Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2607

talazoparib hard capsules (Talzenna®)

Pfizer Ltd

09 February 2024

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in NHSScotland. The advice is summarised as follows:

ADVICE: following a full submission assessed under the end of life medicine process

talazoparib (Talzenna®) is accepted for use within NHSScotland.

Indication under review: as monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Patients should have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments. Patients with hormone receptor (HR)-positive breast cancer should have been treated with a prior endocrine-based therapy, or be considered unsuitable for endocrine-based therapy.

In a phase III study in patients with germline *BRCA1/2*-mutations and HER2-negative locally advanced or metastatic breast cancer who had received previous treatment with an anthracycline and/or a taxane), talazoparib significantly improved radiographic progression-free survival compared with physician's choice of chemotherapy.

This advice applies only in the context of an approved NHSScotland Patient Access Scheme (PAS) arrangement delivering the cost-effectiveness results upon which the decision was based, or a PAS/ list price that is equivalent or lower.

This advice takes account of the views from a Patient and Clinician Engagement (PACE) meeting.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Talazoparib is an inhibitor of poly ADP-ribose polymerase (PARP) enzymes, PARP-1 and PARP-2, which limits PARP-mediated DNA repair and ultimately results in apoptosis and cancer cell death.[1-3]

The recommended dose of talazoparib is 1 mg orally once daily, with or without food. Patients should be treated until disease progression or unacceptable toxicity. Patients should be selected for treatment based on the presence of deleterious or suspected deleterious germline BRCA mutations determined by an experienced laboratory using a validated test method. Genetic counselling for patients with BRCA mutations should be performed according to local regulations, as applicable.[1, 2]

1.2. Disease background

In 2021, breast cancer was the second most common cancer and the fourth most common cause of cancer-related deaths in Scotland.[4] Most breast cancer diagnoses (approximately 80%) occur at an early stage (stage I or II) however, it is estimated that around 30% of these patients will experience a recurrence and develop locally advanced (stage III) or metastatic breast cancer (stage IV).[3, 5, 6] In 2021, 5,143 females were diagnosed with breast cancer in Scotland, of which 6.3% with metastatic (stage IV) disease.[5]

Established prognostic factors, which guide treatment choice, include disease stage, hormone receptor (HR) status, human epidermal growth factor receptor 2 (HER2) receptor status, and the presence of germline mutations in the breast cancer susceptibility genes 1 and 2 (*BRCA1* and *BRCA2*). It is estimated that approximately 70% of patients with breast cancer have HR-positive and HER2-negative disease; 15% have HR-negative and HER2-negative disease (known as triple negative breast cancer [TNBC]); and 15% have HER2-positive disease (this subpopulation is outwith the scope of this submission).[7, 8] Approximately 5% to 10% of all patients with breast cancer,[9, 10] and approximately 9% to 18% of patients with TNBC, have germline mutations in *BRCA1* and *BRCA2*.[11, 12] Most patients (70%) with a germline *BRCA1* mutation present with TNBC, whilst *BRCA2*-mutated breast cancer is more commonly associated with HR-positive disease.[3, 13] The reported 5-year survival rates are 26% (for all patients with metastatic breast cancer)[14], and 12% (metastatic TNBC).[12]

1.3. Treatment pathway and relevant comparators

Metastatic breast cancer is incurable and therefore treatment is palliative, with the aim of extending the length of life whilst preserving quality of life. There are different treatment pathways for germline *BRCA*-mutated, advanced breast cancer (depending on patients' HR- and HER2-status). Available treatment options are also based on other factors, such as PD-L1 status, menopausal status, visceral disease and prior treatments.

For patients with germline *BRCA* mutations with HER2-negative locally advanced or metastatic breast cancer, the choice of initial treatment depends on HR-status. For HR-positive patients, the

standard first-line treatment is endocrine therapy with or without cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors, unless there is an imminent risk of organ failure in which case chemotherapy is used.[15-17] Subsequent treatment options after disease progression include targeted therapies such as everolimus plus exemestane (SMC 872/13), sequential single-agent chemotherapy or further endocrine therapy, depending on the extent and aggressiveness of disease and associated toxicity profile. Eribulin is restricted to use in NHSScotland for patients who have received prior treatments including capecitabine (SMC 1065/15). Guidelines advise that at least two lines of endocrine-based treatment is preferred before moving to chemotherapy. Available agents for systemic chemotherapy include anthracyclines, taxanes, capecitabine, eribulin, vinorelbine, platinums and other agents.[16, 17]

For patients with HR-negative disease (and HER2-negative that is TNBC) who have germline *BRCA* mutations, first-line treatment includes immunotherapy (only if PD-L1 disease positive) with pembrolizumab (SMC2460) or atezolizumab (SMC2267), in combination with chemotherapy; platinum (carboplatin)-based chemotherapy with taxanes is an alternative. Second and later-line options include chemotherapy with capecitabine, eribulin or vinorelbine; sacituzumab govitecan is also accepted for use by SMC for patients who have received at least two prior lines of systemic therapy (SMC2446).[15-17] Olaparib is another PARP inhibitor that is licensed for patients with germline *BRCA* mutations, who have HER2-negative, locally advanced or metastatic breast cancer, but in the absence of a submission from the holder of the marketing authorisation it was not recommended by SMC (SMC2436).

The submitting company considered that chemotherapy (capecitabine, vinorelbine or eribulin) is the only relevant comparator for this submission. Clinical experts consulted by SMC listed these three chemotherapy treatments as options for patients with TNBC (PDL-1 positive and negative) and HR-positive breast cancer who have received prior treatments. However, clinical experts also considered platinum-based chemotherapy (carboplatin) as a relevant comparator for this population.

1.4. Category for decision-making process

Eligibility for a PACE meeting
Talazoparib meets SMC end of life criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

The key evidence to support the efficacy and safety of talazoparib comes from the EMBRACA study, details of which are summarised in Table 2.1.

Table 2.1. Overview of relevant study.

Criteria	EMBRACA[3, 18, 19]
Study design	International, open-label, randomised, phase III study.
Eligible patients	• Adults aged ≥ 18 years with histologically or cytologically confirmed breast cancer. • Locally advanced, HER2-negative breast cancer not amenable to curative radiation or surgical cure and/or metastatic breast cancer appropriate for single systemic cytotoxic chemotherapy. • Documentation of a germline *BRCA1* or *BRCA2* mutation. • No HER2-positive breast cancer. • Prior treatment with a taxane and/or anthracycline in the (neo)adjuvant, locally advanced, or metastatic setting unless medically contraindicated. • Maximum of three prior chemotherapy-inclusive regimens for locally advanced and/or metastatic breast cancer. • No patients who relapsed within 6 months of their last dose of prior platinum therapy. • ECOG performance status ≤2.
Treatments	Talazoparib 1 mg orally once daily (n=287) or physician's choice of chemotherapy (n=144) which comprised one of the following selected before randomisation: • Capecitabine 1,250 mg/m² orally twice daily on Days 1 to 14 of 21-day cycles. • Eribulin mesylate 1.4 mg/m² (equivalent to eribulin 1.23 mg/m²) IV on Days 1 and 8 of 21-day cycles. • Gemcitabine 1,250 mg/m² IV on Days 1 and 8 of 21-day cycles. • Vinorelbine 30 mg/m² IV on Days 1, 8 and 15 of 21-day cycles. Study treatment continued until disease progression or unacceptable toxicity.
Randomisation	Patients were randomised 2:1, stratified according to the number of previous cytotoxic chemotherapy regimens for advanced disease received (0 versus 1 to 3), HR-status (TNBC versus HR-positive) and history of CNS metastases (yes or no).
Primary outcome	IRF-assessed PFS, defined as the time between date of randomisation to the date of first radiologic progressive disease (according to RECIST v1.1) or death due to any cause, whichever occurred first.
Secondary outcomes	• OS defined as time from randomisation to death from any cause. • ORR defined as CR or PR assessed by investigator according to modified RECIST v1.1 in patients with measurable disease.
Statistical analysis	The primary and key secondary outcomes (PFS and OS) were controlled for multiplicity, using a gatekeeping procedure. No multiplicity adjustment was performed for other secondary or exploratory outcomes.

Abbreviations: CNS = central nervous system; CR = complete response; ECOG = Eastern Cooperative Oncology Group; HR = hormone receptor; IRF = independent radiology facility; ORR = objective response rate; OS = overall survival; PFS = progression-free survival; PR = partial response; RECIST v1.1 = Response Evaluation Criteria in Solid Tumours version 1.1; TNBC = triple negative breast cancer.

At the primary progression-free survival (PFS) analysis (data cut-off 15 September 2017), talazoparib demonstrated a statistically significant improvement in radiologic PFS, compared with physician's choice of chemotherapy. There was no statistically significant difference in overall survival (OS) at the final OS analysis (data cut-off 30 September 2019).[18, 19] Detailed results are presented in Table 2.2.

Table 2.2. Primary and relevant secondary outcome results from the EMBRACA study.[1-3, 18, 19]

	Talazoparib (n=287)	Physician's choice of chemotherapy (n=144)
Data cut-off: 15 September 2017		
Primary outcome: IRF-assessed PFS		
Median follow-up, months	13.0	7.2
Events, n	186	83
Median PFS, months	8.6	5.6
HR (95% CI), p-value	0.54 (0.41 to 0.71), p<0.001	
KM estimated PFS at 12 months	37%	20%
Secondary outcome: ORR[a,b]		
ORR (unconfirmed), %	63% (137/219)	27% (31/114)
Complete response, %	5.5%	0%
Partial response, %	57%	27%
Odds ratio (95% CI)	4.99 (2.93 to 8.83)	
Median duration of response[c], months	5.4	3.1
Data cut-off: 30 September 2019		
Secondary outcome: Overall survival (OS)		
Median follow-up, months	44.9	36.8
Deaths, n	216	108
Median OS, months	19.3	19.5
HR (95% CI), p-value	0.85 (0.67 to 1.07), p=0.169	
KM estimated OS at 12 months	71%	74%
KM estimated OS at 24 months	42%	38%
KM estimated OS at 36 months	27%	21%

[a] ORR defined as the proportion of patients with a complete response or partial response as defined by the modified Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST 1.1) in the ITT with measurable disease population by investigator. Confirmation of complete or partial response was not required.
[b] for objective response rate, the number of evaluable patients were 219 (talazoparib) and 114 (physician's choice of chemotherapy).
[c] exploratory outcome assessed only in patients who had an objective response.
Abbreviations: CI = confidence interval; HR = hazard ratio; IRF = independent radiology facility; ITT = intention-to-treat; KM = Kaplan-Meier; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

The study did not allow for crossover but patients could receive subsequent anticancer therapy on disease progression; 81% (talazoparib group) and 76% (chemotherapy group) of patients had subsequent systemic anticancer treatments[18]. The submitting company also presented results adjusting OS using the Rank Preserving Structural Failure Time (RPSFT) method for subsequent PARP inhibitor treatment (received by 4.5% of talazoparib and 33% of chemotherapy patients), which informs the economic base case analysis. These results were consistent with the final OS analysis (hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.62 to 1.05). When adjusting for both subsequent PARP inhibitor and/or platinum treatment (the latter received by 46% and 42% of patients respectively), the HR for OS was reduced to 0.76 (95% CI 0.50 to 1.03).[18]

Prespecified subgroup analyses of PFS according to age, geographic region, HR status, BRCA status and number of prior cytotoxic regimens were generally consistent with the analysis in the ITT population. Although, there was a smaller treatment benefit in the subgroup of patients who had

received prior platinum treatment (n=76; HR 0.76 [95% CI 0.40 to 1.45]), compared with those who had not received prior platinum (n=355; HR 0.52 [95% CI 0.39 to 0.71]).[19, 20] However, this subgroup included small patient numbers and the analyses were exploratory, therefore these results should be interpreted with caution.[3, 18, 20]

2.2. Health-related quality of life outcomes

Health-related quality of life (HRQoL) was assessed as exploratory outcomes using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the breast cancer-specific module (EORTC QLQ-BR23) at baseline, at Day 1 of each cycle and at the end of treatment.

Up to cycle 12, the proportion of patients who had completed at least one question on the EORTC QLQ-C30 or EORTC QLQ-BR23 was ≥81% for both questionnaires in the talazoparib group and ≥73% for both questionnaires in the chemotherapy group, respectively.

Overall, patients in the talazoparib group appeared to have greater improvements in HRQoL, including global health status and breast symptom scale scores, compared with the chemotherapy group. However, the medians were not reached in either treatment group for the time to deterioration in the breast symptom scale for the EORTC QLQ-BR23; the majority of patients were also censored.[3, 19]

3. Summary of Safety Evidence

In the EMBRACA study at data cut-off 30 September 2019, the median duration of treatment was 6.9 months in the talazoparib group and 3.9 months in the chemotherapy group. Any treatment-emergent adverse event (AE) was reported by 99% (282/286) of patients in the talazoparib group and 98% (123/126) of patients in the chemotherapy group. In the talazoparib and chemotherapy groups respectively, patients reporting a serious AE were 35% and 31%; reporting a serious and treatment-related AE was 10% and 8.7%; and a grade 3 or 4 serious AE was 28% and 27% respectively. Patients discontinuing therapy due to an AE was 7.7% and 9.5%.[18]

The most frequently reported grade 3 or 4 AEs with an incidence >2% in the talazoparib group versus the chemotherapy group were: anaemia (40% versus 4.8%), neutropenia (22% versus 35%), thrombocytopenia (15% versus 1.6%), leukopenia (7.3% versus 8.7%), lymphopenia (3.8% versus 0.8%), fatigue (2.4% versus 3.2%), diarrhoea (0.7% versus 5.6%), hand and foot syndrome (0.3% versus 3.2%), vomiting (2.4% versus 2.4%), back pain (2.4% versus 1.6%), dyspnoea (2.4% versus 2.4%), pulmonary embolism (3.1% versus 0.8%), pleural effusion (1.7% versus 4.0%).[18]

It was noted that more patients in the talazoparib group compared with the chemotherapy group required at least one red blood cell (RBC) transfusion (39% versus 5.6% respectively).[18] Talazoparib's summary of product characteristics states that treatment should be stopped if haemoglobin falls below 8 g/dL (treatment would be resumed at a lower dose when the haemoglobin value is 9 g/dL or higher).[1, 2]

Overall, the regulators considered that the safety profile of talazoparib (mainly characterised by myelosuppression) appears to be manageable with appropriate risk minimisation measures. It was

noted that the precise risk of second primary malignancies is not well characterised and monitoring will continue in the post marketing setting. Please refer to the SPC for more details.[1-3]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- Direct evidence from a phase III study is available against single-agent chemotherapy (consisting of capecitabine, vinorelbine, gemcitabine or eribulin); these are generally relevant comparators in Scottish practice.
- The EMBRACA study demonstrated a statistically significant improvement in radiologic PFS (as determined by blinded independent central review), with talazoparib compared with physician's choice of chemotherapy, with a 46% relative risk reduction and 3 months increase in median PFS. These results were considered to be modest but clinically meaningful in this patient population.[3, 19]
- Investigator-assessed ORR, a secondary outcome in the EMBRACA study, is also supportive, numerically favouring talazoparib. Of note, in the EMBRACA study, no patients in the chemotherapy group achieved complete response compared to 12 patients (5.5%) in the talazoparib group.[3]

4.2. Key uncertainties

- At the final OS analysis, after a median follow-up of 44.9 months in the talazoparib group and 36.8 months in the physician's choice of chemotherapy group, there was no statistically significant difference in OS. Moreover, median OS was slightly shorter in the talazoparib group (19.3 months) compared with the chemotherapy group (19.5 months), with 3-year survival rates of 27% and 21%, respectively. The submitting company has indicated that no further data cuts are planned.[3, 18]
- The open-label design of EMBRACA may have affected subjective outcomes such as safety and HRQoL.[3, 19]
- There are no comparative data (direct or indirect) against other treatments that may be used in Scottish practice. Sacituzumab govitecan is accepted for use by SMC for patients with locally advanced or metastatic TNBC who have failed at least two systemic. Clinical experts consulted by SMC listed this as a potential treatment option for TNBC patients. No platinum agents were included in the comparator arm in the EMBRACA study however these may be a relevant comparator in Scottish practice, for both TNBC and HR-positive patients.
- Approximately 39% of patients in the talazoparib group required RBC transfusions, which the submitting company advised is likely to be higher than would be observed in clinical practice (estimated at approximately 8.3% based on a US real-world study funded by Pfizer[22]) and can be partly explained by the EMBRACA protocol requirements being more stringent than UK and US transfusion guidelines.[23, 24] However, there is still uncertainty over the RBC transfusion requirements in clinical practice and associated service implications.

4.3. Clinical expert input

There were mixed responses from experts contacted by SMC, with some feeling it would fulfil an unmet need for this population, given the need for more treatment options. However, others felt the EMBRACA study limitations and results meant this could not be considered a therapeutic advancement.

4.4. Service implications

Experts contacted by SMC anticipated some service implications based on the safety profile, for example the need for transfusion support.

5. Summary of Patient and Carer Involvement

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of talazoparib (Talzenna®), as an end of life medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- Breast cancer with a BRCA1/2 germline mutation is rare and affects only approximately 5% to 10% of all cases. Patients with metastatic breast cancer and a BRCA1/2 germline mutation have a poor prognosis; this is even lower in those who also have HER-2 (human epidermal growth factor receptor 2) negative and HR (hormone receptor) negative disease (known as triple negative breast cancer, TNBC).
- Patients with an inherited BRCA1/2 germline mutation tend to be diagnosed at a younger age than other breast cancer types, which can significantly impact their social life, relationships, and fertility (for women). Additionally, these patients are likely to be working and have families, many with young dependent children; this can result in anxiety about reaching key family milestones. We also heard from PACE participants about the guilt these patients experience secondary to potentially passing on an altered gene to their family. The physical, psychological, and emotional impact of this diagnosis, and its associated poor prognosis, cannot be underestimated.
- There are currently no specific SMC-accepted targeted therapies for patients with germline BRCA1/2-mutations, who have HER2-negative locally advanced or metastatic breast cancer. Given metastatic breast cancer is incurable, there is an unmet need for more effective and tolerable targeted treatments. Talazoparib could offer an extra line of targeted therapy for the treatment of this life-threatening disease to improve quality of life and delay the progression of the disease. Additionally, an effective targeted treatment could provide benefits for future generations of family members affected by this condition and who carry the BRCA1/2-mutation.
- The EMBRACA study showed significant improvements in progression free-survival; if realised this would mean a delay in the development of cancer-related symptoms and would result in an improved quality of life. PACE participants spoke about the value of improvements in quality of life, even in the absence of any increase in overall survival.

- In the EMBRACA study, more patients on talazoparib reported grade 3 to 4 haematological adverse events (AE) and received red blood cell transfusions, compared to the chemotherapy group. However, these did not seem to adversely affect quality of life as patients in the talazoparib group reported greater improvements in health-related quality of life outcomes. Additionally, the rates of serious AEs, treatment-related AEs were comparable between the two groups, with less patients discontinuing treatment due to an AE in the talazoparib group. This relatively well-tolerated side effect profile means that the disruption to daily life is minimal; most patients can return to work, continue family responsibilities and function well during treatment.
- Talazoparib is an oral formulation which avoids the need for frequent hospital visits for parenteral administration and allows patients to spend more valuable time with their family. A PACE participant who is currently receiving talazoparib highlighted how this treatment has allowed them to live a relatively normal life, has reduced hospital visits, and ultimately improved their quality of life. They also highlighted that they would be apprehensive about stopping talazoparib and going back onto chemotherapy.
- Whilst on treatment, monthly blood monitoring and reviews, as well as regular CT scans to assess for treatment response, are advised. Use of an oral treatment in place of chemotherapy will reduce the burden on chemotherapy units, though may still impact on clinic capacity. It was also noted that, over time and with greater experience of use, it may be that other service pressures in oncology units could be eased further with the use of talazoparib.

Additional Patient and Carer Involvement

We received patient group submissions from Breast Cancer Now and METUP UK, both organisations are registered charities. Breast Cancer Now has received 0.7% pharmaceutical company funding in the past two years, including from the submitting company. METUP UK has received 23% pharmaceutical company funding in the past two years, with none from the submitting company. Representatives from both organisations participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

The submitting company provided an economic case as described in Table 6.1.

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis.
Time horizon	Lifetime (10 years).
Population	Adult patients with deleterious or suspected deleterious germline BRCA1/2 mutation HER2- locally advanced breast cancer or metastatic breast cancer who have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant, locally advanced or metastatic setting.

Comparators	Physician's choice of chemotherapy (PCT) comprising: capecitabine (48%), eribulin (44%) or vinorelbine (8%) according to proportions from EMBRACA reweighted to exclude gemcitabine whilst assuming all chemotherapies were of equivalent efficacy.
Model description	A cohort-based partitioned survival model was used with three health states: progression free, progressed disease (PD) and death.
Clinical data	PFS, OS, safety data and baseline patient characteristics were obtained from the EMBRACA study[1-3, 18, 19].
Extrapolation	Long-term PFS was initially extrapolated using parametric survival modelling and curve selection was based on goodness of fit statistics (AIC/BIC). This resulted in the selection of the log-normal distribution in the talazoparib arm and the log-logistic distribution for PCT. For long-term OS a log-normal was selected in the talazoparib arm. A cross over adjusted hazard ratio derived using the RPSFTM was applied to the talazoparib OS extrapolation in the PCT arm. The model estimated that overall survival rates at 3 and 5 years were 27% and 12% respectively for the talazoparib arm and 20.32% and 3.76% in the PCT arm. An exponential distribution was initially fitted to the median time to treatment discontinuation (TTD) from EMBRACA in both arms. However, following concerns raised by the New Drugs Committee (NDC) noting the uncertainty associated with the parametric modelling approach adopted in the base case, the company subsequently modelled PFS, OS and TTD using KM data from EMBRACA directly in the model.
Quality of life	EORTC-QLQ-C30 data were collected in the EMBRACA study from progression free patients and mapped to EQ-5D using a published algorithm to derive utility values. The utility value for the PD health state was based on published literature. Disutilities due to adverse events were also taken from published literature.
Costs and resource use	Costs included medicine acquisition and administration, management of adverse events, terminal care and monitoring and disease management costs. Costs of subsequent treatment was included and was assumed to be ongoing PCT in both arms. The cost of red blood cell (RBC) transfusions were included at a rate of 23.3% based on the midpoint between proportions observed from real-world evidence data that reported fewer patients treated with talazoparib receiving RBC transfusions (8%), and the proportion observed in EMBRACA (38%).
PAS	A Patient Access Scheme (PAS) was submitted by the company and assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the list price. A PAS discount is in place for eribulin and this was included in the results used for decision-making by using estimates of the comparator PAS price.

6.2. Results

The base case results estimated by the company are summarised in Table 6.2 below. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the results using the talazoparib PAS and list prices for comparators can be presented.

Table 6.2 Base case results (with talazoparib PAS, list prices for comparators)

Treatments	ICER (£/QALY)
Talazoparib	dominant
PCT combined	

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; PCT, physician's choice of chemotherapy; dominant = talazoparib was dominant compared to PCT meaning it was estimated as resulting in lower costs and better health outcomes for patients.

6.3. Sensitivity analyses

Selected sensitivity analysis provided by the company are summarised in table 6.3 below.

Table 6.3 Selected sensitivity analysis results (with talazoparib PAS, list prices for comparators)

	Scenario Analysis	Base case assumption	ICER (£/QALY)
1	Impact of response to treatment not considered in the model	Treatment management costs varied by response to treatment (complete response/partial response)	dominant
2	Red blood cell transfusion rate of 38.1% for the talazoparib arm as per EMBRACA	RBC transfusion rate for talazoparib arm midpoint between EMBRACA and RWE data (8.3%)	dominant
3	Talazoparib PFS utility value applied to both arms	EMBRACA PFS utility value for PCT	dominant
4	Combined scenario		dominant

QALY = quality-adjusted life-year, ICER = incremental cost-effectiveness ratio; PAS = patient access scheme; PCT = physicians' choice chemotherapy; PFS = progression-free survival; RBC, red blood cell; dominant = talazoparib was dominant compared to PCT meaning it was estimated as resulting in lower costs and better health outcomes for patients.

6.4. Key strengths

- The model structure was appropriate and consistent with the approach used in the assessment of other oncology treatments.

6.5. Key uncertainties

- There is some uncertainty regarding the choice of comparator used in the analysis. SMC clinical expert responses indicated that sacituzumab govitecan and platinum agents may also be displaced. The proportions of chemotherapies assumed to comprise PCT in the model was also uncertain.

- Due to the open label nature of the EMBRACA study, necessitated by the administration methods of the medicines, health-related quality of life data are at risk of bias. Therefore, the company's approach to treatment-specific utility values in the PFS health state is uncertain. A scenario was provided that used the talazoparib PFS utility value for PFS in the PCT arm (scenario 3).
- The number of patients who would receive RBC transfusions in practice whilst receiving talazoparib is uncertain. The company stated that the EMBRACA study protocol was more stringent in terms of having a higher haemoglobin threshold for RBC transfusion and preferred transfusion rates observed in RWE, although it is somewhat uncertain that the efficacy of talazoparib would be maintained with a less stringent RBC transfusion threshold. However, the company also provided PFS results from the RWE study that reported a similar median PFS to that reported by the EMBRACA study and a scenario was provided using the RBC transfusion rate according to the proportion observed in the EMBRACA study (scenario 2).

7. Conclusion

After considering all the available evidence and the output from the PACE process, the Committee accepted talazoparib for use in NHSScotland.

8. Guidelines and Protocols

The Scottish Intercollegiate Guidelines Network (SIGN) published "Treatment of primary breast cancer: a national clinical guideline (SIGN 134)" in September 2013. However, it is noted that some of these recommendations may be out-of-date.[25]

The National Institute for Health and Care Excellence (NICE) published clinical guideline number 81: "Advanced breast cancer: diagnosis and treatment" in February 2009, which was last updated in August 2017.[16]

The European Society for Medical Oncology (ESMO) published the "ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer" in October 2021.[17]

9. Additional Information

9.1. Product availability date

20 June 2019.

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per 28 days (£)
Talazoparib	1 mg orally once daily, until disease progression or unacceptable toxicity.	£4,634

Costs from BNF online on 12 October 2023. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated 12 patients would receive treatment each year.

SMC is unable to publish the with PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS. This template does not incorporate any PAS discounts associated with comparator medicines.

*Other data were also assessed but remain confidential.**

References

1. Pfizer Limited. Talzenna 0.25 mg hard capsules. Summary of product characteristics. Electronic Medicines Compendium. Available at: https://www.medicines.org.uk/emc/product/10734/smpc. Last updated: 10 March 2022.
2. Pfizer Limited. Talzenna 1 mg hard capsules. Summary of product characteristics. Electronic Medicines Compendium. Available at: https://www.medicines.org.uk/emc/product/10735 Last updated: 10 March 2022.
3. European Medicines Agency (EMA). European Public Assessment Report: Talazoparib (Talzenna®). EMEA/H/C/004674/0000. Published: 26 April 2019. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/talzenna [Accessed: 24 July 2023].
4. Public Health Scotland (PHS). Cancer Mortality in Scotland: Annual update to 2021. Available from: https://publichealthscotland.scot/publications/cancer-mortality/cancer-mortality-in-scotland-annual-update-to-2021/ Published: 25 October 2022. .
5. Public Health Scotland (PHS). Cancer Incidence and Prevalence in Scotland: To December 2021. Available from: https://publichealthscotland.scot/publications/cancer-incidence-in-scotland/cancer-incidence-in-scotland-to-december-2021/ Published: 28 March 2023 (Updated 13 June 2023).
6. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist. 2005; 10:20-29.
7. Simon J, Chaix M, Billa O, Kamga AM, Roignot P, Ladoire S, et al. Survival in patients with HR+/HER2- metastatic breast cancer treated with initial endocrine therapy versus initial chemotherapy. A French population-based study. Br J Cancer. 2020; 123:1071-1077.
8. Cancer Research UK (CRUK). Triple negative breast cancer. Last reviewed: 22 June 2023. Available at: https://www.cancerresearchuk.org/about-cancer/breast-cancer/types/triple-negative-breast-cancer [Accessed: 26 October 2023]. .
9. Easton DF. How many more breast cancer predisposition genes are there? Breast Cancer Res. 1999;1(1):14-17. doi: 10.1186/bcr6.
10. Kemp Z, Turnbull A, Yost S, Seal S, Mahamdallie S, Poyastro-Pearson E, et al. Evaluation of cancer-based criteria for use in mainstream BRCA1 and BRCA2 genetic testing in patients with breast cancer. JAMA Netw Open. 2019; 2:e194428.
11. Hahnen E, Hauke J, Engel C, Neidhardt G, Rhiem K, Schmutzler RK. Germline mutations in triple-negative breast cancer. Breast Care. 2017; 12:15-19.
12. American Cancer Society. Triple-negative Breast Cancer. Available at: https://www.cancer.org/cancer/types/breast-cancer/about/types-of-breast-cancer/triple-negative.html [Accessed: 26 October 2023].
13. Mavaddat N, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, et al.; Consortium of Investigators of Modifiers of BRCA1/2. Pathology of breast and ovarian cancers among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). Cancer Epidemiol Biomarkers Prev. 2012 Jan;21(1):134-47. doi: 10.1158/1055-9965.EPI-11-0775.
14. Cancer Research UK (CRUK). Breast cancer statistics: Breast cancer survival. Available at: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer#heading-Three [Accessed: 26 October 2023].
15. European Medicines Agency (EMA). European Public Assessment Report: Elacestrant (Orserdu®). EMEA/H/C/005898/0000. Published: 20 July 2023. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/orserdu [Accessed: 26 October 2023].
16. National Institute for Health and Care Excellence (NICE). Advanced breast cancer: diagnosis and treatment - Clinical guideline 81 [CG81]. Published: 23 February 2009; Last updated: 16 August 2017. Available at: https://www.nice.org.uk/guidance/CG81 [Accessed: 26 October 2023].

17. Gennari A, André F, Barrios CH, Cortés J, de Azambuja E, DeMichele A, et al; ESMO Guidelines Committee. ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer. Ann Oncol. 2021 Dec;32(12):1475-1495. doi: 10.1016/j.annonc.2021.09.019.
18. Litton JK, Hurvitz SA, Mina LA, Rugo HS, Lee KH, Gonçalves A, et al. Talazoparib versus chemotherapy in patients with germline BRCA1/2-mutated HER2-negative advanced breast cancer: final overall survival results from the EMBRACA trial. Ann Oncol. 2020 Nov;31(11):1526-1535. doi: 10.1016/j.annonc.2020.08.2098.
19. Litton JK, Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, et al. Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation. N Engl J Med. 2018 Aug 23;379(8):753-763. doi: 10.1056/NEJMoa1802905.
20. Rugo HS, Ettl J, Hurvitz SA, Gonçalves A, Lee KH, Fehrenbacher L, et al. Outcomes in Clinically Relevant Patient Subgroups From the EMBRACA Study: Talazoparib vs Physician's Choice Standard-of-Care Chemotherapy. JNCI Cancer Spectr. 2019 Oct 21;4(1):pkz085. doi: 10.1093/jncics/pkz085.
21. Turner NC, Telli ML, Rugo HS, Mailliez A, Ettl J, Grischke EM, et al; ABRAZO Study Group. A Phase II Study of Talazoparib after Platinum or Cytotoxic Nonplatinum Regimens in Patients with Advanced Breast Cancer and Germline BRCA1/2 Mutations (ABRAZO). Clin Cancer Res. 2019 May 1;25(9):2717-2724. doi: 10.1158/1078-0432.CCR-18-1891.
22. Savill KMZ, Ivanova J, Asgarisabet P, Falkenstein A, Balanean A, Niyazov A, et al. Treatment, and Outcomes of Real-World Talazoparib-Treated Patients With Germline BRCA-Mutated Advanced HER2-Negative Breast Cancer. Oncologist. 2023 May 8;28(5):414-424. doi: 10.1093/oncolo/oyad021.
23. Carson JL, Guyatt G, Heddle NM, Grossman BJ, Cohn CS, Fung MK, et al. Clinical Practice Guidelines From the AABB: Red Blood Cell Transfusion Thresholds and Storage. JAMA. 2016 Nov 15;316(19):2025-2035. doi: 10.1001/jama.2016.9185.
24. National Institute for Health and Care Excellence (NICE). Blood transfusion - NICE guideline 24 [NG24]. Published: 18 November 2005; Last reviewed: March 2020. Available at: https://www.nice.org.uk/guidance/NG24 [Accessed: 26 October 2023].
25. Scottish Intercollegiate Guidelines Network (SIGN). Treatment of primary breast cancer - SIGN guideline 134. Published: September 2013. Available at: https://www.sign.ac.uk/our-guidelines/treatment-of-primary-breast-cancer/ [Accessed: 26 October 2023].

This assessment is based on data submitted by the applicant company up to and including 14 December 2023.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal:*https://www.scottishmedicines.org.uk/about-us/policies-publications/

Medicine prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a medicine and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG), established under the auspices of NHS National Services Scotland reviews and advises NHSScotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHSScotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.