package size 2	Price 1	Price 2
Vinorelbine	25 mg/m2	10 mg	50 mg	£5.25	£15.77

# Vials min unit	Max BSA for dose	Cumulative	Per dose	Dose required for BSA value	Total cost for BSA value	# Dose 1	# Dose 2	Resulting dose
-								
1	0.40	0.00%	0.00%	10	£5.25	1	0	10
2	0.80	0.00%	0.00%	20	£10.51	2	0	20
3	1.20	0.38%	0.38%	30	£15.76	3	0	30
4	1.60	23.11%	22.74%	40	£21.02	4	0	40
5	2.00	88.52%	65.40%	50	£15.77	0	1	50
6	2.40	99.91%	11.40%	60	£21.02	1	1	60
7	2.80	100.00%	0.09%	70	£26.28	2	1	70
8	3.20	100.00%	0.00%	80	£31.53	3	1	80
9	3.60	100.00%	0.00%	90	£36.79	4	1	90
		Per Dose Cost (vial sharing not allowed/include			**£17.57**			

National Institute for Health and Care Excellence

Centre for Health Technology Evaluation

ERG report – factual accuracy check and confidential information check

Sacituzumab govitecan for treating metastatic or unresectable triple-negative breast cancer after 2 or more therapies [ID3942]

'*Data owners will be asked to check that confidential information is correctly marked in documents created by others in the technology appraisal process before release; for example, the technical report and ERG report.*' (Section 3.1.29, Guide to the processes of technology appraisals).

You are asked to check the ERG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on insert date** using the below comments table.

All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and separately highlight information that is submitted as 'commercial in confidence' in turquoise, all information submitted as 'academic in confidence' in yellow, and all information submitted as 'depersonalised data' in pink.

Issue 1 Inaccuracies related to conduct of the ASCENT trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Early stopping of the Trial • Section 1.4; Issue 7; p18 Text: "Caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment" • Section 3.2.6; p63 Text: "The caution should be exercised as the ASCENT trial was stopped early for showing benefits of the SG treatment. Evidence show that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment." • Section 3.6.1; p82 Text: "The caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment"	We would ask that this issue and associated paragraphs be removed from the ERG report as they are misleading	ASCENT was stopped after it was fully recruited, according to a robust statistical plan with a high number of survival events having taken place and is by the ERG's own estimate mature data since medians have been exceeded across all endpoints in both arms. In addition, the median follow-up was 17.7 months, which is a significant period of time in the context of previously treated mTNBC. It is therefore misleading to equate the "early" stopping of ASCENT with those trials noted in the cited paper, and to suggest that this may have exaggerated the magnitude of benefit.	ERG recommends not to remove the associated paragraphs. It's a cautionary note; ERG does not assert that the PFS/OS benefit of SG in ASCENT trial is overestimated, but it cannot be excluded either. The ASCENT trial was a basis for regulatory market approval and therefore besides ethical considerations there was a vested commercial interest to market the drug faster. There is large body of empirical evidence from clinical trials and statistical stimulations indicating that trials stopped early for benefit tend to overestimate the treatment effect {Wilcox 2008; Montori 2005; Segota 2006; Bassler 2010; Pocock 1989; Schulz 2005; Grant 2004; Pocock 2005;Trotta 2008} The adequate rule for stopping the trial early for benefit should be based on

This text contains errors in interpretation of the evidence presented.			extremely stringent criteria, which are unlikely to be met for trials of small to moderate size and before 500 events have accumulated even if recruitment is complete with sufficient long follow-up, and clearly reported pre-specified interim analysis/stopping rules. Both O'Brien/Fleming stopping boundaries should be based on overall two-sided type I error of 1% rather than the conventional 5% (Pocock 2005).
<u>Tumour location in the lymph node higher in TPC arm</u> • Section 1.4; Issue 6; p18 Text: "There were more patients who had tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location." • Section 3.2.5; p55	We would ask that this issue and associated paragraphs be removed from the ERG report as they are misleading	This is a misinterpretation of the cited literature, two of which are single-centre studies with very low patient numbers. The actual conclusions were that lymph node involvement during primary, early stage breast cancer results in earlier and more likely metastatic recurrence, and poorer outcomes when this occurs. Clinical expert opinion supports this - location of mets such as visceral organs vs bones may affect prognosis in mTNBC, but not mets in lymph nodes. There is therefore no basis for implying bias towards SG here.	There is sufficient evidence showing the negative prognostic value of lymph node metastasis in TNBC patients in general. We need to remove {Karihtala 2020} and add instead the following citations {Al-Mahmood 2018; Costa 2021; De-La-Cruz-Ku 2020; Aziz 2020; Doval 2016; Goncalves 2018; Koca 2021; Mousavi 2019; Ovcaricek 2011; Qiu 2016}

Text: “There were more patients with tumour location in mediastinal lymph node (26.0% vs. 22.8%) and axillary lymph node (29.8% vs. 22.1%) in the TPC compared to SG arm, respectively. Previous research has shown that patients with metastatic breast cancer located in lymph nodes had poorer prognosis in survivall.[21-23] If this is the case in the ASCENT study, then the true clinically beneficial treatment effects of SG compared to TPC may have been inflated at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.” • Section 3.2.6; p64 Text: “Since tumour’s lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.” • Section 3.6.1; p81 “There were more patients tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour’s lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration			

of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location." This text contains errors in interpretation of the evidence presented and the wider literature.			
<u>Frequency of high grade neutropenia was more frequent in the SG.</u> • Section 1.4; Issue 5; p17 Text: "Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the TPC arm the treatment was discontinued and no G-CSF was administered (potentially dropped out)." • Section 3.2.2; p48 Text: "The treatment dose reduction/modification rules differed across the SG and TPC arms. For example, for the first episode of neutropenic toxicity of grade 3 or more, the SG arm was allowed 25% dose reduction and received granulocyte colony-stimulating factor (G-CSF), whereas for the same episode the treatment in the TPC arm was discontinued and no G-CSF was administered"	We would ask that this issue and associated paragraphs be removed from the ERG report as they are misleading	To state that no G-CSF was administered and that treatment in the TPC arm was discontinued for neutropenic toxicity is incorrect. G-CSF was administered to treat neutropenia and neutropenic sepsis arising in the TPC arm as well as the SG arm (19.8% of TPC patients received G-CSF vs 47.2% of SG patients). In addition, adverse events for individual therapies were treated according to their respective prescribing information, as would be expected both in clinical practice and in trials for these drugs.	The ERG was unable to verify this statement. Can the company indicate where in the submission "G-CSF was administered in TPC arm to treat hematologic toxicity" is stated?

• Section 3.6.1; p82 Text: “High grade neutropenia was more frequent in the SG vs. TPC arm. Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the TPC arm the treatment was discontinued and no G-CSF was administered” This text contains errors in interpretation of the evidence presented.			
<u>TTR and DOR Statistical Significance</u> • Section 3.2.6; p57 Text: “Only patients achieving either a CR or PR (ITT population: SG n=83 vs. TPC n=11) were included in the calculation for DOR and TTR. Given the small sample and wide variability in estimates, the findings suggested a prolonged DOR in the SG vs. TPC (6.3 vs .3.6), however, the corresponding HR estimates did not reach the pre-specified level of statistical significance (HR=0.39, 95% CI: 0.14, 1.06, p=0.057). For patients with a confirmed/partial response, the median time (in months) to first response (TTR) was similar between the SG and TPC groups (1.54 vs. 1.45) in both the ITT and primary	We would ask that this paragraph be removed from the ERG report as it is misleading	TTR and DOR statistics are descriptive only, therefore it cannot be stated that they did not reach a pre-specified level of statistical significance. The protocol states ‘using RECIST 1.1 criteria to classify tumor response, time to onset of objective response, duration of objective response, and time to progression. Using descriptive statistics, these metrics will be tabulated and compared between the two treatment arms.’	This is not a factual error. In the protocol [ClinicalTrials.gov] these outcomes are listed as secondary outcome measures for inferential (not descriptive) purposes, however, in the company’s CSR on page 49 states that TTR was summarized using descriptive statistics and on page 50, the CSR states that DOR was estimated using the KM method to generate 95%

analysis population. No HR and 95% CIs were reported" This text contains errors in interpretation of the evidence presented.			CI, which indicates inferential but not descriptive purpose. The ERG believe that both TTR and DOR were used for inferential rather than descriptive statistics analysis. It remains unclear why HR and 95% CIs for TTR could not be generated.
Additional Work on Clinical Effectiveness Undertaken by ERG • Section 5.2; p116 Text: "A relatively large number of women in TCP did not receive treatment, for reasons that are also not explained." This statement is not correct	Delete the sentence or edit for clarity and specificity of meaning	This is not considered to be correct by the company however the use of 'relatively' makes it difficult to accurately challenge as it subjectifies the statement	Amended

Issue 2 Inaccuracies related to description of the EORTC-QLQ-C30 data and utility analyses based on the ASCENT trial

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
Attrition of data for EORTC-QLQ-C30 assessment • Section 1.4; Issue 4; p16 • Section 1.4; issue 9; p20; description of issue and Page 21, under "what additional evidence or analyses might help to resolve the key issue"	Remove references to excess attrition and lack of investigation: "The EORTC QLQ data were strongly affected by attrition (in excess of 30% of the initial sample in TPC but far lower in SG) No	The reduction in patient numbers is due to patients' progression and not study drop out. The completion rates were high (generally ≥ 90%) for both treatment arms and were similar between the SG and TPC arm across the visits up to C10D1 (at which both arms had n ≥ 10). The reason TPC patients provide much less data over	The impact of the progression sate on data availability is extremely clear. All ERG estimated completion rates are calculates using denominators for patients that did not progress (at each point in time). Denominators used by the ERG are estimated because they are

• Section 3.2.5; p53; Paragraph. “Because of missing values…” • Section 3.6.1; p81 • Section 5.2; p116 “As described in the clinical section, the EORTC QLQ trial data [2.2] were strongly affected by attrition (in excess of 30% of the initial sample in TPC but far lower in SG) with unexplained consequence. The company does not explore how attrition has affected the comparability of the two treatment arms in ASCENT and specifically, whether patient characteristics, prognostic factors or other treatment effect modifiers may have become unbalanced.” • Section 5.3; p118; “It is unclear how progression was impacted…” Factual error and misinterpretation	exploration of how attrition affected the comparability of the two groups whose QLQ values were mapped to obtain utility values.“	time in progression free state is because they progress much faster compared to SG arm (See KM for PFS). The attrition due to loss of follow up or other reasons is extremely low in ASCENT. See PRO report section 8.1.	not presented in the relevant graphs/ Sections etc.. and therefore the ERG, who do not hold the data, have made their assessment based on modelled numbers of patients not progressed at each therapy cycle from the model, and compared these to evaluable patient data in relevant tables in the CSR. The objective of the ERG’s assessment is that the relevant denominators become available for each therapy cycle so an informed assessment can be made. Using data provided so far and model denominators, progression and completion rates are estimated using ITT numbers as denominators at the beginning of each treatment cycle. Given study design, all participants should have at least one baseline reading and one end of treatment reading. Yet the numbers of people that have at least two readings is well short of 90%, the % declared for data completion. 90% completion at baseline gives approximately 476 patients that should have a baseline measurement, all patients should also have an end of treatment

			measurement, so the same number of data points should be available for people who had at least one therapy cycle. Whilst the number of people who had a baseline EORTC QLQ C30 measurement was 464 (87% of ITT sample, data available for safety population only, 247 SG and 217 TPC, Table 14.2.6.1, IMMU -132-05 CSR Post text tables) seems in line with 90%, end of treatment measurement were available for 320 participants, 60.5% of ITT, well below 90%. When applying the conversion from EORTC QLQ to utilities, a further reduction in the numbers at baseline occurs (from 476 to 411, where 411 is 78% of the ITT sample) and the reduction is not even by treatment arm – 87% in SG (similar to overall sample) and 68% in TPC, 22% below the 90% overall completion rate. This drop is 1. Differential, 2. Large and 3. At baseline, so not affected by progression in any measure. The split of % values at the beginning of each therapy cycle - the denominators that are expected to decrease because of progression – are not presented.

			The assessment of dropout dynamics is a key issue in the appraisal, not a factual error. No changes made.
<u>Data available for utility analyses</u> • Section 5.3, p.117 and 120 "The ERG preference would be to have an appropriately developed regression model for utilities that would adjust for attrition" Text mischaracterises the data missingness and extrapolation of that to the utility data derived.		Since the EORTC survey completion rate was high, correspondingly, there were relatively little missingness in the mapped utilities. The reduction in patient numbers correspond to patients who progress on therapy. Overall, using the Longworth mapping algorithm, the mapping was unsuccessful in generating a utility value in only 65 cases out of the 3,104 observations (i.e. in less than 2% of the cases). Since reduction in the sample is due to progression, which consequence of treatment, the suggestion of missing data imputation, recommended, would be inappropriate.	Amended. The difference between decreasing numbers at risk, response rates for each EORTC data point relative to the expected number of people still in pre-progression and the difference between biases introduced by missingness and biases introduced by differences in the rate of other confounding factors (performance biases) that may or may not be related to missingness, are all very well understood and are a key issue in the appraisal.
<u>Additional Work on Clinical Effectiveness Undertaken by ERG</u> Section 5.2; p116 "Utility values were included in the regression analysis if at least two measurements were collected during the trial, i.e. the analysis included only people who had at least two treatment cycles." Factual error	This is factually inaccurate and should be edited or removed	The analyses included all patients who had baseline and at least one post-baseline utility value. Baseline utility was collected prior to treatment initiation.	Amended
<u>Interpretation of the EORTC-QLQ-C30 data.</u>	Remove sentence:	As the attached PRO report and Table 10 in the CS (p50) shows, in a linear mixed-effect regression model for	Amended

• Section 1.5; issue 9; p20; description of the problem. The statement does not adequately characterize the quality of life of patients on SG vs TPC as captured by the EORTC-QLQ-C30.	"An analysis was presented which shows that the difference is statistically significant for utilities, despite the conclusion in the ASCENT CSR that EORTC QLQ C30 are, essentially, similar for SG and TPC" Replace with "An analysis was presented which shows that the difference is statistically significant for utilities, reflecting the clinically meaningful improvement on SG in all primary domains of global health status/QoL, physical functioning, fatigue and pain, and the importance of these relative to the secondary domains"	repeated measures the SG arm showed statistically significantly (i.e., $p < 0.05$) and clinically meaningfully (i.e., mean difference exceeded the superiority margin) greater improvement than that in the TPC arm in all primary domains (global health status/QoL, physical functioning, fatigue, and pain), except for role functioning for which the SG arm showed statistically significant greater improvement than the TPC arm although the difference did not reach clinically meaningful threshold (5.6 vs. 6). The SG arm also showed a trend of greater improvement than the TPC arm in most secondary domains, including emotional functioning, dyspnea, insomnia, appetite loss, no difference between the treatment arms in cognitive functioning, constipation, or social functioning, and inferiority in terms of nausea/vomiting and diarrhea.	
<u>Additional Work on Clinical Effectiveness Undertaken by ERG</u> • Section 5.2; p116 "Given that the two groups (SG, TCP) appear to have different mean utility at baseline, it is important to know whether different utility at baseline is the result of imbalances in baseline characteristics, due to attrition or other reasons, and specifically,	Amend the sentence to reflect that utility values were adjusted to account for imbalances. 2nd quoted statement should be amended to reflect that utility values were not crude averages.	The utility values were generated with an RRMM model that adjusted for baseline and progression status. Adjustment by including baseline utility value was made. If disbalances in patient characteristics are captured by higher utility values at baseline for SG vs TPC, these were adjusted for, by including baseline in the utility model.	A key issue in the appraisal, not a factual error. No changes. The RRMM model used progression status and overall baseline utility (not by treatment) as predictors, obviously in addition to treatment group. The clinical study design was such that values for utility post-progression were not collected.

whether adjusted analyses of utility values are warranted." • Section 5.3; p120 "However, a comparison remains difficult because the TPC group, has, on average, lower utilities at baseline, and it is possible that apparently higher crude average utilities with SG may in fact be compounded with higher utility at baseline." Text error plus factual error/misinterpretation			It is unclear how a model can be adjusted for a disease stage when those values are not available. The only other adjustment operated involved baseline utilities and treatment. The incorporation of utilities at baseline in the model was done using the overall distribution of baseline utilities across patients, not the distribution by treatment group. Therefore, by design, the RRMM assumes no difference in baseline utilities by group. It is also unclear if the model accounts for patient histories, or whether the assumption was tested that the most significant predictor of utility during follow up may be the patient utility at baseline. The use of the term 'crude' refers to the calculations that were done by the ERG based on the utility x measurement (therapy cycle) provided in Document B, to clarify the fact that the ERG conducted a sense check for the difference between crude (not modelled) values read off the graphs, where crude measures are of course subject to sampling errors.

			Not factual errors, but a key issue to be explored in the appraisal. No changes.
Utility analyses • Issue 9. Page 20, "alternative approach" section of table. • Section 5.3; p120 "The graph also shows that, at each assessment visit, average utilities for people that remain on treatment remain constant" • Section 5.5. p.129 Statements about the company utility analyses are misleading and factually incorrect.	Remove sentence: "In the absence of robust demonstration that SG is associated with an independent treatment effect on utility scores, the ERG preferred approach is to use the same utility values for SG and TPC, consistently with prior appraisals (TA639, TA423) where no treatment effect was demonstrated on the utility scale" Remove: In the absence of robust demonstration that SG is associated with an independent treatment effect on utility scores, the same utility values should be used during treatment with SG or TPC, consistently with prior appraisals (TA639) where no treatment effect was demonstrated on the utility scale	The independent treatment effect has been demonstrated robustly in several statistical analyses. A repeated-measures mixed model was developed to obtain health-state and treatment specific utilities, adjusting for baseline utility value, that identified a significant treatment effect. Furthermore, several models were submitted as part of the response to clarification requests stage with regression analysis of utility data for patients while on treatment (i.e. excluding EOT visit). The model for the change from baseline int utility that included all stratification factors various interaction terms of treatment and baseline etc (see B.1.8) and the resulting model confirmed that mean change from baseline in utility while progression free across all visits was [redacted] for SG and [redacted] for TPC, which suggest a statistically significant effect of treatment of at least [redacted] during PFS state. This provided robust evidence of highly statistically significant utility difference between patients on SG vs TPC.	We agree that statements based using visual assessment are not robust, and we recognise this. This is why the ERG opinion is that the utility regression should be presented in extreme detail and all possible predictors should be identified, relevant data presented and an assessment is made. Stratification factors in the additional interactions models were the same as in the general model – so treatment and visit. Importantly, the baseline equality does not guarantee that subsequent selection biases are not at play. The impact of differences in utilities due to selection after baseline, not just at baseline, are not assessed and these are the objective of additional assessment, given the 30% drop in utility data used in the assessment of the difference between baseline and last measurement (net of progression rates) with TPC during follow up (see point above).

	Remove statement: The graph also shows that, at each assessment visit, average utilities for people that remain on treatment remain constant.	Statements made based on a visual interpretation does not reflect information provided in the response to ERG questions	Not a factual error, but a key issue for the appraisal. No change.
<u>Additional Work on Clinical Effectiveness Undertaken by ERG</u> Section 5.3; p119 "The graph was used in the submission to argue that utility with SG is 'consistently higher than baseline' during follow-up. The comparison with the baseline average, however, is misleading, because at each utility assessment, people who remain on treatment are a (selected) subset of people who contributed values at baseline. In other words, the baseline values for people with values at, e.g., cycle 5, is not represented in the graph. It is not possible to conclude whether baseline values for people whose values are assessed at each cycle, was lower or higher than at each assessment." Factual error and misinterpretation	Remove or update paragraph to reflect information that was included as part of the responses to the ERG	As above: as part of our response to clarification requests we fitted extra utility model for change from baseline in utility that included all stratification factors various interaction terms of treatment and baseline etc and the resulting model confirmed that mean change from baseline in utility while progression free across all visits was [redacted] for SG and [redacted] for TPC, which suggest a statistical significant effect of treatment of at least [redacted] during PFS state.	None of the fitted models included patient histories or additional stratification factors other than treatment / visits. Not a factual error but a key issue in the appraisal. No change.
<u>The status of patients at the EOT visit.</u> • Section 1.5; issue 10; p22, description of issue	Replace: The evidence for this utility gain with SG after SG has been stopped is unclear. EORTC QLQ data collection in ASCENT was stopped just after progression.	The End of Treatment evaluation was within 4 weeks of treatment discontinuation. Most patients discontinued treatment due to progression. Large number of patients were available for assessment: 172 patients on SG and 152 patients on TPC, as also noted by the ERG. The	The time to treatment discontinuation (TTD) curve and the PFS curve are not overlapping, the PFS curve falls after TTD, hence after the last treatment. It is easy to plot the time to EOT measurement, similarly to any

Additional Work on Clinical Effectiveness Undertaken by ERG • Section 5.1; p115 Misunderstanding of the issue here	Women receive a similar mix of therapies in SG and TPC in ASCENT. With statement: "The evidence for this utility gain with SG after SG has been stopped comes from the EOT measurements of EORTC-QLQ-C30 data that mostly included patients who progressed on therapy.	EQ-5D scores could be estimated for 167 and 148 of these patients, respectively, based on their EORTC measure. Of these, 315 patients, only 21 (7 on SG and 14 on TPC) were progression-free.	other survival curve. If time to EOT measurement falls between time to last dose and time to progression, then EOT still falls within the pre-progression period, taking into account the lag in measurement of up to 4 weeks. If time to EOT falls after PFS, then the committee will be in the position to decide whether this curve is representative of post-progression utility or not. The difference between average time to treatment discontinuation and time of last measurement is not available, but it is required to assess whether the EOT measurement is a valid estimate for utility post-progression. The curves may still be affected differentially, due to 22% difference in the proportion of participants for whom EOT data are available in the TPC arm compared to SG. Therefore, time to EOT, TTD and PFS should be compared by treatment arm, and not for the overall study. Not a factual error, but a key issue for the appraisal. No changes.

<u>Post-progression utility difference supported by data</u> Section 5.1; p115 “The second argument is that the evidence that improved utility with SG carries over undiminished after progression is not supported by any data.” Misunderstanding of the issue here	Statement should be modified: The evidence that improved utility with SG carries over undiminished after progression is supported by the mixed-model utility regression provided by the manufacturer.	The regression analyses showed that utility at progression is higher for SG vs. TPC even after adjusting for baseline (i.e. estimated utility calculated from the model that included progression and treatment). In a model including interaction of progression and treatment, the interaction term was not statistically significant suggesting that decrement in utility due to progression is similar for both treatment arm. Since in PFS gain in the utility was higher for SG than TPC the post progression utility is higher for SG.	The key fundamental question is whether differential loss to follow up after baseline measurement has affected the comparison, introducing differences between the SG and TPC groups at EOT, involving factors that were balanced at the start of the trial but have become imbalanced because of differential loss to follow-up. Therefore differences in the utility at EOT may be due to the compound effect of treatment and of differences between SG and TPC patient groups. A regression adjusting for baseline utilities is insufficient to clarify whether / how these potential imbalances have accrued during the period of the trial. The demonstration that EOT is also the measurement at progression is not given (but easy to verify, as per point above); the application of utility at EOT to the period after end of treatment is an assumption and as such, the validity of this assumption remains a key issue. Not a factual error, no changes.

Additional Work on Clinical Effectiveness Undertaken by ERG Section 5.3; p119 "The comparison shows that utility scores for all people on treatment, including values for all people the progressed or not, on average, declined between first and last measurement from [redacted] [redacted] with an overall decline of [redacted] [redacted] (Figure 22). It is necessary however to caveat this argument with the possible high number of missing values" Misinterpretation of the data	Remove or reword to reflect accurate understanding of utility and progression	This statement is mischaracterizing the quality of life experience for patients in the trial. The model requires health state utilities for progression-free and progressed health states. Since most pts who filled in the EORTC-QLQ-C30 at the EOT visit and had corresponding utility measure were patients who progressed, the difference in baseline and EOT is evidence for the impact of progression.	As point above. All patients that filled in the EOT questionnaire were patients who were still alive at that point in time; however whether the measurements were taken ***before***, ***at*** or ***after*** progression, and if so, at which point in time in the post-progression period, cannot be verified with the analyses provided; the data gap should be filled to allow for the validity of this assumption to be verified. Not a factual error. No changes

Issue 3 Inaccuracies related to cost-effectiveness modelling

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
<u>The costs of post-progression therapies applied in the model</u> • Section 1.4; Issue 11; p23 Text "the duration of post-progression treatment applied to SG (10.6 weeks on average) is generally shorter than that applied to TPC (13.2 weeks on average). This is implausible, because women treated with SG live longer in the post-progression state (average 25 weeks) compared with TPC (average 19 weeks). This translates in 14 weeks off treatment before death with SG and 6 weeks off treatment with TPC. This assumption implies that women receiving TPC are treated to end of life, whilst in SG, therapies are interrupted well before time of death." This statement omits that the source of these assumptions is the ASCENT trial.	Context is missing from this assertion – we would ask that the paragraph is amended to clarify the source of the data	These data were derived directly from the ASCENT Trial	Some data applied in the model are taken from the trial and some are not (i.e. the duration of post-progression therapies is taken from the trial but not the proportions of such therapies). Therefore the justification is used selectively. An assessment of the overall consistency of the use of data from the trial should be done. Not a factual error, no changes.
<u>ERG preferred distribution of post-progression therapies</u> • Section 1.5; issue 11; p23.	We would suggest to remove the following text: Post-progression costs for TPC are assumed to be made up by eribulin for 66% of women.	The model calculated the post progression therapy in a step-wise manner: 66.4% TPC patients among those who progressed received post-progression	According to clinical opinion received by the company, a rechallenge with eribulin used

Discussion around post-progression therapies does not take into account that the post-progression therapy distribution was calculated in two steps: there was a given % that received subsequent therapies, and a distribution of therapies were set among those, who did receive it. Therefore, the report mischaracterizes the assumption about subsequent therapies.	This is incompatible with trial data, as approximately 33% of women (both arms) received eribulin before the study and 53% (TPC arm) during the study, leaving approximately 15% eribulin-naïve. The company's proportions implicitly assume that in the TPC arm, up to 50% of the cohort is treated with eribulin (the most expensive treatment) twice. Post-progression therapy proportions favour SG.	treatment (based on the ASCENT trial and reported in the CS), and 46.9% of TPC patients received eribulin. That is, about 31% of patients overall received subsequent therapies on TPC, according to the company submission. The source of both figures is the ASCENT trial. Finally, because in the UK eribulin is only possible to receive a 3rd line so no one would be eligible for eribulin previously, we disagree with the ERG argumentation to reduce the number of eribulin use after TPC, because patients in ASCENT received it earlier.	in multiple therapy lines in the same patient is not plausible. In the ASCENT trial, about 30% of participants received eribulin, essentially, as first line therapy, inconsistently with clinical use of eribulin in the UK. This is a general key issue for the appraisal, with larger implications than just the choice of a % of people who receive eribulin post-progression. To ensure the internal consistency of the cost-effectiveness, a higher % of post-progression eribulin can be applied to TPC if and only if the subgroup of people who received eribuln first line in ASCENT is excluded from any of the analyses supporting the cost effectiveness. Whether the use of data from this subgroup as the main evidence base in the appraisal is a key issue. Not a factual error, no change.
<u>Method of calculating RDI for SG and application in the model</u>	Remove this statement as it is incorrect	The method of RDI calculation was reported as per the ASCENT trial. According to ASCENT trial CSR,	The CSR states very clearly that any dose discarded because of interrupted

• Section 1.5; Issue 13; p26 Section 5.4.3; p124 Text: "The methods used to calculate the RDI applied in the model are not described" "In the absence of a correctly quantified RDI, the RDI has been reset to 100%. " "The relevant RDI, with all cost components accounted for, should be recalculated and RDI calculation methods should be provided and thoroughly described." The ERG's statement about RDI is missing critical context and is inaccurate.		RDI for SG was calculated as "cumulative dosage received / total assigned dosage*100". Total assigned dosage for each patient is defined as the product of the starting assigned dose and number of doses the patient was scheduled to receive during the patient's treatment period (number of infusions actually received by the patient plus the number of infusions the patient missed between the first and last infusion). Acknowledging the uncertainty in RDI inputs, the company submission has presented two scenarios related to RDI for SG and TPC: 1) 94.2% for SG and 84% for TPC; 84% was extracted from eribulin trial EMBRACE (safety population) which was also used in eribulin NICE submission (TA423). The RDI for eribulin in EMBRACE trial was calculated as "actual dose intensity/planned dose intensity". 2) 100% for SG and TPC as extreme value testing. Therefore, with the method defined in the ASCENT trial being comparable to the method adopted in the other relevant trials (e.g., eribulin), it should be considered as an input with uncertainty which has	infusions was subtracted from the total dose. These subtractions still correspond to a cost. The company should present data on the average number of days between doses and the average ***prescribed*** dose as this is the cost supported by the NHS.

		been properly tested in the sensitivity analysis, rather than inaccuracy, whilst the ERG's description of "in the absence of a correctly quantified RDI" is misleading.	
<u>Statement regarding applying wastage for drug cost calculation</u> • Section 5.4.4, p125/126; paragraph 1 "Although it is customary to use vial sharing in clinical practice, this practice should not be used to decrease the cost of therapy." The statement is inaccurate.	Proposed amendment: Remove the statement as it is incorrect	Acknowledging the absence of data to accurately inform drug wastage, the company model adopted the same approach as a recent NICE submission in the related disease area (trastuzumab deruxtecan NICE submission TA704). The assumption of 50% vial sharing feasible and 50% vial sharing not allowed was broadly accepted by the ERG and the Committee of TA704. This assumption was supported by a clinical expert in UK who confirmed that “in clinical practice drug wastage is recognized and efforts are made to minimize it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain” (TA523).	The incorporation of drug wastage in this appraisal reflected a hospital perspective. The methods used in other appraisals may have been relevant in that context, this does not imply that the replication of those methods in this appraisal may rely on the same assumptions. Not a factual error No changes
<u>Weight distribution for the cost calculation of SG and TPC</u> • Section 1.5; Issue 15; p27	Proposed amendment: Amend: “This distribution is slightly skewed towards lower weight percentiles compared	The company used the best available evidence based on the patient-level data of ASCENT trial, in order to estimate the SG cost accurately by assigning a weight	This issue concerns the application of two different distributions for weight in the two treatment groups. The use of a parametric

Text: "This distribution is slightly skewed towards lower weight percentiles compared with the parametric (using the same mean and standard deviation) normal distribution used for TPC. " • Section 5.4.2; p123 This ERG statement may be misinterpreted because it only provides a description with partial fact.	with the parametric (using the same mean and standard deviation) normal distribution used for TPC. ” To: “This distribution is slightly skewed towards lower weight percentiles compared with the parametric (using the same mean and standard deviation) normal distribution used for TPC. The range of the company used weight distribution for SG also slightly shifts to the right comparing to the normal distribution range, with fewer patients on the end of lower bound and also includes a few outliers beyond the upper bound."	distribution that was derived specifically to be aligned with the required dosage per number of vials for SG patients (i.e., 19.1kg-38.21kg, 38.21-57.31kg, so on so forth).	distribution in one group and of a non parametric distribution in the other group involves costing differentially and specifically, costing based on measurement error in ne group and not in the other (regardless of which group is costed parametrically or not). Not a factual error, no change.
<u>Cost calculation of vinorelbine</u> • Section 1.5; Issue 16; p28 Text: "The cost of vinorelbine and capecitabine were incorrectly calculated." "The cost of vinorelbine used a distribution of doses with erroneous values. " The ERG implemented a revision to the model for the preferred vinorelbine cost calculation. According to the screenshot provided by the ERG to the end of the report, 4 vials of 10mg strength vial were assumed for patients with a requirement of 40mg resulting dosage (BSA based). However, this is not	Remove the statement as it is incorrect. Remove the revision to the model.	In the company submission model, the dose distribution was arranged based on a rule of applying the vial combination that is with the lowest cost first. This assumption was also from a conservative perspective by assuming the lowest possible cost for a comparator drug.	In principle, the difference Is minimal, however it is important to keep consistency in the calculations and avoid ad hoc solutions, not to create a precedent that can then be misunderstood in other contexts. Not a factual error, no change.

considered to be practical because for patients requiring 40mg dosage, one vial of 50mg strength vial would cost less (£15,77 with Company's assumption vs £21.02 in the ERG preferred assumption)			
<u>Cost calculation of capecitabine</u> • Section 1.5; Issue 16; p28 Text: "The cost of vinorelbine and capecitabine were incorrectly calculated." "The cost of capecitabine used a fixed cost, whilst in practice, capecitabine is weight-based." "Dose by weight tables are provided in the capecitabine SMPC; these have been used to recalculate the cost of this oral treatment." The ERG stated that capecitabine should be calculated weight based. However, according to SmPC, it is recommended to be given 1250mg/m^2 twice daily as monotherapy for mTNBC patients. This aligns with the dosing regimen assumption that the company made in the model and the cost calculations performed	Remove the statement. Remove the revision to the model.	The company acknowledge that capecitabine drug acquisition cost was not adjusted by population BSA distribution for wastage. However, this was a conscious decision from a conservative perspective by applying the lowest per mg cost and assuming no wastage for a comparator drug.	The difference between the two approaches is minimal, but there may be unintended consequences of using the company's approach, for example, the costs of subsequent therapies may be underestimated / biased, in which case the approach would not be conservative. Not a factual error, no change

accordingly (i.e., body surface area based).			
<u>Statement that company has not provided the individual Kaplan-Meier data of PFS, OS, and TTD.</u> • Section 3.5.2; p72; paragraph 1. The ERG statement is incorrect. The company has provided detailed PFS, OS, and TTD data for the ITT population in the initial submission, and further to that provided more detailed data to meet the ERG's subsequent request on data for subgroups.	Proposed amendment: Amend: “The ERG requested the company to provide the individual Kaplan-Meier data to accurately construct curves, and allow a more reliable comparison between the models chosen by the company and those chosen by the ERG. However, the company did not provide the data” To: “The individual Kaplan-Meier data was submitted along with parametric survival extrapolations in the company submission model. Upon ERG's request, the company has subsequently provided further data (i.e., including individual Kaplan-Meier data, parametric survival extrapolations) for subgroups."	In the company submission model, individual Kaplan-Meier data has been provided for PFS, OS, and TTD, in <PFS Details>, <OS Details>, and <TTD Details> worksheet, respectively. Data provided includes: 1) individual Kaplan-Meier data; 2) survival extrapolation parameters for six standard distributions; 3) extrapolated curves and data point per each model cycle.	The model does not have IPD data. The ERG requested for IPD data but this was not supplied. Please refer to clarification questions.
<u>Additional Work on Clinical Effectiveness Undertaken by ERG</u> • Section 5.3; p121 Text: “In the absence of this model, the ERG’s preferred approach would be to use the average utility for SG during treatment” This statement is incorrect. The model was provided to the ERG.	Remove this statement as it is incorrect	The model was provided to the ERG with the submission	This comment refers to the statistical model(s) used to estimate a treatment effect on utilities – with the requirement that the model ‘[..] appropriately [..] ***<u>adjusts for attrition and potential selection biases</u>*** by means of an appropriate exploration of clinical prognostic factors and treatment modifiers. This is not available.

			It is also clear that this model requires complete testing of whether or not there are imbalanced and whether or not adjusting those imbalances do not generate trivial results. This assessment is necessary to minimize uncertainty in the decision because it incorporates in the cost-effectiveness only those claims that are robust to challenges. For claims that are not robust, uncertainty is minimized assuming that no effects apply.

Issue 4 Textual and data clarifications

Description of problem	Description of proposed amendment	Justification for amendment	ERG comment
<u>Inaccurate characterisation of wastage and use of 'special packs' designation</u> • Section 1.5; Issue 14; p27 The cost-effectiveness assumes that a fraction of drugs used for IV are 'redeployed' to other patients. However, all drugs used in this appraisal are prescribed in packs classified as 'special containers', as such, they are reimbursed as full vials, in the minimum quantity required to fulfil the prescribed dose, regardless as to whether wastage is discarded or redeployed. Therefore, the NHS perspective is not	Remove reference to special container status and any implied restrictions this has on the ability to share vials of SG.	The PSNC is an organisation whose work is limited to NHS community pharmacies. Any regulations, recommendations or restrictions arising from this organisation are therefore irrelevant to an appraisal for a drug that is administered in hospital, and reference to such in	Drugs in the UK are reimbursed as full packs, not as partial packs. This applies to vials in particular. This system differs from that of other Countries, where only the dose injected is reimbursed. If a pack is reimbursed, wastage is not relevant for costing purposes. Hospital drugs and specifically, chemotherapy, are not distributed via community pharmacies.

maintained when the cost of vials is reduced below the amount paid by the NHS at the point of filling the prescription • Section 5.4.4; p126 The UK Pharmaceutical Services Committee (PSNC) states that, as per the Pharmaceutical Services Regulations, when a prescription is filled in, only the original pack should be supplied (or a multiple).56 All drugs classified as dispensed via 'special containers' should be supplied as full pack. For reimbursement, the special container rules are automatically applied, implying that reimbursement will be set at nearest pack or combination of packs necessary to fulfil the dose. For this reason, even if vials may be shared at the point of delivery, the NHS reimbursement is always set at the nearest full pack for a dose that requires the use of a fraction of the pack (or combinations or multiple packs). The assumption of vial sharing in fact is from the hospital perspective, as the hospital may support lower costs to deliver a dose than the full pack, but not the NHS perspective as the NHS will always reimburse the full pack. For this reason, the ERG set wastage to 100% (**Error! Reference source not found.**) as any amount wasted does not translate into a reduction in the acquisition cost to the NHS		the ERG report is highly misleading.	No factual errors. No change.
<u>Inaccurate description of ASCENT inclusion criteria</u> • Section 3.2.2; Table 6; p47 Error in "Following a protocol amendment, only patients with known brain metastases at baseline were eligible to enrol in the trial as long as their	Remove text "Following a protocol amendment, only patients with known brain metastases at baseline were eligible to enrol in the trial as long as their central nervous system (CNS) disease was	Statement is factually incorrect. The use of 'only' gives the impression that only brain metastases positive patients were eligible for enrolment following the	Text amended

central nervous system (CNS) disease was treated and stable for at least 4 weeks prior to randomization”	treated and stable for at least 4 weeks prior to randomisation. The proportion of patients with known brain metastasis at baseline was limited to 15% and this subgroup was not included in the primary efficacy analysis population Include text “Protocol amendment 1 removed the requirement for baseline brain imaging requirement to rule out brain metastases, thereby allowing patients with brain metastases into the study as long as their central nervous system (CNS) disease was treated and stable for at least 4 weeks prior to randomisation. Protocol amendment 3 subsequently limited the number of patients with brain metastases in the trial to 15%. This subgroup was not included in the primary efficacy analysis population."	amendment. This is not correct. The amendment allowed patients with known brain metastases to enter the trial. Prior to the amendment they were excluded. Several amendments were made in the protocol during the study. We propose further clarification is required.	
<u>Inaccurate description of ASCENT permitted concomitant medication</u> • Section 3.2.2; Table 6; p48	Include Hematopoietic growth factors or blood transfusions	Permitted use of hematopoietic growth factors or blood transfusions was omitted from the table	Added

Inaccurate description of patient population for treatment discontinuation • Section 3.2.4; p51 and p52 Error in "Most frequent reason for treatment discontinuation was the occurrence of disease progression (78.0%) and it was more frequent in SG (84.7%) vs. TPC (71.2%) group of patients"	Clarify that these data represent the primary analysis population (BM-ve)	Missing context. The data presented in this paragraph related to the BM-ve population, however the text does not refer to this fact. It could mislead the reader as to the population referred to.	This is not a factual error. The text in the ERG report on page 51 just above Table 8 states: "Details on patient disposition in the ASCENT study are presented in Table 8 (for primary analysis BM-ve population, n=468 patients). Moreover, the title of Table 8 refers to BM-ve as follows: "Study sample disposition (primary analysis, BM-ve population)".
Inaccurate description of data availability on study patient disposition • Section 3.2.4; p51 and p52 Error in "No similar data are provided for the ITT population"	Remove statement	Statement is factually incorrect. Table 14.1.1.1 of CSR post-text tables document provides patient disposition for the screened population, which are presented in Figure 4 of the CS. This figure provides the disposition for all randomised patients (i.e., ITT analysis set), including reason for discontinuation.	This is not a factual error. Table 14.1.1.1 does not present the data presented in CSR (Table 17, page 58) and Erg report (Table 8, page 51). Therefore, no similar data as in Table 8 (ERG report) or Table 17 (CSR) for ITT was presented.
Data error: PFS disposition • Section 3.2.4; p52 Error in "the risk of disease progression or death was significantly reduced in the SG vs. TPC arm (HR=0.41, 95% CI: 0.32, 0.51)"	Change upper CI from 0.51 to 0.52 Modify to include additional context that this is the primary endpoint in the BM-ve population	Rounding error on 0.519. No context that data represents the primary endpoint in the BM-ve population	Amended
Data error: ASCENT study: baseline patient characteristics	Change wording to: Overall, 69.0% of patients had received 2-3 prior	Data appears to be presented for the BM-ve population. Data are	Amended

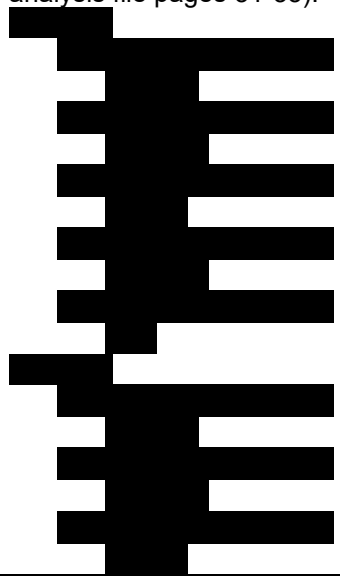
• Section 3.2.5; p53 Error in “Overall, 70.5% of patients had received 2-3 prior chemotherapies and 29.5% had received >3 prior chemotherapies”	chemotherapies and 31.0% had received >3 prior chemotherapies	available for the ITT population that is most relevant to the decision problem: • 2-3 prior therapies: 69.0% for ITT population (per CS table 6; CSR post-text tables p32; p48; Table 14.1.4.1) • >3 prior therapies: 31.0% for ITT population (per CS table 6; CSR post-text tables p32p48; Table 14.1.4.1)	
<u>Data error: ASCENT study: baseline patient characteristics</u> • Section 3.2.5; p53 Error in “Patients had a median age of 54 years (SD=11.7)”	Change wording to: Patients had a median age of 54 years (SD=11.5)	SD should be 11.5 per CS table 6; CSR post-text tables p32; Table 14.1.3.1	Amended
<u>Data error: ASCENT study: baseline patient characteristics</u> • Section 3.2.5; p53 Error in “Creatinine clearance: 110.5 mL/min”	Change wording to: creatinine clearance: 110.6 mL/min	Mean creatinine clearance should be 110.6 (CS table 6; CSR post-text tables p32; p35; Table 14.1.3.1)	Amended
<u>Data error: ASCENT study: baseline patient characteristics</u> • Section 3.2.5; p54	Change wording to: • eribulin 115 (43.1%)	Though 0 patients in the SG arm received TPC, all patients were allocated a TPC prior to randomisation. In SG arm: eribulin 115	This is not a factual error. The table provides baseline characteristics. Clarification response confirmed that 0 patients in the SG group received TPC. This table does not present prior

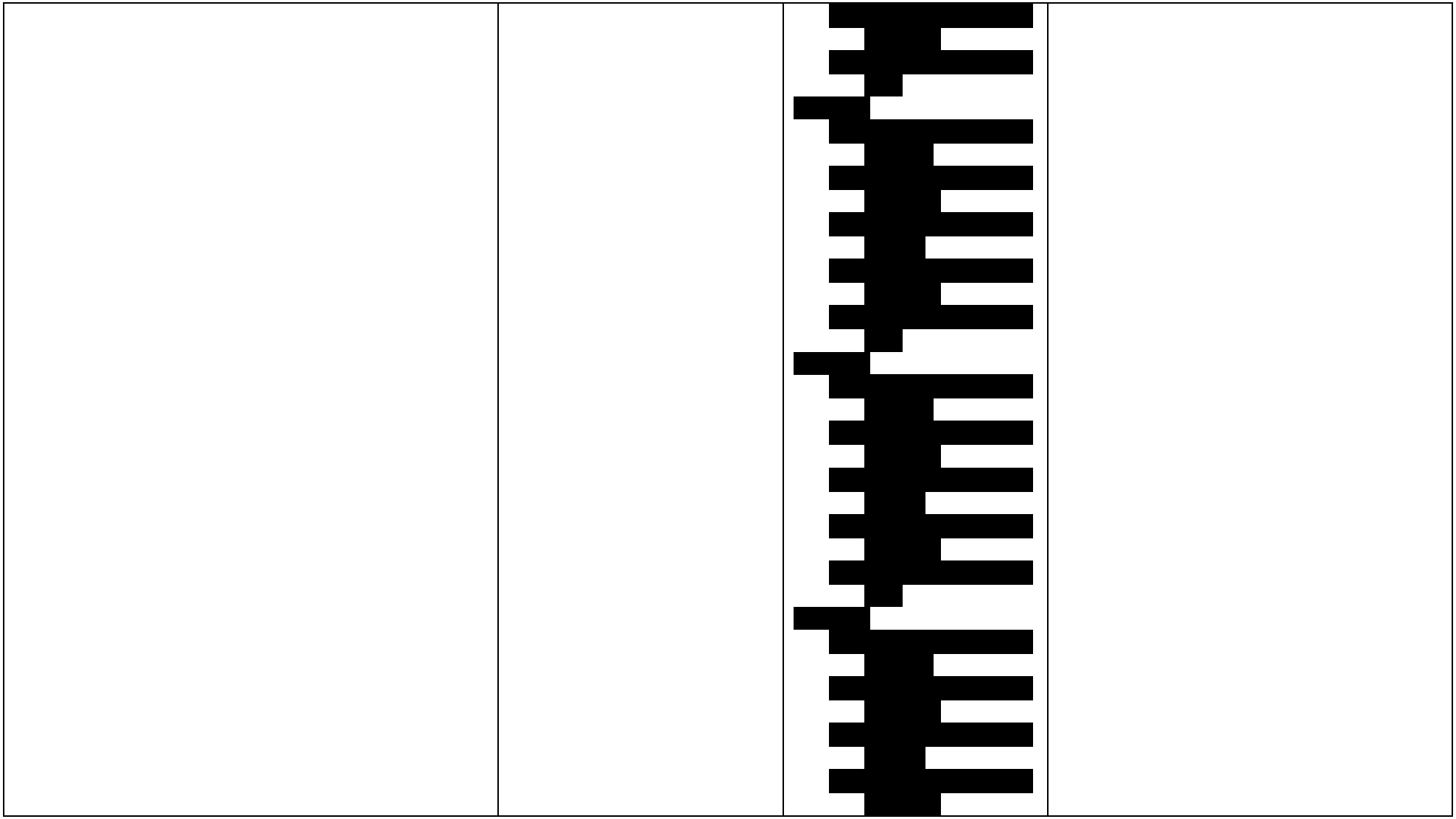
Error in Treatment of physician choice [n (%)] in data table, 0% recorded for SG for all TPC treatments	• capecitabine 48 (18.0%) • gemcitabine 46 (17.2%) • vinorelbine 58 (21.7%)	(43.1%), capecitabine 48 (18.0%), gemcitabine 46 (17.2%), vinorelbine 58 (21.7%)	randomisation data. If we were to present prior randomisation data then this will be required to the overall sample or stratified for both arms rather than presenting one arm only.
<u>Data error: ASCENT study: PFS outcomes</u> • Section 3.2.6; Table 10 p56 Error in "The median time (in months) to disease progression was significantly longer with SG vs. TPC in the ITT ([redacted]) and primary analysis population ([redacted])." • Table 10 p57 Error in hazard ratios quoted for ITT population and BM-ve population	Change text to: The median time (in months) to disease progression was significantly longer with SG vs. TPC in the ITT (5.6 vs. 2.1; HR for disease progression=0.43, 95% CI: 0.34, 0.55) and primary analysis population (5.8 vs. 2.1; HR for disease progression=0.41, 95% CI: 0.32, 0.53). Change Hazard ratio and CI in text and table to: • ITT population: 0.43 (0.34, 0.55) • BM-ve population: 0.41 (0.32, 0.53)	Hazard ratio and CI contain errors in reporting (CS Table 9; Bardia 2021 Table 2)	Amended
<u>Data error: ASCENT study: OS outcomes</u> • Section 3.2.6; p56	Change wording to: 49% reduction in ITT	Data error: This should 49% as the Hazard Ratio is 0.51 (CS Table 9; Bardia 2021 Table	Amended

Error in “associated with a significantly reduced risk of death in patients treated with SG vs. TPC (50% reduction in ITT and 52% reduction in primary analysis population)” • Table 10 p57 Error in hazard ratios quoted for ITT population and BM-ve population	Change hazard ratio and CI to: • ITT population: 0.51 (0.41, 0.62) • BM-ve population: 0.48 (0.38, 0.59)	2), further errors in Cis compared with sources	
<u>Data error: ASCENT study: ORR outcomes</u> • Section 3.2.6; p56 Error in “Patients treated with SG achieved a significantly greater rate of objective response (ORR, either complete or partial) compared to those treated with TPC in the ITT (OR=10.99, 95% CI: 5.65, 21.35) and primary analysis population (OR=10.85, 95% CI: 5.59, 21.09).” • Table 10 p57 Error in odds ratios quoted for ITT population and BM-ve population	Change text to: • Patients treated with SG achieved a significantly greater rate of objective response (ORR, either complete or partial) compared to those treated with TPC in the ITT (31.1% vs 4.2%, OR=10.99, 95% CI: 5.65, 21.35) and primary analysis population (34.9% vs 4.7%, OR=10.85, 95% CI: 5.59, 21.09). Change odds ratio and CI in table to: • ITT population: 10.99 (5.66, 21.36) • BM-ve population: 10.86 (5.60, 21.10)	Odds ratio and CI contain errors in reporting (CS Table 9) We also recommend adding actual ORR % figures in this paragraph.	Amended

Data error: ASCENT study: CBR outcomes • Section 3.2.6; p56 Error in text “Similar improvement was observed with respect to clinical benefit rate (CBR), which was significantly greater in the SG vs. TPC treatment arm for the ITT (OR=8.06, 95% CI: 4.83, 13.45) and primary analysis population (OR=8.54, 95% CI: 5.05, 14.43)”. • Table 10 p57 Error in hazard ratios quoted for ITT population and BM-ve population	Change text to: • Similar improvement was observed with respect to clinical benefit rate (CBR), which was significantly greater in the SG vs. TPC treatment arm for the ITT (OR=8.07, 95% CI: 4.84, 13.46) and primary analysis population (OR=8.54, 95% CI: 5.06, 14.44). Change odds ratio and CI in text and table to: • ITT population: 8.07 (4.84, 13.46) • BM-ve population: 8.54 (5.06, 14.44)	Odds ratio and CI contain errors in reporting (CS Table 9)	Amended
Data error: ASCENT study: DOR outcomes • Section 3.2.6; p56 Error in text “the corresponding HR estimates did not reach the pre-specified level of statistical significance (HR=0.39, 95% CI: 0.14, 1.06, p=0.057).” • Table 10 p57	Change text to: • the corresponding HR estimates did not reach the pre-specified level of statistical significance (HR=0.39, 95% CI: 0.14, 1.07, p=0.057).	CI contains errors in reporting (CS Table 9)	Amended

Error in hazard ratios quoted for ITT population and BM-ve population	Change hazard ratio and CI in text and table to: • ITT population: 0.39 (0.14, 1.07) • BM-ve population: 0.39 (0.14, 1.07)		
<u>Data error: ASCENT study: TTP outcomes</u> • Table 10 p57 Error in hazard ratios quoted for ITT population and BM-ve population	Change hazard ratio and CI in table to: • ITT population: [redacted] • BM-ve population: [redacted]	Hazard ratio and CI contain errors in reporting (CS Table 9)	Amended
<u>Data error: ASCENT study: HRQoL outcomes</u> • Section 3.2.6 p59 Error in text "[redacted]	Change text to: [redacted]	Data errors for reported CIs for physical functioning, role functioning and pain	Amended

	[redacted]		
Text error: Clinical Effectiveness • Section 3.5.1; p69 Error in “The company averaged the mean changes across Cycles 2 and 6. (Document B, Table 7; PRO analysis file, figures on page 25-29).”	Change “Table 7” to “Table 10”	Text error, table reference incorrect	Amended (please note that this is not in track changes)
Factual Error: Clinical Effectiveness • Section 3.5.1; p72 Error in “This analysis is based on the same baseline (at Cycle 1) sample as the unadjusted analysis (SG n=236 vs. TPC n=183). The mean EORTC QLQ-C30 score changes were analysed across Cycle 2 (SG n=216 vs. TPC n=157), Cycle 3 (SG n=189 vs. TPC n=94), Cycle 4 (SG n=178 vs. TPC n=71), Cycle 5 (SG n=145 vs. TPC n=48), and Cycle 6 (SG n=143 vs. TPC n=36). (PRO analysis file, figures on page 31-35)”	Statement is inaccurate and should be amended accordingly	Note that this is not completely accurate, as the n varied by domain (PRO analysis file pages 31-35): 	Added



<table>
<tr><td></td><td></td><td>• [redacted]</td><td></td></tr>
<tr><td><u>Factual Error: Clinical Effectiveness</u>
• Section 3.5.2; p71
Error in “This section describes the ERG’s approach to modelling PFS, OS, and TTD. The ERG requested the company to provide the individual Kaplan-Meier data to accurately construct curves, and allow a more reliable comparison between the models chosen by the company and those chosen by the ERG. However, the company did not provide the data. The ERG digitised figure 7 (PFS), figure 8 (OS), and figures 36 and 37 (TTD).”</td><td>Statement is inaccurate and should be deleted</td><td>KM data for overall population was in the original model submitted; additional KM data were provided at clarifications stage.</td><td>This is not a factual error. The ERG requested twice for the data to be supplied in a specific format (IPD) and this was not provided. Please refer to clarification requests and NICE technology appraisal team. For example:<table><tr><td></td><td></td><td>Events</td></tr><tr><td>Timepoint</td><td>N at risk</td><td>Lost to follow-up</td></tr><tr><td>Day=0</td><td>N=?</td><td>N=?</td></tr><tr><td>Day=?</td><td>N=?</td><td>N=?</td></tr><tr><td>Day=?</td><td>N=?</td><td>N=?</td></tr><tr><td>Etc…</td><td>N=?</td><td>N=?</td></tr></table></td></tr>
<tr><td><u>Data Error: Clinical Effectiveness</u>
• Section 3.5.3; Table 19 p73
Error in “PFS Extrapolation for ASCENT “TPC, company” value for 12 months”</td><td>Update 12month PFS value to correct value of 1.74%</td><td>Data Error: Value entered is 0.23% for 12 months cannot be correct as the 20-month entry is 0.70%</td><td>Amended</td></tr>
<tr><td><u>Factual Error: Resources and Costs</u>
• Section 4.9.8.1; p110
Error in “A non-parametric weight distribution was used for SG, taken directly from ASCENT. In the calculation of the cost of therapy using the weight distribution, an RDI of [redacted] is used as well, to represent the impact of dose reductions and adjustments.”</td><td>Change [redacted] to [redacted]</td><td>Data Error: Should be [redacted]</td><td>Amended</td></tr>
<tr><td><u>Text Error:</u>
<u>Company cost-effectiveness results</u></td><td>TCP replaced with TPC</td><td>TPC is correct abbrev for Treatment of Physicians Choice</td><td>Amended throughout the report</td></tr>
</table>

• Section 4.3; p86 Additional Work on Clinical Effectiveness Undertaken by ERG • Section 5.2; p116 • Section 5.3; p119 • Section 5.4.5; page 128 Error in text “TCP”			
Text Error: Additional Work on Clinical Effectiveness Undertaken by ERG • Section 5.4.5; Table 42 p128 “ERG Preferred Distribution” Column incorrectly headed	Change column headings to match those of the ‘Company Base Case’ section	This will correctly label the column headings	Amended

Location of incorrect marking	Description of incorrect marking	Amended marking	ERG comment
Missing AiC marking (page 58-59): [redacted]	This should be marked as Academic in Confidence (AiC)	Data are not publicly available	Marking amended

NICE National Institute for Health and Care Excellence

Technical engagement response form

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 21 January 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Variation in prior therapy. The number and types of prior therapies that patients received varied across the countries that participated in the trial. This limits the generalisability of ASCENT trials results to the UK setting	No	The mainstay of metastatic triple negative breast cancer (mTNBC) treatment in the UK and internationally is single-agent chemotherapy.(1-3) This has remained largely unchanged for many years due to the lack of innovation in TNBC treatment, with the recent exceptions of immunotherapy plus chemotherapy in first-line treatment of PD-L1 positive patients and PARP inhibitors in *BRCA* mutation-positive patients.(1-3) The prior therapies used before sacituzumab govitecan (SG; Trodelvy) and treatment of physician's choice (TPC) in ASCENT are highly generalisable to UK clinical practice. Prior to second or third line therapy, almost all patients, regardless of geography, typically receive a taxane and an anthracycline-based therapy, whether in neoadjuvant treatment for early-stage disease, or as first or second line therapy for metastatic disease.(1-3) This is well reflected in the ASCENT trial, where 100% of patients had received a prior taxane and 82% had received an anthracycline.(4, 5) Another commonly used early-line therapy used by UK clinicians is carboplatin, which had been used in 65% of patients.(5) Approximately 29% and 7% of patients had received a prior immunotherapy or PARP inhibitor.(5) These figures demonstrate that patients in ASCENT had received optimal standard prior treatment, similar to what would be expected in England according to clinical expert feedback on the treatment

		pathway in this country. Consequently, this issue has no bearing on the generalisability of the ASCENT population to clinical practice in England, or on the cost-effectiveness of SG in its licensed indication.
Key issue 2: Long term effectiveness/safety data uncertainties. Lack of longer-term effectiveness/safety data. The median (range) of ASCENT study follow-up was 8.38 (0-24) months	Yes	The median study follow-up for ASCENT at the March 2020 data cut used in this submission was approximately 17.7 months, which is mature considering the very poor prognosis in this disease setting, and is considerably longer than the median SG values for overall survival (OS; 11.8 months) and progression-free survival (PFS; 4.8 months), meaning there is a high degree of confidence in these results.(4) The median follow-up time of 8.38 months reported in the ASCENT CSR is actually the median duration of individual patient follow-up rather than of the whole study.(6) This issue is further addressed by a later OS data cut from the final database lock in February 2021 with a median follow-up of approximately 27 months, which shows the same survival benefit of SG vs. TPC in terms of median survival outcomes:(7) • Median PFS was 4.8 months vs 1.7 months in patients treated with SG and TPC, respectively (HR: 0.41; 95% CI: 0.33, 0.52) • The median OS was 11.8 months vs 6.9 months in patients treated with SG and TPC, respectively (HR: 0.51; 95% CI: 0.42, 0.63) This additional survival follow-up validates the company's initial OS extrapolations and is described in more detail in Issue 8.
Key issue 3: Imbalance in the randomised but untreated patients across groups. There was a notably higher proportion of randomised but untreated patients (consent withdrawals) in TPC (14.5%)	Yes	In the case report form (CRF) employed in ASCENT, patients that were randomised but not treated were classified as discontinuing treatment. The reasons that patients discontinued treatment could be chosen from a series of preset categories. The information available from the CRFs regarding these reasons is presented below no further information was formally captured in this regard: • Of 38 patients randomized to the TPC group who were not treated, their "Primary Reason for Discontinuing Treatment" selected was: 32 patients with "Study drug not administered (after randomisation)" and 6 patients with "Withdrawal of Consent".

vs. SG (3.4%) treatment group. The ERG is uncertain how the company handled these data in terms of follow-up, inclusion, imputation, or censoring matters.		• Of 9 patients randomized to the SG group who were not treated, their "Primary Reason for Discontinuing Treatment" selected for all 9 patients was "Study drug not administered (after randomisation)". Per protocol, patients who prematurely discontinued from ASCENT underwent the final visit assessments and long-term follow-up every 4 weeks thereafter for survival status.(8) Although the majority of patients who prematurely discontinued prior to treatment did not have final assessments (physical exam, electrocardiogram, etc) performed for the study, they did have follow-up information provided on their survival status. Of the patients who discontinued prior to treatment, 8 had final visit assessments performed (4 of 9 patients in the SG group and 4 of 38 patients in the TPC group) and there were 8 patients who were lost to follow-up and had no available OS data (1 patient in the SG group and 7 patients in the TPC group). In the ITT population, all patients were included in both the PFS and OS analyses.(6) As described above, OS status was available for most SG and TPC patients that withdrew at the start of the study. For the PFS analysis, withdrawn patients were subject to the follwing censoring rule described in the original submission, "no adequate response assessment after randomisation", i.e., they were censored at date of death if they died prior to what would have been their second scheduled assessment, or censored at randomisation if they survived beyond what would have been their second scheduled assessment.(6) It should be noted that these censoring rules are commonly implemented in oncology studies in order to meet FDA requirements. To demonstrate that this issue does not affect the results and conclusions of ASCENT, the PFS and OS analyses (median survival, hazard ratios, and Kaplan-Meier plots) are provided in the Appendix for all patients who received allocated treatment (i.e., the safety population). These results are consistent with the PFS and OS analyses in the ITT population; the PFS hazard ratio (HR) was 0.43 and the OS HR was 0.51 for both populations.(6, 9) The patients in the TPC arm who were randomised but not treated are therefore not considered to have affected the results and conclusions of ASCENT.

<table>
<tr>
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<td>Table 1: List of tables and figures with PFS and OS analyses for the Safety Population(9)
<table>
<tr><th>Table or figure in CSR</th><th>Analysis</th><th>Table or figure in this document</th></tr>
<tr><td>Table 15.2.2.2a</td><td>Analysis of OS</td><td>Table 6</td></tr>
<tr><td>Figure 15.2.2.2c</td><td>KM estimates of OS</td><td>Figure 10</td></tr>
<tr><td>Figure 15.2.1.2a</td><td>KM estimates of PFS – independent review committee</td><td>Figure 11</td></tr>
<tr><td>Table 14.2.1.19</td><td>Sensitivity analysis of PFS – independent review analysis</td><td>Table 7</td></tr>
</table></td>
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<tr>
<td>Key issue 4: Differential attrition for the EORTC QLQ-C30 score. There was a differential attrition of ITT sample due to missing values for EORTC QLQ-C30 score at a follow-up in the SG arm (11.7%) and TPC arm (30.2%).</td>
<td>Yes/No</td>
<td>The completion rates, using the number of ITT patients who were expected to provide an HRQoL assessment at a given timepoint as denominator, were high (generally ≥90%) for both treatment arms across visits until C10D1 (i.e., the assessment visit with n ≥10 in both arms).(10) The completion rates were similar between the SG and TPC arms across visits up to C10D1.(10)

The available data rates of the EORTC QLQ-C30, using the number of ITT patients as denominator, decreased considerably over time in both treatment arms (from 95% at baseline to 18% at C10D1 and 2% at C24D1; the number of patients beyond Cycle 24 was less than 10), reflecting the decreasing number of patients who remained on treatment and alive.(10) As expected, the available data rates were much higher in the SG arm than in the TPC arm, generally reflecting that the median PFS was much longer in the SG arm than the TPC arm (4.8 months vs. 1.7 months) with chemotherapy.(4, 10) The higher rate of progression and death events early on in TPC vs SG arm also led to fewer patients providing at least one post baseline QLQ-C30 measure, resulting in a smaller proportion of patients included in PRO evaluable for TPC (69.8%) vs. SG (88.4%; Figure 1).(10)</td>
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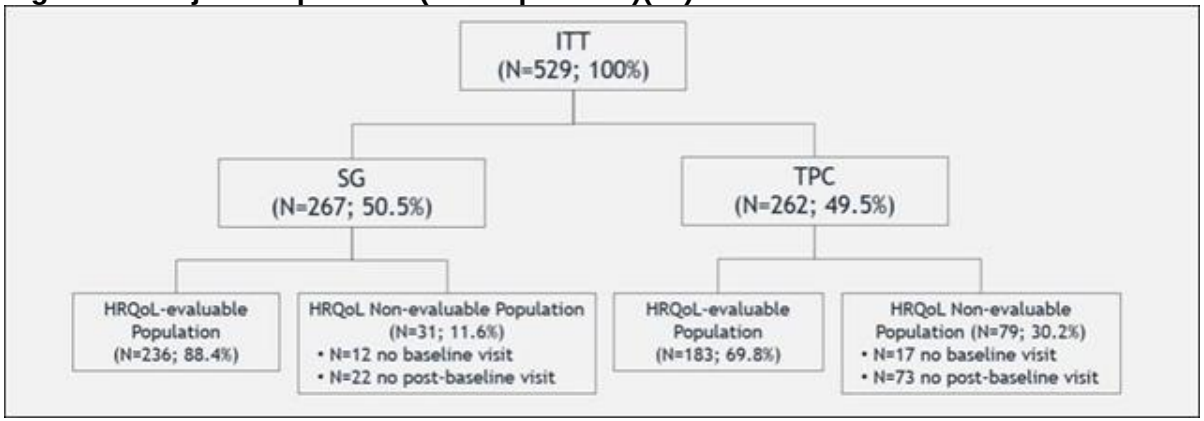
Figure 1: Subject Disposition (ITT Population)(10)



HRQoL = health-related quality of life; ITT = intent to treat; SG = sacituzumab govitecan; TPC = treatment of physician choice

Also, Table 7 and Table 8 in the PRO report provide detailed comparison of the PRO evaluable vs. ITT population and concludes that "there were no marked differences in the baseline demographic characteristics between the HRQoL evaluable population and the ITT population."(10) Therefore, even though the PRO population was a subset of ITT, it was representative of the ITT population.(10)

As specified in the PRO report, the primary reason for missing information and increased attrition in the TPC arm was earlier disease progression.(10) The linear mixed-effect models for repeated measures (MMRM) analysis assumed that patients who discontinued study treatment and stopped completing HRQoL assessments during the first six cycles of treatment would have similar HRQoL score changes as patients who continued to receive study treatment.(10) However, patients who discontinued study treatment prematurely had worse HRQoL than those who remained on treatment; therefore the HRQoL estimates from the MMRM analysis may be better than what would have been obtained if HRQoL data had been collected after treatment discontinuation and included in the analysis.(10) For this

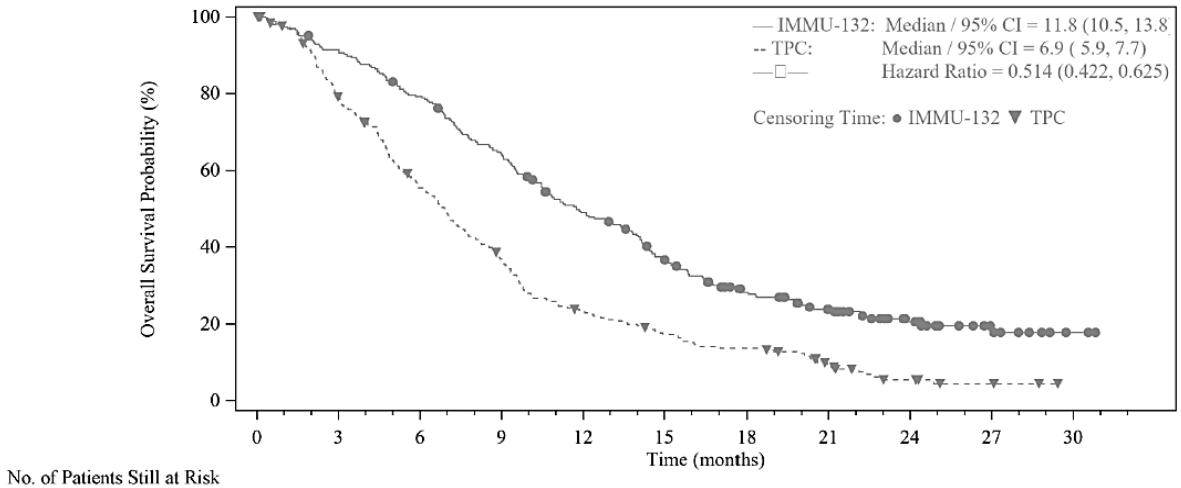
		reason, the HRQoL analysis conducted in ASCENT is likely to be biased against SG in favour of TPC.(10)
Key issue 5: Frequency of high-grade neutropenia was more frequent in the SG. High grade neutropenia was more frequent in the SG (47.20%) vs. TPC (19.80%) arm. Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the TPC arm the treatment was discontinued and no G-CSF was administered (potentially dropped out).	No	This issue misrepresents how haematological toxicities were treated in the ASCENT study and is therefore irrelevant. It is incorrect to state that neutropenic episodes in the TPC arm were treated solely by discontinuation of therapy, and not with dose reduction or G-CSF administration.(6) Any consequent inference of bias against TPC by assuming premature termination of comparator treatment (i.e., before progression occurs), or improved QoL on SG due to better treatment of neutropenia, is therefore unfounded. Neutropenia was treated optimally in the TPC arm in accordance with product labelling, as would be expected both in clinical trials and clinical practice;(8) it would be unethical and unscientific to mandate undertreatment with comparator therapies. As stated in our initial company submission, concomitant G-CSF support was administered to 23% of TPC patients, and neutropenia led to dose interruption and dose reduction in 21.4% and 19.2% of the TPC group, respectively;(4, 6) this includes 17% of patients in the TPC arm who received G-CSF as treatment for neutropenia, and 10% who received it as secondary prophylaxis.(11) Only four patients in the TPC arm were discontinued due to neutropenia, one of which was a case of febrile neutropenia.(6) In summary, neutropenia was treated appropriately and in accordance with clinical practice both for SG and TPC. The incidence and treatment of neutropenia, as well as all associated costs, have been accurately documented and modelled in the cost-effectiveness analysis.
Key issue 6: Tumour location in the lymph node was higher in the TPC arm. There were more patients	No	The small difference identified in the prevalence of lymph node metastases between the SG and TPC populations is of no consequence to the interpretation of the ASCENT clinical data, and has no influence on actual and modelled outcomes. This issue is a result of misinterpretation of the cited literature regarding the significance of lymph node metastases

who had tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.		in TNBC. The studies cited by the ERG focus on early stage TNBC where, generally, lymph node metastases are prognostic indicators for a higher risk of metastatic relapse and poorer outcomes than those without lymph node metastases(12-20). However, once a patient has been diagnosed with metastatic disease, the presence of metastases in lymph nodes is of little relevance to the subsequent course of the disease. TNBC typically metastasises to visceral organs such as the lung and liver, the central nervous system and sometimes bones,(21) and the location and distribution of these metastases are far more relevant to a patient's prognosis in mTNBC than the presence of disease in the lymph nodes.(22, 23)
Key issue 7: Early stopping of the trial. Caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment	Yes	At the time of the original submitted analysis (data cut-off 11 March 2020), 316 PFS events and 340 OS events had occurred in the primary analysis population.(6) Therefore, according to a robust statistical plan, ASCENT was stopped after it was fully recruited, with a high number of survival events having taken place.(4, 8) While the independent Data Monitoring Committee unanimously recommended stopping the trial early, additional PFS and OS events occurred during database cleaning that exceeded the original targeted event numbers.(4, 6) Further, it is by the ERG's own estimate that the data presented in the submission was mature as medians for PFS and OS have been exceeded across all endpoints in both arms.(4) In addition, the median follow-up in the primary analysis population was 17.7 months, which is a significant period of time in the context of previously treated mTNBC, which has an extremely poor prognosis and a median OS of just 15 months from diagnosis of metastatic disease, dropping to 7 months at 2nd or 3rd line treatment.(4, 24-26)

		It is therefore misleading to equate the “early” stopping of ASCENT with those trials noted in the cited paper, and to suggest that this may have exaggerated the magnitude of benefit.(27) The 105 trials described in the cited systematic review were stopped prematurely after enrolling an average of 63% of the planned sample size, in contrast to the fully enrolled ASCENT trial.(6, 27) The authors also noted a very strong correlation between number of events and magnitude of treatment effect, suggesting that the risk of overestimating clinical benefit is markedly reduced with a large event number (e.g., over 200 events).(27) As noted above in the response to Issue 2, results from the final database lock in February 2021 confirmed a sustained OS and PFS benefit of SG vs. TPC, comparable to the March 2020 data cut used in the submission, suggesting that the initial results were in no way exaggerated.(7)

Key issue 8: Log-logistic OS parametric extrapolations overestimate survival. The use of the log-logistic distribution for OS overestimates (overall) survival in the model, which extends the period over which SG accrues a survival benefit compared with TPC.		Extended survival follow-up provided in this response validates and is strongly supportive of our base case use of a joint log-logistic method to model survival extrapolation.(28) The slight exception to this is that the joint log-logistic extrapolation may overestimate long-term survival outcomes in the TPC arm, for which the generalised Gamma appears to be a better fit, as suggested by the ERG. In line with clinical expert opinion, the extended survival follow-up also clearly rules out the use of Weibull modelling for SG survival extrapolation. The choice of log-logistic curve in the base case of the economic analysis took into consideration statistical fit, clinical plausibility based on real-world evidence and input from six practicing UK clinical experts. Based on the data cut from March 11 2020, UK clinical experts suggested that the log-logistic distribution was reasonable, with none considering the Weibull as viable. Of note, one clinical expert explicitly suggested that the Weibull distribution was too pessimistic at earlier time points, with another stating that plausible extrapolations should allow for longer-term survivors as there is some long-term survivorship among these patients. More importantly, analysis of the updated data with an additional 11 months of follow-up for OS provides very strong support for the choice of the log-logistic joint fits (see Issue 2, and New Evidence Form). **1. Observed milestone estimates:** The comparison of the new OS Kaplan-Meier (KM) curves (Figure 2) vs. the parametric curves fitted to OS data available before the update (Table 2) shows that the observed OS rate for SG at 24 months (0.205; 95% CI: 0.154, 0.261) is matched by the jointly fitted log-logistic model (0.206), while the Weibull distribution (0.157) underestimates SG survival at 24 months.(28)

Figure 2: OS KM curves derived from an updated data cut with additional 11 months follow-up (February 2021 data cut)(28)



IMMU-132 = sacituzumab govitecan; KM = Kaplan-Meier; OS = overall survival; TPC = treatment of physician's choice

Table *2:* Updated OS KM (February 2021 data cut) vs. parametric estimates of OS at 24 months based on earlier data cut (March 2020 data cut)(28)

SG treatment arm			TPC treatment arm		
Observed OS rate (updated OS KM curve)	**Log-logistic treatment as a predictor***	**Weibull as stratified fit** (ERG preference)	**Observed OS rate (updated OS KM curve)**	**Log-logistic model with treatment as a predictor***	**Gen. gamma stratified** (ERG preference)*
0.205 95% CI: 0.154, 0.261	**0.206**	**0.157**	**0.055** 95% CI: 0.028, 0.094	0.083	0.057

*Parametric estimates were derived based on previous data cut (before adding 11 months of follow-up)

Additionally, for the TPC arm, the use of the log-logistic model overestimates the observed OS rate at 24 months (0.083 vs. 0.055), while the observed rate would be captured by the stratified generalised Gamma model (0.057). Since the log-logistic model overestimates the OS for TPC, its use in the base case economic analysis represents a conservative approach.

The ERG's preferred Weibull model considerably underestimates the observed 24-month rate for SG. In particular, it performed much weaker in capturing the tail after 24 months in the SG arm than the log-logistic distribution (Figure 3 and Figure 4), justifying its exclusion by clinical experts.

2. Parametric extrapolations

The exercise described in the original Company Submission, Section B.3.3, has been repeated on the new dataset. All previous conclusions in terms of model diagnostics still hold true, for the data with longer follow-up (not presented). The AIC/BICs of all fits are presented in Table 3. Based on the statistical criteria (Akaike's Information Criteria [AIC]/Bayesian Information Criteria [BIC]), the joint log-logistic distribution still fits the data best.

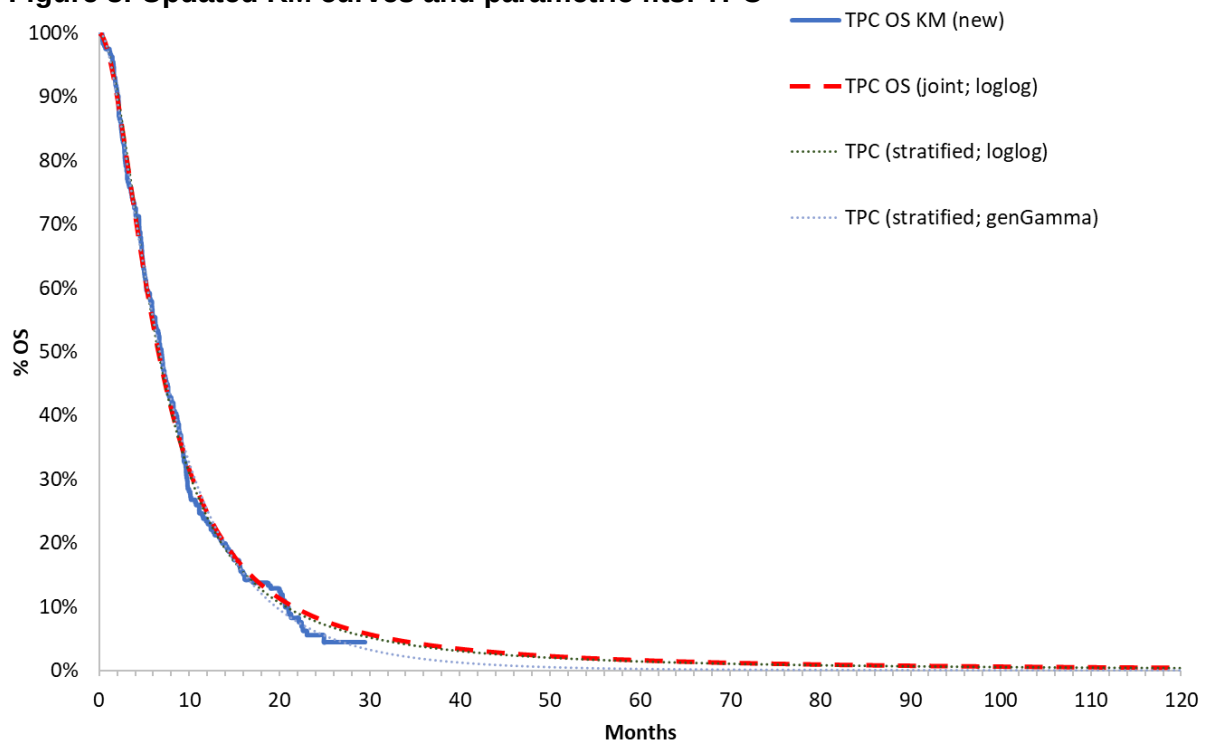
		In response to the ERG comments, we also present results of the parametric extrapolation based on the separately fitted curves (Table 3). The log-logistic model appears as the best distribution for each of the arms separately, although the generalised Gamma has very small difference, and likely a very close contender. It should be noted that the AIC for the joint log-logistic fit is lower than the sum of the AIC across the two separately fitted log-logistic curves, suggesting a preference for joint fit. Most importantly, the difference in the mean OS between SG and TPC is smaller with the jointly fitted log-logistic curves compared with separately fitted models. The joint log-logistic model overestimates the tail of the TPC arm, compared to the separate fitted models or the generalised Gamma, resulting in a higher mean OS for TPC. Therefore, the joint log-logistic model is a conservative assumption when predicting the benefit of SG. As suggested by the ERG, the generalised Gamma is a better visual fit for TPC (shown in AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; SG = sacituzumab govitecan; TPC = treatment of physician's choice Figure 3). A scenario where OS is modelled with the separately fitted generalised gamma distribution for TPC and the log-logistic curve for SG results in a -12% drop in our base case ICER, to £43,574. In summary, clinical expert opinion and new data strongly supports the use of joint log-logistic model projection in the economic analysis, clearly rules out the use of the Weibull distribution for SG and shows that the joint log-logistic model is a conservative approach as it overestimates TPC efficacy and thereby likely underestimates the efficacy benefit of SG. **Table 3: OS in the ITT population: Goodness-of-fit statistics with treatment arm as predictor and stratified models**

Joint Fits: Distribution	AIC	BIC	Median (months)		Mean (months)	
			SG	TPC	SG	TPC
Weibull	2931.42	2944.19	12.29	7.37	15.01	9.01
Log-normal	2935.70	2948.47	11.23	6.48	17.59	10.14
Log-logistic	**2916.79**	**2929.56**	**11.64**	**6.58**	**18.35**	**10.38**
Exponential	2967.07	2975.59	11.45	6.44	16.36	9.21
Gen. gamma	2920.45	2937.46	11.87	6.87	15.74	9.11
Gompertz	2956.85	2969.62	12.31	7.08	14.77	9.01

Stratified Fits: Distribution	AIC	BIC	Median (month)	Mean (month)
SG				
Weibull	1513.84	1520.97	12.37	14.94
Log-normal	1524.46	1531.59	11.37	18.80
Log-logistic	**1510.88**	**1518.01**	**11.67**	**19.10**
Exponential	1531.30	1534.87	11.45	16.36
Gen. gamma	1513.77	1524.44	12.04	15.43
Gompertz	1525.08	1532.21	12.42	14.68
TPC				
Weibull	1419.36	1426.45	7.31	9.00
Log-normal	1410.65	1417.74	6.45	9.64
Log-logistic	**1407.09**	**1414.18**	**6.58**	**10.05**

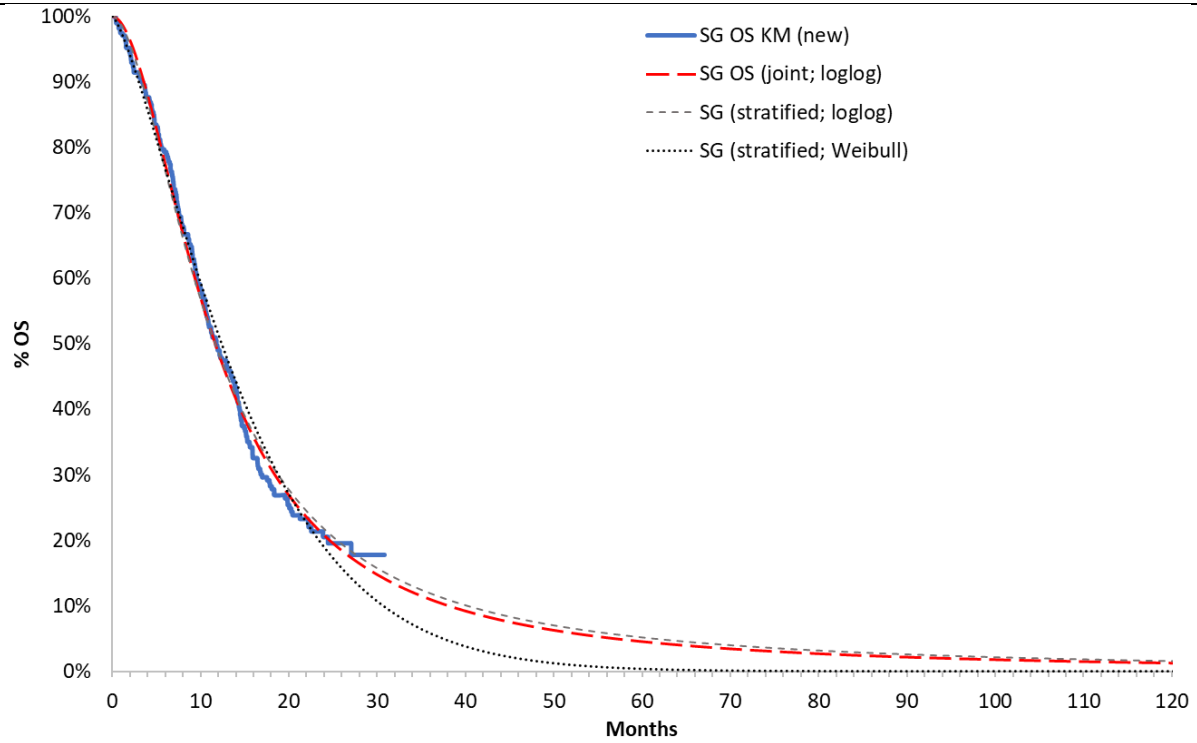
		Exponential: 1435.78 / 1439.33 / 6.44 / 9.21 Gen. gamma: 1408.75 / 1419.36 / 6.75 / 9.17 Gompertz: 1433.58 / 1440.67 / 6.98 / 9.02 AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Figure 3: Updated KM curves and parametric fits: TPC



genGamma = generalised Gamma; KM = Kaplain-Meier; loglog = log-logistic; OS = overall survival; TPC = treatment of physician's choice

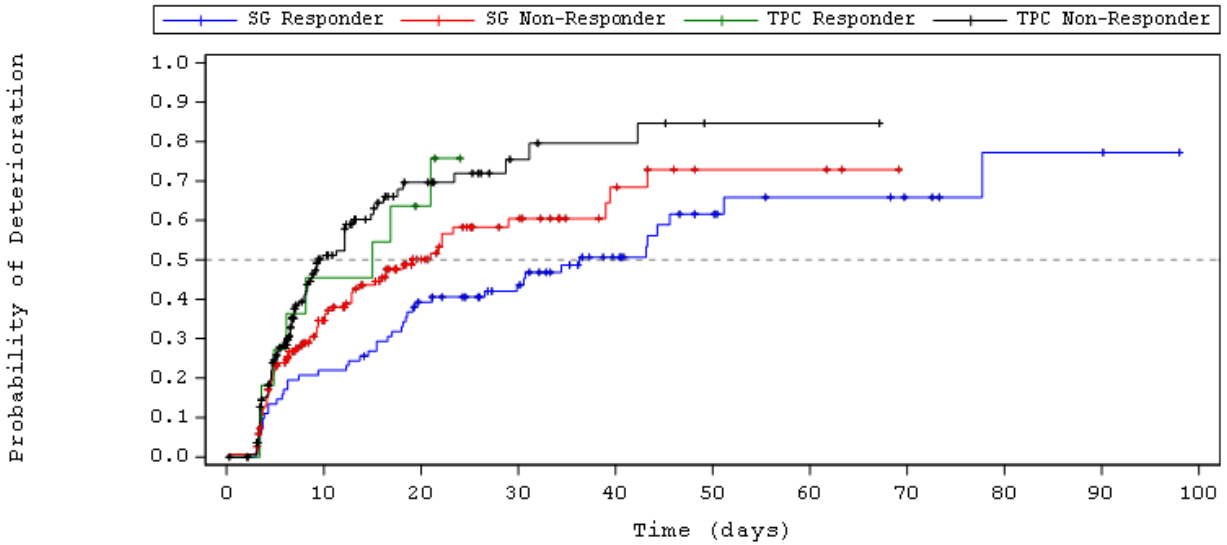
Figure 4: Updated KM curves and parametric fits: SG

		 genGamma = generalised Gamma; KM = Kaplain-Meier; loglog = log-logistic; OS = overall survival; SG = sacituzumab govitecan
Key issue 9: Pre-progression utilities with SG may not be higher than utilities with TPC. The cost-effectiveness model incorporates pre-	Yes	Higher pre-progression utility for SG vs TPC is firmly justified by the HRQoL data from the ASCENT study, which was collected using the EORTC-QLQ-C30 tool, a robust, objective, commonly used questionnaire.(29) In a linear mixed-effect regression model for repeated measures, the SG arm showed statistically significantly ($p<0.05$) and clinically meaningfully (i.e., mean difference exceeded the superiority margin) greater improvement than the TPC arm in all primary domains (global health status/QoL, physical functioning, fatigue, and pain)

progression utilities for SG of [redacted], 0.084 higher than those used for TPC, [redacted], with the difference being attributable to treatment with SG. EQ-5D utilities were obtained from a mapping algorithm which used EORTC QLQ C-30 scores from ASCENT. An analysis was presented which shows that the difference is statistically significant for utilities, despite the conclusion in the ASCENT CSR that EORTC QLQ C30 are, essentially, similar for SG and TPC.		except for role functioning, for which the SG arm still showed statistically significantly greater improvement than the TPC arm but did not reach the clinically meaningful threshold.(29) In addition, there is a strong clinical and mechanistic rationale for patients' quality of life being better in the pre-progression health state for SG vs. TPC due to the seven times greater objective response rate for SG vs TPC (31.1% vs 4.2%) in ASCENT.(6) Tumour shrinkage in patients with metastatic breast cancer has been shown to have a direct impact on quality of life through a reduction in symptoms such as pain, breathlessness and mood disturbance.(30, 31) Therefore, patients demonstrating a partial or complete treatment response based on RECIST-defined objective response criteria often experience improved quality of life compared with patients who do not achieve a deep treatment response.(30) This is further supported by a vignette study based on responses from 100 members of the general public in the UK which found that utility in metastatic breast cancer increases significantly following a treatment response ($p<0.0001$).(32) This study has been used in the analysis of previous breast cancer NICE submissions such as eribulin (TA423).(33) In addition, there were many more patients treated with SG vs. TPC with stable disease whose tumours shrunk in the pre-progression health state while not meeting the stringent criteria for response, as shown in Figure 5.(6, 34)

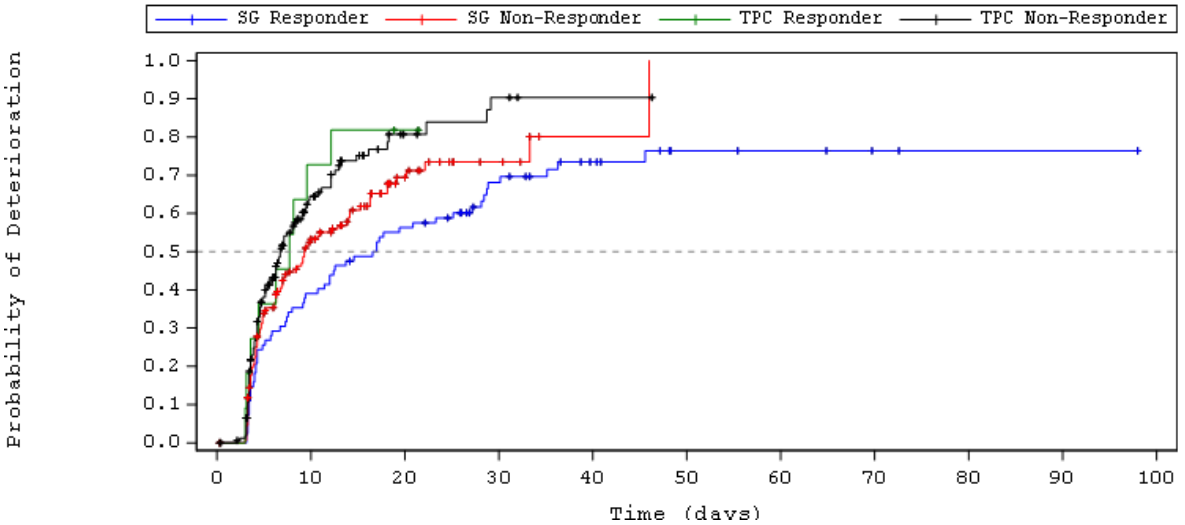
		Figure 5: Best percent change in size of the target lesion by IRC assessment (ASCENT; ITT population)(34)  Dashed lines represent ±30% change from baseline in tumour diameter IRC = independent review committee; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice Furthermore, therapeutic impact on quality of life is not only dependent on RECIST-defined objective response. A superior therapy may also maintain a patient's initial quality of life merely by delaying progression for longer than a comparator therapy. This was demonstrated by a new analysis of the ASCENT HRQoL by Loibl et al, in which patients treated with SG generally showed more favourable score changes and longer time to deterioration than patients who received TPC, regardless of clinical response status (see Figure 6 and Figure 7).(35)

Figure 6: Time to first deterioration in EORTC QLQ-C30 Physical Functioning by treatment response(35)



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Figure 7: Time to first deterioration in EORTC QLQ-C30 Role Functioning by treatment response(35)



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SG = sacituzumab govitecan; TPC = treatment of physician's choice

In summary, the pre-progression health state for SG comprises substantially deeper and broader responses compared with TPC, as well as many more patients with stable disease whose tumours have shrunk while not meeting the stringent criteria for response.(6, 34) This strongly supports a higher utility value for SG than TPC in the pre-progression state. These factors have also been independently verified by multiple Consultant Medical and Clinical Oncologists from major treatment centres across the UK, all of whom agree that it is highly plausible that treatment with SG will result in noticeably better HRQoL than with existing chemotherapies. As discussed in Issue 4, additional insight from clinical experts also suggested that the HRQoL analysis in ASCENT may actually be biased somewhat against SG due to the fact that the attrition rates in the TPC arm were much higher than SG,

		meaning patients with much worse QoL in the TPC arm were not captured in the analysis.(10)
Key issue 10: Evidence does not support higher post-progression utilities for women who received SG instead than TPC. The cost-effectiveness analysis incorporates higher post-progression utilities with SG compared with TPC (by the same factor (0.084) used for pre-progression utility. The evidence for this utility gain with SG after SG has been stopped is unclear. EORTC QLQ data collection in ASCENT was stopped just after progression.	Yes	As discussed in response to Issue 9, a higher pre-progression utility for SG vs TPC is firmly justified by the HRQoL data derived from the EORTC-QLQ-C30 tool and there is a strong rationale for patients' quality of life being better in the pre-progression health state for SG vs TPC.(6, 10, 34) Therefore, though the utility decrease post progression is similar in both arms, since the pre-progression utilities are significantly higher with SG vs. TPC, a similar drop will retain some benefit. A panel of Consultant Medical and Clinical Oncologists from major treatment centres across the UK agreed that higher quality of life for patient progressing on SG vs TPC was clinically plausible based the HRQoL data derived from ASCENT. A rationale for this is that a greater proportion of SG patients experienced a reduction in their tumour diameters, and these reductions were greater in magnitude than for TPC patients (Figure 8).(34) As a result, patients in the SG group were in general entering their progressed health state with a lower tumour burden than their TPC counterparts, consequently justifying a better quality of life in this health state.(30, 31, 34) It should be noted that, as demonstrated in Figure 8, tumour response is a continuum rather than a binary state, and that even a reduction that does not meet the threshold for confirmed response (i.e., a reduction of >30% in tumour diameter) may result in alleviation of symptoms and improved quality of life.(34)

		Figure 8: Best percent change in size of the target lesion by IRC assessment (ASCENT; ITT population)(34)  Dashed lines represent ±30% change from baseline in tumour diameter IRC = independent review committee; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Key issue 11: Post-progression therapy costs applied to TPC assume a very high proportion of people receiving eribulin. This is clinically incompatible with rates of prior and within trial eribulin, and assume more intensive therapy for longer, compared with SG.	Yes/No	The comment from the ERG touches on three separate points that have been addressed individually below. **1. Eribulin use prior to the trial:** The rate of prior eribulin use in ASCENT reflects that the study enrolled a heavily pre-treated population; patients in ASCENT received a mean of 4.5 prior systemic therapies (maximum of 17) when including neoadjuvant therapy.(5) The proposed place of therapy of SG is for patients who have received two prior lines of systemic therapy for locally advanced or metastatic TNBC. As eribulin is restricted by NICE to third-line treatment of locally advanced or metastatic breast cancer, prior eribulin use in patients eligible for SG treatment in the real-world setting would be lower than that observed in the ASCENT study.(33) **2. Post-progression therapy mix:** The ERG quote figure of [redacted] of TPC patients subsequently receiving eribulin which is inaccurate as this figure is for post-SG therapy; the actual rate of subsequent eribulin after TPC, assumed to be the proportion that did not get it as part of TPC, is 46.9%.(6) It is also important to note that these percentages are proportions of patients that actually went on to receive a subsequent therapy, not a proportion of the TPC group as a whole, and to quote these percentages without this context suggests a much higher post-progression eribulin rate than observed. Per the original company submission, only [redacted] of TPC patients went on to receive a subsequent therapy. In England, eribulin has a fixed place in the treatment algorithm as a third line therapy for metastatic disease and patients cannot receive it in earlier lines.(33, 36) Therefore, in order to better reflect the real world, the model accounted for a use of eribulin that is larger than what was observed in the trial for both arms. The values that were discussed with clinical experts as the likely proportions were [redacted] of patients, after SG, and 46.9% after TPC. We believe that this is reflective of the costs of post-progression therapies. The post-progression therapy mix has been reanalysed based on the new data cut with longer follow-up (February 2021). As expected, the proportion of patients who discontinued treatment due to progression with subsequent therapy increased to [redacted] and

[redacted] for the TPC and SG arms, respectively. The sum of the proportions of subsequent therapies in this new analysis exceeds 100% in both arms ([redacted] for TPC and SG, respectively), reflecting multiple active therapies for some patients, and suggest slightly higher subsequent therapy use after SG than TPC.

Note that the above proportions of eribulin use were retained to reflect UK treatment practice, as per the original discussions with clinical experts.

Table 4: Subsequent therapy proportions and their duration*

Treatment	Eribulin	Paclitaxel	Carboplatin	Capecitabine	Epirubicin	Vinorelbine
Subsequent therapy use						
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	46.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration (weeks)						
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: epirubicin numbers reflect doxorubicin patients as well.
*Based on final Feb 25 2021 datacut and UK clinical opinion for eribulin use, among the patients who had discontinued treatment due to progression, and had at least one recorded subsequent therapy. The sum of the proportions of subsequent therapies in the new exceeds 100% in both arms (144.8% and 150.7% for TPC and SG, respectively), reflecting multiple active therapies for some patients.
Source: Trial data analysis, Gilead, data on file. Eribulin treatment percentage: UK clinicians.

A scenario using trial-based post-progression therapy distribution was run, with eribulin use among those who received subsequent therapy of [redacted] after SG and [redacted] after TPC. This had a marginal impact on the ICER (£51,057; see Table 5).

3. Duration of post-progression therapies

Analysis of more complete subsequent therapy duration data from the new data cut shows that any post-progression therapy was taken for a similar treatment duration in both arms,

		which is to be expected as there is no clinical or scientific reason to believe that treatment with either SG or TPC would result in a different subsequent therapy duration. We considered the ERGs suggestion as reasonable and have run a scenario with their assumption (see Table 5). Overall, the following modifications are made to post-progression therapy modelling. • Proportion of patients receiving subsequent therapy: [redacted] and [redacted] for SG and TPC respectively based on updated data-cut • Proportion of eribulin use post-progression: no change as it reflects the UK clinical pathway • Duration of post-progression therapy: use updated data, reflecting several more episodes of subsequent therapies (see Table 4) • Scenarios: 1) ERG recommended durations; 2) fully trial based analysis
Key issue 12: Acquisition and administration costs of SG and TPC are incorrectly underestimated. Acquisition and administration costs are applied in the model as a cost per (model) cycle (equal to 1 week), calculated as the total cost per therapy cycle (generally over 3 weeks) divided by 3. However, this approach underestimates acquisition and	No	The drug acquisition cost, administration cost and concomitant medication cost are calculated by assigning per model cycle average cost (converted from treatment cycle cost) to the proportion of patients who remain on treatment for each model cycle. It is indeed a simplified approach, but it was selected because the administration schedules with SG and TPC (eribulin, vinorelbine, gemcitabine, and capecitabine) are relatively evenly spread within each treatment cycle: SG is given on Week 1 and Week 2 of a 3-week treatment cycle; similarly, eribulin is given on Week 1 and Week 2 of a 3-week treatment cycle; vinorelbine is given weekly; gemcitabine is given on Week 1, 2, 3 of a 4-week treatment cycle; capecitabine is given daily.(4) Therefore, it was expected that the proportion of patients who might die during the break of each treatment cycle would have reasonably minimal impact on cost estimations. The extent to which the underestimation would differ on both arms (i.e., incremental) and consequently the impact on ICER is essentially neglectable. For the cost-effectiveness analysis where the incremental cost is used for generating ICER result, it is considered an appropriate approach. It is incorrect to state “incorrectly

administration costs because costing by model cycle does not assign a proportion of the costs to people that die in (model) cycle 2 and 3 of every therapy cycle. Overall, the model generates underestimates of therapy costs, however the underestimates differ by therapy due to differences in prices, in administration patterns and costs and by type of prescriptions (oral vs IV).		underestimated".
Key issue 13: The relative dose intensity (RDI) applied to the cost of SG and TPC may not be calculated correctly. The methods used to calculate the RDI applied in the model are not described. The use of the safety / exposure RDI may underestimate treatment costs because doses discarded result in lower exposure but not in lower	No	The ASCENT trial showed very few patients with dose interruptions (i.e., 10 out of 258 patients in SG arm).(5) 64 patients in the SG arm had dose reductions and 157 had dose delays.(5) The company understands that any dose discarded because of interrupted infusions is associated with a cost, however, given the very small number of patients with interrupted doses in ASCENT trial SG arm, the extent of the potential underestimation would be minimal. Therefore, the RDI of 94.2% reported in ASCENT for SG and used in the model should still be a solid input for base case.(5) The company submission has also presented two scenarios related to RDI for SG and TPC: • 94.2% for SG and 84% for TPC; 84% was extracted from eribulin trial EMBRACE (safety population) which was also used in eribulin NICE submission (TA423). The RDI for eribulin in EMBRACE trial was calculated as "actual dose intensity/planned dose intensity".

costs.		• 100% for SG and TPC as extreme value testing.
Key issue 14: Wastage, for drugs used in this appraisal, is not part of the NHS perspective	No	Vial sharing does take place to minimise wastage in UK clinical practice. Acknowledging the absence of data to precisely quantify the percentage, the company model adopted the same approach as a recent NICE submission in a related disease area (trastuzumab deruxtecan in HER2-positive metastatic breast cancer, NICE submission TA704).(37) The assumption of 50% vial sharing was broadly accepted by the ERG and the Committee of TA704.(37) The acceptance of 50% vial sharing is a directly relevant precedent to the current appraisal, since the formulations of both SG and trastuzumab deruxtecan are powder for concentrate for solution for infusion, and dosage for both products is calculated using a weight-based approach.(38, 39) There is therefore no justification for inconsistency with the approach taken in TA704. This assumption was supported by a clinical expert in the UK quoted in NICE submission TA704 who confirmed that "in clinical practice drug wastage is recognized and efforts are made to minimize it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain".(37) In terms of perspective, vial sharing ultimately over time reduces the amount of product ordered at individual hospitals, consequently reducing the cost to the NHS.
Key issue 15: The model uses different weight distributions for the cost calculation of SG and TPC. The cost of SG is calculated using a non-parametric distribution directly calculated using percentiles of weight from the ASCENT trial (non-US) population. This distribution is slightly skewed towards lower	No	The company used the best available evidence based on the patient-level data of ASCENT trial, in order to estimate the SG cost accurately by assigning a weight distribution that was derived specifically to be aligned with the required dosage per number of vials for SG patients (i.e., 19.1kg-38.21kg, 38.21-57.31kg, so on so forth). Overall, using a parametric distribution versus using the trial-observed non-parametric weight distribution has almost neglectable impact on SG cost estimation. Given the treatments in the TPC arm are generally very low in their costs, parametric versus non-parametric BSA distribution would make even smaller impact. The company has also tested using parametric weight distribution (normal) for SG drug cost calculation, and the ICER would improve/reduce from £49,651 (original base case) to £49,354 (new using ERG preferred approach). This further proves that the company's

weight percentiles compared with the parametric (using the same mean and standard deviation) normal distribution used for TPC.		selected approach is from a conservative perspective.
Other issues identified by NICE technical team (not included in the ERG report): **Ongoing rollover study**. Please could you provide more details on the ongoing rollover study. Did this allow people in the comparator arm to crossover to the treatment arm? Or the study only includes people originally randomsied to have sacituzumab govitecan? What additional data will it provide?	No	The rollover study (IMMU-132-14) evaluates safety outcomes in patients who were initiated on SG in another study, are continuing to receive clinical benefit from continuation of SG therapy and are tolerating therapy at the time of enrolment.(40) The study captures patients from multiple "parent" studies of SG in solid tumours, including the ASCENT study.(40) The objective of this study is to evaluate long-term safety in patients with metastatic solid tumours who are benefitting from continuation of SG.(40) The study is not intended to allow cross-over from comparator therapy to SG. Therefore, there is no follow-up of TPC patients from ASCENT in this rollover study.(40) The data that the rollover study will provide are the percentage of patients experiencing any adverse events, serious adverse events or laboratory abnormalities for a period of up to approximately three years from a patient's first dose of SG.(40) Further information regarding the rollover study can be found on ClinicalTrials.gov.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
-	-	-	-

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

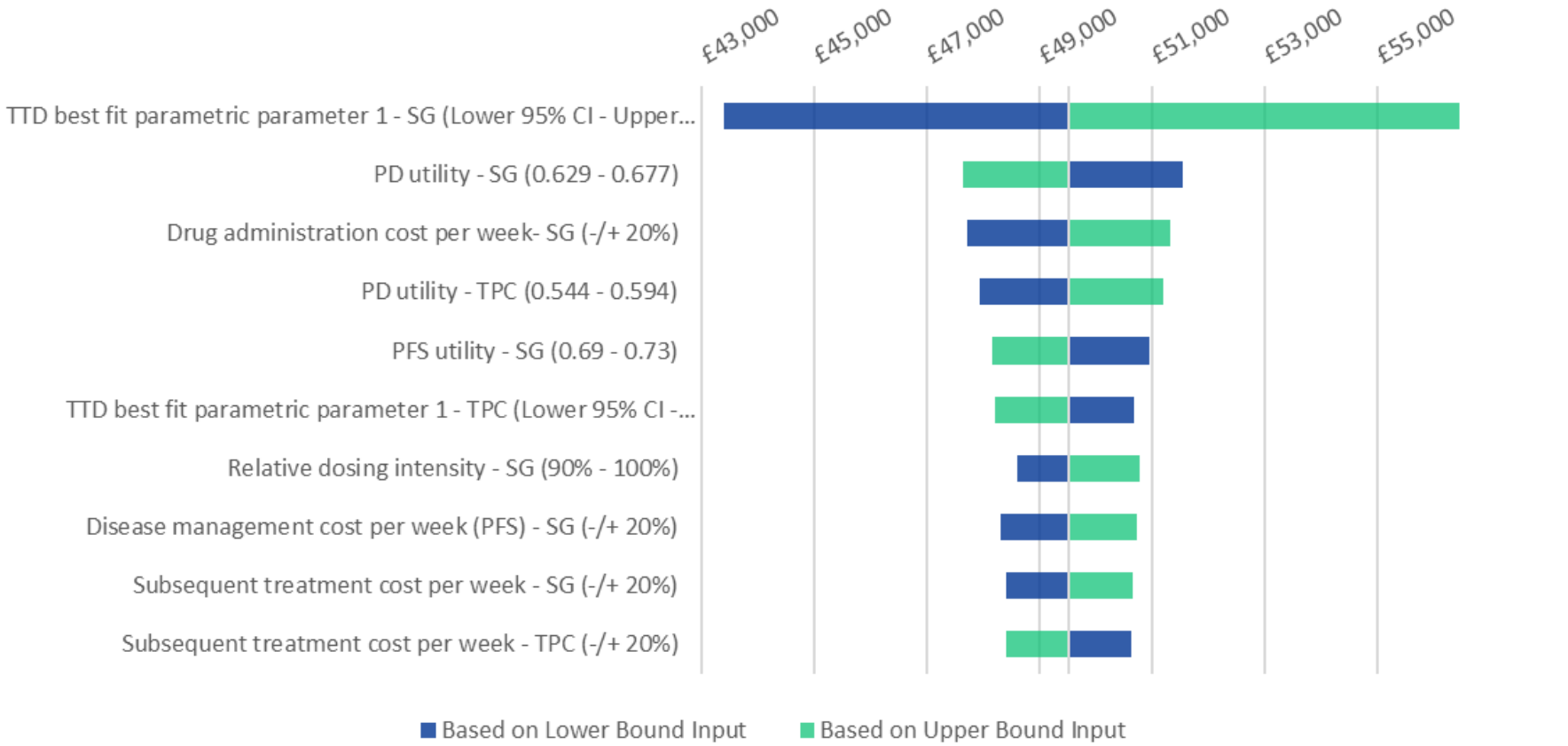
Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
ERG report Table 43 "ERG's revised ICERs, QC and corrections" (Section 5.5)	Vinorelbine cost calculation (considering wastage) did not include a dose option of 40 mg	Changes made to include a dose of 40 mg as an option in the cost calculation (according to ERG's preference)	£49,673 (after the change) versus £49,651 (original base-case ICER) +£22; +0.04%
ERG report Table 43 "ERG's revised ICERs, QC and corrections" (Section 5.5)	Half cycle correction was applied to the drug costs (acquisition, administration, and concomitant drugs)	Half cycle correction removed.	£49,181 (after the change) versus £49,651 (original base-case ICER) -£470; -0.96%
Company's base case after incorporating ERG's QC comments and corrections	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Corrected base-case ICER: **£49,202** -£449; -0.91%
ERG report Issue 8 "Log-logistic OS parametric extrapolations	OS long-term extrapolations for SG and TPC were estimated by a jointly fitted parametric model log-logistic distribution (i.e., best	OS extrapolations for SG and TPC updated based on new trial data cut (with additional 11 months of follow-up). Jointly fitted	£48,783 (with new data cut for OS and treatment duration) versus £49,202 (corrected base-case ICER)

overestimate survival" (Section 4.9.2)	statistical fit), based on trial data from the March 2020 datacut.	parametric model log-logistic distribution is still deemed to be the most appropriate estimation (see details in Company's response to Issue 8). Treatment duration estimation updated accordingly using the new data cut, though it is not a part of issue discussion.	-£419; -0.86%
ERG report Issue 11 "Post-progression therapy costs applied to TPC…" (Section 5.4.5)	Post-progression therapy (e.g., treatment distribution and duration) was informed by trial data that was available at the time of the original submission, as well as consultations with UK clinical experts.	Subsequent treatment cost estimation (including the percentage of patients receiving subsequent treatment in each arm, treatment distribution, and duration on subsequent treatment) updated based on new trial data (with additional 11 months of follow-up). Details can be found in company's response to Issue 11.	£49,938 (with new data for post-progression therapy) versus £49,202 (corrected base-case ICER) +£736; +1.47%
Company's base case following technical engagement (or revised base case)	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**Revised base-case ICER including all changes above: £49,516**

Sensitivity analyses around revised base case

Sensitivity analyses have been re-run based on the revised base case. Results are presented in this section (Table 5 and Figure 9).

Figure 9. Tornado diagram for the new base case (PAS price)



CI = confidence interval; PAS = patient access scheme; PD = progressive disease; PFS = progression-free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTD = time to discontinuation

Table 5. Scenario analysis around the new base case (PAS price)

Parameter	Base case	Scenario	ICER/QALY (PAS price)	% Change from base case
Base case			**£49,516**	**--**
Model settings				
Time horizon	10 years	5 years	£53,597	8.24%
		15 years	£48,373	-2.31%
Discounting	3.5% for both costs and outcomes	1.5% for both costs and outcomes	£48,530	-1.99%
PFS extrapolation	Stratified fit model: lognormal for SG and log logistic for TPC (best statistical fit)	Stratified fit model: Weibull for SG and TPC (pessimistic assumption for long-term estimation)	£50,671	2.33%
		Stratified fit model: log logistic for SG and lognormal for TPC (2nd best statistical fit)	£49,323	-0.39%
		KM + Parametric fit (Stratified fit model: lognormal for SG and log logistic for TPC)	£50,642	2.27%
OS extrapolation	Joint fit model: log logistic for both SG and TPC (best statistical fit)	Joint fit model: generalised Gamma for both SG and TPC (pessimistic assumption for long-term estimation and 2nd best statistical fit)	£53,552	8.15%
		KM + Parametric fit (Joint fit model: log logistic for both SG and TPC)	£44,390	-10.35%

Parameter	Base case	Scenario	ICER/QALY (PAS price)	% Change from base case
Base case			**£49,516**	**--**
		Stratified fit model: log-log for SG (best stats fit based on new data cut and clinical plausible) and generalised Gamma for TPC **This scenario is newly added in response to ERG's preference**	£43,574	-12.00%
Treatment duration	Based on TTD parametric fitting model separately fitted to trial observed data: exponential for both SG and TPC (best statistical fit)	Based on TTD parametric fitting model separately fitted to trial observed data: KM + Parametric fit (exponential for both SG and TPC)	£49,730	0.43%
		Based on TTD parametric fitting model separately fitted to trial observed data: Weibull for both SG and TPC (second best statistical fit)	£49,605	-0.02%
		Based on TTD KM curve (mature) for both SG and TPC **This scenario is newly added since KM curves are now complete.**	£49,585	0.14%
Post-progression therapy mix **This scenario is newly added to explore the impact of subsequent treatment on model result (in response to Issue 11)**	Based on ASCENT trial (new data cut) and UK clinicians' opinions	Fully trial-based subsequent treatment distribution	£51,057	2.91%
		Duration on subsequent treatment: 12.5 weeks (SG) and 9.5 weeks (TPC) **This scenario is newly added using ERG preferred settings (assumption not supported by the trial data or clinical opinion).**	£51,062	2.92%
Relative dosing intensity	94.2% for SG; assumed the same for TPC	84% for TPC (assumed equal to the RDI presented in Eribulin NICE TA423)	£50,075	1.13%

Parameter	Base case	Scenario	ICER/QALY (PAS price)	% Change from base case
Base case			**£49,516**	**--**
		100% for SG and TPC	£50,365	1.71%
% of wastage (likelihood of vial sharing not feasible in clinical practice)	50% of wastage	100% of wastage	£52,125	5.27%
		0% of wastage	£46,907	-5.27%
Utility analysis mapping algorithm from EORTC QLQ-C30 collected in ASCENT trial to EQ-5D-3L	Longworth et al. 2014	Crott et al. 2010	£45,963	-7.18%
AE disutility	Exclude	Include	£49,588	0.14%

AE = adverse event; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = European Quality of Life Five Dimension; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year; RDI = relative dose intensity; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTD = time to discontinuation;

Appendix

Table 6: Table 15.2.2.2a analysis of OS - safety population(9)

Figure 10: Figure 15.2.2.2a KM estimates of OS – safety population(9)

Figure 11: Figure 15.2.1.2a KM estimates of PFS – independent review committee safety population(9)

Table 7: IMUU-132-05 Final. Sensitivity analysis of PFS - independent review analysis 5 safety population(9)

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39. Daiichi Sankyo UK Limited. Enhertu 100 mg powder for concentrate for solution for infusion - Summary of Product Characteristics. 2021.

40. ClinicalTrials.gov. Rollover Study in Subjects With Metastatic Solid Tumors Benefiting From Therapy With Sacituzumab Govitecan 2021 [Available from: https://clinicaltrials.gov/ct2/show/NCT04319198.

NICE National Institute for Health and Care Excellence

Clinical expert statement and technical engagement response form

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

Thank you for agreeing to comment on the evidence review group (ERG) report for this appraisal, and for providing your views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature. The ERG report and stakeholder responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

In part 1 we are asking for your views on this technology. The text boxes will expand as you type.

In part 2 we are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report (listed in 1.1 with more explanation in sections 1.4 and 1.5). You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

A clinical perspective could help either:

- resolve any uncertainty that has been identified OR

- provide missing or additional information that could help committee reach a collaborative decision in the face of uncertainty that cannot be resolved.

In part 3 we are asking you to provide 5 summary sentences on the main points contained in this document.

Please do not embed documents (such as a PDF) in a submission because this may lead to the information being mislaid or make the submission unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include **journal articles** in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Please note, part 1 can be completed at any time. We advise that **part 2** is completed after the expert engagement teleconference (if you are attending or have attended). At this teleconference we will discuss some of the key issues, answer any specific questions you may have about the form, and explain the type of information the committee would find useful.

Clinical expert statement

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

NICE National Institute for Health and Care Excellence

Deadline for comments by **5pm** on **<<insert deadline>>**. Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

NICE National Institute for Health and Care Excellence

Part 1: Treating locally advanced or metastatic triple-negative breast cancer and current treatment options

Table 1 About you, aim of treatment, place and use of technology, sources of evidence and equality

1. Your name	Dr Alicia Okines
2. Name of organisation	The Royal Marsden Hospital, London
3. Job title or position	Consultant medical oncologist
4. Are you (please tick all that apply)	☐ An employee or representative of a healthcare professional organisation that represents clinicians? ☒ A specialist in the treatment of people with triple-negative breast cancer? ☐ A specialist in the clinical evidence base for triple-negative breast cancer or technology? ☐ Other (please specify):
5. Do you wish to agree with your nominating organisation's submission? (We would encourage you to complete this form even if you agree with your nominating organisation's submission)	☒ Yes, I agree with it ☐ No, I disagree with it ☐ I agree with some of it, but disagree with some of it ☐ Other (they did not submit one, I do not know if they submitted one etc.)
6. If you wrote the organisation submission and/or do not have anything to add, tick here. (If you tick this box, the rest of this form will be deleted after submission)	☐ Yes
7. Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None

8. What is the main aim of treatment for triple-negative breast cancer? (For example, to stop progression, to improve mobility, to cure the condition, or prevent progression or disability)	To improve symptoms, improve or maintain quality of life and to prolong life
9. What do you consider a clinically significant treatment response? (For example, a reduction in tumour size by x cm, or a reduction in disease activity by a certain amount)	A reduction in tumour size will usually correlate with improved symptoms, but the magnitude of reduction required to improve symptoms depends upon other factors including the site of the metastatic disease, overall cancer burden and symptom burden at initiation of therapy. RECIST criteria used in clinical trial reporting require a 30% reduction in the sum of the diameter of target lesions. This usually correlates well with symptomatic benefit, although patients with more minor responses may also have symptomatic improvement.
10. In your view, is there an unmet need for patients and healthcare professionals in triple-negative breast cancer?	Undoubtably. The median survival for patients with metastatic TNBC of around 18 months from diagnosis falls very short of that now expected for metastatic ER+ breast cancer or HER2+ breast cancer (each approximately 5 years). This is a rapidly progressive, aggressive and relentless disease against which many standard treatments are either ineffective or only briefly effective, followed by early progression.
11. How is triple-negative breast cancer currently treated in the NHS? • Are any clinical guidelines used in the treatment of the condition, and if so, which? • Is the pathway of care well defined? Does it vary or are there differences of opinion between professionals across the NHS? (Please state if your experience is from outside England.)	Early TNBC: Except for small (<20mm) node negative tumours, neo-adjuvant chemotherapy (NAC) with an anthracycline, taxane and carboplatin is now the standard of care. For patients without a complete pathological response to NAC, adjuvant capecitabine is recommended. This is fairly standard across the NHS, although the incorporation of carboplatin is likely incomplete across the UK as the data supporting a longer-term benefit of this addition was only presented in 2021. Locally advanced or metastatic TNBC:

• What impact would the technology have on the current pathway of care?	1st line therapy is determined by PDL-1 status: Patients with PDL-1 positive cancers are advised nab-paclitaxel and atezolizumab (TA639) due to improved PFS and OS. Patients with PDL-1 negative cancers have an even greater unmet need, especially those who have previously received an anthracycline, taxane, platinum and capecitabine as treatment for early breast cancer. Such patients may be offered a re-challenge of any one of these agents depending on the relapse-free interval and response in the neo-adjuvant setting. For patients with de novo TNBC (ie no prior treatment for early breast cancer) with PDL-1 negative disease may be offered a taxane, anthracycline or capecitabine (the latter if they prefer an oral therapy without hair loss, noting that this is outside the license and NICE guidance) 2nd line therapy will again be one of the standard chemotherapy regimens 3rd line therapy is eribulin (TA515) Fewer patients with metastatic TNBC receive treatment beyond 3rd line. Eribulin should ideally be an option in the first/second-line setting for patients who have already received anthracycline, taxane, platinum +/- capecitabine for early breast cancer, as is the standard of care in many other countries. Guidelines: The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines (ABC5, 2020) are used for treatment of the condition. The American Society of Clinical Oncology (ASCO) also provide guidelines for the condition (Moy B et al., J Clin Oncol 2021)
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice? • How does healthcare resource use differ between the technology and current care?	• Currently used for selected patients via a compassionate access scheme. • Secondary care/specialist clinics only • Training on drug preparation required, nil else.

• In what clinical setting should the technology be used? (for example, primary or secondary care, specialist clinic) • What investment is needed to introduce the technology? (for example, for facilities, equipment, or training)	
13. Do you expect the technology to provide clinically meaningful benefits compared with current care? • Do you expect the technology to increase length of life more than current care? • Do you expect the technology to increase health-related quality of life more than current care?	Yes, the ASCENT trial demonstrated a clear survival benefit over the therapy of physician's choice, which, other than gemcitabine monotherapy, was representative of the standard of care in the UK. Yes. Responses to therapy improve health-related quality of life and this treatment has approximately 7x the chance of giving patients a response to therapy. It is well-tolerated in clinical practice and prolongs the duration of disease control and therefore the duration of good quality of life.
14. Are there any groups of people for whom the technology would be more or less effective (or appropriate) than the general population?	No, Trop 2 testing is not an established biomarker for SG and the Forest plot demonstrated benefit across all clinical subgroups.
15. Will the technology be easier or more difficult to use for patients or healthcare professionals than current care? Are there any practical implications for its use? (For example, any concomitant treatments needed, additional clinical requirements, factors affecting patient acceptability or ease of use or additional tests or monitoring needed)	The technology is just as easy to use for patients and clinicians as current care. The drug preparation and infusion times are slightly longer, but otherwise there are no differences.

16. Will any rules (informal or formal) be used to start or stop treatment with the technology? Do these include any additional testing?	No, scans and blood tests will be used to determine response and clinical benefit as per the current standard of care.
17. Do you consider that the use of the technology will result in any substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation? • Do the instruments that measure quality of life fully capture all the benefits of the technology or have some been missed? For example, the treatment regimen may be more easily administered (such as an oral tablet or home treatment) than current standard of care	The psychological benefit of receiving a therapy that you know has a high chance of efficacy cannot be ignored.
18. Do you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits and how might it improve the way that current need is met? • Is the technology a 'step-change' in the management of the condition? • Does the use of the technology address any particular unmet need of the patient population?	Yes, the response rate and overall survival benefit make this technology a step-change in the management of this condition Patients with metastatic TNBC have an unmet need for effective therapies and a poorer median survival than other patients with advanced breast cancer, as outlined above. Patients with PDL-1 negative TNBC who cannot benefit from immunotherapy have a particular unmet need.
19. How do any side effects or adverse effects of the technology affect the management of the condition and the patient's quality of life?	The side effects are manageable with supportive medications and dose reductions when needed. They are very unlikely to negatively impact on most patients' QoL
20. Do the clinical trials on the technology reflect current UK clinical practice? • If not, how could the results be extrapolated to the UK setting?	Yes, the study population is representative of the UK TNBC population in terms of both demographics and previous treatments. The high rate of eribulin as TPC in the study confirms a fair comparator as this is the most effective chemo drug we have for previously treated TNBC. The most important outcomes of RR, PFS, OS and HRQoL were measured.

• What, in your view, are the most important outcomes, and were they measured in the trials? • If surrogate outcome measures were used, do they adequately predict long-term clinical outcomes? • Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently?	No surrogate outcome measures were used. No additional AEs have come to light; the drug has been available to patients in the USA for almost 2 years and ongoing clinical trials in ER+ breast cancer and other tumour types have not revealed any new safety information.
21. Are you aware of any relevant evidence that might not be found by a systematic review of the trial evidence?	No
22. How do data on real-world experience compare with the trial data?	None available that I am aware of
23. NICE considers whether there are any equalities issues at each stage of an appraisal. Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics. Please state if you think this appraisal could • exclude any people for which this treatment is or will be licensed but who are protected by the equality legislation	None that I am aware of

• lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population • lead to recommendations that have an adverse impact on disabled people. Please consider whether these issues are different from issues with current care and why. More information on how NICE deals with equalities issues can be found in the NICE equality scheme. Find more general information about the Equality Act and equalities issues here.	

Part 2: Technical engagement questions for clinical experts

We welcome your comments on the key issues below, but you may want to concentrate on issues that are in your field of expertise. If you think an issue that is important to clinicians or patients has been missed in the ERG report, please also advise on this in the space provided at the end of this section.

The text boxes will expand as you type. Your responses to the following issues will be considered by the committee and may be summarised and presented in slides at the appraisal committee meeting.

For information: the professional organisation that nominated you has also been sent a technical engagement response form (a separate document) which asks for comments on each of the key issues that have been raised in the ERG report. These will also be considered by the committee.

Table 2 Issues arising from technical engagement

Key issue 1: Variation in prior therapy The number and types of prior therapies that patients received varied across the countries that participated in the trial. This limits the generalisability of ASCENT trials results to the UK setting.	I disagree. All patients had received taxanes, the majority had received an anthracycline and cyclophosphamide and capecitabine, which is what we would expect in the UK in this setting. The rate of PDL-1 use is slightly lower than we would expect, but not significantly as although approximately 40% of TNBC are PDL1 positive, not all will receive immunotherapy.
Key issue 2: Long term effectiveness/safety data uncertainties Lack of longer-term effectiveness/safety data. The	Regrettably the disease and setting under study has a very poor prognosis, so longer term follow up is not required.

median (range) of ASCENT study follow-up was 8.38 (0-24) months.	The median follow-up reported in the NEJM was 17.7 months (range 5.8-28.1 months). The majority of patients had therefore already sadly died when the study was reported.
Key issue 3: Imbalance in the randomised but untreated patients across groups There was a notably higher proportion of randomised but untreated patients (consent withdrawals) in TPC (14.5%) vs. SG (3.4%) treatment group. The ERG is uncertain how the company handled these data in terms of follow-up, inclusion, imputation, or censoring matters.	This is inevitable for an open label study when the investigational agent has shown such promise in phase 2 (Bardia et al., NEJM 2019), which both patients and clinicians will have been aware of following presentation of the results during study recruitment. The study could not be blinded due to the variety of regimens (including oral cape) in the TPC arm.
Key issue 4: Differential attrition for the EORTC QLQ-C30 score There was a differential attrition of ITT sample due to missing values for EORTC QLQ-C30 score at a follow-up in the SG arm (11.7%) and TPC arm (30.2%).	Patients on the TPC arm deteriorated and died much earlier than those on the SG arm, therefore this attrition is inevitable.
Key issue 5: Frequency of high-grade neutropenia was more frequent in the SG	The TPC arm also included oral capecitabine which rarely causes high grade neutropenia. These are different drugs and the rates of toxicity including grade 3-4 neutropenia are inevitably different. More patients will have required GCSF on the SG arm as patients received the

Clinical expert statement

High grade neutropenia was more frequent in the SG (47.20%) vs. TPC (19.80%) arm. Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the TPC arm the treatment was discontinued and no G-CSF was administered (potentially dropped out).	treatment for longer due to the higher efficacy combined with 13% of patients on the TPC arm receiving capecitabine, which almost never required GCSF. Management of TPC in trials is usually matched to routine clinical practice, which would involve dose reductions and where necessary, secondary prophylaxis with GCSF. The permitted use of GCSF in the study was in keeping with routine clinical practice for both study arms. More patients did not drop out of the TPC arm due to adverse events such as grade 3-4 neutropenia (5% drop out due to AEs for both arms); patients in the TPC arm mostly dropped out due to progressive disease as they were receiving less effective therapy.
Key issue 6: Tumour location in the lymph node was higher in the TPC arm There were more patients who had tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically	Axillary lymph node involvement confers a poorer prognosis in early (operable) breast cancer but does not impact on prognosis in metastatic breast cancer. Liver metastases are associated with a poorer prognosis in advanced breast cancer and the rates were well matched between the arms.

beneficial treatment effect of SG compared to TPC is exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.	
Key issue 7: Early stopping of the trial Caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment.	The IDMC recommended the study was terminated early as the benefit of SG had already reached statistical significance. Patient accrual had been completed and the median follow up was over 17 months. Early presentation was permitted to ensure earlier access to this effective drug for a patient population with significant unmet need. I do not think this has influenced the positive results of the study.
Key issue 8: Log-logistic OS parametric extrapolations overestimate survival The use of the log-logistic distribution for OS overestimates (overall) survival in the model, which extends the period over which SG accrues a survival benefit compared with TPC.	

Key issue 9: Pre-progression utilities with SG may not be higher than utilities with TPC The cost-effectiveness model incorporates higher pre-progression utilities for SG than those used for TPC, with the difference being attributable to treatment with SG. EQ-5D utilities were obtained from a mapping algorithm which used EORTC QLQ C-30 scores from ASCENT. The EORTC QLQ data were strongly affected by attrition (in excess of 30% of the initial sample in TPC but far lower in SG).	Higher pre-progression utilities are to be expected with a more effective treatment with a much (x7) higher response rate. This is an aggressive cancer which rapidly progresses and frequently causes patients symptoms such as pain. Patients with response to therapy usually gain symptomatic benefit from the treatment, so have better utilities. When this response is maintained for several months as it is commonly with SG, the utilities may continue to rise as patients return to higher levels of functioning at home/at work.
Key issue 10: Evidence does not support higher post-progression utilities for women who received SG instead than TPC The cost-effectiveness analysis incorporates higher post-progression utilities with SG compared with TPC.	Higher post progression utilities are also to be expected after an effective therapy. Due to the higher response rate and longer duration of response, patients will have a lower disease/symptom burden at progression than those who never responded to chemo and progressed radiologically and symptomatically on the TPC arm. It will therefore take loinger to deteriorate post-progression and higher utilities will therefore be maintained for longer. Again, this is to be expected when effective therapies are compared to much less effective ones in advanced cancer treatment

Clinical expert statement

The evidence for this utility gain with SG after SG has been stopped is unclear. EORTC QLQ data collection in ASCENT was stopped just after progression. Women receive a similar mix of therapies in SG and TPC in ASCENT.	Whilst it's a pity that utilities were not collected for long after progression, patients will have started new therapies which would then influence utilities due to side effects or clinical benefit from the new treatment
Key issue 11: Post-progression therapy costs applied to TPC assume a very high proportion of people receiving eribulin, clinically incompatible with rates of prior and within trial eribulin, and assume more intensive therapy for longer, compared with SG. The costs of post-progression therapies applied in the model are not consistent with the time left in the model before death.	As eribulin is only available in the 3rd line in the UK, high rates of eribulin use are to be expected; most patients who have progressed on TPC will receive eribulin if they have not already received it, as would be the case for patients in the UK. Eribulin is the most effective chemotherapy drug we have available in the UK for TNBC at present, so most oncologists will recommend it after progression on standard first and second line therapies.
Key issue 12: Acquisition and administration costs of SG and TPC are incorrectly underestimated Acquisition and administration costs are applied in the model as a cost per (model) cycle	The risk of death during the first 3 cycles was very low on both arms in the study

(equal to 1 week), calculated as the total cost per therapy cycle (generally over 3 weeks) divided by 3. However, this approach underestimates acquisition and administration costs because costing by model cycle does not assign a proportion of the costs to people that die in (model) cycle 2 and 3 of every therapy cycle. Overall, the model generates underestimates of therapy costs, however the underestimates differ by therapy due to differences in prices, in administration patterns and costs and by type of prescriptions (oral vs IV).	
Key issue 13: The relative dose intensity (RDI) applied to the cost of SG and TPC may not be calculated correctly The methods used to calculate the RDI applied in the model are not described. The use of the safety / exposure RDI may underestimate treatment costs	

because doses discarded result in lower exposure but not in lower costs.	
Key issue 14: Wastage, for drugs used in this appraisal, is not part of the NHS perspective The cost-effectiveness assumes that some of the IV drugs are redeployed to other patients. However they are reimbursed as full vials so this assumption reduces the cost to below that paid by the NHS.	Vial sharing is usual in NHS practice
Key issue 15: The model uses different weight distributions for the cost calculation of SG and TPC The cost of SG is calculated using a non-parametric distribution directly calculated using percentiles of weight from the ASCENT trial (non-US) population. This distribution is slightly skewed towards lower weight percentiles compared with the parametric (using the same mean and standard deviation)	

normal distribution used for TPC.	
Are there any important issues that have been missed in ERG report?	

Part 3: Key messages

In up to 5 sentences, please summarise the key messages of your statement:

- Metastatic TNBC is an aggressive cancer with a very poor prognosis and subsequent unmet need for novel, effective therapies
- SG is a highly effective antibody-drug conjugate that represents a real step-change in the management of metastatic TNBC
- All subgroups of patients with TNBC benefit from SG
- The toxicities are manageable and patient QoL is improved and maintained for longer by SG
- Not approving this drug would be devastating for the many women in the UK living with TNBC who have been waiting for this drug which they know has a good chance of prolonging their life with good QoL.

Thank you for your time.

Your privacy

The information that you provide on this form will be used to contact you about the topic above.

☒ **Please tick this box** if you would like to receive information about other NICE topics.

For more information about how we process your personal data please see our privacy notice.

NICE National Institute for Health and Care Excellence

Technical engagement response form

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Thursday 27 January 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

Technical engagement response form

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

NICE National Institute for Health and Care Excellence

About you

Table 1 About you

Your name	Holly Heath
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	Breast Cancer Now
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 9: Pre-progression utilities with SG may not be higher than utilities with TPC. The cost-effectiveness model incorporates pre-progression utilities for SG of 0.710, 0.084 higher than those used for TPC, 0.626, with the difference being attributable to treatment with SG. EQ-5D utilities were obtained from a mapping algorithm which used EORTC QLQ C-30 scores from ASCENT. An analysis was presented which shows that the difference is statistically significant for utilities, despite the conclusion in the	No	Sacituzumab govitecan (Trodelvy) compared with single agent chemotherapies has shown an increase in progression-free survival and overall survival. This could increase the time that the patient's disease and symptoms are controlled for and support a better quality of life. This could enable the patient to continue to do the things that matter to them for longer. The value of this for both the patient and their family and friends cannot be underestimated. Many patients are acutely aware of the clinical benefits associated with this new treatment. Therefore, this treatment being routinely available on the NHS would provide reassurance to them but also their family that they are receiving an optimum treatment following prior therapies which can have a positive impact on emotional wellbeing. Alongside this, patients can receive significant hope from an increase in progression-free survival and overall survival – in that it could provide a bridge to a time when more new and effective medicines may become available. Quality of life is an important factor for this group of patients. The trial has shown a favourable objective response rate for sacituzumab govitecan versus standard

ASCENT CSR that EORTC QLQ C30 are, essentially, similar for SG and TPC.		chemotherapy which could provide patients with tumour shrinkage, which can help with symptom control and support them in carrying out their day to day activities. In terms of side effects, patients tell us that the potential risk of experiencing a range of side effects is outweighed by the hope of this new treatment working. A patient currently receiving the treatment told us "even if I experience side effects, now that I know it's working it makes it much more bearable. If it's doing a good job, that's what's important". Patients who have received at least two prior lines of treatment have few treatment options, currently limited to single agent chemotherapies which tend to have limited efficacy. There is a significant unmet need for new effective treatment options.
Key issue 10: Evidence does not support higher post-progression utilities for women who received SG instead than TPC. The cost-effectiveness analysis incorporates higher post-progression utilities with SG compared with TPC (by the same factor (0.084) used for pre-progression utility. The evidence for this utility gain with SG after SG has been stopped is unclear. EORTC QLQ data collection in ASCENT was stopped just after progression. Women receive a similar mix of	No	If a patient receives sacituzumab govitecan, they may experience tumour shrinkage and a good quality of life whilst on the treatment. As discussed by the clinical and patient experts at the technical engagement call, this could mean that when a patient progresses and needs to move onto a different treatment, that they are better physically and emotionally than someone that may have to start the subsequent treatment having been on a standard chemotherapy. A patient who receives sacituzumab govitecan may therefore feel stronger to start the new treatment. A patient currently receiving sacituzumab govitecan also explains "being on Trodelvy has enabled me at the moment to avoid radiotherapy to the brain – so I've been able to avoid the tiredness, steroids and side effects of that contributing to me maintaining a better quality of life for longer. I might need it [radiotherapy] later, but Trodelvy is buying me time and giving me something to keep in my back pocket for when I might need it."

therapies in SG and TPC in ASCENT.		

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
Additional issue 1: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue 2: Insert additional issue	Please indicate the section(s) of the ERG report that discuss this issue	Yes/No	Please include your response, including any new evidence, data or analyses, and a description of why you think this is an important issue for decision making
Additional issue N: Insert additional issue			[INSERT / DELETE ROWS AS REQUIRED]

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Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
Insert key issue number and title as described in the ERG report	Briefly describe the company's original preferred assumption or analysis	Briefly describe the change(s) made in response to the ERG report	Please provide the ICER resulting from the change described (on its own), and the change from the company's original base-case ICER.
Insert key issue number and title as described in the ERG report	…	…	[INSERT / DELETE ROWS AS REQUIRED]
Company's base case following technical engagement (or revised base case)	Incremental QALYs: [QQQ]	Incremental costs: [£££]	Please provide company revised base-case ICER

Sensitivity analyses around revised base case
[PLEASE DESCRIBE HERE]

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Technical engagement response form

Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

As a stakeholder you have been invited to comment on the evidence review group (ERG) report for this appraisal.

Your comments and feedback on the key issues below are really valued. The ERG report and stakeholders' responses are used by the appraisal committee to help it make decisions at the appraisal committee meeting. Usually, only unresolved or uncertain key issues will be discussed at the meeting.

Information on completing this form

We are asking for your views on key issues in the ERG report that are likely to be discussed by the committee. The key issues in the ERG report reflect the areas where there is uncertainty in the evidence, and because of this the cost effectiveness of the treatment is also uncertain. The key issues are summarised in the executive summary at the beginning of the ERG report.

You are not expected to comment on every key issue but instead comment on the issues that are in your area of expertise.

If you would like to comment on issues in the ERG report that have not been identified as key issues, you can do so in the 'Additional issues' section.

If you are the company involved in this appraisal, please complete the 'Summary of changes to the company's cost-effectiveness estimates(s)' section if your response includes changes to your cost-effectiveness evidence.

Please do not embed documents (such as PDFs or tables) because this may lead to the information being mislaid or make the response unreadable. Please type information directly into the form.

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Do not include medical information about yourself or another person that could identify you or the other person.

We are committed to meeting the requirements of copyright legislation. If you want to include journal articles in your submission you must have copyright clearance for these articles. We can accept journal articles in NICE Docs. For copyright reasons, we will have to return forms that have attachments without reading them. You can resubmit your form without attachments, but it must be sent by the deadline.

Combine all comments from your organisation (if applicable) into 1 response. We cannot accept more than 1 set of comments from each organisation.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, all information submitted under 'academic in confidence' in yellow, and all information submitted under 'depersonalised data' in pink. If confidential information is submitted, please also send a second version of your comments with that information replaced with the following text: 'academic/commercial in confidence information removed'. See the Guide to the processes of technology appraisal (sections 3.1.23 to 3.1.29) for more information.

Deadline for comments by **5pm** on **Friday 21 January 2022.** Please log in to your NICE Docs account to upload your completed form, as a Word document (not a PDF).

Thank you for your time.

We reserve the right to summarise and edit comments received during engagement, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during engagement are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Sacituzumab govitecan for treating unresectable locally advanced or metastatic triple-negative breast cancer after 2 or more therapies [ID3942]

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About you

Table 1 About you

Your name	
Organisation name: stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder, please leave blank)	
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	

Key issues for engagement

All: Please use the table below to respond to the key issues raised in the ERG report.

Table 2 Key issues

Key issue	Does this response contain new evidence, data or analyses?	Response
Key issue 1: Variation in prior therapy. The number and types of prior therapies that patients received varied across the countries that participated in the trial. This limits the generalisability of ASCENT trials results to the UK setting	No	The mainstay of metastatic triple negative breast cancer (mTNBC) treatment in the UK and internationally is single-agent chemotherapy.(1-3) This has remained largely unchanged for many years due to the lack of innovation in TNBC treatment, with the recent exceptions of immunotherapy plus chemotherapy in first-line treatment of PD-L1 positive patients and PARP inhibitors in *BRCA* mutation-positive patients.(1-3) The prior therapies used before sacituzumab govitecan (SG; Trodelvy) and treatment of physician's choice (TPC) in ASCENT are highly generalisable to UK clinical practice. Prior to second or third line therapy, almost all patients, regardless of geography, typically receive a taxane and an anthracycline-based therapy, whether in neoadjuvant treatment for early-stage disease, or as first or second line therapy for metastatic disease.(1-3) This is well reflected in the ASCENT trial, where 100% of patients had received a prior taxane and 82% had received an anthracycline.(4, 5) Another commonly used early-line therapy used by UK clinicians is carboplatin, which had been used in 65% of patients.(5) Approximately 29% and 7% of patients had received a prior immunotherapy or PARP inhibitor.(5) These figures demonstrate that patients in ASCENT had received optimal standard prior treatment, similar to what would be expected in England according to clinical expert feedback on the treatment

		pathway in this country. Consequently, this issue has no bearing on the generalisability of the ASCENT population to clinical practice in England, or on the cost-effectiveness of SG in its licensed indication.
Issue 1: ERG response		No additional evidence was submitted. A proportion of the trial population may have received Eribulin as first line therapy in the post metastatic therapy as presented in the CS and CSR.
Key issue 2: Long term effectiveness/safety data uncertainties. Lack of longer-term effectiveness/safety data. The median (range) of ASCENT study follow-up was 8.38 (0-24) months	Yes	The median study follow-up for ASCENT at the March 2020 data cut used in this submission was approximately 17.7 months, which is mature considering the very poor prognosis in this disease setting, and is considerably longer than the median SG values for overall survival (OS; 11.8 months) and progression-free survival (PFS; 4.8 months), meaning there is a high degree of confidence in these results.(4) The median follow-up time of 8.38 months reported in the ASCENT CSR is actually the median duration of individual patient follow-up rather than of the whole study.(6) This issue is further addressed by a later OS data cut from the final database lock in February 2021 with a median follow-up of approximately 27 months, which shows the same survival benefit of SG vs. TPC in terms of median survival outcomes:(7) • Median PFS was 4.8 months vs 1.7 months in patients treated with SG and TPC, respectively (HR: 0.41; 95% CI: 0.33, 0.52) • The median OS was 11.8 months vs 6.9 months in patients treated with SG and TPC, respectively (HR: 0.51; 95% CI: 0.42, 0.63) This additional survival follow-up validates the company's initial OS extrapolations and is described in more detail in Issue 8.
Issue 2: ERG response		The company submitted a second wave of data with longer follow up. This is no longer an issue.
Key issue 3: Imbalance in the randomised but untreated patients across	Yes	In the case report form (CRF) employed in ASCENT, patients that were randomised but not treated were classified as discontinuing treatment. The reasons that patients discontinued treatment could be chosen from a series of preset categories. The information available from

groups. There was a notably higher proportion of randomised but untreated patients (consent withdrawals) in TPC (14.5%) vs. SG (3.4%) treatment group. The ERG is uncertain how the company handled these data in terms of follow-up, inclusion, imputation, or censoring matters.		the CRFs regarding these reasons is presented below no further information was formally captured in this regard: • Of 38 patients randomized to the TPC group who were not treated, their "Primary Reason for Discontinuing Treatment" selected was: 32 patients with "Study drug not administered (after randomisation)" and 6 patients with "Withdrawal of Consent". • Of 9 patients randomized to the SG group who were not treated, their "Primary Reason for Discontinuing Treatment" selected for all 9 patients was "Study drug not administered (after randomisation)". Per protocol, patients who prematurely discontinued from ASCENT underwent the final visit assessments and long-term follow-up every 4 weeks thereafter for survival status.(8) Although the majority of patients who prematurely discontinued prior to treatment did not have final assessments (physical exam, electrocardiogram, etc) performed for the study, they did have follow-up information provided on their survival status. Of the patients who discontinued prior to treatment, 8 had final visit assessments performed (4 of 9 patients in the SG group and 4 of 38 patients in the TPC group) and there were 8 patients who were lost to follow-up and had no available OS data (1 patient in the SG group and 7 patients in the TPC group). In the ITT population, all patients were included in both the PFS and OS analyses.(6) As described above, OS status was available for most SG and TPC patients that withdrew at the start of the study. For the PFS analysis, withdrawn patients were subject to the follwing censoring rule described in the original submission, "no adequate response assessment after randomisation", i.e., they were censored at date of death if they died prior to what would have been their second scheduled assessment, or censored at randomisation if they survived beyond what would have been their second scheduled assessment.(6) It should be noted that these censoring rules are commonly implemented in oncology studies in order to meet FDA requirements. To demonstrate that this issue does not affect the results and conclusions of ASCENT, the PFS and OS analyses (median survival, hazard ratios, and Kaplan-Meier plots) are provided in the Appendix for all patients who received allocated treatment (i.e., the safety population).

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These results are consistent with the PFS and OS analyses in the ITT population; the PFS hazard ratio (HR) was 0.43 and the OS HR was 0.51 for both populations.(6, 9) The patients in the TPC arm who were randomised but not treated are therefore not considered to have affected the results and conclusions of ASCENT.

Table 1: List of tables and figures with PFS and OS analyses for the Safety Population(9)

Table or figure in CSR	Analysis	Table or figure in this document
Table 15.2.2.2a	Analysis of OS	Table 6
Figure 15.2.2.2c	KM estimates of OS	Figure 10
Figure 15.2.1.2a	KM estimates of PFS – independent review committee	Figure 11
Table 14.2.1.19	Sensitivity analysis of PFS – independent review analysis	Table 7

Issue 3: ERG response

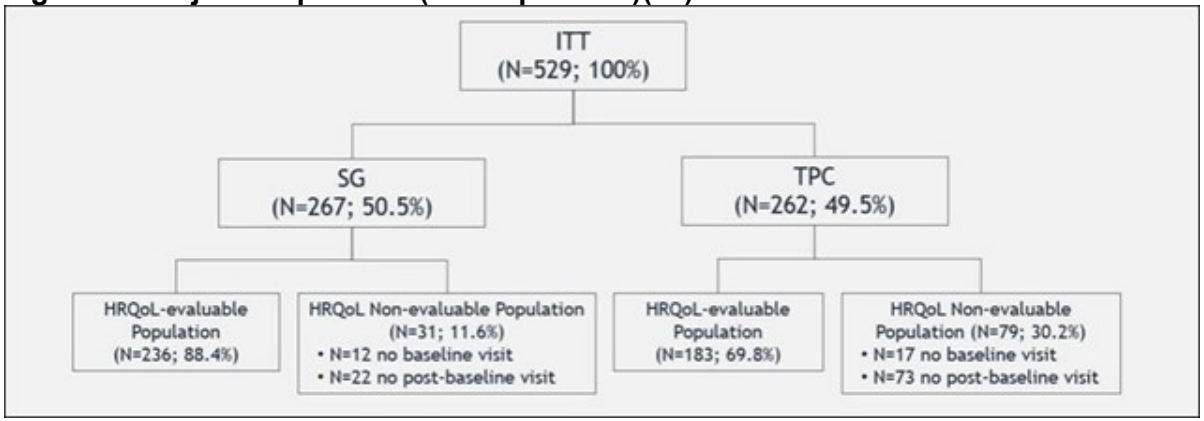
The company presents results for OS and PFS outcomes in the safety population. The results of the safety population are similar to the ITT population, however randomisation is broken. In the TPC group: 12% (32/262) of participants did not receive the allocated treatment. In the SG group: 3.4% (9/267) of participants did not receive the allocated treatment. It is still not clear if this proportion of participants were on another active treatment as this may influence quality of life.

Endpoint		ITT population		Safety population	
		SG	TPC	SG	TPC
PFS	n	267	262	258	224
	Median months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	5.4 (4.2, 5.9)	1.8 (1.5, 2.7)
	HR	0.43 (0.34, 0.54)		0.43 (0.34, 0.54)	

<table>
<tr><td></td><td></td><td>
<table>
<tr><td></td><td>(95% CI)</td><td colspan="2"></td><td colspan="2"></td></tr>
<tr><td rowspan="3">OS</td><td>n</td><td>267</td><td>262</td><td>258</td><td>224</td></tr>
<tr><td>Median months (95% CI)</td><td>11.8 (10.5, 13.8)</td><td>6.9 (5.9, 7.7)</td><td>11.9 (10.5, 14.0)</td><td>7.1 (6.2, 8.2)</td></tr>
<tr><td>HR (95% CI)</td><td colspan="2">0.50 (0.41, 0.62)</td><td colspan="2">0.51 (0.41, 0.63)</td></tr>
</table>
</td></tr>
<tr><td>Key issue 4: Differential attrition for the EORTC QLQ-C30 score. There was a differential attrition of ITT sample due to missing values for EORTC QLQ-C30 score at a follow-up in the SG arm (11.7%) and TPC arm (30.2%).</td><td>Yes/No</td><td>The completion rates, using the number of ITT patients who were expected to provide an HRQoL assessment at a given timepoint as denominator, were high (generally ≥90%) for both treatment arms across visits until C10D1 (i.e., the assessment visit with n ≥10 in both arms).(10) The completion rates were similar between the SG and TPC arms across visits up to C10D1.(10)

The available data rates of the EORTC QLQ-C30, using the number of ITT patients as denominator, decreased considerably over time in both treatment arms (from 95% at baseline to 18% at C10D1 and 2% at C24D1; the number of patients beyond Cycle 24 was less than 10), reflecting the decreasing number of patients who remained on treatment and alive.(10) As expected, the available data rates were much higher in the SG arm than in the TPC arm, generally reflecting that the median PFS was much longer in the SG arm than the TPC arm (4.8 months vs. 1.7 months) with chemotherapy.(4, 10) The higher rate of progression and death events early on in TPC vs SG arm also led to fewer patients providing at least one post baseline QLQ-C30 measure, resulting in a smaller proportion of patients included in PRO evaluable for TPC (69.8%) vs. SG (88.4%; Figure 1).(10)</td></tr>
</table>

Figure 1: Subject Disposition (ITT Population)(10)



HRQoL = health-related quality of life; ITT = intent to treat; SG = sacituzumab govitecan; TPC = treatment of physician choice

Also, Table 7 and Table 8 in the PRO report provide detailed comparison of the PRO evaluable vs. ITT population and concludes that "there were no marked differences in the baseline demographic characteristics between the HRQoL evaluable population and the ITT population."(10) Therefore, even though the PRO population was a subset of ITT, it was representative of the ITT population.(10) Number of people before progression.

As specified in the PRO report, the primary reason for missing information and increased attrition in the TPC arm was earlier disease progression.(10) The linear mixed-effect models for repeated measures (MMRM) analysis assumed that patients who discontinued study treatment and stopped completing HRQoL assessments during the first six cycles of treatment would have similar HRQoL score changes as patients who continued to receive study treatment.(10) However, patients who discontinued study treatment prematurely had worse HRQoL than those who remained on treatment; therefore the HRQoL estimates from the MMRM analysis may be better than what would have been obtained if HRQoL data had been collected after treatment discontinuation and included in the analysis.(10) For this

		reason, the HRQoL analysis conducted in ASCENT is likely to be biased against SG in favour of TPC.(10)
Issue 4: ERG response		No additional evidence submitted. Heavy sample attrition in the EORTC QLQ-C30 data analysis is present. Uncertainty remains (wide 95% CIs) in the EORTC QLQ-C30 mean change estimates beyond Cycle 6. The ERG remains uncertain what effective sample size was used for the adjusted analysis (MMRM LS mean changes). The company reports the baseline sample size (at Cycle 1: SG n=236 vs. TPC n=183) used for the unadjusted analysis. The ERG believes that the adjusted analysis of MMRM LS mean change would be based on a smaller baseline sample (Cycle 1) and consequent samples (Cycles 2-6) than the corresponding samples in unadjusted analysis simply due to missing covariate data.
Key issue 5: Frequency of high-grade neutropenia was more frequent in the SG. High grade neutropenia was more frequent in the SG (47.20%) vs. TPC (19.80%) arm. Different dose reduction/modification rules applied across the SG and TPC arms for the first episode of high grade toxicities (hematologic) might have favored the SG arm more than the TPC arm, since in the SG arm in case of such toxicity the dose reduction was recommended and G-CSF was administered, whereas in the	No	This issue misrepresents how haematological toxicities were treated in the ASCENT study and is therefore irrelevant. It is incorrect to state that neutropenic episodes in the TPC arm were treated solely by discontinuation of therapy, and not with dose reduction or G-CSF administration.(6) Any consequent inference of bias against TPC by assuming premature termination of comparator treatment (i.e., before progression occurs), or improved QoL on SG due to better treatment of neutropenia, is therefore unfounded. Neutropenia was treated optimally in the TPC arm in accordance with product labelling, as would be expected both in clinical trials and clinical practice;(8) it would be unethical and unscientific to mandate undertreatment with comparator therapies. As stated in our initial company submission, concomitant G-CSF support was administered to 23% of TPC patients, and neutropenia led to dose interruption and dose reduction in 21.4% and 19.2% of the TPC group, respectively;(4, 6) this includes 17% of patients in the TPC arm who received G-CSF as treatment for neutropenia, and 10% who received it as secondary prophylaxis.(11) Only four patients in the TPC arm were discontinued due to neutropenia, one of which was a case of febrile neutropenia.(6) In summary, neutropenia was treated appropriately and in accordance with clinical practice both for SG and TPC. The incidence and treatment of neutropenia, as well as all associated costs, have been accurately documented and modelled in the cost-effectiveness analysis.

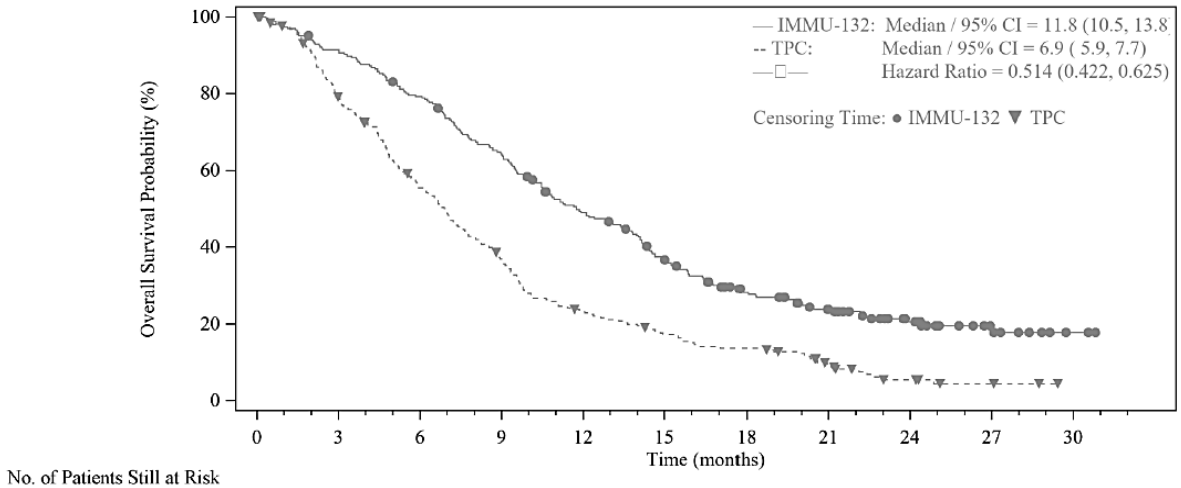
TPC arm the treatment was discontinued and no G-CSF was administered (potentially dropped out).		
Issue 5: ERG response		No additional evidence submitted. The company submission does state that [redacted] Concomitant growth-factor support was given to 49% of the patients treated with SG and 23% of those with TPC. [redacted] SG population received twice as G-CSF because they experienced a higher number of adverse events. The number of patients that stayed on treatment, discontinued treatment or missed treatment remains unclear. Therefore, the overall effect of receiving differential treatment (G-CSF differential rates), dose interruption and reduction on utilities, and perhaps, progression free survival, remain unclear.
Key issue 6: Tumour location in the lymph node was higher in the TPC arm. There were more patients who had tumour location in lymph nodes in the TPC arm (26%-30%) compared to the SG arm (23%). Since tumour's lymph node location has been shown to be associated with poorer prognosis, it is possible that the observed clinically beneficial treatment effect of SG compared to TPC is	No	The small difference identified in the prevalence of lymph node metastases between the SG and TPC populations is of no consequence to the interpretation of the ASCENT clinical data, and has no influence on actual and modelled outcomes. This issue is a result of misinterpretation of the cited literature regarding the significance of lymph node metastases in TNBC. The studies cited by the ERG focus on early stage TNBC where, generally, lymph node metastases are prognostic indicators for a higher risk of metastatic relapse and poorer outcomes than those without lymph node metastases(12-20). However, once a patient has been diagnosed with metastatic disease, the presence of metastases in lymph nodes is of little relevance to the subsequent course of the disease. TNBC typically metastasises to visceral organs such as the lung and liver, the central nervous system and sometimes bones,(21) and the location and distribution of these metastases are far more relevant to a patient's prognosis in mTNBC than the presence of disease in the lymph nodes.(22, 23)

exaggeration of the true effect at some degree at least partially due to confounding imparted by the between-arm imbalance in lymph node tumour location.		
Issue 6: ERG response		No additional evidence submitted. The qualitative difference on the prevalence of tumour lymph nodes location (26% - 30% in TPC vs 23% in SG) was a cautionary argument. The company validated clinical evidence around the prognostic factors in TNBC and mTNBC. This is no longer an issue.
Key issue 7: Early stopping of the trial. Caution should be exercised in the interpretation of the ASCENT study efficacy results as this trial was stopped early for showing benefits of the SG treatment. The evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment	Yes	At the time of the original submitted analysis (data cut-off 11 March 2020), 316 PFS events and 340 OS events had occurred in the primary analysis population.(6) Therefore, according to a robust statistical plan, ASCENT was stopped after it was fully recruited, with a high number of survival events having taken place.(4, 8) While the independent Data Monitoring Committee unanimously recommended stopping the trial early, additional PFS and OS events occurred during database cleaning that exceeded the original targeted event numbers.(4, 6) Further, it is by the ERG's own estimate that the data presented in the submission was mature as medians for PFS and OS have been exceeded across all endpoints in both arms.(4) In addition, the median follow-up in the primary analysis population was 17.7 months, which is a significant period of time in the context of previously treated mTNBC, which has an extremely poor prognosis and a median OS of just 15 months from diagnosis of metastatic disease, dropping to 7 months at 2nd or 3rd line treatment.(4, 24-26) It is therefore misleading to equate the "early" stopping of ASCENT with those trials noted in the cited paper, and to suggest that this may have exaggerated the magnitude of benefit.(27) The 105 trials described in the cited systematic review were stopped prematurely after enrolling an average of 63% of the planned sample size, in contrast to the fully enrolled ASCENT trial.(6, 27) The authors also noted a very strong correlation between number of

		events and magnitude of treatment effect, suggesting that the risk of overestimating clinical benefit is markedly reduced with a large event number (e.g., over 200 events).(27) As noted above in the response to Issue 2, results from the final database lock in February 2021 confirmed a sustained OS and PFS benefit of SG vs. TPC, comparable to the March 2020 data cut used in the submission, suggesting that the initial results were in no way exaggerated.(7)
Issue 7: ERG response		The company submitted a second wave of data with longer follow up. This is no longer an issue.

Key issue 8: Log-logistic OS parametric extrapolations overestimate survival. The use of the log-logistic distribution for OS overestimates (overall) survival in the model, which extends the period over which SG accrues a survival benefit compared with TPC.		Extended survival follow-up provided in this response validates and is strongly supportive of our base case use of a joint log-logistic method to model survival extrapolation.(28) The slight exception to this is that the joint log-logistic extrapolation may overestimate long-term survival outcomes in the TPC arm, for which the generalised Gamma appears to be a better fit, as suggested by the ERG. In line with clinical expert opinion, the extended survival follow-up also clearly rules out the use of Weibull modelling for SG survival extrapolation. The choice of log-logistic curve in the base case of the economic analysis took into consideration statistical fit, clinical plausibility based on real-world evidence and input from six practicing UK clinical experts. Based on the data cut from March 11 2020, UK clinical experts suggested that the log-logistic distribution was reasonable, with none considering the Weibull as viable. Of note, one clinical expert explicitly suggested that the Weibull distribution was too pessimistic at earlier time points, with another stating that plausible extrapolations should allow for longer-term survivors as there is some long-term survivorship among these patients. More importantly, analysis of the updated data with an additional 11 months of follow-up for OS provides very strong support for the choice of the log-logistic joint fits (see Issue 2, and New Evidence Form). **1. Observed milestone estimates:** The comparison of the new OS Kaplan-Meier (KM) curves (Figure 2) vs. the parametric curves fitted to OS data available before the update (Table 2) shows that the observed OS rate for SG at 24 months (0.205; 95% CI: 0.154, 0.261) is matched by the jointly fitted log-logistic model (0.206), while the Weibull distribution (0.157) underestimates SG survival at 24 months.(28)

Figure 2: OS KM curves derived from an updated data cut with additional 11 months follow-up (February 2021 data cut)(28)



IMMU-132 = sacituzumab govitecan; KM = Kaplan-Meier; OS = overall survival; TPC = treatment of physician's choice

Table *2:* Updated OS KM (February 2021 data cut) vs. parametric estimates of OS at 24 months based on earlier data cut (March 2020 data cut)(28)

SG treatment arm			TPC treatment arm		
Observed OS rate (updated OS KM curve)	**Log-logistic treatment as a predictor***	**Weibull as stratified fit** (ERG preference)	**Observed OS rate (updated OS KM curve)**	**Log-logistic model with treatment as a predictor***	**Gen. gamma stratified** (ERG preference)*
0.205 95% CI: 0.154, 0.261	**0.206**	**0.157**	**0.055** 95% CI: 0.028, 0.094	0.083	0.057

*Parametric estimates were derived based on previous data cut (before adding 11 months of follow-up)

Additionally, for the TPC arm, the use of the log-logistic model overestimates the observed OS rate at 24 months (0.083 vs. 0.055), while the observed rate would be captured by the stratified generalised Gamma model (0.057). Since the log-logistic model overestimates the OS for TPC, its use in the base case economic analysis represents a conservative approach.

The ERG's preferred Weibull model considerably underestimates the observed 24-month rate for SG. In particular, it performed much weaker in capturing the tail after 24 months in the SG arm than the log-logistic distribution (AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Figure 3 and Figure 4), justifying its exclusion by clinical experts.

2. Parametric extrapolations

The exercise described in the original Company Submission, Section B.3.3, has been repeated on the new dataset. All previous conclusions in terms of model diagnostics still hold true, for the data with longer follow-up (not presented). The AIC/BICs of all fits are presented in Table 3. Based on the statistical criteria (Akaike's Information Criteria [AIC]/Bayesian Information Criteria [BIC]), the joint log-logistic distribution still fits the data best.

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		In response to the ERG comments, we also present results of the parametric extrapolation based on the separately fitted curves (Table 3). The log-logistic model appears as the best distribution for each of the arms separately, although the generalised Gamma has very small difference, and likely a very close contender. It should be noted that the AIC for the joint log-logistic fit is lower than the sum of the AIC across the two separately fitted log-logistic curves, suggesting a preference for joint fit. Most importantly, the difference in the mean OS between SG and TPC is smaller with the jointly fitted log-logistic curves compared with separately fitted models. The joint log-logistic model overestimates the tail of the TPC arm, compared to the separate fitted models or the generalised Gamma, resulting in a higher mean OS for TPC. Therefore, the joint log-logistic model is a conservative assumption when predicting the benefit of SG. As suggested by the ERG, the generalised Gamma is a better visual fit for TPC (shown in AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; SG = sacituzumab govitecan; TPC = treatment of physician's choice Figure 3). A scenario where OS is modelled with the separately fitted generalised gamma distribution for TPC and the log-logistic curve for SG results in a -12% drop in our base case ICER, to £43,574. In summary, clinical expert opinion and new data strongly supports the use of joint log-logistic model projection in the economic analysis, clearly rules out the use of the Weibull distribution for SG and shows that the joint log-logistic model is a conservative approach as it overestimates TPC efficacy and thereby likely underestimates the efficacy benefit of SG.

Table 3: OS in the ITT population: Goodness-of-fit statistics with treatment arm as predictor and stratified models

Joint Fits: Distribution	AIC	BIC	Median (months)		Mean (months)	
			SG	TPC	SG	TPC
Weibull	2931.42	2944.19	12.29	7.37	15.01	9.01
Log-normal	2935.70	2948.47	11.23	6.48	17.59	10.14
Log-logistic	**2916.79**	**2929.56**	**11.64**	**6.58**	**18.35**	**10.38**
Exponential	2967.07	2975.59	11.45	6.44	16.36	9.21
Gen. gamma	2920.45	2937.46	11.87	6.87	15.74	9.11
Gompertz	2956.85	2969.62	12.31	7.08	14.77	9.01
Stratified Fits: Distribution	**AIC**	**BIC**	**Median (month)**		**Mean (month)**	
SG						
Weibull	1513.84	1520.97	12.37		14.94	
Log-normal	1524.46	1531.59	11.37		18.80	
Log-logistic	**1510.88**	**1518.01**	**11.67**		**19.10**	
Exponential	1531.30	1534.87	11.45		16.36	
Gen. gamma	1513.77	1524.44	12.04		15.43	
Gompertz	1525.08	1532.21	12.42		14.68	
TPC						
Weibull	1419.36	1426.45	7.31		9.00	

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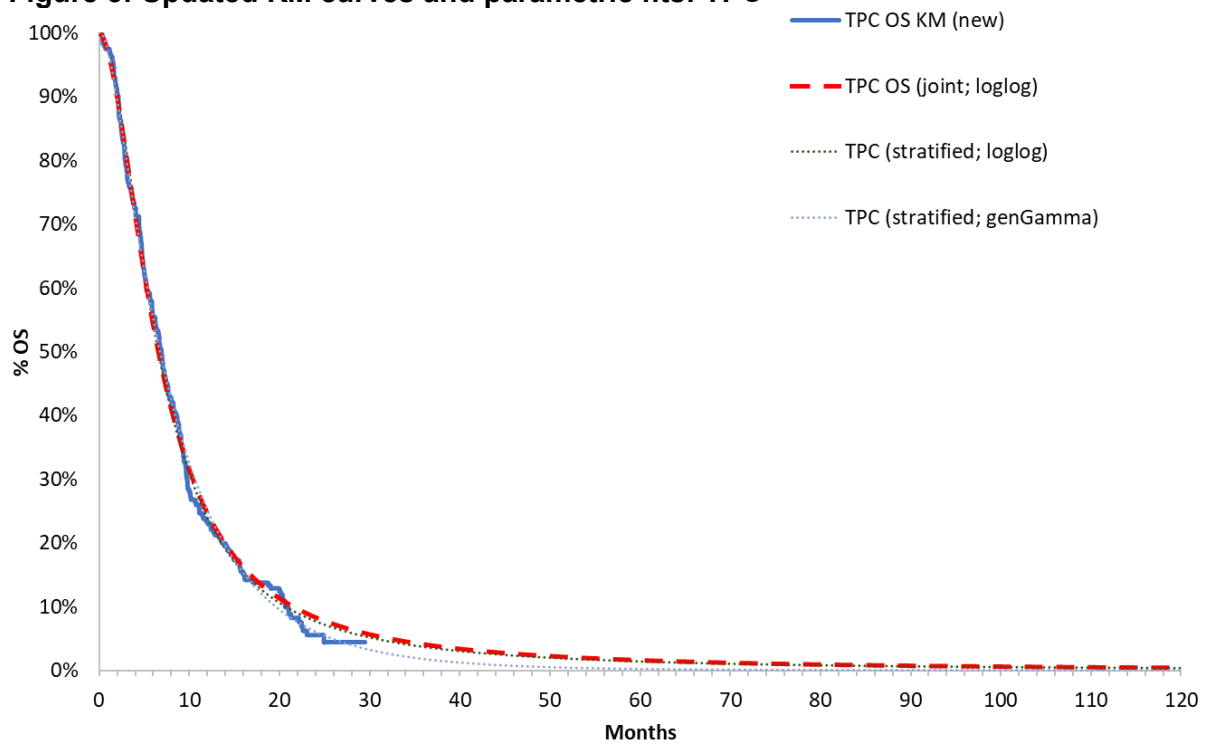
Log-normal	1410.65	1417.74	6.45	9.64
Log-logistic	**1407.09**	**1414.18**	**6.58**	**10.05**
Exponential	1435.78	1439.33	6.44	9.21
Gen. gamma	1408.75	1419.36	6.75	9.17
Gompertz	1433.58	1440.67	6.98	9.02

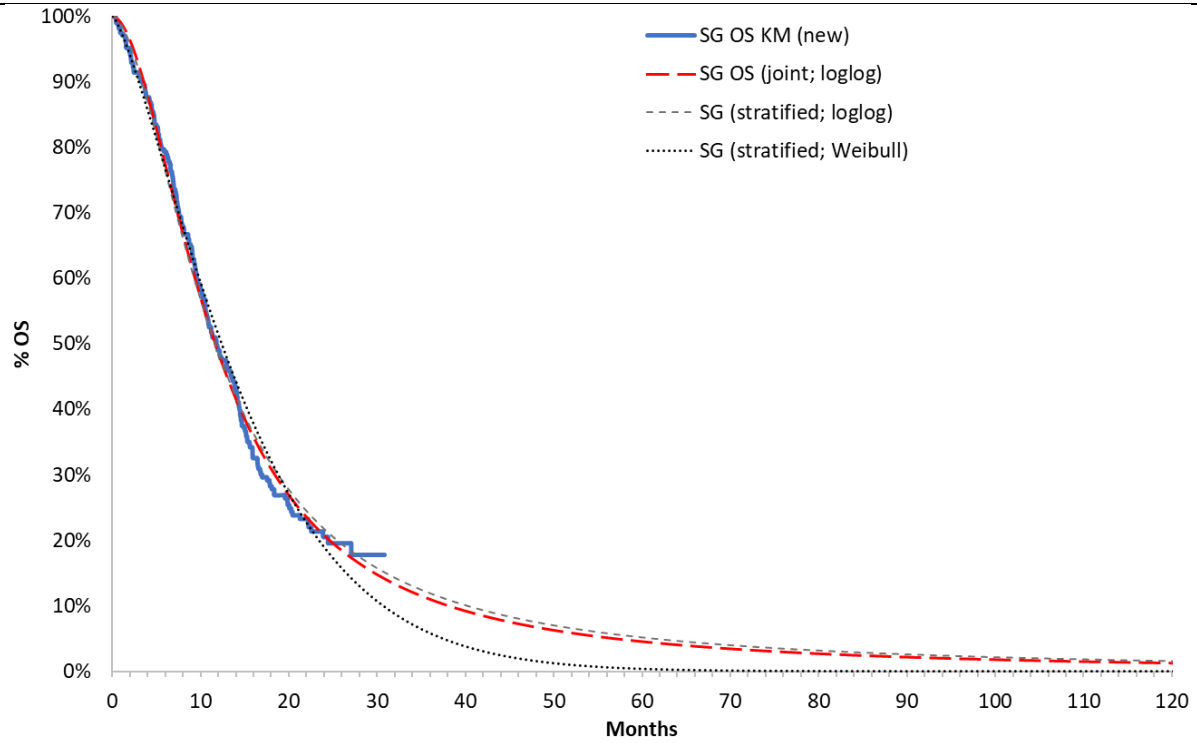
AIC = Akaike's Information Criteria; BIC = Bayesian Information Criteria; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Figure 3: Updated KM curves and parametric fits: TPC



genGamma = generalised Gamma; KM = Kaplain-Meier; loglog = log-logistic; OS = overall survival; TPC = treatment of physician's choice

Figure 4: Updated KM curves and parametric fits: SG

		 genGamma = generalised Gamma; KM = Kaplain-Meier; loglog = log-logistic; OS = overall survival; SG = sacituzumab govitecan
Issue 8: ERG response		The Company provided new curves based on a new data cut. These curves were incorporated in a version of the model that was superseded at the completion of the ERG report. For this reason, it is impossible to evaluate the impact of curve selection in the

		context of other changes made to the model by the ERG and incorporated in the model version submitted for consultation. It is also impossible to evaluate visual fit given that the company did not incorporate the complete set of both the jointly fitted and the independently fitted distributions. When assessing the visual fit for the previous set of curves, the ERG found that some models were overall inferior fits when AIC and BIC criteria were considered, and yet, better choices for one arm when considering the visual fit, because the joint model fitted one arm very well and the other arm poorly. This fact is strongly suggestive that an independent fit was preferable. The omission of independently estimated curves from the model biases the assessment of which distribution fits better, and therefore the choice of distributions and extrapolations cannot be completed at this point. The curves based on the new data cuts must be included in all forms, both independent and joint fits, in the most recent version of the economic model which also incorporates the changes in the model made by the ERG.
Key issue 9: Pre-progression utilities with SG may not be higher than utilities with TPC. The cost-effectiveness model incorporates pre-progression utilities for SG of [redacted], 0.084 higher than those used for TPC, [redacted], with the difference being attributable to treatment with	Yes	Higher pre-progression utility for SG vs TPC is firmly justified by the HRQoL data from the ASCENT study, which was collected using the EORTC-QLQ-C30 tool, a robust, objective, commonly used questionnaire.(29) In a linear mixed-effect regression model for repeated measures, the SG arm showed statistically significantly ($p<0.05$) and clinically meaningfully (i.e., mean difference exceeded the superiority margin) greater improvement than the TPC arm in all primary domains (global health status/QoL, physical functioning, fatigue, and pain) except for role functioning, for which the SG arm still showed statistically significantly greater improvement than the TPC arm but did not reach the clinically meaningful threshold.(29) In addition, there is a strong clinical and mechanistic rationale for patients' quality of life being better in the pre-progression health state for SG vs. TPC due to the seven times greater objective response rate for SG vs TPC (31.1% vs 4.2%) in ASCENT.(6) Tumour shrinkage in patients with metastatic breast cancer has been shown to have a direct impact on quality of

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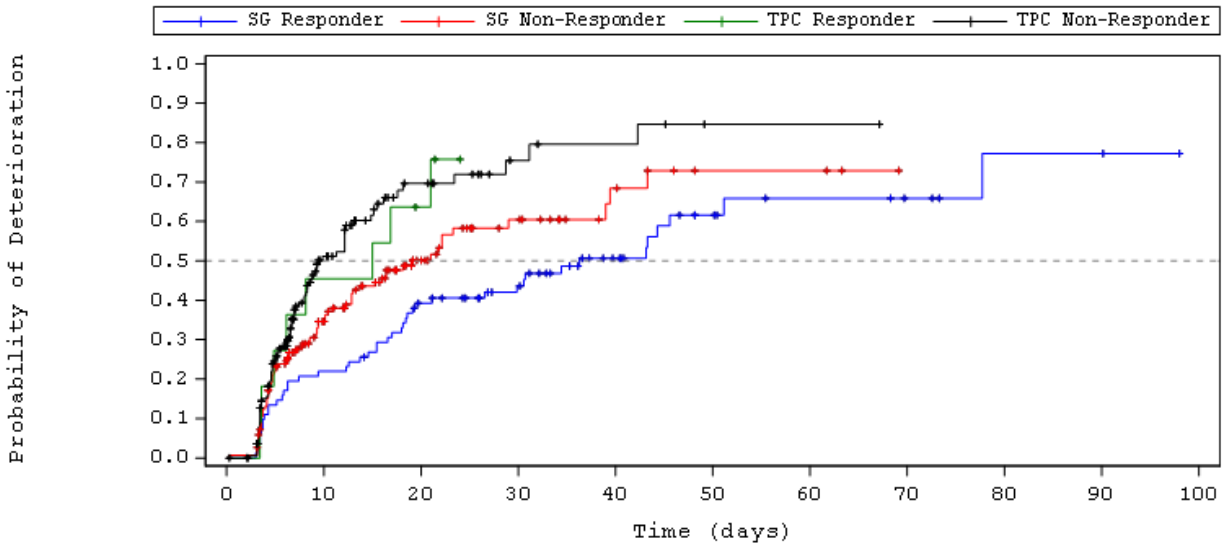
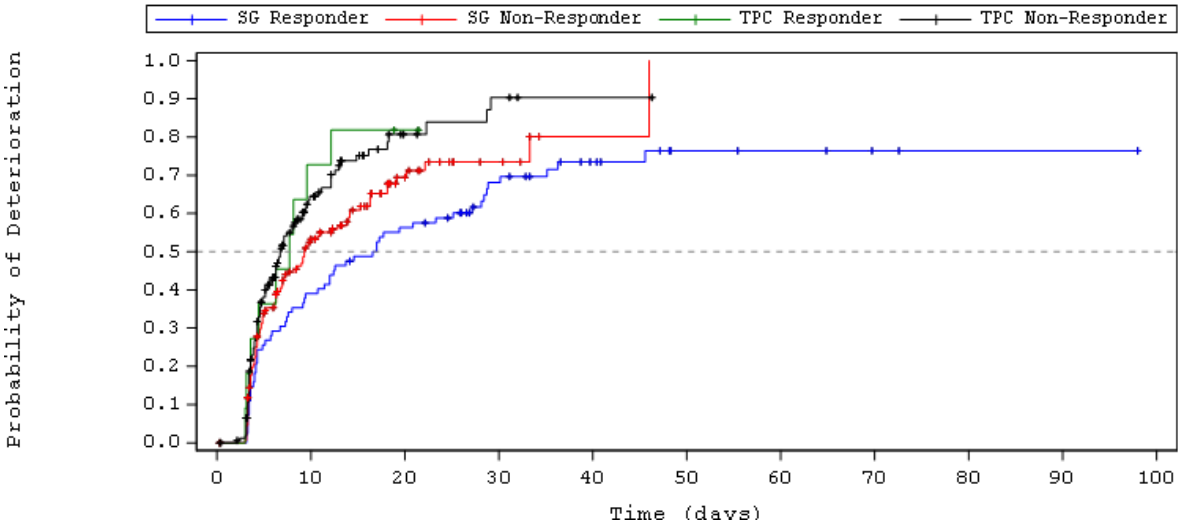
SG. EQ-5D utilities were obtained from a mapping algorithm which used EORTC QLQ C-30 scores from ASCENT. An analysis was presented which shows that the difference is statistically significant for utilities, despite the conclusion in the ASCENT CSR that EORTC QLQ C30 are, essentially, similar for SG and TPC.		life through a reduction in symptoms such as pain, breathlessness and mood disturbance.(30, 31) Therefore, patients demonstrating a partial or complete treatment response based on RECIST-defined objective response criteria often experience improved quality of life compared with patients who do not achieve a deep treatment response.(30) This is further supported by a vignette study based on responses from 100 members of the general public in the UK which found that utility in metastatic breast cancer increases significantly following a treatment response ($p<0.0001$).(32) This study has been used in the analysis of previous breast cancer NICE submissions such as eribulin (TA423).(33) In addition, there were many more patients treated with SG vs. TPC with stable disease whose tumours shrunk in the pre-progression health state while not meeting the stringent criteria for response, as shown in Figure 5.(6, 34) **Figure 5: Best percent change in size of the target lesion by IRC assessment (ASCENT; ITT population)(34)** 

		Dashed lines represent ±30% change from baseline in tumour diameter IRC = independent review committee; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice Furthermore, therapeutic impact on quality of life is not only dependent on RECIST-defined objective response. A superior therapy may also maintain a patient's initial quality of life merely by delaying progression for longer than a comparator therapy. This was demonstrated by a new analysis of the ASCENT HRQoL by Loibl et al, in which patients treated with SG generally showed more favourable score changes and longer time to deterioration than patients who received TPC, regardless of clinical response status (see Figure 6 and Figure 7).(35) **Figure 6: Time to first deterioration in EORTC QLQ-C30 Physical Functioning by treatment response(35)**



EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SG = sacituzumab govitecan; TPC = treatment of physician's choice

Figure 7: Time to first deterioration in EORTC QLQ-C30 Role Functioning by treatment response(35)

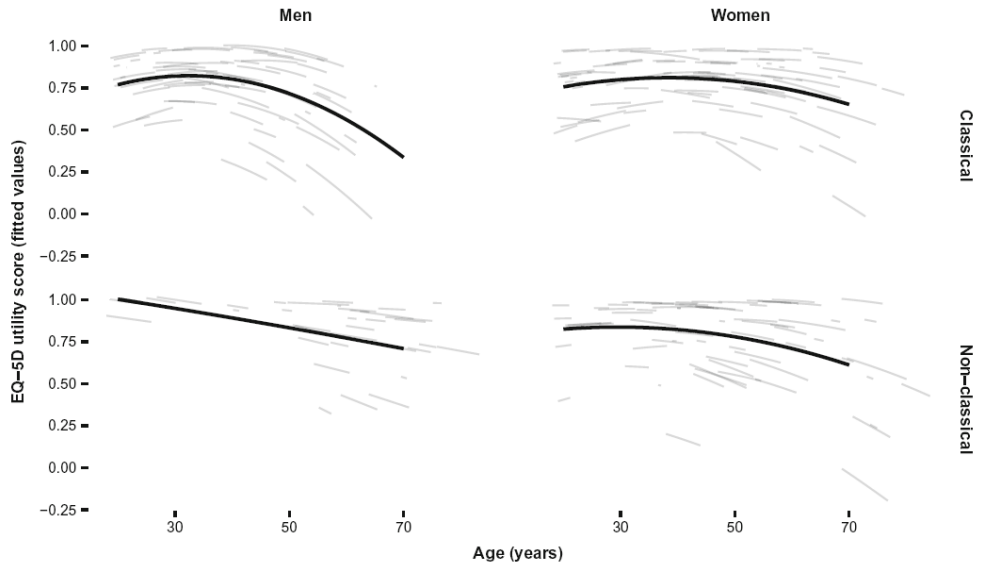


EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire; SG = sacituzumab govitecan; TPC = treatment of physician's choice

In summary, the pre-progression health state for SG comprises substantially deeper and broader responses compared with TPC, as well as many more patients with stable disease whose tumours have shrunk while not meeting the stringent criteria for response.(6, 34) This strongly supports a higher utility value for SG than TPC in the pre-progression state. These factors have also been independently verified by multiple Consultant Medical and Clinical Oncologists from major treatment centres across the UK, all of whom agree that it is highly plausible that treatment with SG will result in noticeably better HRQoL than with existing chemotherapies. As discussed in Issue 4, additional insight from clinical experts also suggested that the HRQoL analysis in ASCENT may actually be biased somewhat against SG due to the fact that the attrition rates in the TPC arm were much higher than SG,

		meaning patients with much worse QoL in the TPC arm were not captured in the analysis.(10)
Issue 9: ERG response		No additional evidence submitted. The ERG's assessment of the utility regression analysis is that the naïve linear mixed-effect regression model is invalid in the case of data points not missing at random. The high attrition rate of utility values is evident in Table 14.2.6.1 Summary of EORTC-QLQ-C30 Scores by Visit Safety Population. At baseline, 247 people out of 258 who received SG and 217 people out of 224 had an EORTC QLQ reading. The first issue is that 17% of the people allocated to TPC never received a dose. This proportion is large enough to break randomisation, therefore an unadjusted comparison, based on the safety population, is most likely biased. Second, the ASCENT trial was open label, this means that patients and physicians knew the allocated treatment. As stated in the ASENT CSR (Page 57), these patients elected to not participate in the study when they were not randomised to SG. It is entirely possible that these patients believed they would be better off not receiving TPC, and that therefore they had better health than people who accepted to take part in the trial. The End of treatment EORTC values should be available for any participant who started treatment, so similar numbers to completion rates at baseline are expected for the last reading. Yet, End of Treatment values are available only for 169 (SG) and 151 (TPC). These are 63% and 63% of people who were started on treatment with SG or TPC,

		respectively, substantially below the 90% declared by the company; given that utilities are derived from the EORTC values, it is possible that missing utility values may be even higher. It is impossible to assess the denominators at each visit listed in Table 14.2.6.1, other than obtaining data regarding people **still not progressed** at each point in time when the QLQ measures were obtained. The importance of this issue is that it is uncertain whether missing values should be imputed before the analysis is conducted, and if so, how. Values not missing at random require that a missingness explanatory model is estimated. To start the assessment as to whether such alternative analysis is required, it is important that descriptive data are provided. First, the provision of denominators for each visit, together with a comparison of baseline patients characteristics by allocation x completion (yes/no) and with a graph representing the utility data in such a way that eventual changes in the composition of the population over time can be assessed. Below is an example of a possible representation of EQ-5D values that could help resolve the assessment of systematic differences in utility values between arms, at least at the visual level, in such a way that the need of subsequent modelling efforts may be assessed by the AC (The graph should be understood as an example, not construed as the request of an analysis by factors used in this particular example).

		 **Fig. 1** Relation between EQ-5D and age. Polynomial mixed effect model of EQ-5D in relation to age, stratified for sex and phenotype. Large lines represent fitted values at group level, the smaller lines represent the fitted values at individual patient level
Key issue 10: Evidence does not support higher post-progression utilities for women who received SG instead than TPC. The cost-effectiveness analysis incorporates higher	Yes	As discussed in response to Issue 9, a higher pre-progression utility for SG vs TPC is firmly justified by the HRQoL data derived from the EORTC-QLQ-C30 tool and there is a strong rationale for patients' quality of life being better in the pre-progression health state for SG vs TPC.(6, 10, 34) Therefore, though the utility decrease post progression is similar in both

post-progression utilities with SG compared with TPC (by the same factor (0.084) used for pre-progression utility. The evidence for this utility gain with SG after SG has been stopped is unclear. EORTC QLQ data collection in ASCENT was stopped just after progression.		arms, since the pre-progression utilities are significantly higher with SG vs. TPC, a similar drop will retain some benefit. A panel of Consultant Medical and Clinical Oncologists from major treatment centres across the UK agreed that higher quality of life for patient progressing on SG vs TPC was clinically plausible based the HRQoL data derived from ASCENT. A rationale for this is that a greater proportion of SG patients experienced a reduction in their tumour diameters, and these reductions were greater in magnitude than for TPC patients (Figure 8).(34) As a result, patients in the SG group were in general entering their progressed health state with a lower tumour burden than their TPC counterparts, consequently justifying a better quality of life in this health state.(30, 31, 34) It should be noted that, as demonstrated in Figure 8, tumour response is a continuum rather than a binary state, and that even a reduction that does not meet the threshold for confirmed response (i.e., a reduction of >30% in tumour diameter) may result in alleviation of symptoms and improved quality of life.(34) **Figure 8: Best percent change in size of the target lesion by IRC assessment (ASCENT; ITT population)(34)** 

		Dashed lines represent ±30% change from baseline in tumour diameter IRC = independent review committee; ITT = intent-to-treat; SG = sacituzumab govitecan; TPC = treatment of physician's choice
Issue 10: ERG response		No additional evidence submitted. The Appraisal suffers from the lack of utility data after treatment discontinuation. The cost-effectiveness model is not structured to incorporate the effects alluded to. The model takes a fixed value for utility for the period before progression and after progression, respectively. This means that if a benefit acquired pre-progression is carried over, a similar benefit is assumed in the post-progression state despite treatment being discontinued. However, this contradicts the RECIST definition of progression, which occurs because the size of tumour lesion increases. Therefore, all patients who progress report an increase in their lesions and this is inconsistent with the assumption that lesions reduction is maintained unchanged after treatment; in other words, a rebound effect is assumed. This is a common assumption in economic models, when modelling utilities after treatment discontinuation. In this particular appraisal, whether lesion size differs by treatment arm after progression is unknown, as it is unknown whether residual differences in lesion sizes post-progression translate in effective differences in utility by arm. In the absence of this evidence, it is difficult to argue for different utilities in post-progression after the original treatment has been interrupted.

Key issue 11: Post-progression therapy costs applied to TPC assume a very high proportion of people receiving eribulin. This is clinically incompatible with rates of prior and within trial eribulin, and assume more intensive therapy for longer, compared with SG.	Yes/No	The comment from the ERG touches on three separate points that have been addressed individually below. **1. Eribulin use prior to the trial:** The rate of prior eribulin use in ASCENT reflects that the study enrolled a heavily pre-treated population; patients in ASCENT received a mean of 4.5 prior systemic therapies (maximum of 17) when including neoadjuvant therapy.(5) The proposed place of therapy of SG is for patients who have received two prior lines of systemic therapy for locally advanced or metastatic TNBC. As eribulin is restricted by NICE to third-line treatment of locally advanced or metastatic breast cancer, prior eribulin use in patients eligible for SG treatment in the real-world setting would be lower than that observed in the ASCENT study.(33) **2. Post-progression therapy mix:** The ERG quote figure of [redacted] of TPC patients subsequently receiving eribulin which is inaccurate as this figure is for post-SG therapy; the actual rate of subsequent erbulin after TPC, assumed to be the proportion that did not get it as part of TPC, is 46.9%.(6) It is also important to note that these percentages are proportions of patients that actually went on to receive a subsequent therapy, not a proportion of the TPC group as a whole, and to quote these percentages without this context suggests a much higher post-progression eribulin rate than observed. Per the original company submission, only [redacted] of TPC patients went on to receive a subsequent therapy. In England, eribulin has a fixed place in the treatment algorithm as a third line therapy for metastatic disease and patients cannot receive it in earlier lines.(33, 36) Therefore, in order to better reflect the real world, the model accounted for a use of eribulin that is larger than what was observed in the trial for both arms. The values that were discussed with clinical experts as the likely proportions were [redacted] of patients, after SG, and 46.9% after TPC. We believe that this is reflective of the costs of post-progression therapies. The post-progression therapy mix has been reanalysed based on the new data cut with longer follow-up (February 2021). As expected, the proportion of patients who discontinued treatment due to progression with subsequent therapy increased to [redacted] and

[redacted] for the TPC and SG arms, respectively. The sum of the proportions of subsequent therapies in this new analysis exceeds 100% in both arms ([redacted] for TPC and SG, respectively), reflecting multiple active therapies for some patients, and suggest slightly higher subsequent therapy use after SG than TPC.

Note that the above proportions of eribulin use were retained to reflect UK treatment practice, as per the original discussions with clinical experts.

Table 4: Subsequent therapy proportions and their duration*

Treatment	Eribulin	Paclitaxel	Carboplatin	Capecitabine	Epirubicin	Vinorelbine
Subsequent therapy use						
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	46.9%	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Treatment duration (weeks)						
SG	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TPC	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Note: epirubicin numbers reflect doxorubicin patients as well.
*Based on final Feb 25 2021 datacut and UK clinical opinion for eribulin use, among the patients who had discontinued treatment due to progression, and had at least one recorded subsequent therapy. The sum of the proportions of subsequent therapies in the new exceeds 100% in both arms (144.8% and 150.7% for TPC and SG, respectively), reflecting multiple active therapies for some patients.
Source: Trial data analysis, Gilead, data on file. Eribulin treatment percentage: UK clinicians.

A scenario using trial-based post-progression therapy distribution was run, with eribulin use among those who received subsequent therapy of [redacted] after SG and [redacted] after TPC. This had a marginal impact on the ICER (£51,057; see Table 5).

3. Duration of post-progression therapies

Analysis of more complete subsequent therapy duration data from the new data cut shows that any post-progression therapy was taken for a similar treatment duration in both arms,

		which is to be expected as there is no clinical or scientific reason to believe that treatment with either SG or TPC would result in a different subsequent therapy duration. We considered the ERGs suggestion as reasonable and have run a scenario with their assumption (see Table 5). Overall, the following modifications are made to post-progression therapy modelling. • Proportion of patients receiving subsequent therapy: [redacted] and [redacted] for SG and TPC respectively based on updated data-cut • Proportion of eribulin use post-progression: no change as it reflects the UK clinical pathway • Duration of post-progression therapy: use updated data, reflecting several more episodes of subsequent therapies (see Table 4) • Scenarios: 1) ERG recommended durations; 2) fully trial based analysis

Issue 11: ERG response		No new data provided. 1. The ERG agrees that eribulin in the UK is reimbursed as post-progression therapy in the model only. Yet, in the ASCENT study population, slightly more than 30% of patients receive eribulin prior to SG/TPC – therefore these patients are not patients that would be seen in the UK clinical practice. Therefore, the exclusion of patients who received eribulin prior to SG would realign trial data with the decision problem. In the absence of this restriction, only 14% of the TPC sample size would be eligible to receive eribulin after the conclusion of the TPC phase of the study. The assumed proportion incorporated in the model, based on assumptions, did not consider this restriction and introduced a bias in the cost-effectiveness, because a proportion of people in SC were assumed to receive eribulin twice, as first line and as third line. This is clearly clinically implausible. The new rates incorporated by the ERG (assuming that people who received and did not receive subsequent therapy would be equally eligible for eribulin) amended the bias. 2. The model only allows for one line of subsequent therapy. The addition of two or more subsequent therapies requires the restructuring of the way subsequent therapy costs are structured, to not double count therapies for people who in the meantime have moved to the 'dead' state. Further data will be considered once they will be incorporated in the ERG model of the 18th November that is used in this submission.
Key issue 12: Acquisition and administration costs of SG and TPC are incorrectly underestimated. Acquisition and administration costs are applied in the model as a cost per (model) cycle (equal	No	The drug acquisition cost, administration cost and concomitant medication cost are calculated by assigning per model cycle average cost (converted from treatment cycle cost) to the proportion of patients who remain on treatment for each model cycle. It is indeed a simplified approach, but it was selected because the administration schedules with SG and TPC (eribulin, vinorelbine, gemcitabine, and capecitabine) are relatively evenly spread within each treatment cycle: SG is given on Week 1 and Week 2 of a 3-week treatment cycle; similarly, eribulin is given on Week 1 and Week 2 of a 3-week treatment cycle; vinorelbine is given weekly; gemcitabine is given on Week 1, 2, 3 of a 4-week treatment cycle; capecitabine is given daily.(4) Therefore, it was expected that the proportion

to 1 week), calculated as the total cost per therapy cycle (generally over 3 weeks) divided by 3. However, this approach underestimates acquisition and administration costs because costing by model cycle does not assign a proportion of the costs to people that die in (model) cycle 2 and 3 of every therapy cycle. Overall, the model generates underestimates of therapy costs, however the underestimates differ by therapy due to differences in prices, in administration patterns and costs and by type of prescriptions (oral vs IV).		of patients who might die during the break of each treatment cycle would have reasonably minimal impact on cost estimations. The extent to which the underestimation would differ on both arms (i.e., incremental) and consequently the impact on ICER is essentially neglectable. For the cost-effectiveness analysis where the incremental cost is used for generating ICER result, it is considered an appropriate approach. It is incorrect to state "incorrectly underestimated".
Issue 12: ERG response		No additional evidence submitted. The error in the cost calculation has been corrected in the ERG model; the correction is easy to implement and avoids the underestimation of therapy costs due to deaths intervened in each cycle in the model.
Key issue 13: The relative dose intensity (RDI) applied to the cost of SG and TPC may not be calculated correctly.	No	The ASCENT trial showed very few patients with dose interruptions (i.e., 10 out of 258 patients in SG arm).(5) 64 patients in the SG arm had dose reductions and 157 had dose delays.(5) The company understands that any dose discarded because of interrupted infusions is associated with a cost, however, given the very small number of patients with interrupted doses in ASCENT trial SG arm, the extent of the potential underestimation would

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The methods used to calculate the RDI applied in the model are not described. The use of the safety / exposure RDI may underestimate treatment costs because doses discarded result in lower exposure but not in lower costs.		be minimal. Therefore, the RDI of 94.2% reported in ASCENT for SG and used in the model should still be a solid input for base case.(5) The company submission has also presented two scenarios related to RDI for SG and TPC: • 94.2% for SG and 84% for TPC; 84% was extracted from eribulin trial EMBRACE (safety population) which was also used in eribulin NICE submission (TA423). The RDI for eribulin in EMBRACE trial was calculated as "actual dose intensity/planned dose intensity". • 100% for SG and TPC as extreme value testing.
Issue 13: ERG response		Document B of the submission, also cited in this document in Issue 5, states that [redacted]. The cost reduction assigned in the model should be recalculated and the methods should be fully reported.
Key issue 14: Wastage, for drugs used in this appraisal, is not part of the NHS perspective	No	Vial sharing does take place to minimise wastage in UK clinical practice. Acknowledging the absence of data to precisely quantify the percentage, the company model adopted the same approach as a recent NICE submission in a related disease area (trastuzumab deruxtecan in HER2-positive metastatic breast cancer, NICE submission TA704).(37) The assumption of 50% vial sharing was broadly accepted by the ERG and the Committee of TA704.(37) The acceptance of 50% vial sharing is a directly relevant precedent to the current appraisal, since the formulations of both SG and trastuzumab deruxtecan are powder for concentrate for solution for infusion, and dosage for both products is calculated using a weight-based approach.(38, 39) There is therefore no justification for inconsistency with the approach taken in TA704. This assumption was supported by a clinical expert in the UK quoted in NICE submission TA704 who confirmed that “in clinical practice drug wastage is recognized and efforts are made to minimize it by carefully scheduling patients for treatment where vial sharing is possible, although the proportion of drug cost saved through vial share is uncertain”.(37)

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		In terms of perspective, vial sharing ultimately over time reduces the amount of product ordered at individual hospitals, consequently reducing the cost to the NHS.
Issue 14: ERG response		No additional evidence submitted. According to current reimbursement rules, vial sharing does not have an effect on the number of prescriptions – and therefore of vials – reimbursed. This is different than the number of vials used, and it amounts to a cost to the NHS regardless of the sharing rules applied in the hospitals.
Key issue 15: The model uses different weight distributions for the cost calculation of SG and TPC. The cost of SG is calculated using a non-parametric distribution directly calculated using percentiles of weight from the ASCENT trial (non-US) population. This distribution is slightly skewed towards lower weight percentiles compared with the parametric (using the same mean and standard deviation) normal distribution used for TPC.	No	The company used the best available evidence based on the patient-level data of ASCENT trial, in order to estimate the SG cost accurately by assigning a weight distribution that was derived specifically to be aligned with the required dosage per number of vials for SG patients (i.e., 19.1kg-38.21kg, 38.21-57.31kg, so on so forth). Overall, using a parametric distribution versus using the trial-observed non-parametric weight distribution has almost neglectable impact on SG cost estimation. Given the treatments in the TPC arm are generally very low in their costs, parametric versus non-parametric BSA distribution would make even smaller impact. The company has also tested using parametric weight distribution (normal) for SG drug cost calculation, and the ICER would improve/reduce from £49,651 (original base case) to £49,354 (new using ERG preferred approach). This further proves that the company's selected approach is from a conservative perspective.
Issue 15: ERG response		No additional evidence submitted. The comment of the ERG does not concern the nature or source of data – it concerns the application of two different distributions of weight to the SG and TPC arms in the model. Whilst in a clinical trial there are differences, due to randomness, the model considers the counterfactual, so the distribution of weight should be identical for the two arms – whether real data or parametric. The use of real data in addition was hardcoded in the model, preventing model costs to adapt to changes in the RDI and

		introducing computation errors.
Other issues identified by NICE technical team (not included in the ERG report): **Ongoing rollover study**. Please could you provide more details on the ongoing rollover study. Did this allow people in the comparator arm to crossover to the treatment arm? Or the study only includes people originally randomsied to have sacituzumab govitecan? What additional data will it provide?	No	The rollover study (IMMU-132-14) evaluates safety outcomes in patients who were initiated on SG in another study, are continuing to receive clinical benefit from continuation of SG therapy and are tolerating therapy at the time of enrolment.(40) The study captures patients from multiple "parent" studies of SG in solid tumours, including the ASCENT study.(40) The objective of this study is to evaluate long-term safety in patients with metastatic solid tumours who are benefitting from continuation of SG.(40) The study is not intended to allow cross-over from comparator therapy to SG. Therefore, there is no follow-up of TPC patients from ASCENT in this rollover study.(40) The data that the rollover study will provide are the percentage of patients experiencing any adverse events, serious adverse events or laboratory abnormalities for a period of up to approximately three years from a patient's first dose of SG.(40) Further information regarding the rollover study can be found on ClinicalTrials.gov.

Additional issues

All: Please use the table below to respond to additional issues in the ERG report that have not been identified as key issues. Please do **not** use this table to repeat issues or comments that have been raised at an earlier point in this appraisal (for example, at the clarification stage).

Table 3 Additional issues from the ERG report

Issue from the ERG report	Relevant section(s) and/or page(s)	Does this response contain new evidence, data or analyses?	Response
-	-	-	-

Summary of changes to the company's cost-effectiveness estimate(s)

Company only: If you have made changes to the base-case cost-effectiveness estimate(s) in response to technical engagement, please complete the table below to summarise these changes. Please also provide sensitivity analyses around the revised base case. If there are sensitivity analyses around the original base case which remain relevant, please re-run these around the revised base case.

Table 4 Changes to the company's cost-effectiveness estimate

Key issue(s) in the ERG report that the change relates to	Company's base case before technical engagement	Change(s) made in response to technical engagement	Impact on the company's base-case incremental cost-effectiveness ratio (ICER)
ERG report Table 43 "ERG's revised ICERs, QC and corrections" (Section 5.5)	Vinorelbine cost calculation (considering wastage) did not include a dose option of 40 mg	Changes made to include a dose of 40 mg as an option in the cost calculation (according to ERG's preference)	£49,673 (after the change) versus £49,651 (original base-case ICER) +£22; +0.04%
ERG report Table 43 "ERG's revised ICERs, QC and corrections" (Section 5.5)	Half cycle correction was applied to the drug costs (acquisition, administration, and concomitant drugs)	Half cycle correction removed.	£49,181 (after the change) versus £49,651 (original base-case ICER) -£470; -0.96%
Company's base case after incorporating ERG's QC comments and corrections	Incremental QALYs: [redacted]	Incremental costs: [redacted]	Corrected base-case ICER: **£49,202** -£449; -0.91%
ERG report Issue 8 "Log-logistic OS parametric extrapolations	OS long-term extrapolations for SG and TPC were estimated by a jointly fitted parametric model log-logistic distribution (i.e., best	OS extrapolations for SG and TPC updated based on new trial data cut (with additional 11 months of follow-up). Jointly fitted	£48,783 (with new data cut for OS and treatment duration) versus £49,202 (corrected base-case ICER)

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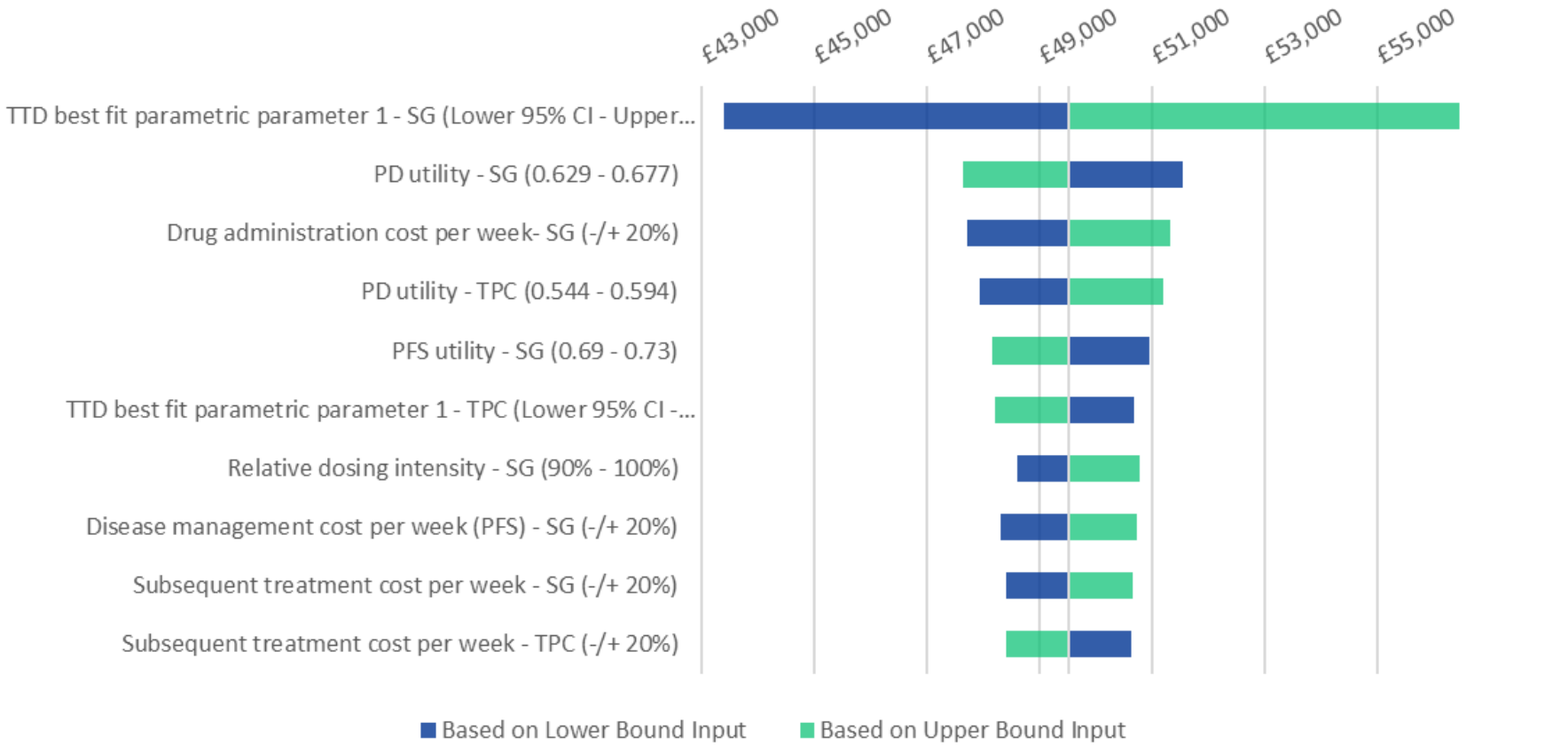
overestimate survival" (Section 4.9.2)	statistical fit), based on trial data from the March 2020 datacut.	parametric model log-logistic distribution is still deemed to be the most appropriate estimation (see details in Company's response to Issue 8). Treatment duration estimation updated accordingly using the new data cut, though it is not a part of issue discussion.	-£419; -0.86%
ERG report Issue 11 "Post-progression therapy costs applied to TPC…" (Section 5.4.5)	Post-progression therapy (e.g., treatment distribution and duration) was informed by trial data that was available at the time of the original submission, as well as consultations with UK clinical experts.	Subsequent treatment cost estimation (including the percentage of patients receiving subsequent treatment in each arm, treatment distribution, and duration on subsequent treatment) updated based on new trial data (with additional 11 months of follow-up). Details can be found in company's response to Issue 11.	£49,938 (with new data for post-progression therapy) versus £49,202 (corrected base-case ICER) +£736; +1.47%
Company's base case following technical engagement (or revised base case)	**Incremental QALYs:** [redacted]	**Incremental costs:** [redacted]	**Revised base-case ICER including all changes above: £49,516**

Sensitivity analyses around revised base case

Sensitivity analyses have been re-run based on the revised base case. Results are presented in this section (Table 5 and Figure 9).

Figure 9. Tornado diagram for the new base case (PAS price)



CI = confidence interval; PAS = patient access scheme; PD = progressive disease; PFS = progression-free survival; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTD = time to discontinuation

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Table 5. Scenario analysis around the new base case (PAS price)

Parameter	Base case	Scenario	ICER/QALY (PAS price)	% Change from base case
Base case			**£49,516**	**--**
Model settings				
Time horizon	10 years	5 years	£53,597	8.24%
		15 years	£48,373	-2.31%
Discounting	3.5% for both costs and outcomes	1.5% for both costs and outcomes	£48,530	-1.99%
PFS extrapolation	Stratified fit model: lognormal for SG and log logistic for TPC (best statistical fit)	Stratified fit model: Weibull for SG and TPC (pessimistic assumption for long-term estimation)	£50,671	2.33%
		Stratified fit model: log logistic for SG and lognormal for TPC (2nd best statistical fit)	£49,323	-0.39%
		KM + Parametric fit (Stratified fit model: lognormal for SG and log logistic for TPC)	£50,642	2.27%
OS extrapolation	Joint fit model: log logistic for both SG and TPC (best statistical fit)	Joint fit model: generalised Gamma for both SG and TPC (pessimistic assumption for long-term estimation and 2nd best statistical fit)	£53,552	8.15%
		KM + Parametric fit (Joint fit model: log logistic for both SG and TPC)	£44,390	-10.35%

Parameter	Base case	Scenario	ICER/QALY (PAS price)	% Change from base case
Base case			**£49,516**	**--**
		Stratified fit model: log-log for SG (best stats fit based on new data cut and clinical plausible) and generalised Gamma for TPC **This scenario is newly added in response to ERG's preference**	£43,574	-12.00%
Treatment duration	Based on TTD parametric fitting model separately fitted to trial observed data: exponential for both SG and TPC (best statistical fit)	Based on TTD parametric fitting model separately fitted to trial observed data: KM + Parametric fit (exponential for both SG and TPC)	£49,730	0.43%
		Based on TTD parametric fitting model separately fitted to trial observed data: Weibull for both SG and TPC (second best statistical fit)	£49,605	-0.02%
		Based on TTD KM curve (mature) for both SG and TPC **This scenario is newly added since KM curves are now complete.**	£49,585	0.14%
Post-progression therapy mix **This scenario is newly added to explore the impact of subsequent treatment on model result (in response to Issue 11)**	Based on ASCENT trial (new data cut) and UK clinicians' opinions	Fully trial-based subsequent treatment distribution	£51,057	2.91%
		Duration on subsequent treatment: 12.5 weeks (SG) and 9.5 weeks (TPC) **This scenario is newly added using ERG preferred settings (assumption not supported by the trial data or clinical opinion).**	£51,062	2.92%
Relative dosing intensity	94.2% for SG; assumed the same for TPC	84% for TPC (assumed equal to the RDI presented in Eribulin NICE TA423)	£50,075	1.13%

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Parameter	Base case	Scenario	ICER/QALY (PAS price)	% Change from base case
Base case			**£49,516**	**--**
		100% for SG and TPC	£50,365	1.71%
% of wastage (likelihood of vial sharing not feasible in clinical practice)	50% of wastage	100% of wastage	£52,125	5.27%
		0% of wastage	£46,907	-5.27%
Utility analysis mapping algorithm from EORTC QLQ-C30 collected in ASCENT trial to EQ-5D-3L	Longworth et al. 2014	Crott et al. 2010	£45,963	-7.18%
AE disutility	Exclude	Include	£49,588	0.14%

AE = adverse event; EORTC QLQ = European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire; EQ-5D = European Quality of Life Five Dimension; ICER = incremental cost-effectiveness ratio; KM = Kaplan-Meier; OS = overall survival; PAS = patient access scheme; PFS = progression-free survival; QALY = quality-adjusted life year; RDI = relative dose intensity; SG = sacituzumab govitecan; TPC = treatment of physician's choice; TTD = time to discontinuation;

Appendix

Table 6: Table 15.2.2.2a analysis of OS - safety population(9)

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Figure 10: Figure 15.2.2.2a KM estimates of OS – safety population(9)

Figure 11: Figure 15.2.1.2a KM estimates of PFS – independent review committee safety population(9)

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Table 7: IMUU-132-05 Final. Sensitivity analysis of PFS - independent review analysis 5 safety population(9)

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All analyses below here are conducted using the revised efficacy data submitted by the Company during Technical Engagement (TE). It has been agreed that the Appraisal will be taken forwards using the revised efficacy data. To situate the impact of the new efficacy data, the ERG requested a comparison of old vs revised dataset. The assessment of the impact of new data in comparison with the old will be addressed in due course in this document.

Base case ICER

The Company base case, using the revised efficacy dataset, is £49,651.

In the previous iteration, the ERG had found two material errors in the model. During TE, the Company accepted both corrections. The ICER, once the essential modelling errors are corrected, is **£49,516**. This is the ICER that will be used to assess the impact of additional Issues that have not been resolved during Technical Engagement.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
ICER initially submitted (pre-TE discussions)					
Correction of error in Vinorelbine cost calculation	[redacted]	[redacted]	[redacted]	[redacted]	£49,651
No half cycle correction for drug acquisition cost, administration cost and concomitant drugs cost	[redacted]	[redacted]	[redacted]	[redacted]	£49,516

Details

1. The correction of costs for vinorelbine was accepted by the company before TE. The difference is minimal however the model has been amended to exclude hard coded values used by the company. The correction is necessary to ensure that changes to the price of vinorelbine are propagated correctly in the model.
2. The Company did not implement the half cycle correction correctly, resulting in a cost of 1.5 times the cost of one chemotherapy session assigned to cycle 1 in the original model.

Issue 12. Acquisition and administration costs of SG and TPC are incorrectly underestimated.

The original model used a cost per cycle to calculate drug acquisition and administration costs.

The ERG recalculated drug acquisition and administration costs assigning a cost based on the real frequency of therapy cycles. The ERG also showed that the calculation based on cycles results in underestimation of costs because the proportion of drug given to people who die in the cycles between an administration and another is assumed to be 'returned' or 'recouped' cost-wise. This is clearly impossible.

The Company debated that this approach is incorrect because costing by cycle would represent the delays that occur in the administration of treatment cycles due to practical arrangements such as for example when day 1 of a therapy cycle falls on a Sunday. Therefore, some people would be treated not on day (for example) 21 precisely, but on day 22 or perhaps 20.

However,

1. The RDI already incorporates treatment delays resulting from variability in the duration of the therapy cycle. The use of costing by cycle is effectively a double count;
2. The company did not present evidence that therapy cycles, in real practice, are substantially delayed for *a substantial* proportion of trial participants.
3. Pragmatic arrangements work in both directions – some people see their administration delayed; some see it advanced. It is also possible that a delayed administration is followed by an advance administration. In both these examples, the impact of therapy delays cancels out; this is the general approach taken in models;
4. Treatment by cycle is incorrect not because it assumes that people are given a therapy exactly at the beginning of the cycle, but because treatment by cycle inappropriately subtracts therapy costs for people that die *after* having received the dose. Receiving one dose is an irreversible cost;
5. For the reason above, delays in therapy cycle duration and fractionated therapy costs are essentially rather different issues and are not mutually exclusive.

Costing by cycle favours SG. The company also argues that the difference of using the cost per therapy cycle is small. The assessment of what constitutes 'small' should be assessed in context. Specifically, costing the model appropriately has an impact of £900 approximately (5% difference), should be assessed in the light that this difference is sufficient to push the ICER above the cost-effectiveness threshold and that several justified difference, when cumulatively considered, have a large impact all jointly considered.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Costing using treatment cycles	[redacted]	[redacted]	[redacted]	[redacted]	£50,377

Issue 13. The relative dose intensity (RDI) applied to the cost of SG and TPC may not be calculated correctly.

The company argued that the ASCENT trial showed very few patients with dose interruptions (i.e., 10 out of 258 patients in SG arm). 64 patients in the SG arm had dose reductions and 157 had dose delays. The company also cites prior RDI values used for eribulin in EMBRACE trial “was calculated as "actual dose intensity/planned dose intensity”".

The incorporation of the RDI in the model directly translates as a reduction of drug acquisition cost. The ERG already explained in the ERG report that:

1. Dose interruptions are counted as ‘reduced exposure’ in safety datasets (from which the Company RDI is derived), so they are subtracted from 100% when the exposure-RDI is calculated. These dose interruptions should not be counted as reduced costs, therefore should not be used as RDI in a model;
2. 64 patients had dose reductions. The economic RDI will be impacted if and only if these dose reductions translate in a lower number of vials required. Because the Company model assumed that all dose reductions translate as a decrease in the number of vials needed, the exposure-RDI certainly overestimates the economic RDI (although the ERG does not have the data to say by how much);
3. 157 had dose delays: dose delays translate in reduced costs if and only if they translate in skipping a dose entirely during a therapy cycle, or over the course of the entire period on treatment. In the model it is irrelevant if a dose is delivered on day 1 or on day 3 in a therapy cycle; dose delays may be relevant if they push the *average* number of days between a therapy cycle and the next over the 21 days considered in this submission. In addition, the average duration of therapy cycles should also consider cycles that are shorter than the 21 days. As explained in the prior Issue, delays and anticipated doses may cancel out, at least in part.

Therefore, the ERG considers that the RDI used in the model is not transparent, and may be incorrectly estimated with respect to economic costing.

The Company’s reference to the precedent of eribulin does not provide elements to clarify how the SG RDI was calculated.

The most appropriate account of duration of therapy cycles would be best resolved abandoning the cost per cycle feature and assuming a different duration of therapy cycle than 21 days (currently implemented in the ERG costing). This approach does require evidence that therapy cycles are delayed systematically and no cancel out effects are seen. If delays are of just a few days, it is unlikely that the RDI would be substantially lower than 100%. This evidence would be extremely easy to obtain from the trial safety datasets. The RDI is simply a pragmatic way to take this source of dilution of therapy costs into account.

The ERG agrees with the Company that the RDI may be somewhat lower than 100%, therefore requested that the RDI is transparently recalculated using effective duration of therapy cycles as observed in the ASCENT study. This revised estimate has not been provided, therefore the uncertainty about how this value impacts the cost-effectiveness remains unresolved.

Reducing the RDI below 100% favours SG; reversing the RDI to 100% for both SG and TPC increases the ICER by of about £1,700

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Costing using treatment cycles	[redacted]	[redacted]	[redacted]	[redacted]	£50,377
Setting RDI =100% for SG and TPC	[redacted]	[redacted]	[redacted]	[redacted]	£51,228

Issue 14: Wastage, for drugs used in this appraisal, is not part of the NHS perspective.

The company states that "In terms of perspective, vial sharing ultimately over time reduces the amount of product ordered at individual hospitals, consequently reducing the cost to the NHS".

The Company's argument is correct only in the case when hospitals are reimbursed based on itemised billing, like in the US or Canada, or in the special case of the Cancer Drug Fund in the UK. In all other cases, the hospital is reimbursed per session (HRG) not per itemised billing, therefore any costs saved because of vial sharing remain in the hospital budgets. The argument of ultimate savings accruing to the NHS apply if reimbursement via the CDF is assumed.

This assumption favours SG. The isolated impact of this assumption on the ICER is of about £3,500.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Costing using treatment cycles	[redacted]	[redacted]	[redacted]	[redacted]	£50,377
Full wastage, 100%	[redacted]	[redacted]	[redacted]	[redacted]	£53,015

Issue 15: The model uses different weight distributions for the cost calculation of SG and TPC

The point of this issue is that the Company used *different* weight distributions for SG and TPC (regardless of which distribution was chose, parametric or non parametric) *and at the same time* the weight distribution was calculated using the RDI shifting the weights bounds towards higher values as a result of setting the RDI.

The reason why this approach is incorrect is that the dilution of treatment intensity represented by the RDI is due to doses being more spaced out in time compared

with a perfect world where every patient is treated precisely every 21 days. The Company's method instead models doses as if dilution accrued as lower strength of treatment received. This is unrealistic, because a patient who weights a (per hypothesis, and constant) weight (e.g. 100kgs) will not receive a lower dose per session but will continue to receive the relevant doses, just spaced out in time. Therefore the distribution of patient weight should not be modelled as if it translated in dilution of the strength of therapy. In addition, the model already discounts the cost of one dose by the RDI (cells H26-H36, Sheet Drug Costs Calcs) therefore introducing a double count.
The Company also applies higher utility to SG after treatment has been discontinued, on grounds that people on SG start from higher utility during treatment. This explanation is inconsistent with the fact that progression implies treatment stopping working and therefore a drop in utility.

The impact of this implicit assumption when modelling the weight distribution, and double count of the RDI, favours SG.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Costing using treatment cycles	[redacted]	[redacted]	[redacted]	[redacted]	£50,377
Same weight distribution for SG and TPC, delinking	[redacted]	[redacted]	[redacted]	[redacted]	£51,363

Summary
The Table below reports the cumulative effect on the ICER of costing assumptions.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
No half cycle correction for drug acquisition cost, administration cost and concomitant drugs cost	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Costing using treatment cycles	[redacted]	[redacted]	[redacted]	[redacted]	£50,377
Setting RDI =100% for SG and TPC	[redacted]	[redacted]	[redacted]	[redacted]	£51,228
Setting patient weight to normal distribution (SG)	[redacted]	[redacted]	[redacted]	[redacted]	£52,213
Full wastage, 100%	[redacted]	[redacted]	[redacted]	[redacted]	£54,497

Issue 9 – Pre-progression utilities with SG may not be higher than utilities with TPC.

With regards to pre-progression and post progression utilities, the ERG reiterates that no explanations nor descriptions nor data are provided regarding the issue of high attrition rates affecting specifically the regression models used to estimate the benefit of SG on the treatment scale.
Clearly the ERG does not hold data sufficient to assess or estimate the potential impact on utilities differential treatment effects.
The ERG bases the request on simple basic data:
In the clarification questions documents, the company stated that of 3,014 data points (EORTC QLQ-C30) collected in the trial, 2,496 were used in the models for estimating utilities and treatment effects. The proportion of data points used in the utility models is 82% of the total available data. This contrasts with the 90% or above maintained by the Company.
In the TE documents, the ERG provided extensive summaries of potential data attrition and why there are strong reasons to believe data attrition may be differential and may bias the utilities estimation models.
There are at this point no further data or explanation to reassure that that analysis may be unbiased despite the high attrition rates.

The impact on the ICER is as detailed in the Tables below.
Assuming the validity of utility estimation models favours SG. Compared with the base case, assuming no difference in utilities by treatment *during treatment* (but still with longer time with better utility due to treatment with SG) causes a net increase in the ICER of £7,000. Removing the assumption of different utilities by treatment after treatment has been discontinued causes a net increase in the ICER of about £3,000.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
No effect on utility post-progression, using value from drop-down (ERG=TA639)	[redacted]	[redacted]	[redacted]	[redacted]	£56,512
No treatment difference, utility pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	£52,843

Cumulative impact on the ICER

Jointly considered, these two assumptions alone increase the ICER by £10,000 compared with the Company's base case.

Cumulative	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
No effect on utility post-progression, using value from drop-down (ERG=TA639)	[redacted]	[redacted]	[redacted]	[redacted]	£56,512
No treatment difference, utility pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	£59,633

When considered together with the costing assumptions in the previous Section, the incremental ICERs are as illustrated in the Table below:

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Including assumptions on wastage, costing RDI	[redacted]	[redacted]	[redacted]	[redacted]	£54,497
No effect on utility post-progression, using value from drop-down (ERG=TA639)	[redacted]	[redacted]	[redacted]	[redacted]	£61,133
No treatment difference, utility pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	£64,510

Issue 11: Post-progression therapy costs applied to TPC assume a very high proportion of people receiving eribulin. This is clinically incompatible with rates of prior and within trial eribulin, and assume more intensive therapy for longer, compared with SG.

The ERG raised the key argument that the proportion of rates of post-progression of

eribulin in the model, given that 32% of participants had received eribulin as first line therapy, was inappropriate. This is because assuming 50% of post-progression eribulin meant assuming that a large proportion of participants in the study would receive eribulin twice, once in first line and then again in second line.
Two key objections are related in this point:

1. Women who received eribulin first line in the ASCENT study are not a population in scope in the UK, therefore a model scenario should be developed using exclusively women who did not receive prior eribulin in the trial. These women would be a plausible population for this decision problem;
2. If the whole ASCENT dataset is used, then the rate of eribulin, essentially, in 3rd line or above, should be much reduced in the model. This is to make the model consistent, but it also reflects questions on the relevance of the ASCENT trial efficacy data for the UK population in scope.

The importance of removing women who received eribulin first line in the ASCENT trial is because these women are likely to have a different prognosis than the general UK population in scope, and not just to avoid the double count in costs.
There are no issues in preservation of randomisation if women who received first line eribulin were removed, because randomisation occurred *after* clinician assigned one of the potential TPC therapies to any woman recruited. Therefore the internal validity of the trial in the subgroup 'women who did not receive eribulin prior to the trial' is preserved.

The distribution of post-progression therapies in the Company base case favours SG.

The impact of changing post-progression therapies to eliminate repeated treatment with eribulin, keeping the whole ASCENT trial sample, is of about £5,000.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Subsequent therapies adjusted to exclude repeat eribulin	[redacted]	[redacted]	[redacted]	[redacted]	£54,372

Efficacy extrapolations

The company submitted a new version of the model incorporating data from a more mature dataset. The major improvement in the model though was the inclusion of stratified and joint fits (previously not provided) that allow an assessment of statistical curve fits for OS.

The difference between the two datasets is one year follow-up.
The ASCENT data are mature data, in a population with very poor prognosis.
The comparison of old and new data in the Graph below shows that the Kaplan-Meier curves are very similar; the new data do not appear to have modified the

median of the distributions, with some marginal changes to the mean. As anticipated, the difference between the two datasets may amount to censoring with more patients being censored in the shorter timeframe.

Revised extrapolation curves were estimated and incorporated in the model. Two statistical models were estimated, using joint fits and independent (stratified) fits. The AIC and BIC statistics are reported in the Tables here below, both for the joint models and for the stratified models.

According to strict statistical fit criteria, the Gompertz and exponential are not plausible models in any scenario. The log-logistic and generalised gamma appear to perform very similarly.

Joint Fits: Distribution	**AIC**	**BIC**	**Median (months)**		**Mean (months)**	
			SG	**TPC**	**SG**	**TPC**
Log-logistic	**2916.8**	**2929.6**	**11.64**	**6.58**	**18.35**	**10.38**
Gen. gamma	2920.5	2937.5	11.87	6.87	15.74	9.11
Weibull	2931.4	2944.2	12.29	7.37	15.01	9.01
Log-normal	2935.7	2948.5	11.23	6.48	17.59	10.14
Gompertz	2956.9	2969.6	12.31	7.08	14.77	9.01
Exponential	2967.1	2975.6	11.45	6.44	16.36	9.21

Stratified fits: SG				
	AIC	BIC	Median (months)	Mean (months)
Log-logistic	**1510.88**	**1518.01**	**11.67**	**19.1**
Gen. gamma	1513.8	1524.4	12.04	15.43
Weibull	1513.8	1521.0	12.37	14.94
Log-normal	1524.5	1531.6	11.37	18.80
Gompertz	1525.1	1532.2	12.42	14.68
Exponential	1531.3	1534.9	11.45	16.36

Stratified fits: TPC				
	AIC	BIC	Median (months)	Mean (months)
Log-logistic	**1407.1**	**1414.2**	**6.58**	**10.05**
Gen. gamma	1408.8	1419.4	6.75	9.17
Log-normal	1410.7	1417.7	6.45	9.64
Weibull	1419.4	1426.5	7.31	9.00
Gompertz	1433.6	1440.7	6.98	9.02
Exponential	1435.8	1439.3	6.44	9.21

When considering the three most plausible distributions for the joint fits, the log-logistic and the generalised gamma appear to fit the data well.

The two models differ by the magnitude of treatment effect: the log-logistic reports a better treatment effect, 7.97 months increased survival with SG vs TPC, compared with the treatment effect with the generalised gamma, 6.63 months increased survival with SG vs TPC. (£53,552 compared with company base case).
The generalised gamma however seems to replicate trial means more closely than the log-logistic, this could be the indication of a better performing model, also given the maturity of the data.
In terms of plausibility of estimated survival rates, the joint log-logistic gives 14.7% (SG) and 5.8% (TPC) survival at 30 months, 6.8% survival at 48 months and 4.7% at 60 months with SG.
The generalised gamma, on the contrary, assumes that the entire cohort treated with TPC is dead from 40 months onward, with 3.5% still alive at month 48 and 2% still alive at 48 months with SG.

The joint Weibull model seems to fit less well; it produces an OS treatment difference of 6 months, with an ICER of £57,210 (compared with company base case).

When looking at stratified fits, the purely statistical rankings offer a slightly different picture.

First of all, AIC and BIC values are very similar for log-logistic and generalised gamma, essentially confirming that statistical criteria alone are not sufficient to inform the choice of distribution.
Second, whilst Gompertz and exponential appear consistently not to be good choices, the Weibull and log normal models appear to appropriately fit the SG and TPC arm respectively, and statistical fit for those models appears indeed very close to that of the log-logistic and generalised gamma. Therefore, these two curves cannot be excluded from the visual assessment.

The log-logistic model, when fitted separately for SG and TPC, appears to fit SG similarly to the joint fit (ICER is decreased to £46,390 compared with company base case).
The log logistic model and the log-normal model fit the TPC arm identically, essentially leaving the choice between log-logistic and generalised gamma. When the log-logistic model is used for SG, the ICER with the generalised gamma for TPC decreases to £43,573 because the generalised gamma estimates lower survival for TPC.

When considering the generalised gamma for SG, the ICER increases in all scenarios. The ICER, with the stratified generalised gamma for both SG and TPC, is increased to £55,600, by approximately £6,000.
Using the generalised gamma for SG and log-logistic for TPC gives an ICER of £60,800 and when using the lognormal the ICER is reduced to £58,500 approximately.
Finally, the Weibull does not seem to be a suitable fit to trial data for SG.

Essentially, the conclusion is that the choice of distribution is reduced to a choice between joint vs stratified models and the log-logistic vs the gamma.
The log-logistic is the most optimistic scenario (for both joint and stratified models), whilst the generalised gamma is more conservative but no less plausible.

The choice is driven by whether or not there would be women in this population that reach a survival at 4 years and 5 years, and in which proportion.
In this respect, there may be two factors at play. On one hand, it is not impossible that very few women would reach such survival timeframe. This fact is not incompatible with the generalised gamma. On the other hand, the ASCENT trial had more than 30 women that refused treatment with TCP once their allocation became known. The prognosis of those women is not known and data were not provided in that respect; however if they had a different prognosis than the rest of the TCP group, a stratified fit would be appropriate for TCP.
It is also possible that the TCP curve in this model would be underestimated and therefore the log-logistic curve would be more appropriate.

Second, the generalised gamma is also a suitable model for SG. However, it is difficult to assess the proportion of women that would be alive at 4 or 5 years with SG. The combination generalised gamma for SG and log logistic for TCP is plausible (survival curves come close but to not cross).

There are two additional scenarios that combine log-logistic and generalised gamma curves.

The scenario SG (generalised gamma) and TPC (log-logistic) is a scenario where

survival curves merge at approximately 50 months. After that time point, there are no differences in survival rates between the SG and TPC group, with survival with SG or TPC converging to 0%.

In alternative, the combination with SG (log-logistic) and TPC (generalised gamma) generates the most optimistic scenario, with SG maintaining a sustained higher survival compared with TPC and a long-term survival of about 5% at 5 years, whilst survival with TPC converges to 0% at 40 months and thereafter.

In summary, the following scenarios are plausible:

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Joint fit, log-logistic (Company base case)	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Joint fit, generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£53,552
Stratified fit, log logistic (	[redacted]	[redacted]	[redacted]	[redacted]	£46,390
Stratified fit, generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£55,654
Stratified fit, log-logistic (SG) generalised gamma (TPC)	[redacted]	[redacted]	[redacted]	[redacted]	£43,974
Stratified fit, generalised gamma (SG) log-logistic (TPC)	[redacted]	[redacted]	[redacted]	[redacted]	£61,478

Cumulative analyses

The following Table illustrates the cumulative incremental analysis.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
Including assumptions on wastage, costing RDI etc..	[redacted]	[redacted]	[redacted]	[redacted]	£54,497
No effect on utility post-progression, using value from drop-down (ERG=TA639)	[redacted]	[redacted]	[redacted]	[redacted]	£61,133
No treatment difference, utility pre-progression	[redacted]	[redacted]	[redacted]	[redacted]	£64,510

Subsequent therapies adjusted to exclude repeat eribulin	[redacted]	[redacted]	[redacted]	[redacted]	£69,861
Joint fit, log-logistic (Company base case)	As above				
Joint fit, generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£75,147
Stratified fit, log logistic (	[redacted]	[redacted]	[redacted]	[redacted]	£64,193
Stratified fit, generalised gamma	[redacted]	[redacted]	[redacted]	[redacted]	£78,965
Stratified fit, log-logistic (SG) generalised gamma (TPC)	[redacted]	[redacted]	[redacted]	[redacted]	£58,643
Stratified fit, generalised gamma (SG) log-logistic (TPC)	[redacted]	[redacted]	[redacted]	[redacted]	£90,332

Scenario analyses

The Table below provides some initial scenario analyses. All scenarios assume the company's OS distributions as in base case.

	Cost (SG)	Cost (TPC)	QALY (SG)	QALY (TPC)	ICER
Company Base case	[redacted]	[redacted]	[redacted]	[redacted]	£49,516
ERG assumptions, with:	[redacted]	[redacted]	[redacted]	[redacted]	
- vial sharing (50% Company preferred)	[redacted]	[redacted]	[redacted]	[redacted]	£66,789
- vial sharing at 50%, - treatment effect on utilities pre-progression, same utilities post-progression	[redacted]	[redacted]	[redacted]	[redacted]	£63,293
- subsequent therapies as in company's base case (1st and 3rd line eribulin)	[redacted]	[redacted]	[redacted]	[redacted]	£64,510
- subsequent therapies as in company's base case (1st and 3rd line eribulin) - vial sharing at 50%	[redacted]	[redacted]	[redacted]	[redacted]	£61,807

- subsequent therapies as in company's base case (1st and 3rd line eribulin) - vial sharing at 50% - treatment effect on utilities pre-progression, same utilities post-progression	[redacted]	[redacted]	[redacted]	[redacted]	£58,572