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

Slides for PUBLIC – redacted

Technology appraisal committee A 07 June 2021

Chair: Jane Adam

Lead team: Ana Duarte, Alan Thomas, Fiona MacPherson

Evidence assessment group: Warwick Evidence Review Group

Technical team: Claire Hawksworth, Eleanor Donegan, Raphael Egbu, Joanna Richardson, Janet Robertson

Company: Gilead

NICE

Sacituzumab govitecan is not recommended

Clinical effectiveness

- Highly effective treatment for people with triple-negative locally advanced or metastatic breast cancer who have a poor prognosis
- Uncertainty in quality of life data collected in ASCENT, particularly post-progression

Cost effectiveness

- Uncertainty about whether quality of life was better post-progression for people who have had SG compared with those who had standard of care
- Uncertainty in most appropriate distribution to extrapolate survival outcomes
- Results of the economic model with the committee's preferred assumptions showed that SG was not a cost-effective use of NHS resources
- End of life criteria are met

Recap from 1st meeting

NICE National Institute for Health and Care Excellence

Sacituzumab govitecan (Trodelvy, Gilead)

RECAP

Table 1 Technology details

Marketing authorisation	For unresectable locally advanced or metastatic triple-negative breast cancer after two or more prior lines of systemic therapies, at least one for advanced disease
Mechanism of action	Monoclonal antibody linked to a topoisomerase inhibitor SN-38 which attaches to Trop-2 expressed on many breast cancer cells. SN-38 blocks topoisomerase I which cells use to replicate their DNA
Administration	Intravenous infusion (IV) once weekly on days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity
Dose	10mg/kg
Price	£793 per 180mg vial (a confidential discount is in place for sacituzumab govitecan, some if its comparators, and subsequent treatments)

Treatment pathway for metastatic TNBC

RECAP

First line

- Anthracyclines (or single-agent docetaxel if anthracyclines are contraindicated)
- Gemcitabine + paclitaxel, (where docetaxel or docetaxel + capecitabine is appropriate)
- Atezolizumab + nab-paclitaxel (PD-L1 positive disease- TA639)

Second line

- Single-agent vinorelbine or capecitabine
- **Sacituzumab govitecan?-** people who have had one line of therapy for advanced disease plus adjuvant or neoadjuvant chemotherapy

Third line

- Single-agent vinorelbine or capecitabine (whichever was not used second line)
- Eribulin
- **Sacituzumab govitecan?-** people with metastatic disease at presentation

Clinical experts - majority of people will receive SG 2nd line in the UK

NICE

5

Pivotal trial: ASCENT

ASCENT was stopped early (in March 2020) due to compelling evidence of efficacy of SG over TPC

RECAP

Table 2 Clinical trial design and outcomes

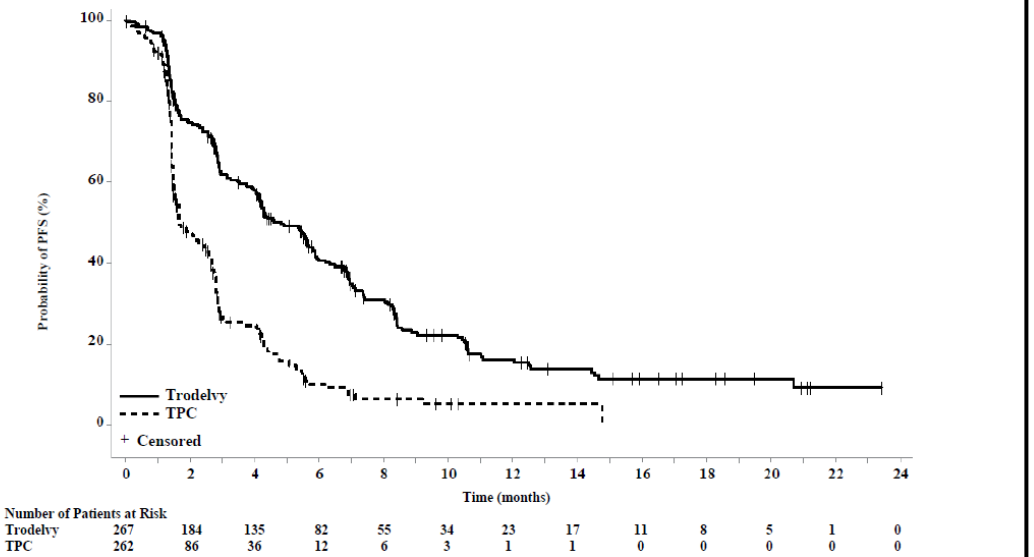
	ASCENT
Design	Open-label, phase III RCT, randomised 1:1; completed
Population	Aligned with population under appraisal
Intervention	Sacituzumab govitecan (SG)
Comparator(s)	Treatment of physician's choice (TPC)- eribulin, capecitabine, gemcitabine or vinorelbine
Outcomes (in model)	• Progression free survival • Time to progression • Overall survival • Health related quality of life
Statistical populations	• ITT- survival analyses; N=529 (SG; n=267 and TPC; n=262) • Safety- QoL analyses (excluded those who did not receive treatment); n=482 (SG; n=258 and TPC; n=224).

RCT, randomised controlled trial, mTNBC, metastatic triple-negative breast cancer, ITT, intention-to-treat, QoL, quality of life

Kaplan-Meier plots used in model (ITT population, February 2021 data cut)

RECAP

KM plot PFS (ITT population)



KM plot OS (ITT population)

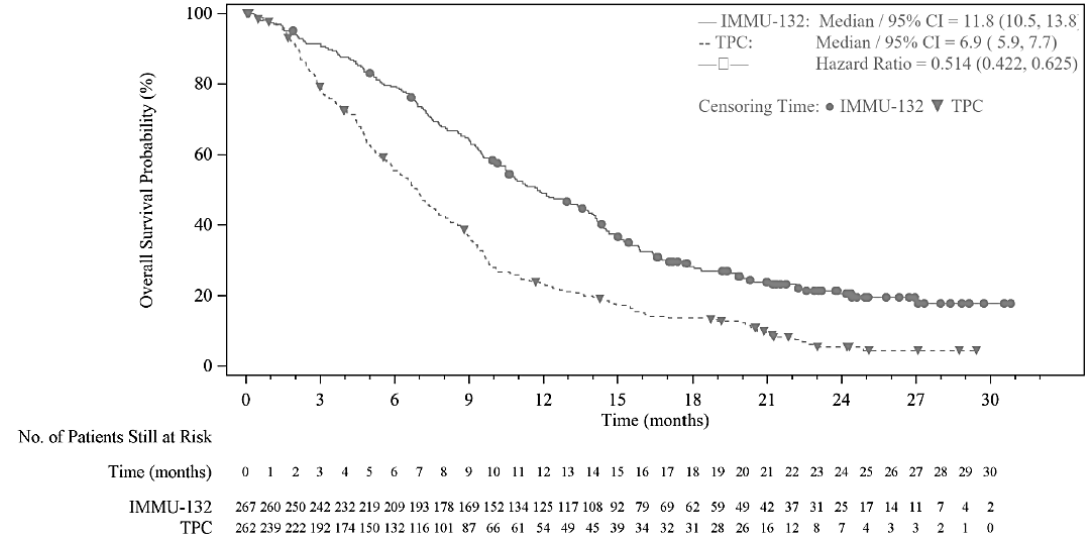


Table 3 Progression-free survival (PFS) and overall survival (OS) results (ITT population)

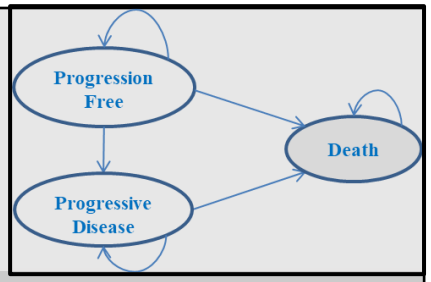
	PFS		OS	
	SG	TPC	SG	TPC
Median, months (95% CI)	4.8 (NA)	1.7 (NA)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)
Number of events (%)	NA	NA	201 (75.3%)	222 (84.7%)
HR (95% CI) SG vs TPC	0.41 (0.33, 0.52)		0.51 (0.42, 0.63)	

NA= not available

Company's economic model

RECAP

Table 4 Model description

Model structure	3-state partitioned survival model: • progression-free • progressed disease • death 
Time horizon	10 years
Model cycle	one-week
Discount rates	3.5% for costs and QALYs
Population	locally advanced or mTNBC as per ASCENT trial
Intervention	sacituzumab govitecan
Comparators	treatment of physician's choice (eribulin, vinorelbine, capecitabine, or gemcitabine)
Utility values	mapped to EQ-5D from the EORTC QLQ-C30 data collected in ASCENT
Subsequent treatments	eribulin, paclitaxel, carboplatin, capecitabine, epirubicin and vinorelbine. eribulin drives the model for subsequent treatment cost

Consultation responses

NICE National Institute for Health and Care Excellence

ACD consultation responses

Patient organisation (n=2)

- Breast Cancer Now, including patient testimony
- METUPUK

Web comments (n=17)

Clinical expert (n=1)

- Dr Alicia Okines, National Cancer Research Institute (NCRI)

Company (n=1)

- Gilead

Breast Cancer Now perspectives on ACD (1/2)

Disappointed SG not recommended –high unmet need, limited treatment options and poor prognoses. Improved post-progression quality of life is reasonable

- People living with TNBC have poor prognosis, limited treatment options and high unmet need
- Decision to not recommend is NOT a sound and suitable basis for guidance to the NHS considering that NICE recognised the high unmet need in TNBC, and need for effective treatments
- SG is highly effective and offers considerable benefit compared with standard of care
- Several pages of personal testimony on the value of delayed progression with SG for patients
- SMC made this available in Scotland in March 2022, patients in England and Wales could be left behind
- Reasonable that reduced symptom burden can have a positive impact on quality of life for a certain period of time after progression. The value of this should not be underestimated
- TNBC is more common in black women, women under 40 and those who have inherited an altered BRCA gene, therefore a negative recommendation would disproportionately impact certain groups
- **114,366 people signed an open letter calling on Gilead, NICE and NHS England to urgently find a solution to this drug becoming routinely available**
    - ‘there is a risk that patients could miss out on the hope of more time with their loved ones’

Breast Cancer Now perspectives on ACD (2/2)

Statements from people with TNBC express fear of disease recurrence and the lack of treatment options

People who are currently receiving sacituzumab govitecan

- *"For me, even after 1 cycle/2 infusions I can already 'feel' things are better. For someone who has had immunotherapy and a chemotherapy prior to this…Trodelvy is going to be an absolute lifeline for me…it means I haven't yet got to tell my sons I'm dying…It'll hopefully mean and show them I'm living and will live for as long as possible. I really hope Trodelvy is approved otherwise we're left with nothing"*

People with secondary TNBC who may need sacituzumab govitecan in the future

- *"I've had every NICE approved chemotherapy since my secondary TNBC diagnosis…there has been very little progress with TNBC. It feels like an extra burden on top of the cancer being terminal that it has less treatment options"*

People with experience of primary TNBC

- *"I am now 9 years post the second occurrence, and having been told I have a very high chance of it returning am incredibly disappointed that this drug may not be available should I or others need it in the future as part of their treatment. Living with the ever increasing fear of cancer returning and learning that a new drug may not be readily available is, quite frankly, horrendous and frustrating in my mind"*

METUPUK perspectives on ACD

A negative recommendation for SG exacerbates inequality- younger and black women, and already available in Scotland

- Patients are very distressed at the prospect of Trodelvy being unavailable to them
- One patient who is currently failing her 3rd line treatment said: “I am absolutely devastated, Trodelvy is my only hope of surviving until the end of the year. I want to spend precious time with my partner and two children aged 12 and 14. NICE’s decision not to fund Trodelvy has a massive impact on patients like me who have run out of options. We are supposed to have patient centred care, this is totally the opposite”
- How has NICE reached a different decision? Inequality of access to SG in England vs. Scotland.
- SG one of first Project Orbis drugs intended to deliver faster patient access to innovative cancer drugs
- Difficult to comment on the clinical and cost-effectiveness ACD due to confidential discounts and redactions
- TNBC disproportionately affects younger people, almost always women, and people of colour. Younger people, particularly in their 20s and 30s are most likely to have a delayed, missed, or late stage diagnosis and are most likely to be pregnant or post pregnancy. These groups are also most likely to have the poorest outcomes and shortest disease free survival

17 web comments from patients- themes (1/2)

Disappointment about provisional recommendation

"I hope you can come to some agreement with Gilead to give every patient with TNBC the treatment and hope they deserve"

Availability elsewhere

"…Patients in the USA are having amazing results…This feels like a massive backwards step for the cancer community and will drive private funding which will bring financial divisions"

"This evidence in Scotland is accepted and this treatment is being offered. It does not make sense that England and Scotland have looked at the same evidence and come to such a different conclusion"

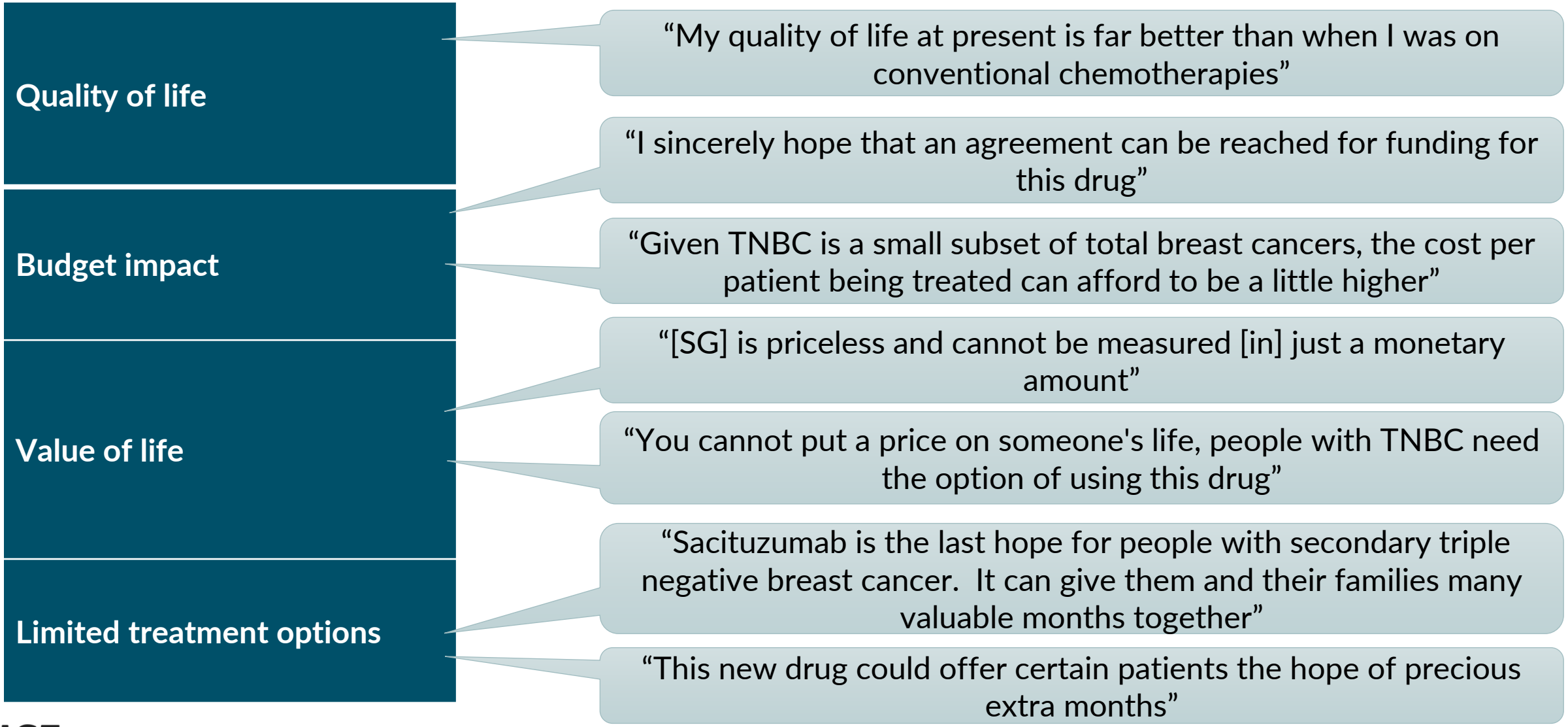
Anxiety and fears

"[TNBC] causes anxiety in patients, friends and family members. Not having access to life saving/life extending treatment cause more anxiety than is necessary"

Equality

"The disease more commonly affects younger women and provides them with vital time with their families"

17 web comments from patients- themes (2/2)



Clinical expert perspectives on ACD

The quality of life of patients treated with SG is expected to be better during and after treatment

Invited clinical expert attending first appraisal committee meeting

- Post-progression utility data from the trial should not be discounted even though there is just one data point
- Patients who respond to treatment have a reduced tumour burden and improved quality of life
- OS benefit demonstrates that people who do not have this technology will deteriorate and die sooner, therefore their quality of life will also deteriorate sooner
- A positive recommendation is critical for people living with advanced TNBC

Clinical expert response by web comment

- Quality of life is likely dependent on tumour burden/response rate. Quality of life is expected to be better during the treatment phase **and** up to 3-6 months post progression but will remain higher in those to those who had had SG vs those who have not
- Beneficial for drug to be made available for needing patient despite uncertainty in survival extrapolation

Summary of company response to ACD

There is evidence to support the approach used in the revised base case. SG is a ground-breaking treatment for people with TNBC

- SG is a ground-breaking therapy, and a negative recommendation disproportionately impacts young, and black women
- People receiving SG vs TPC should have continued quality of life improvement after progression
- Higher post-progression utilities for SG vs TPC is plausible due to a lower tumour burden at the time of progression. This is supported by clinical experts
- In the revised base case, this higher post-progression utility lasts for up to 6 months
- Strong evidence that using the joint log-logistic to estimate long-term survival is robust and represents the most reasonable interpretation of the evidence
    - Observed 30 month survival rates from ASCENT more closely align with the joint log-logistic . Not ‘optimistic’ as described in ACD
    - Joint generalised gamma has been dismissed by clinical experts as too pessimistic
- Improved patient access scheme offered

Issues for discussion

one unresolved, and one area of uncertainty

Table 5 Summary of issues for discussion

Assumption	Company base case	EAG base case	Committee decision	Discuss?
Utility values-post-progression	Higher utility value for SG	Same utility values for SG and TPC	Same utility values	Yes
Overall survival	Jointly fitted log-logistic model	Log-logistic or generalised gamma jointly or independently fitted	Joint fit either log-logistic or generalised gamma	Company and EAG use joint log-logistic in their base case

Post-progression utility

ACD 3.13

NICE National Institute for Health and Care Excellence

Key issue: Utilities- trial data affected by dropout (1/3)

ACD

- Uncertainty in the QoL data due to EORTC QLQ-C30 scores missing for 11.7% of the SG arm and 30.2% of the TPC arm
- Committee concluded 'this uncertainty would impact the analysis of the EORTC QLQ-C30 data and therefore the utility values used in the model.' (assumed post-progression as well as pre-progression values came from the trial where the last HRQOL measurement was collected 4 weeks post last dose)

Company response to ACD

- Post-hoc analysis (n=62/79) of QoL unevaluable patients (not followed up due to withdrawal or progression vs. those completing ≥1 post-baseline assessment) in TPC arm showed:
  - more prior therapies
  - lower baseline quality of life
  - progressed more rapidly on treatment
- This suggests worse overall prognosis in the group not contributing to QoL data

QoL (those followed up vs those who were not): TPC arm OS from ASCENT

Overview of original utility values and clarification

Table 6 Original utility values used in model at ACM1

	Pre-progression			Post-progression			Source of utility data
	SG	TPC	Difference	SG	TPC	Difference	
Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	• **Company stated**: Pre- and post-progression - analysis of EORTC QLQ-C30 data collected in ASCENT, mapped to utilities and analysed in a regression model
	Committee preference						
EAG	[redacted]	[redacted]	-	0.653	0.653	-	• Pre-progression - same as the company but without a decrement for TPC • Post-progression - TA639
				Committee preference			

Key issue: post-progression utilities- reasoning for difference (2/3)

ACD

- Committee concluded that data collected in ASCENT did not appropriately reflect longer-term post-progression utilities and preferred the EAG approach (same post-progression utility value for SG and TPC)

Company response to ACD

- Carry-over effect clinically plausible due to improved tumour status/symptom burden
- Supported by 3 clinical experts - utilities between SG and TPC would converge post-progression
- Identical utilities immediately after progression unreasonable (not valid interpretation of evidence/clinical opinion)
- **Revised base case includes convergence of post-progression utility at 6 months**
  - Using two tunnel states tracking people alive for: (a) exactly 6 months (b) beyond 6 months
  - Utility model applied the following predictors: (a) exactly 6 months – treatment arm **and** progressed status; (b) beyond 6 months – progressed status **only**

Stakeholder/clinician comments

- Feasible that people having SG retain improved quality of life into the progressed state due to reduced tumour and symptom burden compared to people having standard of care
- QoL expected to be better not only during the treatment phase but up to 3-6 months post progression

Key issue: post-progression utilities- summary and concept

1. Committee accepted that people 'felt better' on SG than on chemotherapy and had higher HRQOL (pre-progression)
2. However, once the disease progresses HRQOL declines
3. The company originally proposed that the difference in utility pre-progression is maintained throughout the post-progression phase (that is, people continue to have a higher HRQOL if they had previously taken SG, lasting throughout progression)
4. EAG suggested that on progression, the utility would immediately be the same irrespective of the treatment they had received pre-progression
5. The company now proposes that the utility remains higher for 6 months post-progression after treatment with SG compared to TPC, and then the utility for both arms converge to somewhere in the middle

- Why might there be a carry over effect?
- Could it be related to people having a better response with SG - is there evidence of utility being directly related to the measurement of target lesions on scans?
- Could it be related to side effects of the pre-progression treatment?
- Could people who progressed after initially feeling better on SG (compared to chemotherapy) take time to lose any HRQOL benefit?
- If any improved HRQOL benefit exist, how long might it last?
- Is it plausible that different utilities might be applied within, and beyond 6 months?

★ EAG preference

Key issue: post-progression utilities- implementation (3/3)

EAG

- Company convergence argument based on tumour response but method not coherently supported by clinical data
- Implausible for TPC utilities to rebound ([redacted] pre-progression, [redacted] for 0- 6 months post progression and [redacted] for post 6 months to death)
- Unclear on source of utility ([redacted]) applied to people surviving beyond 6 months post-progression
- ASCENT average duration of response 6.65 months **measured from time of response not from progression (5.5 months are spent in pre-progression therefore 1.2 months is the upper bound for post-progression improvement)**
- All people responding is implausible. Should the correct proportion of people experiencing benefit due to tumour shrinkage be 35% (ORR) or 50% (CBR)?
- Produced scenarios with higher utility for SG during period of response with no rebound for TPC using TA639 values with company's preferred decrement ([redacted])
- Preferred base case is no difference in post-progression utility values (0.653 for both SG and TPC)

EAG considered two assumptions for scenario analyses:

1. Post-progression duration of response	2. Proportion of responders with higher utilities
★ a) 1.2 months (corresponds to 6.65 months average duration of response)	a) 35 % (corresponds to objective response rate)
b) 3 months (corresponds to 8.5 months average duration of response)	★ b) 50 % (corresponds to clinical benefit rate)

ORR, objective response rate (complete response or partial response); CBR, clinical benefit rate (ORR or stable disease)

Overview of original and revised utility values

Table 6 Original utility values used in model at ACM1

	Pre-progression			Post-progression			Source of utility data
	SG	TPC	Difference	SG	TPC	Difference	
Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	• **Company stated**: Pre- and post-progression - analysis of EORTC QLQ-C30 data collected in ASCENT, mapped to utilities and analysed in a regression model
	Committee preference						
EAG	[redacted]	[redacted]	-	0.653	0.653	-	• Pre-progression - same as the company but without a decrement for TPC • Post-progression - TA639
				Committee preference			

Table 7 Utility values in company **revised** base case

	SG	TPC
Post-progression (within 6 months)	[redacted]	[redacted]
Post-progression (beyond months)	[redacted]	[redacted]

Table 8 EAG utility values for **revised** scenarios

	SG	TPC
Post-progression (response)	0.653	[redacted]
Post-progression (post-response)	[redacted]	[redacted]

TA639 values with [redacted] decrement

Revised base cases (includes SG PAS only)

Table 9 Company and EAG **revised** incremental base case results

Revised base cases	ICER (£/QALY)
Company	
Assumes higher post-progression utilities for SG converging at 6 months	£48,760
EAG	
Assumes no convergence (0.653 used post-progression in both arms)	£50,876

Results do not include confidential commercial discounts for comparators

ICERs which include confidential commercial discounts for comparators are reported in PART 2

EAG post-progression utility scenarios

EAG explored a combination of 2 assumptions for scenario analyses:

1. Post-progression duration of response: 1.2 months or 3 months
2. Proportion of responders (with higher utilities): 30 % (ORR) or 50% (CBR)

Table 10 EAG post-progression utility scenario analyses results

Assumption	ICER (£/QALY)
1.2 months, 35% response	
	£52,557
★ 1.2 months, 50% response	
	£52,467
3 months, 35% response	
	£52,227
3 months, 50% response	
	£51,998

★ EAG preference

Results do not include confidential commercial discounts for comparators

ICERs which include confidential commercial discounts for comparators are reported in PART 2

ORR, objective response rate (complete response or partial response); CBR, clinical benefit rate (ORR or stable disease)

Other considerations

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End of life (EOL) and equality consideration

SG meets EOL criteria, and TNBC disproportionately affects a certain population of women

EOL criteria

- The company, EAG and committee agree that end of life criteria are met

Equality

- Patient organisations and clinical experts noted that TNBC has high unmet need and disproportionately affects younger, and black women
- Several pages of patient response to the initial committee recommendation support the need for treatment in this population
- It is noted that SG was made available for treating TNBC elsewhere in the UK (Scotland, March 2022)

Backup slides

NICE National Institute for Health and Care Excellence

ACM1- resolved issues

RECAP

Table 13 Summary of issues resolved at ACM1

Assumption	Company base case	EAG base case	Committee decision
Acquisition & admin. costs	Per model cycle (1 wk)	Per treatment cycle	Per treatment cycle
Weight distribution	Non-parametric for SG Parametric for TPC	Should be same. Parametric for SG and TPC	Parametric for both
Vial sharing/ wastage	50% vial sharing (50% cost)	No vial sharing (100% cost)	50% vial sharing
Subsequent treatments- TPC	Eribulin 46.9% (clinical opinion), Others ASCENT Feb 2021	Eribulin- 14% (eribulin naïve in ASCENT). Others assumption	Eribulin 46.9%
Utility values- pre-progression	Higher utility value for SG	Same utility values for SG and TPC	Higher utility value for SG

ACM1- 1st committee meeting

Unresolved issues- for discussion and clarification

Table 14 Summary of unresolved issues for discussion and clarification

Assumption	Company base case	EAG base case	Committee decision
Utility values- post-progression	Higher utility value for SG	Same utility values for SG and TPC	Same utility values
Overall survival	Jointly fitted log-logistic model	Log-logistic or generalised gamma jointly or independently fitted	Joint fit either log-logistic or generalised gamma
Relative dose intensity*	94.2%	100% in absence of detailed description of calculations	94.2%

*Clarification needed

Overall survival extrapolations

ACD 3.14

NICE National Institute for Health and Care Excellence

Key issue: extrapolation of OS- area of uncertainty

ACD

- '…remained an area of high uncertainty, but without a clear rationale for independent fits it was reasonable to consider jointly fitted curves'
- '….true survival extrapolation could be anywhere between the optimistic log-logistic and the more pessimistic generalised gamma models.'

Company response to ACD

- Jointly fitted log-logistic more plausible:
  1. 30 month OS rates from ASCENT aligns better with log-logistic vs generalised gamma models
  2. Clinical expert predicted 60-month survival of 1.4% for TPC, more closely aligns with the 1.7% log-logistic estimate compared to the 0.1% generalised gamma
- Independent log-logistic fits well and is more optimistic, suggesting joint log-logistic is conservative

EAG

- Joint log-logistic model is robust and represents most reasonable interpretation of the available evidence
- Statistical performance of joint vs independent fits never tested and joint fit chosen as default
- Combinations of independently fitted curves now irrelevant
- **Base and scenario analyses apply joint log-logistic model**

Should the jointly fitted log-logistic or generalised gamma be used to generate cost-effectiveness estimates?

Relative dose intensity (RDI)

ACD 3.10

NICE National Institute for Health and Care Excellence

Key issue: method for implementing 94.2% RDI

ACD

- '.....the company included an RDI of 94.2%, which was informed by dose reduction, incomplete infusions and delays in the ASCENT trial.' This was accepted by committee.

Company

- Implemented this RDI in the economic model as dose reductions
- Aligned with data from ASCENT

EAG

- Initially implemented this RDI in the economic model as dose delays
- If committee agreed that the RDI<100% due to dose reductions and not dose delays then the company's modelling approach is correct

Is implementing an RDI of 94.2% as dose reduction committee's preferred approach?

Kaplan-Meier plot for PFS (ITT population) March 2020 data cut

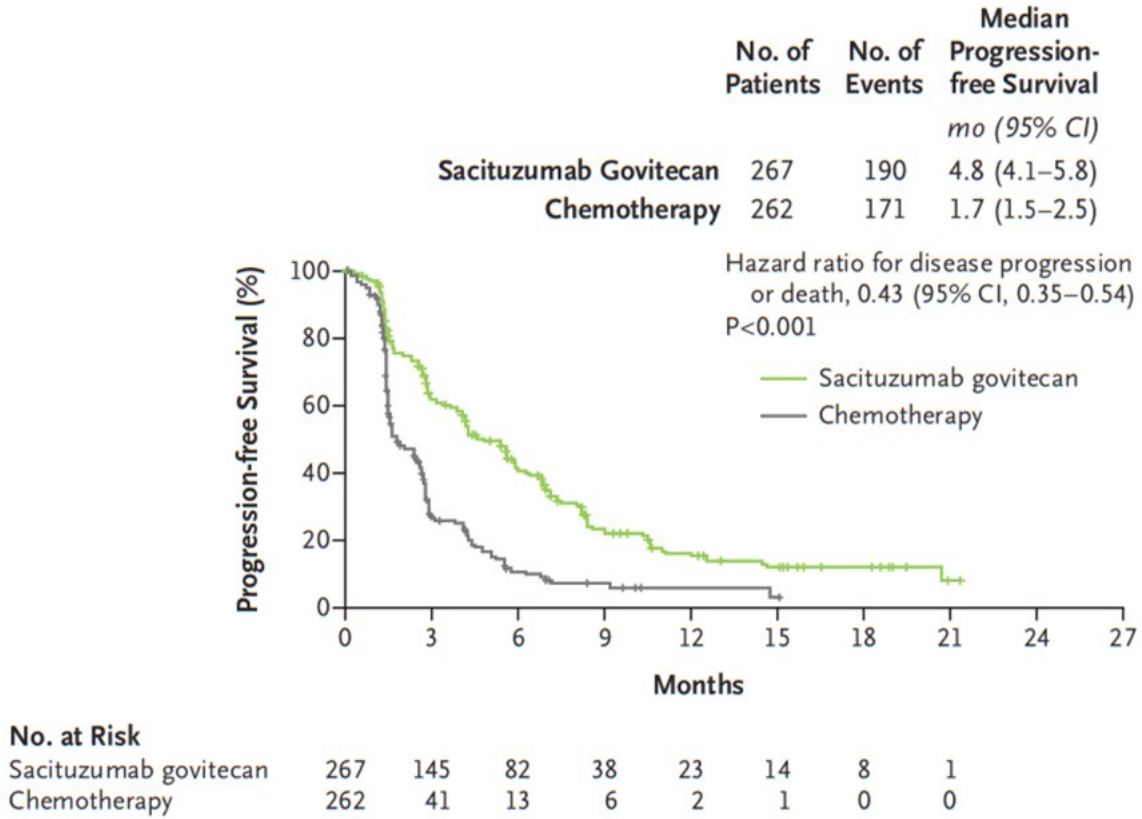

Table 11 Progression-free survival (PFS) results- March 2020 data cut (ITT population)

	SG	TPC
Median PFS, months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)
Number of events (%)	190 (71.2)	171 (65.3)
PFS HR (95% CI) SG vs TPC	0.43 (0.34, 054)	

Kaplan-Meier plot for OS (ITT population) March 2020 data cut

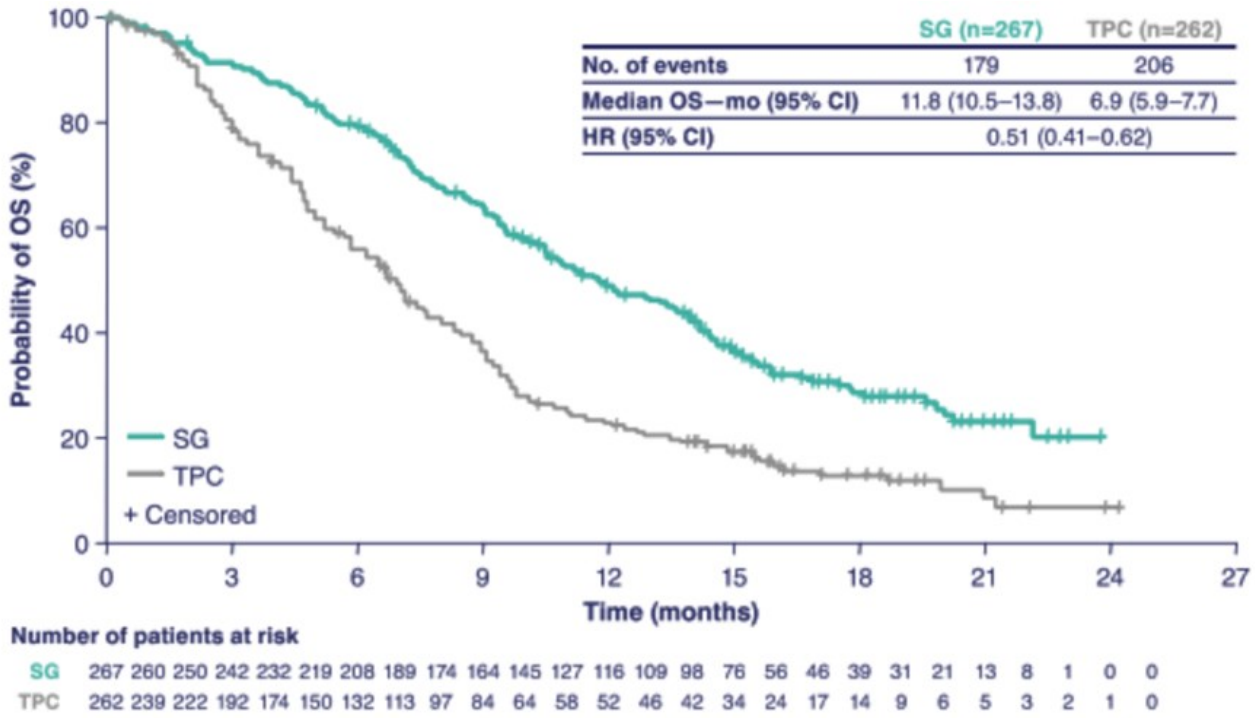

Table 12 Overall survival (OS) results- March 2020 data cut (ITT population)

	SG	TPC
Median OS, months (95% CI)	11.8 (10.5, 13.8)	6.9 (5.9, 7.7)
Number of events (%)	179 (67.0)	206 (78.6)
OS HR (95% CI) SG vs TPC	0.50 (0.41, 0.62)	