Slides for PUBLIC – redacted

NICE National Institute for Health and Care Excellence

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

Lead team presentation

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ERG: Warwick Evidence Review Group

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Company: Gilead

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Key clinical issues

- Are ASCENT data generalisable to a UK setting? (treatment pathways, particularly prior eribulin use)
- 14.5% of people randomised to the TPC arm did not receive treatment vs 3.4% of SG arm. Why was this? How did this impact the results? These people were excluded from the utility analysis.
- There was less pre-progression quality of life data for TPC vs SG. How did this impact the quality of life results?
- The last data point for quality of life was 4 weeks after the last dose of treatment. Does this represent post-progression quality of life?
- Is there evidence that HRQoL is better on SG than other therapies, and if so, before or after stopping treatment at progression?

Patient and carer perspectives

Submission received from Breast Cancer Now

- Triple-negative breast cancer (TNBC) affects younger women
- A diagnosis of TNBC and can be particularly frightening and is hard to come to terms with. It has a huge impact on both the individual and family/friends
- People feel unlucky if they have this compared to breast cancer with molecular targets.

"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."

- People feel like they're living on borrowed time which has a big impact on mental health. Managing TNBC remains one of the greatest areas of unmet need.

"Having brain metastases is especially frightening as the disease can take away who I am as a person as well as my physical abilities."

- New treatment options are desperately needed- trial results indicate a promising treatment that extends survival. More quality time with friends/families outweighs inconvenience of travel to hospital / potential of side effects

"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."

Disease background – triple negative breast cancer (TNBC)

- 4,500-6,750 UK annual incidence accounting for 15% of all breast cancer
- TNBC lacks all three molecular markers: oestrogen receptors (ER), progesterone receptors (PR) and human epidermal growth factor 2 (ERBB2, formerly HER2). These affect treatment and prognosis
- Can be locally advanced, having spread to local areas, or metastatic to organs including brain, bones, lungs or liver
- Not sensitive to endocrine therapy or molecular targeted therapy (due to lack of molecular markers). Chemotherapy is the main systemic treatment
- TNBC is associated with high 5 year mortality of ~40% and a shorter time to relapse than for non-TBNC patients.
- TNBC has high metastatic potential (46% of patients)
- Disproportionately affects younger women, black women and women with the BRCA-1 mutation

Sacituzumab govitecan (Trodelvy, Gilead)

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
Dose	10mg/kg
Administration	Intravenous infusion (IV) once weekly on days 1 and 8 of 21-day treatment cycles until disease progression or unacceptable toxicity
List price	£793 per 180mg vial

Treatment pathway for metastatic TNBC

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 progressed to advanced disease following adjuvant or neoadjuvant chemotherapy

Third line

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

Is this pathway used consistently in clinical practice? Is SG likely to be used in the UK 2nd and/or 3rd line? Is ASCENT representative?

Professional organisation

Submission received from the NCRI Breast Research Group

Important and effective treatment for people with mTNBC who have a poor prognosis with standard chemotherapy

- 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 longer median PFS and longer median OS than standard chemotherapy
- SG is a real breakthrough for patients living with advanced TNBC

mTNBC: metastatic triple negative breast cancer, PFS: progression free survival, OS: overall survival

Pivotal trial: ASCENT

ASCENT was stopped early (in March 2020) due to compelling evidence of efficacy of SG over TPC. Median follow up was 10.55 months in the SG arm and 6.28 months in the TPC arm

Trial design	Open-label, phase III RCT, randomised 1:1. Completed	
Population	Unresectable, locally advanced mTNBC refractory or relapsed after receiving ≥2 prior standard of care chemotherapies (including ≥1 prior therapy locally advanced / metastatic setting).	
Intervention/ comparator	Sacituzumab govitecan	Single agent treatment of physician's choice (TPC)- eribulin, capecitabine, gemcitabine or vinorelbine
Outcomes (in model)	• Progression free survival • Overall survival • Time to progression • 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). • Primary- survival analyses (excluded those with brain metastases); n=468 (SG; n=235 and TPC; n=233)	

QoL: quality of life

ASCENT Key results- March 2020 data cut*

- Trial results demonstrate similar efficacy in those with / without brain metastases (ITT vs. primary analysis population). Small numbers with brain metastases (approx. n=30) each arm (primary population)
- Does sacituzumab govitecan cross the blood brain barrier?

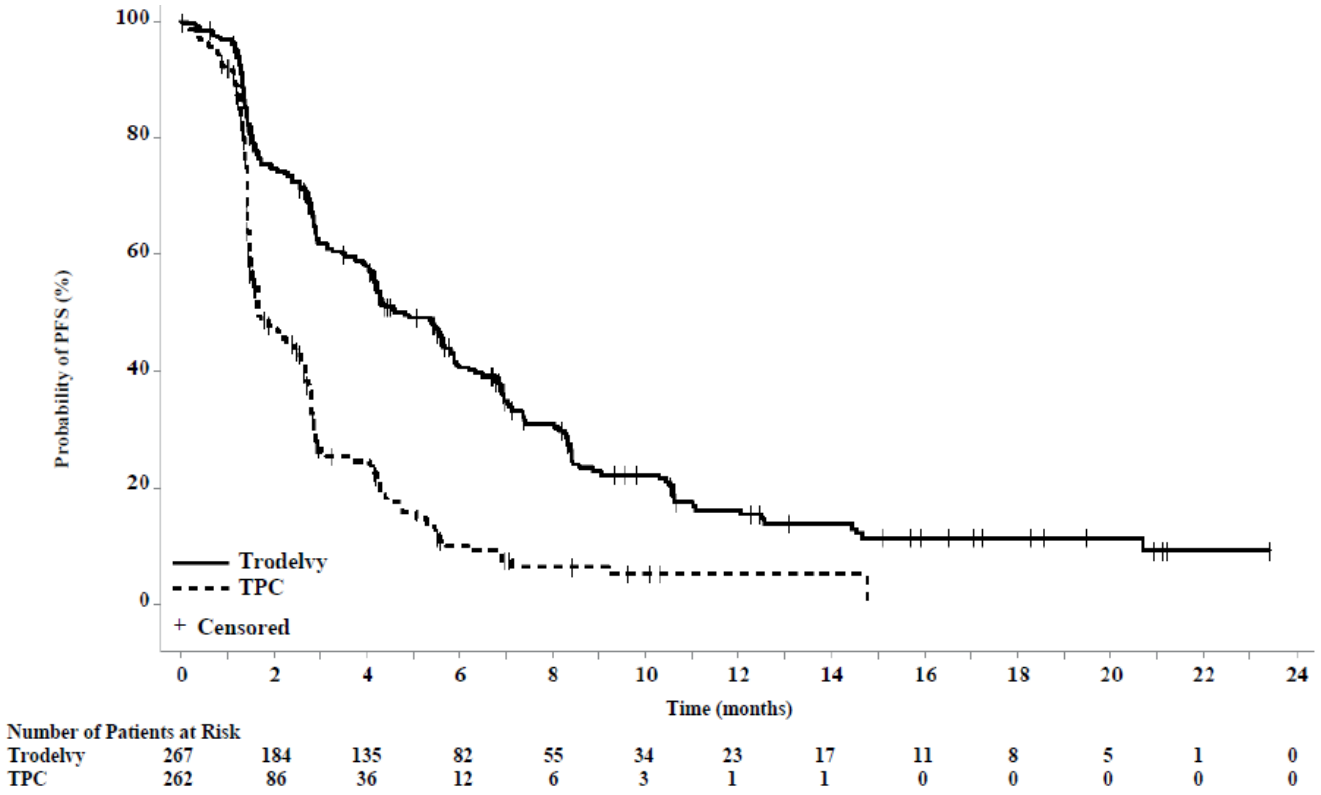
		ITT population (includes brain metastases)		Primary analysis population (excludes brain metastases)	
		SG, n=267	TPC, n=262	SG, n=235	TPC, n=233
PFS	Median PFS, months (95% CI)	4.8 (4.1, 5.8)	1.7 (1.5, 2.5)	5.6 (4.3, 6.3)	1.7 (1.5, 2.6)
	PFS HR (95% CI)	0.43 (0.35, 0.54)		0.41 (0.32, 0.52)	
OS	Median OS, 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)
	OS HR (95% CI)	0.51 (0.41, 0.62)		0.48 (0.38, 0.59)	

*Results from the Feb 2021 data cut were not reported for the primary analysis population

Does sacituzumab govitecan cross the blood brain barrier?

NICE

Kaplan-Meier plot for PFS (ITT population) February 2021 data cut – used in model



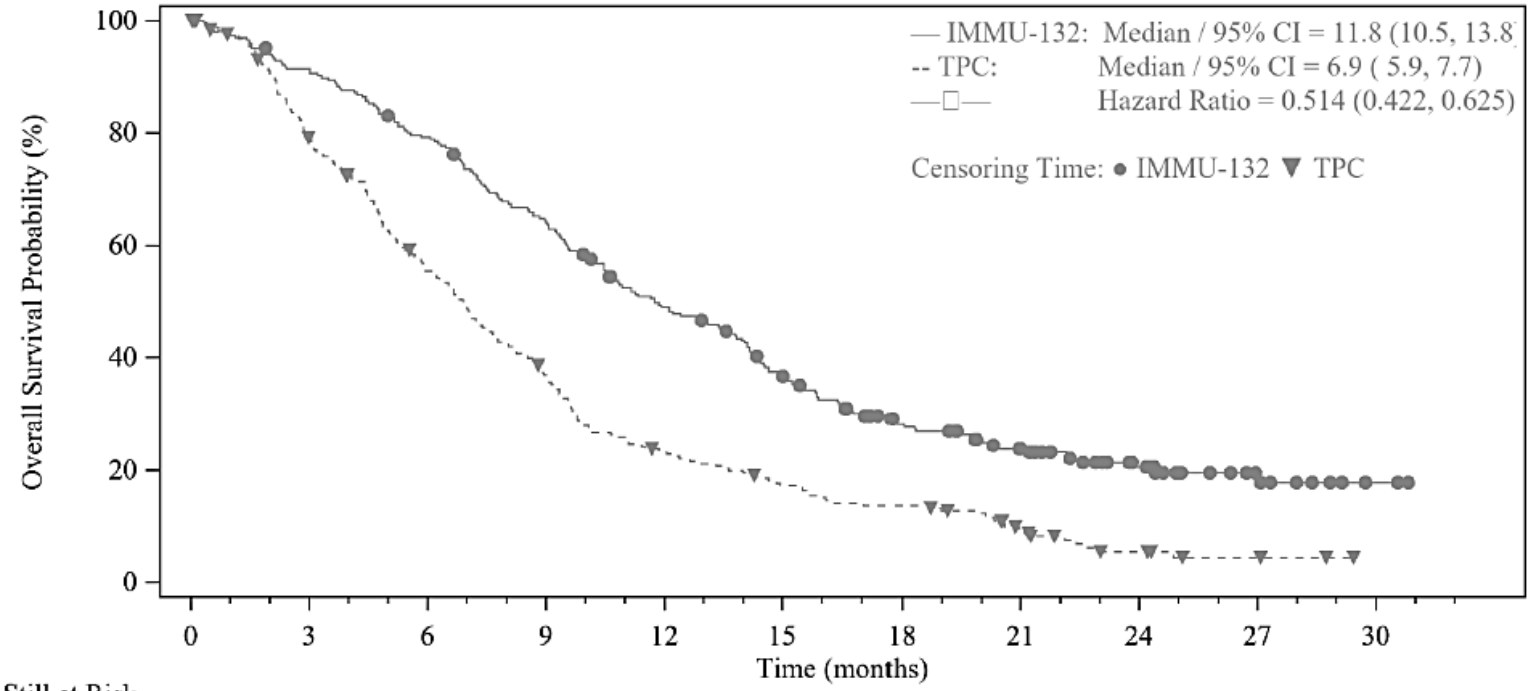
	SG	TPC
Median PFS, months (95% CI)	4.8 (NA)	1.7 (NA)
Number of events (%)	NA	NA
OS HR (95% CI) SG vs TPC	0.41 (0.33, 0.52)	

NA= not available

Kaplan-Meier plot for OS (ITT population) February 2021 data cut – used in model

ERG:

- KM curves are similar to March 2020 data cut
- No change to the medians
- Marginal changes to the means



No. of Patients Still at Risk

Time (months)	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
IMMU-132	267	260	250	242	232	219	209	193	178	169	152	134	125	117	108	92	79	69	62	59	49	42	37	31	25	17	14	11	7	4	2
TPC	262	239	222	192	174	150	132	116	101	87	66	61	54	49	45	39	34	32	31	28	26	16	12	8	7	4	3	3	2	1	0

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

Uncertainty around generalisability of ASCENT data

Background:

- **Issue 1**: ASCENT 32.7% had eribulin prior to enrolling in the study.
- TA423 eribulin only recommended 3rd line (UK no 1st line eribulin for metastatic TNBC) and proposed positioning of SG is before eribulin, not after
- **Issue 2**: After randomisation 14.5% TPC vs 3.4% SG arm chose not to commence treatment

ERG:

- **Issue 1**: 1st line eribulin in the metastatic setting is not UK standard of care
- **Issue 2**: potential bias due to sample attrition and broken randomisation. Were these patients on another active treatment - may influence quality of life and subsequent treatment use

Company comments:

- **Issue 1**: ASCENT prior therapies generalisable (100% taxane and 82% anthracycline)
- **Issue 2**: survival status for n=31/38. Safety population results (those who had treatment) consistent with ITT population

Clinical expert comments:

- **Issue 1**: ASCENT prior therapies are as expected in a UK setting (taxane, anthracycline, cyclophosphamide and capecitabine)
- **Issue 2**: Inevitable for open label study. Could not be blinded

Are the trial data generalisable to the decision problem and UK setting?

Quality of life- differential attrition and post-progression data

Background:

- HRQoL assessed at baseline, day 1 of cycle and final study visit (4 wk after last study drug/ premature study termination)
- **Issue 3:** Missing EORTC QLQ-C30 values for 11.7% of the SG arm vs 30.2% of the TPC arm
- **Issue 4:** Is the last data point representative of post-progression utility?

ERG:

- **Issue 3**: might have biased treatment effect estimates for HRQoL. Uncertainty (wide 95% CIs) in the EORTC QLQ-C30 estimates beyond Cycle 6
- **Issue 4**: ASCENT did not provide post-progression QoL data

Company comments:

- **Issue 3**: Completion rates similar until Cycle 10. Less TPC data due to earlier progression
- Misleading to use ITT as denominator - decreasing number of patients remain on treatment
  - If anything, missing HRQoL data in the TPC arm is biased against SG, in favour of TPC
- **Issue 4**: ASCENT HRQoL data is appropriate to inform post-progression utilities

Clinical expert comments:

- TPC arm deteriorated and died much earlier than those in the SG arm, attrition is inevitable

Did less data in the TPC arm bias HRQoL estimates?
Is the 4 week post progression data sufficient to inform utilities?

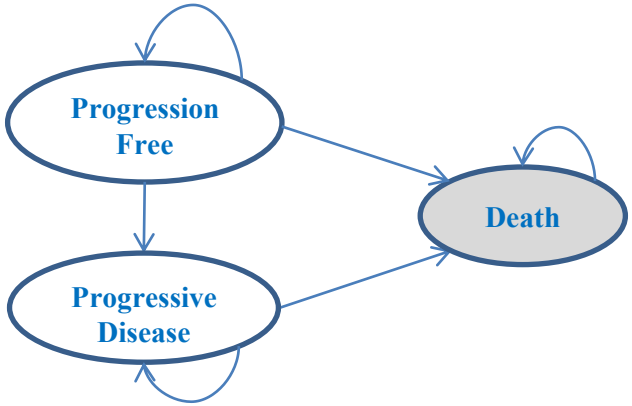
Key clinical issues

- Are ASCENT data generalisable to a UK setting? (treatment pathways, particularly prior eribulin use)
- 14.5% of people randomised to the TPC arm did not receive treatment vs 3.4% of SG arm. Why was this? How did this impact the results? These people were excluded from the utility analysis.
- There was less pre-progression quality of life data for TPC vs SG. How did this impact the quality of life results?
- The last data point for quality of life was 4 weeks after the last dose of treatment. Does this represent post-progression quality of life?
- Is there evidence that HRQoL is better on SG than other therapies, and if so, before or after stopping treatment at progression?

Key cost-effectiveness issues

- Is the company's or ERG's approach to costing drugs more representative of clinical practice?
  - Cycle costs for drugs, RDI and weight distribution?
- Is vial sharing feasible?
- Are the trial data appropriate to inform utility values or should alternative sources be used?
- Is there evidence that HRQoL is better on SG than other therapies, and if so, before or after stopping treatment at progression?
- What assumptions are appropriate for modelling the costs of subsequent eribulin?
  - 46.9% subsequent eribulin or 14% due to prior eribulin?
- How should overall survival be extrapolated?

Company's economic model



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

Company and ERG preferred assumptions

		Company base case assumption	ERG base case assumption
Costing assumptions	Acquisition & administration costs	Cost per model cycle (1 week)	Cost per treatment cycle
	Relative dose intensity	94.2%	100% in absence of detailed description of calculations
	Weight distribution	Non-parametric for SG Parametric for TPC	Should be the same. Used parametric for SG
	Vial sharing/ wastage	50% vial sharing (50% cost)	Vials should be costed by number of prescriptions and assumes vials are not shared (100% cost)
	Utility values	Higher utility value for SG than TPC in both the pre-progression and progressed states	Same utility values for SG and TPC in both the pre-progression and progressed states (TA639 precedence)
	Subsequent treatments	46.9% of people in the TPC arm had eribulin, based on UK clinical opinion. Remaining distributions and treatment duration based on ASCENT Feb 2021 data cut	14% of people in the TPC arm had eribulin reflecting those remaining eribulin naïve in ASCENT. Remaining distributions and durations were assumptions
	Overall survival	Jointly fitted log-logistic model	A range of plausible extrapolations. Log-logistic or generalised gamma either jointly or independently fitted

Costing assumptions- represent UK practice?

- Acquisition and administration costs
  - By model cycle or treatment cycle?
- Relative dose intensity (RDI)
  - 94.2% or 100%?
- Weight distribution
  - Non-parametric for SG and parametric for TPC, or the same for both?

Company:

- Administration schedules are evenly spread within each treatment cycle therefore can use cost per model cycle
- Same impact both arms -no relative difference
- Very few patients in ASCENT had dose interruptions so 94.2% RDI is appropriate
- Used data from ASCENT to assign weight distributions

ERG:

- The cost of each dose should be accrued when incurred. Cost per cycle shifts fraction of dose to later cycles when deaths have occurred for patients that have already had full dose
- Company used RDI to reduce dose for drug cost (incorrect average cost per dose). But:
  - ASCENT- largest proportion of RDI is due to dose delay not interruption
  - Delays of less than 7 days have minimal impact
- The model uses lower weight in SG than TPC to calculate drug costs so confounds RDI error
- Risk that RDI <100% underestimates treatment costs and 100% should be accounted even if exposure is less

Costing assumptions- impact on ICERs

- Is vial sharing feasible?
  - About service delivery
  - Relatively small patient numbers
  - Vial sharing does not reduce no. of prescriptions

Table- ERG's preferred costing assumptions and impact on the ICER (one-way and cumulative)

	One way impact	Cumulative impact
Company base case		£49,516
Costing using treatment cycles	£50,377, (+£861)	£50,377, (+£861)
Setting RDI to 100%	£50,365, (+£849)	£51,228, (+£1,712)
Normal weight distribution for SG	£50,484, (+£967)	£52,213, (+£2,697)
No vial sharing	£52,125, (+£2,609)	£54,497, (+£4,981)

ICERs include PAS for SG and list price all others (cPAS ICERs in part2)

Issues 9 & 10: pre- and post-progression utility values

	Pre-progression		Post-progression		Source of utility data
	SG	TPC	SG	TPC	
Company	[redacted]	[redacted]	[redacted]	[redacted]	• Both pre- and post-progression - Analysis of EORTC QLQ C30 data collected in ASCENT, mapped to utilities and analyses in a regression model
ERG	[redacted]	[redacted]	0.653	0.653	• Pre-progression - same as the company but without a decrement for TPC • Post-progression - TA639 to be consistent with prior appraisals where no treatment effect was demonstrated on the utility scale

Should pre- and post-progression utility values be higher for SG than TPC or the same across arms?

Issue 9: Pre-progression utility values

Background
- EORTC QLQ C30 data collected in ASCENT mapped to EQ-5D utilities
- Company used [redacted] for SG and [redacted] for TPC (0.084 difference)

ERG:
- Utilities should be the same
- CSR concluded that EORTC QLQ C30 scores were similar for SG and TPC
- Data missing not at random (TPC arm) invalidates the analysis
- Differential values not accepted in previous TAs.

Company:
- ASCENT data do evidence a difference
- Greater ORR (31.1% vs 4.2%), tumour shrinkage and reduction in symptoms is clinical rationale for higher utilities in SG

Stakeholder comments:
- Improved PFS, OS and tumour shrinkage show symptom control- people can do the things they enjoy for longer
- Reassurance and potential bridge to future therapies- quality of life benefit

Is ASCENT an appropriate data source? Are higher SG utilities pre-progression appropriate?

CSR: clinical study report, ORR: objective response rate

Issue 10: Post-progression utility values

Background
- Company used [redacted] for SG and [redacted] for TPC, applying the same difference of 0.084

Company:
- People on SG entering post-progression with less tumour burden - higher utility
- You'd expect the drop in utilities to be equal across arms: 0.084

ERG:
- Utilities should be the same:
- EORTC QLQ C30 data collection stopped just after progression (4 weeks)
- Lesion size (SG vs TPC) after progression is unknown and no evidence for lesion size translating into utility differences
- SG and TPC arms had similar mix of post-progression therapies
- Used values from TA639 (atezolizumab)

Stakeholder comments:
- People having SG are better physically and emotionally to start the next treatment
- SG enabled one patient to avoid radiotherapy to the brain and associated tiredness, steroids and other side effects
- Higher post-progression utilities are to be expected after an effective therapy
- Patients on SG will have a lower disease/symptom burden at progression

Is ASCENT an appropriate data source? Should SG have higher utilities post-progression?

Issue 11: Post-progression therapy costs

Background
- February 2021 data cut 73.9% and 71.9% in the SG and TPC had subsequent treatment
- Eribulin is the driver of subsequent therapy costs
- Company assumed 46.9% in the TPC arm had eribulin (from UK clinical experts)

ERG:
- TPC has a very high subsequent eribulin proportion
- Clinically incompatible with rates of prior (not UK practice) and within trial eribulin
- Proportion of people having eribulin post TPC should be capped at 14% (number of people eribulin naïve in ASCENT)

Company:
- Prior eribulin in ASCENT is higher than would be expected in the UK
- Subsequent eribulin proportions in model came from UK clinical experts- [redacted]% SG and 46.9% for TPC
- 46.9% reflects TPC arm who did not get eribulin
- Proportions for other subsequent therapies- ASCENT data
- Trial based scenario - [redacted]% for SG and [redacted]% for TPC

Stakeholder comments:
- High rates of eribulin are to be expected as it is only available 3rd line in the UK
- those who progress on TPC will get eribulin if they have not already received it

Should the proportion of subsequent eribulin in the TPC arm be 46.9% or 14%?

Issue 11: Post-progression therapy costs

		Eribulin	Paclitaxel	Carboplatin	Capecitabine	Epirubicin	Vinorelbine
Proportion (%)							
SG	Company*	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
	ERG	66.0%	0.7%	7.9%	8.6%	8.2%	8.6%
TPC	Company	46.9%	[redacted]%	[redacted]%	[redacted]%	[redacted]%	[redacted]%
	ERG	14.0%	0.7%	7.9%	26.8%	22.6%	28%
Duration (weeks)							
SG	Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG	12.5	12.5	12.5	12.5	12.5	12.5
TPC	Company	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	ERG	9.5	9.5	9.5	9.5	9.5	9.5

Data sources

Company- proportion for eribulin based on UK clinical opinion, the remaining proportions and duration were based on the ASCENT February 2021 data cut

ERG- proportion for eribulin based on 14% cap, the remaining proportions were pragmatic estimation and durations assumed that subsequent therapies are given for half the time between post-progression and death

Should the proportion of subsequent eribulin in the TPC arm be 46.9% or 14%?

Company figures from Table 4 TE response form, ERG figures from Table 42 ERG report

Issue 8: Extrapolation of OS- area of uncertainty

Background

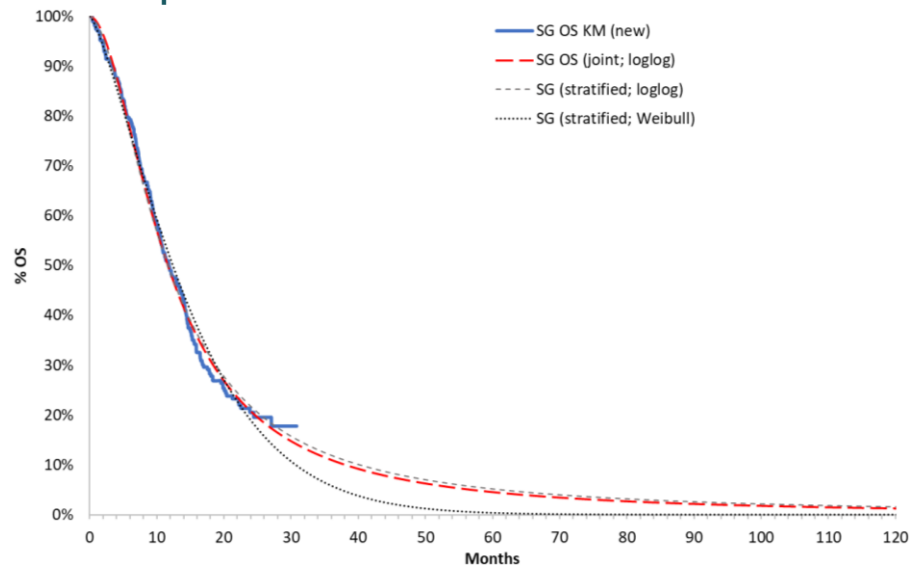
- Log-logistic and generalised gamma best fit observed data
- Company used jointly fitted log-logistic for both arms
- Company selected log-logistic due to its long term survival projections

Company:

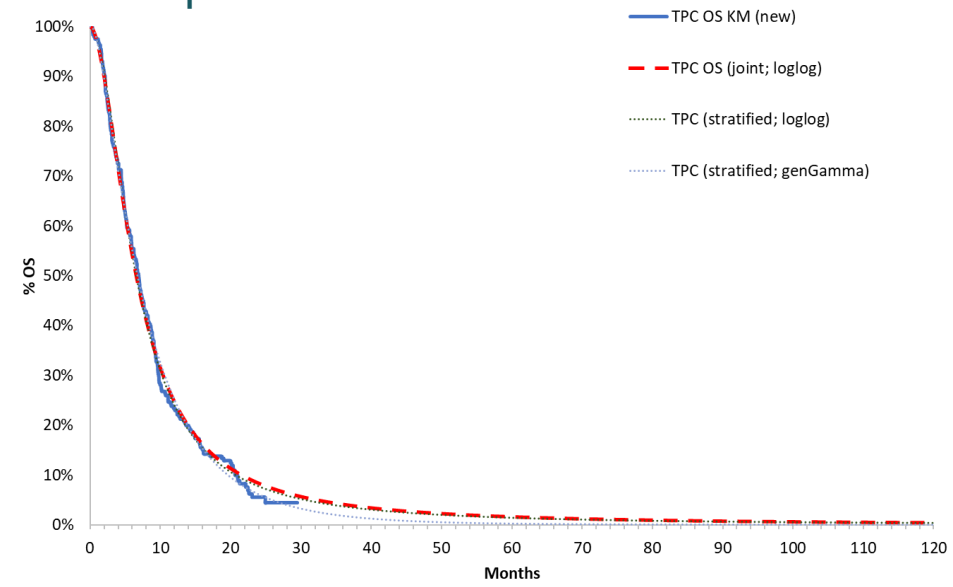
- The AIC for the joint log-logistic fit is lower than the sum of the two separately fitted curves - preference joint fit
- Log-logistic appears to overestimate long-term survival in the TPC arm - conservative approach
- Agree generalised gamma good fit for TPC but still prefer joint log-logistic

Company

OS SG parametric fit Feb 2021 data cut



OS TPC parametric fit Feb 2021 data cut



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OS parametric fits for SG and TPC

ERG:

- Log-logistic most optimistic efficacy (+7.97m vs +6.63m OS with generalised gamma).
- No strong statistical rationale / validation with external data, other distributions fit similarly
- Eg joint generalised gamma- similar statistical fit, better visual fit, more closely replicates trial means and does not overestimate longer term survival
- Individual fits should also be considered

Table- projected survival rates up to 60 months (5 years) with different OS extrapolations

	Estimated survival rates		30 months	48 months	60 months
1	Joint log-logistic	SG	14.2%	6.8%	4.6%
		TPC	5.5%	2.5%	1.7%
2	Joint generalised gamma	SG	12.2%	3.6%	1.6%
		TPC	2.6%	0.4%	0.1%
3	Independent log-logistic	SG	15.1%	7.5%	5.2%
		TPC	4.9%	2.2%	1.4%
4	Independent generalised gamma	SG	11.5%	2.9%	1.1%
		TPC	3.0%	0.6%	0.2%

Plausible options:

1. (joint fit) log-logistic
2. (joint fit) generalised gamma
3. (independent fit) log-logistic for both arms
4. (independent fit) generalised gamma for both arms
5. (independent fit) log-logistic for SG and generalised gamma for TPC
6. (independent fit) generalised gamma for SG and log-logistic for TPC

Which approach? Joint or independent fit? Log-logistic or generalised gamma?

Key cost-effectiveness issues

- Is the company's or ERG's approach to costing drugs more representative of clinical practice?
  - Cycle costs for drugs, RDI and weight distribution?
- Is vial sharing feasible?
- Are the trial data appropriate to inform utility values or should alternative sources be used?
- Is there evidence that HRQoL is better on SG than other therapies, and if so, before or after stopping treatment at progression?
- What assumptions are appropriate for modelling the costs of subsequent eribulin?
  - 46.9% subsequent eribulin or 14% due to prior eribulin?
- How should overall survival be extrapolated?

End-of-life criteria are met

- Both the company and ERG agree that the end of life criteria are met

Life expectancy is shorter than 24 months:

- The expected survival for women with TNBC is between 7 and 13 months
- Median OS in the ASCENT trial (ITT population) was 7 months
- Modelled mean OS in the TPC arm 10.38 months (company preferred approach)

SG extends life by at least 3 months:

- In the ASCENT trial median OS in the SG arm was 4.9 months longer than in the TPC arm
- In the base case analysis SG improved mean OS by 6.9 months compared with TPC

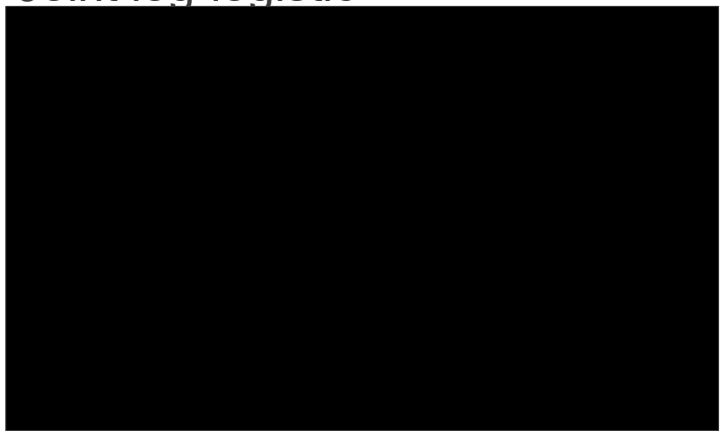
Summary of model drivers to be discussed in part 2 with confidential ICERs (contain comparator PAS discounts)

Issue	Key question
Costing assumptions	ERG or company approach represent UK practice?
Vial sharing	Is vial sharing feasible?
Pre-progression utility values	Should values be the same or higher in SG?
Post-progression utility values	Should values be the same or higher in SG?
Subsequent eribulin	46.9% or 14% subsequent eribulin?
Overall survival	How should OS be modelled?

Back up slides

Different OS extrapolations cntd

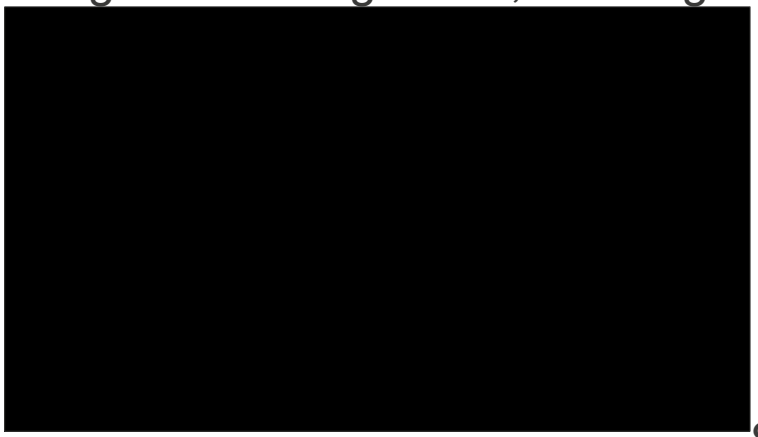
Joint log-logistic



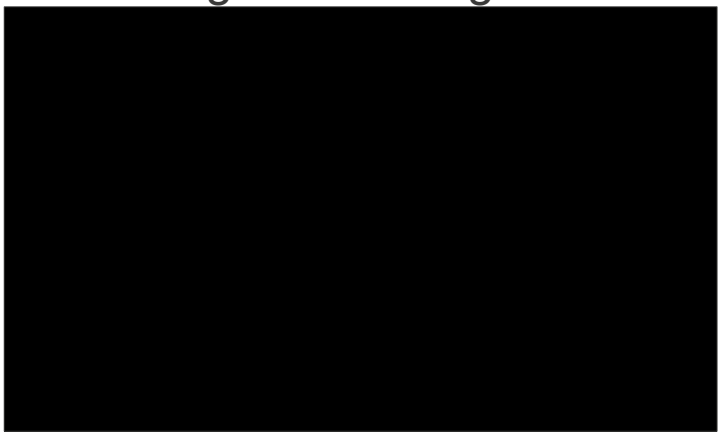
Stratified log-logistic

Joint generalised gamma

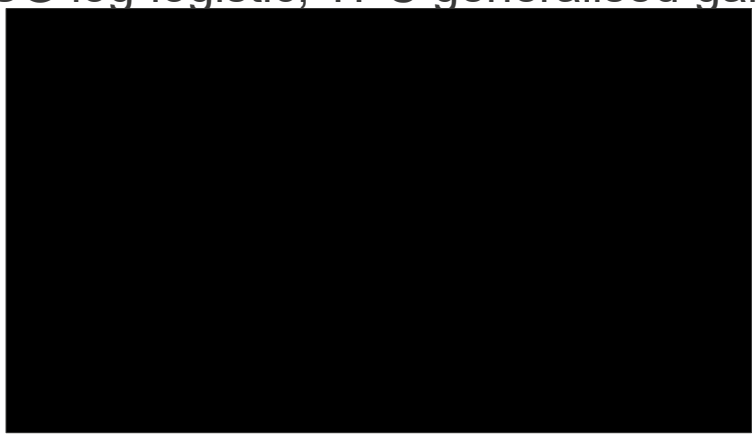
SG generalised gamma, TPC log-logistic



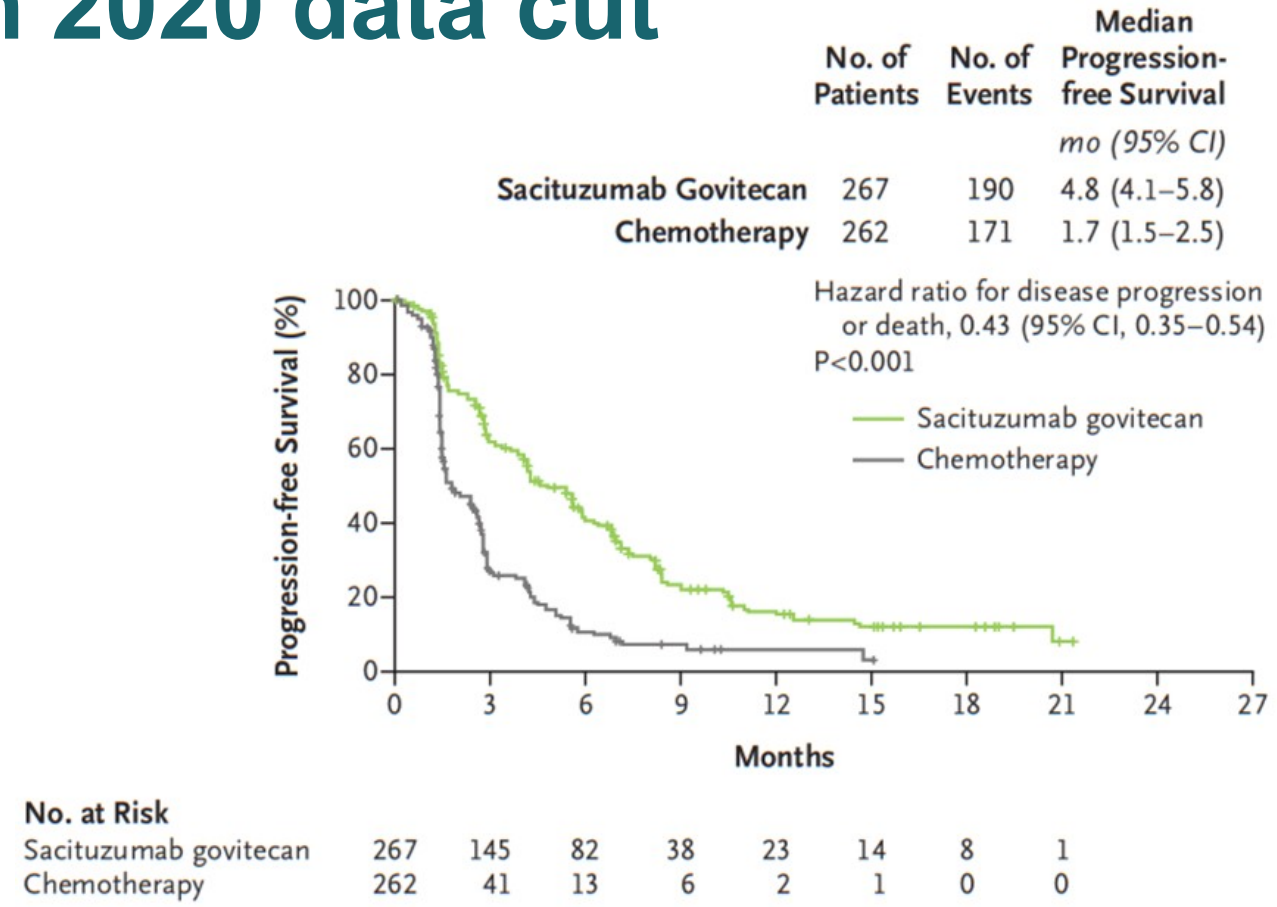
Stratified generalised gamma



SG log-logistic, TPC generalised gamma

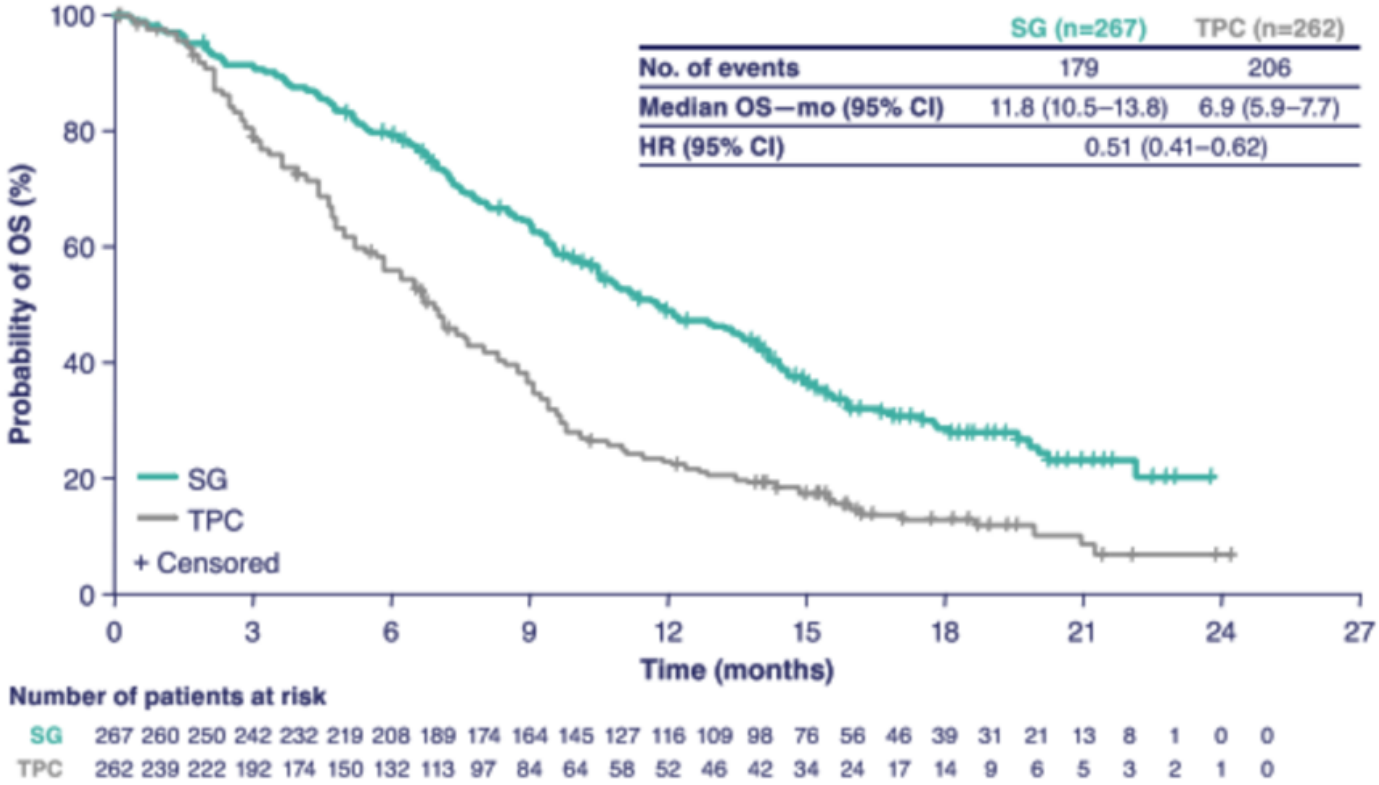


Kaplan-Meier plot for PFS (ITT population) March 2020 data cut



	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



	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)	

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
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.	The company provided a later data cut from ASCENT with longer follow up.	The more mature data cut helps resolve this.	Yes
6	**Tumour location in the lymph node was higher in the TPC arm** Tumour's lymph node location is associated with poorer prognosis and this could bias the relative effectiveness of SG.	Presence of tumours in the lymph nodes is not prognostic.	Satisfied with the company and ERG's position that this is not a prognostic factor.	N/A
7	**Early stopping of the trial** Evidence shows that early stopping of the trial may exaggerate the magnitude of benefit of the experimental treatment	The company provided a later data cut from ASCENT with longer follow up.	The more mature data cut helps resolve this.	Yes

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration	Included in updated base case?
5	**Frequency of high-grade neutropenia was more frequent in the SG arm.** Different dose reduction/modification rules applied across the two arms so the dose was reduced for SG and G-CSF administered but in the TPC the treatment was discontinued and no-GSF was administered	The company clarified that high grade neutropenia had been treated the same in each arm, with dose reduction and administration of G-CSF. Clinical experts confirmed that neutropenia was treated appropriately.	Neutropenia was treated appropriately and in accordance with clinical practice in both arms.	?