1 Recommendations

1.1 Sacituzumab govitecan is not recommended, within its marketing authorisation, as an option for treating unresectable triple-negative locally advanced or metastatic breast cancer in adults after 2 or more systemic therapies, at least one of which was for advanced disease.

1.2 This recommendation is not intended to affect treatment with sacituzumab govitecan that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Usual treatment for triple-negative locally advanced or metastatic breast cancer is chemotherapy.

Clinical trial evidence shows that sacituzumab govitecan increases how long people have before their disease gets worse and how long they live compared with chemotherapy.

At its current price, the cost-effectiveness estimates for sacituzumab govitecan are higher than what NICE usually considers an acceptable use of NHS resources. Therefore, it is not recommended.

2 Information about sacituzumab govitecan

Marketing authorisation indication

2.1 Sacituzumab govitecan (Trodelvy, Gilead Sciences) has a marketing authorisation 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'.

Dosage in the marketing authorisation

2.2 The dosage schedule is available in the summary of product characteristics for sacituzumab govitecan.

Price

2.3 The list price of sacituzumab govitecan is £793.00 per 180 mg vial (excluding VAT; BNF online accessed March 2022).

2.4 The company has a commercial arrangement, which would have applied if the technology had been recommended.

3 Committee discussion

The appraisal committee considered evidence submitted by Gilead, a review of this submission by the evidence review group (ERG), and responses from stakeholders. See the committee papers for full details of the evidence.

Clinical need and treatment pathway

Triple-negative breast cancer has a high disease burden

3.1 Triple-negative breast cancer accounts for about 15% of breast cancers and lacks all 3 molecular markers (oestrogen, progesterone and HER2 receptors) which affects treatment options and prognosis. Chemotherapy is the mainstay of treatment because triple-negative breast cancer is not sensitive to endocrine therapy or molecular targeted therapy. The patient expert explained that being diagnosed with locally recurrent unresectable or metastatic breast cancer is extremely difficult for people, and their family and friends. It can cause considerable anxiety and fear, and the uncertainty of the outcome can be very difficult to deal with. The aim of treatment is to stop progression of the disease, extend life, and maintain or improve quality of life for as long as possible. Treatment is continued

for as long as it is controlling the disease. The committee concluded that there is a high disease burden for people with triple-negative breast cancer.

There is a high unmet need for effective treatments for triple-negative locally advanced or metastatic breast cancer

3.2 The marketing authorisation for sacituzumab govitecan specifies its use after 2 or more prior systemic therapies. For people who have triple-negative advanced or metastatic breast cancer, first-line therapies are paclitaxel, docetaxel, nab-paclitaxel, anthracycline-based chemotherapy, gemcitabine without or without carboplatin, or atezolizumab plus nab-paclitaxel for PD-L1-positive disease (see NICE's technology appraisal guidance on atezolizumab with nab-paclitaxel for untreated PD-L1-positive, locally advanced or metastatic, triple-negative breast cancer [TA639]). Second-line therapies are single-agent vinorelbine or capecitabine. Third-line therapies are eribulin (see NICE's technology appraisal guidance on eribulin for treating locally advanced or metastatic breast cancer after 2 or more chemotherapy regimens [TA423]) or single-agent vinorelbine or capecitabine (whichever was not used previously) (see NICE's clinical guideline on breast cancer: diagnosis and management). In the locally advanced or metastatic setting, the proposed positioning for sacituzumab govitecan is either second line (for people who received a systemic treatment for early disease) or third line (for people who present with de novo metastatic disease). The clinical experts clarified that, in the locally advanced or metastatic setting, most patients would have sacituzumab govitecan as a second-line therapy. Clinicians prefer to use the most effective treatments earlier in the treatment pathway. Therefore, people will have already received anthracyclines, taxanes, and capecitabine . The clinical experts noted that because early triple-negative breast cancer tends to relapse quickly after treatment, rechallenge with these therapies is not appropriate, leaving very few effective treatment options. The committee concluded that there is a high

unmet need for effective treatments for locally advanced or metastatic triple-negative breast cancer.

Clinical evidence

Sacituzumab govitecan offers considerable benefit compared with standard care

3.3 The clinical evidence was based on ASCENT, a randomised, open-label clinical trial for people with relapsed or refractory, unresectable, triple-negative, locally advanced or metastatic breast cancer after 2 or more previous therapies. ASCENT compared sacituzumab govitecan with treatment of physician's choice, which included eribulin, capecitabine, gemcitabine and vinorelbine. The company reported trial results from a March 2020 data cut. This showed a consistent clinically meaningful and statistically significant benefit for sacituzumab govitecan compared with treatment of physician's choice for objective response rate, progression-free survival and overall survival. The objective response rate was considerably greater in the sacituzumab govitecan arm: 31.1% compared with 4.2% in the treatment of physician's choice arm. Median progression-free survival was 4.8 months in the sacituzumab govitecan arm compared with 1.7 months in the treatment of physician's choice arm (hazard ratio 0.43, 95% confidence interval 0.35 to 0.54). Median overall survival was 11.8 months with sacituzumab govitecan compared with 6.9 months in the treatment of physician's choice arm (hazard ratio 0.51, 95% confidence interval 0.41 to 0.62). The patient expert experienced tumour shrinkage while on sacituzumab govitecan, including their brain metastases, and explained that initial gastrointestinal side effects were well managed with a dose reduction and concomitant medication. The company provided a later data cut from February 2021 during technical engagement. The ERG noted that the survival data were similar across the 2 data cuts, with no changes to the median estimates, and marginal changes to the mean estimates. The committee considered sacituzumab govitecan to be a

highly effective treatment for people with triple-negative locally advanced or metastatic breast cancer who have a poor prognosis.

The results of the trial are generalisable to NHS clinical practice

3.4 In ASCENT, 32.7% of people had previously had eribulin, which is only used as a third-line treatment in the UK (after 2 or more chemotherapy regimens in line with TA423). In the UK, eribulin would be given after sacituzumab govitecan. The ERG noted that prior eribulin in ASCENT could impact the trial efficacy results for sacituzumab govitecan. The clinical experts explained that because the trial also included people who had not had prior eribulin, the trial demonstrated that sacituzumab govitecan is effective before and after eribulin. They felt that the efficacy of sacituzumab govitecan is not affected by prior treatment with eribulin. The committee accepted that although approximately a third of the people in ASCENT had received eribulin, which does not reflect UK practice, the results were generalisable to people in the NHS.

The effect of a higher dropout rate in the comparator arm is unknown

3.5 In ASCENT, 14.5% of people randomised to the comparator arm (treatment of physician's choice including eribulin, gemcitabine, capecitabine and vinorelbine) chose not to have treatment, compared with 3.4% of people in the sacituzumab govitecan arm. The ERG noted that this differential dropout rate could introduce bias because it is unclear if common patient characteristics affected the choice to start treatment. The ERG suggested that it may have been people with a better prognosis who felt they had better options outside of participating in ASCENT. The clinical experts disagreed and explained that people who dropped out of the trial were more likely to be those with poor prognosis who chose not to have further chemotherapy as part of the comparator arm. They said that dropout was inevitable in an open-label trial, and that people may be unwilling to remain in the comparator arm when there is already published data showing that sacituzumab govitecan is an effective treatment. The safety population included only those who started treatment, and the

company used this population to conduct the quality-of-life analyses. The committee concluded that the survival data from ASCENT is generalisable to the NHS, and that the effect of differential dropout rates on the measured outcomes is unknown.

ASCENT trial data is appropriate for decision making

3.6 The committee noted issues with the generalisability of ASCENT including previous eribulin use (see section 3.4) and differential dropout rates between sacituzumab govitecan and treatment of physician's choice (see section 3.5) but concluded that the trial data was appropriate for decision making.

There is uncertainty in the quality-of-life data and therefore in the utility values used in the model

3.7 ASCENT collected data on European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 scores, which informed the utilities in the model. Scores were missing for 11.7% of the treatment arm and 30.2% of the comparator arm. The clinical experts explained that this was probably because of people in the comparator arm having earlier disease progression and deteriorating more quickly; attrition for collection of data on quality of life is inevitable when people progress because they are less willing or able to complete questionnaires. The ERG highlighted that this might have biased the treatment effect estimates, and noted the wide confidence intervals around the EORTC QLQ-C30 scores. It deemed the quality-of-life data collected in ASCENT highly uncertain. The committee concluded that this uncertainty would impact the analysis of the EORTC QLQ-C30 data and therefore the utility values used in the model.

It's plausible that quality of life is better while taking sacituzumab govitecan compared with standard chemotherapy, but not necessarily after progression

3.8 The company argued that ASCENT indicated that quality of life was better for those on sacituzumab govitecan. It assumed a quality-of-life benefit for

those on sacituzumab govitecan compared with treatment of physician's choice in both the pre-progression and post-progression health states. The clinical experts explained that this is plausible because of the considerably greater objective response rate for sacituzumab govitecan (31.1% compared with 4.2% for treatment of physician's choice). This increased tumour shrinkage with sacituzumab govitecan would reduce symptoms associated with tumour burden and lead to improved quality of life. They considered it plausible that this would carry over upon disease progression, because people on sacituzumab govitecan enter the progressed health state with a reduced tumour burden compared with those who had treatment of physician's choice. The patient expert agreed that sacituzumab govitecan gave a good quality of life and that they were able to complete normal daily activities. Their initial gastrointestinal symptoms were managed with a dose reduction. The patient expert emphasised the psychological benefits of knowing that you were on an effective treatment compared with standard chemotherapy and added that the hope this brings and potential to act as a bridge to future effective therapies improved their quality of life. The committee noted that to inform the post-progression utility values in the model, the company used a quality of life questionnaire completed 4 weeks after the last dose, which would be in early post-progression. The committee questioned whether this represented the true quality of life throughout the whole post-progression period. The committee concluded that it is plausible that quality of life is better while taking sacituzumab govitecan compared with standard chemotherapy, but that the post-progression effects on quality of life are uncertain.

Cost-effectiveness evidence

The company's model structure is appropriate

3.9 The company submitted a partitioned survival model to estimate the cost effectiveness of sacituzumab govitecan compared with treatment of physician's choice: eribulin, capecitabine, gemcitabine and vinorelbine. It

had 3 health states: progression-free survival, post-progression survival and death. The committee considered that a partitioned survival model is a standard approach to estimate the cost effectiveness of cancer drugs and was appropriate for decision making.

Costs in the economic model

Treatment acquisition and administration costs are between the company and ERG estimates

3.10 Four assumptions contributed to the acquisition and administration costs of treatments in the model: costing by model or treatment cycle, relative dose intensity (RDI), the weight distribution applied to each treatment arm and allowance for any vial sharing.

- Costing by cycle: the company included drug costs in the model as a cost per 1-week model cycle. The ERG explained that this was not appropriate because anyone who died during a model cycle would still have received the full treatment at the start of the treatment cycle, and this should be costed. It preferred a cost per 3-week treatment cycle which removed the risk of underestimating acquisition and administration costs. The Cancer Drugs Fund clinical lead explained that using a cost by treatment cycle was logical and the normal approach for modelling the costs of cancer drugs.
- RDI: the company included an RDI of 94.2%, which was informed by dose reduction, incomplete infusions and delays in the ASCENT trial. The ERG stated it was unclear how the company had calculated the RDI to be 94.2% and preferred 100% to ensure that treatment costs had not been underestimated, noting that 100% of the costs should be included, even if the exposure was less. The Cancer Drugs Fund clinical lead explained that clinical trials do not achieve 100% RDI, and 94.2% seemed reasonable.
- Weight distribution: all treatments included in the model were dosed by weight. The company applied different weight distributions to the

sacituzumab govitecan and treatment of physician's choice arms, which reflected the weight distribution of people in the ASCENT trial. It used a non-parametric distribution for the sacituzumab govitecan arm and a parametric distribution for the treatment of physician's choice arm. The ERG advised that, methodologically, the weight distribution should be identical in both arms and noted that the non-parametric distribution for sacituzumab govitecan was slightly skewed towards lower percentiles. The ERG did not prefer either distribution as long as the same distribution was applied to both arms to accurately model costs. The company did a scenario analysis using parametric distributions for both arms. It noted that this had a minimal impact on the incremental cost-effectiveness ratio (ICER), and that the change was actually in favour of sacituzumab govitecan.

- Vial sharing: the company assumed wastage for 50% of people having sacituzumab govitecan but that vials would be perfectly shared for the remaining 50%. The ERG felt this did not take an NHS perspective because these savings occurred at the hospital level and did not result in a reduced number of prescriptions. The committee considered the feasibility of vial sharing in practice based on the patient numbers. The Cancer Drugs Fund clinical expert agreed with the company, that 50% is a reasonable assumption for vial sharing.

The committee considered costing per treatment cycle (the ERG's approach), and an RDI of 94.2% and 50% vial sharing (the company's approach) to be most appropriate. The committee preferred using the same weight distribution in both arms but noted that varying this assumption had a small impact on the ICER and therefore did not discuss this at length. It concluded that the true treatment acquisition and administration costs would lie between the company and ERG estimates.

The appropriate proportion of people having subsequent eribulin in the treatment of physician's choice arm of the model is 47%

3.11 The model included eribulin, paclitaxel, carboplatin, capecitabine, epirubicin and vinorelbine as subsequent treatments. Eribulin is the most expensive, and so the cost-effectiveness estimates were sensitive to the proportion of people assumed to have eribulin as a subsequent treatment. The committee appreciated that it was difficult to appropriately incorporate subsequent eribulin costs in the model given that a third of patients in the trial had prior eribulin, which does not reflect UK clinical practice (see section 3.4) or the expected treatment pathway (see section 3.2). The committee recalled the clinical experts' view that prior eribulin use would not affect future outcomes and would predominately affect costs. The company sought UK clinical expert opinion about the expected proportions of people having subsequent eribulin in UK practice. The estimated proportion of people having eribulin after sacituzumab govitecan is commercial in confidence and cannot be reported here, but the ERG agreed with the company's estimate. The proportion of people having subsequent eribulin in the comparator arm of the model was 47%; this was based on those who did not get eribulin in the treatment of physician's choice arm in ASCENT, and would therefore get it subsequently. The ERG was concerned that a large proportion of people in the treatment of physician's choice arm of the model had eribulin twice because of the proportion of patients who had it prior to entering the trial. This would overestimate eribulin costs in the comparator arm only and would underestimate the ICER for sacituzumab govitecan. The ERG's preferred approach was to only model subsequent eribulin for the 14% of patients in the treatment of physician's choice arm of ASCENT who had not previously had eribulin. The committee acknowledged the complexity of the issue, but concluded that it was appropriate to assume subsequent eribulin for all who had not had it as part of the treatment of physician's choice (47%) arm, because this reflects what would happen in clinical practice in the NHS.

Utility values in the economic model

Higher pre-progression utilities for sacituzumab govitecan than for treatment of physician's choice are acceptable

3.12 The company used utility values in the pre-progression state that were 0.084 higher for people on sacituzumab govitecan than for those on treatment of physician's choice. These values came from the company's safety population analysis of the EORTC QLQ-C30 data collected in ASCENT. The ERG considered that this health-related quality-of-life analysis was invalid because of the attrition in quality-of-life data (see section 3.7) and the higher dropout rate of people assigned to treatment of physician's choice (see section 3.5), noting that this broke the randomisation. It also noted the clinical study report concluded that EORTC QLQ-C30 scores were similar for sacituzumab govitecan and treatment of physician's choice. The clinical and patient experts provided a rationale to support the company case for higher utilities for people on sacituzumab govitecan compared with treatment of physician's choice (see section 3.8). The committee accepted the biological plausibility and magnitude of quality-of-life benefit, and agreed that utility values would be higher in the pre-progression state for those on sacituzumab govitecan.

Higher post-progression utilities for sacituzumab govitecan than for treatment of physician's choice are not acceptable

3.13 The company used the same analysis to inform the utility values in the post-progression state, meaning the post-progression utility was 0.084 higher for those who had sacituzumab govitecan. The clinical experts stated that it was clinically plausible for sacituzumab govitecan to confer better quality of life in the post-progression state, because people who had sacituzumab govitecan before progression had reduced tumour burden and therefore symptoms, and this quality of life would carry through to the post-progression state. The ERG had the same concerns about the difference in utility between the sacituzumab govitecan and

treatment of physician's choice arms as it had for the pre-progression health state (see section 3.12) and also noted that the data for informing post-progression quality of life had only been collected in ASCENT 4 weeks after the last treatment dose. The ERG did not feel this reliably reflected post-progression utility over the longer term. The clinical experts noted that this was an appropriate time point because it would be before people started subsequent therapies and therefore gave valid estimates for the quality of life after sacituzumab govitecan. However, the Cancer Drugs Fund clinical lead noted that utility would continue to decline in the progressed state as people neared death, and would not be maintained at the 4-week level. The ERG also did not feel that ASCENT health-related quality-of-life data was appropriate to inform post-progression utilities and preferred to use values that had been accepted in a previous appraisal in locally advanced or metastatic triple-negative breast cancer (TA639). It also stated that people would get a similar mix of therapies post-progression regardless of treatment arm, and therefore preferred to use the same utility value for the post-progression state. The committee concluded that the 1 measurement 4 weeks after the last treatment did not appropriately reflect longer-term post-progression utilities in people who had received sacituzumab govitecan; it preferred the ERG's approach.

Long-term survival estimates

The long-term overall survival benefit for sacituzumab govitecan is uncertain

3.14 The company chose a jointly fitted log-logistic model to extrapolate overall survival. It chose this approach based on the goodness of fit statistics and visual fit to the trial data. The company noted that the more mature data from the February 2021 data cut validated the joint log-logistic model. The ERG suggested that many options fitted the data well. It noted what it considered to be an optimistic long-term survival using the log-logistic approach, and said that other curves fitted the data equally well but gave

less optimistic outcomes for sacituzumab govitecan compared with treatment of physician's choice. For example, the jointly fitted generalised gamma had a similar statistical fit, a better visual fit and more closely replicated the mean overall survival results from the trial, but gave lower longer-term survival estimates. Initially the company only explored joint fits, but in the absence of strong rationale the ERG felt that independent fitted curves should also be explored. The ERG did not have a preferred approach, but gave 6 plausible options that could be narrowed down by seeking clinical expert opinion on the expected survival rates at 5 years. The jointly fitted log-logistic curve estimated that 1.7% of people in the treatment of physician's choice arm would be alive at 5 years. The clinical experts agreed that this was optimistic and felt it could be closer to the 1.4% estimated using the independently fitted log-logistic curves. The committee noted that the trial data was mature and therefore the extrapolated overall survival was a true area of uncertainty rather than uncertainty due to data immaturity. It was not able to take a firm view on whether jointly fitted or independently fitted curves were more appropriate, but narrowed the choice to jointly fitted models because the ERG explained they were not clearly inferior to the independent models. The committee concluded that this remained an area of high uncertainty, but without a clear rationale for independent fits it was reasonable to consider the jointly fitted curves. It agreed that the true survival extrapolation could be anywhere between the optimistic log-logistic and the more pessimistic generalised gamma models.

End of life

End of life criteria are met

3.15 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's guide to the methods of technology appraisal. It considered that all scenario analyses presented by the company and the ERG indicated that sacituzumab govitecan offers more than 3 months' extension to life in a population that has a life

expectancy of less than 24 months. Therefore, it concluded that sacituzumab govitecan fulfils the end of life criteria.

Cost-effectiveness results

The cost-effectiveness estimate are higher than what NICE considers a cost-effective use of NHS resources

3.16 The company's base case ICER, using the company's preferred assumptions, and including the confidential patient access scheme discount for sacituzumab govitecan and the list price for the comparators and subsequent treatments, is £49,516 per quality-adjusted life year (QALY) gained. The committee preferred the following ERG assumptions:

- Using a cost per treatment cost, and assuming equal weight distributions for drug acquisition and administration costs (see section 3.10).
- Using the same post-progression utility value for sacituzumab govitecan and treatment of physician's choice (see section 3.13).

This increased the ICER to above what is considered a cost-effective use of NHS resources when using the company's chosen joint log-logistic distribution. Using the generalised gamma distribution increased the ICER further. The committee felt that the true cost-effectiveness estimate could lie anywhere between the ICERs generated using the log-logistic or generalised gamma distribution, and when including all confidential discounts (for the comparators and subsequent treatments), the company's base case and committee's preferred ICERs were well above £50,000 per QALY gained.

Conclusion

Sacituzumab govitecan is not recommended for use in the NHS

3.17 The committee concluded that the cost-effectiveness estimates for sacituzumab govitecan incorporating the committee's preferred

assumptions were higher than what NICE considers a cost-effective use of NHS resources. Therefore, the committee did not recommend sacituzumab govitecan for use in the NHS.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review 3 years after publication of the guidance. NICE welcomes comment on this proposed date. NICE will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Jane Adam
Chair, appraisal committee
March 2022

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee A.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Claire Hawksworth
Technical lead

Eleanor Donegan
Technical adviser

Thomas Feist and Gavin Kenny
Project managers

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