Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2538

pembrolizumab concentrate for solution for infusion (Keytruda®)

Merck Sharp & Dohme (UK) Limited

05 May 2023

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

pembrolizumab (Keytruda®) is accepted for use within NHSScotland.

Indication under review: in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early stage triple-negative breast cancer (TNBC) at high risk of recurrence.

In a randomised, double-blind phase III study, the addition of pembrolizumab to neoadjuvant chemotherapy followed by adjuvant pembrolizumab monotherapy significantly improved the pathological complete response rate and event-free survival compared with placebo.

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.

Chair
Scottish Medicines Consortium

1. Clinical Context

1.1. Medicine background

Pembrolizumab is a humanised monoclonal antibody that blocks the interaction between programmed cell death-1 (PD-1) receptor and its ligands, PD-L1 and PD-L2. This potentiates T-cell responses, including anti-tumour responses of antigen presenting cells and tumours or other cells in the tumour microenvironment.[1]

Neoadjuvant pembrolizumab in combination with chemotherapy is administered for eight doses of 200mg every 3 weeks or four doses of 400mg every 6 weeks or until disease progression that precludes definitive surgery or unacceptable toxicity, followed by adjuvant pembrolizumab as monotherapy for nine doses of 200mg every 3 weeks or five doses of 400mg every 6 weeks or until disease recurrence or unacceptable toxicity. Patients who experience disease progression that precludes definitive surgery or unacceptable toxicity related to pembrolizumab as neoadjuvant treatment in combination with chemotherapy should not receive pembrolizumab monotherapy as adjuvant treatment. Pembrolizumab is administered intravenously. Please see the Summary of product characteristics (SPC) for further information.[1]

Pembrolizumab is also licensed in combination with chemotherapy, for the treatment of locally recurrent unresectable or metastatic triple-negative breast cancer in adults whose tumours express PD-L1 with a combined positive score (CPS)≥10 and who have not received prior chemotherapy for metastatic disease.[1] It has been accepted for restricted use by SMC in combination with paclitaxel or nab-paclitaxel, subject to a two-year clinical stopping rule (SMC2460).

1.2. Disease background

Triple-negative breast cancer (TNBC) is defined by a lack of oestrogen receptor and progesterone receptor expression, and the absence of human epidermal growth factor receptor 2 (HER2) overexpression or amplification. It accounts for 15% to 20% of all breast cancers and is associated with a higher tumour grade at diagnosis and a higher risk of distant disease recurrence, particularly to visceral organs and the central nervous system, with most relapses occurring within the first 3 years after surgery. TNBC is more common in people aged under 40 years, black people and in those with a Breast Cancer 1 (BRCA1) mutation. The 5-year overall survival rate for patients with stage II to III disease is approximately 77%.[2, 3]

1.3. Treatment pathway and relevant comparators

Early breast cancer is treated with a combination of surgery, radiotherapy and chemotherapy depending on tumour and patient characteristics. In patients with operable tumours who have TNBC, neoadjuvant treatment with a sequential anthracycline and taxane chemotherapy regimen is recommended; the addition of a platinum agent may be considered to improve response rate. Following the completion of chemotherapy and surgery, patients receive regular follow up. If a postoperative pathological complete response (pCR) is not achieved, adjuvant off-label capecitabine may be offered. Bisphosphonates are also recommended for post-menopausal patients with low oestrogen expression at high risk of relapse.[2, 4, 5] Olaparib has been licensed as

an adjuvant treatment for patients with HER2-negative, high risk early breast cancer with a germline BRCA1/2 mutation, however SMC has not yet issued advice for this indication (SMC2518).[6]

1.4. Category for decision-making process

Pembrolizumab meets SMC orphan equivalent criteria for this indication.

2. Summary of Clinical Evidence

2.1. Evidence for the licensed indication under review

Evidence to support the efficacy and safety of pembrolizumab for the indication under review is from the KEYNOTE-522 study.[7, 8] Details are summarised in Table 2.1.

Table 2.1. Overview of the KEYNOTE-522 study[2, 7, 8]

Criteria	KEYNOTE-522
Study design	Multicentre, randomised, double-blind, placebo controlled phase III study
Eligible patients	• Adults with centrally confirmed TNBC (defined by ASCO/CAP). • Previously untreated locally advanced non-metastatic disease with tumour stage T1c and nodal stage N1 to N2, or tumour stage T2 to T4 with nodal stage N0 to N2 (according to primary tumour and regional lymph node staging per AJCC) as assessed by the investigator. • ECOG performance status of 0 or 1 within 10 days of treatment initiation.
Treatments	**Neoadjuvant treatment:** Pembrolizumab 200mg or matching placebo every 3 weeks in combination with: • Paclitaxel 80mg/m^2 once weekly plus carboplatin AUC 5mg/mL/min every 3 weeks or AUC 1.5mg/mL/min once weekly. Treatment continued for four 21-day cycles, followed by: • Doxorubicin 60mg/m^2 or epirubicin 90mg/m^2 every 3 weeks plus cyclophosphamide 600mg/m^2 every 3 weeks. Treatment continued for four 21-day cycles followed by surgery. **Adjuvant treatment:** • Pembrolizumab 200mg or matching placebo every 3 weeks for up to nine 21-day cycles. All treatments were administered intravenously and continued until completion of treatment (17 cycles), disease progression that precludes definitive surgery, disease recurrence in the adjuvant phase, or unacceptable toxicity.
Randomisation	Patients were randomised 2:1 to receive pembrolizumab (n=784) or placebo (n=390). Randomisation was stratified according to nodal status (positive or negative), tumour size (T1/T2 or T3/T4) and choice of carboplatin dosing (every 3 weeks or weekly).
Co-primary outcomes	pCR rate, defined as the proportion of patients without residual invasive cancer on haematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes (ypT0/Tis ypN0) following completion of neoadjuvant systemic therapy by AJCC staging criteria assessed by the local pathologist at the time of definitive surgery. Event-free survival, defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause as assessed by the investigator.

Secondary outcomes	Overall survival, defined as the time from randomisation to death due to any cause.
Statistical analysis	A hierarchical statistical testing strategy was applied in the study according to the methodology of Maurer and Bretz to control for multiplicity and to allocate alpha between pre-specified event driven interim and final analyses. Outcomes controlled for multiplicity were tested in the following order: pCR rate, EFS and overall survival. Outcomes were not formally tested until the preceding outcome in the hierarchy had reached a pre-specified significance boundary.
AJCC= American Joint Committee on Cancer; ASCO=American Society of Clinical Oncology; AUC=area under the concentration-time curve; CAP=College of American Pathologists; ECOG= Eastern Cooperative Oncology Group; EFS=event-free survival; pCR=pathological complete response; TNBC=triple negative breast cancer	

The final analysis for pCR rate was at interim analysis 2 (24 April 2019 data cut-off), pCR was not formally tested at interim analysis 4 (23 March 2021 data cut-off). Event-free survival (EFS) crossed the statistical significance boundary for formal testing at interim analysis 4 with 23 March 2021 data cut-off; a final EFS analysis is planned when 327 events have occurred and at least one year has elapsed since the final interim analysis.[2]

The addition of pembrolizumab to neoadjuvant chemotherapy followed by adjuvant pembrolizumab monotherapy was associated with a significant improvement in pCR rate and EFS compared with placebo. Most first EFS events in the pembrolizumab and placebo groups were due to distant (7.7% versus 13%) or local (3.6% versus 4.4%) recurrences. For the secondary outcome, overall survival, a lower proportion of patients in the pembrolizumab group died compared with placebo however, the difference between groups was not statistically significant.[2, 8]

Table 2.1: Primary and selected secondary outcome results for KEYNOTE-522 in the ITT population[2, 7, 8]

	Pembrolizumab plus chemotherapy	**Placebo plus chemotherapy**
Data cut-off: 24 April 2019[A]	n=669	n=333
Primary outcome: pathological complete response rate (ypT0/Tis ypN0)		
pCR rate, % (n)	64% (428)	55% (182)
Difference, % (95% CI)	9.2% (2.8% to 16%), p<0.05	
Data cut-off: 23 March 2021[B]	n=784	n=390
Median follow up	37.8 months	37.6 months
Primary outcome: pathological complete response rate (ypT0/Tis ypN0)		
pCR rate, % (n)	63% (494)	56% (217)
Difference, % (95% CI)	7.5% (1.6% to 13%)	
Primary outcome: event-free survival		
EFS events, n(%)	123 (16%)	93 (24%)
Median EFS	Not reached	Not reached
HR (95% CI)	0.63 (0.48 to 0.82), p<0.001	
KM estimated EFS at 24 months	88%	81%
KM estimated EFS at 42 months	84%	75%

Secondary outcome: overall survival		
Deaths, n	80	55
Median overall survival	Not reached	Not reached
HR (95% CI)	0.72 (0.51 to 1.02), p-value=0.03	
KM estimated OS at 24 months	92%	91%
KM estimated OS at 42 months	89%	84%
CI=confidence interval; EFS=event-free survival; HR=hazard ratio; KM=Kaplan-Meier; pCR=pathological complete response; OS=overall survival. [A]Second interim analysis; final analysis for pCR (included the first 1002 randomised patients) [B]Fourth interim analysis, pCR not formally tested		

Pre-planned subgroup analyses were conducted for the co-primary outcomes based on nodal status, tumour status, choice of carboplatin regimen, tumour PD-L1 status, overall stage, menopausal status, age, geographic region, ethnic origin, ECOG performance status, HER2 status and lactate dehydrogenase (LDH) level. These were generally consistent with the ITT analyses at the March 2021 data cut-off and favoured the pembrolizumab group compared with placebo with the exception of the subgroup of 155 patients with an ECOG performance status of 1 which favoured placebo for pCR rate (difference -7.0 [95% CI: -22.2 to 9.7]). However, the subgroup size is small and therefore results should be interpreted with caution. When EFS was tested in subgroups of patients with various PD-L1 CPS cut offs, the magnitude of benefit with the addition of pembrolizumab was greater for patients with a PD-L1 CPS ≥10 and ≥20 compared with <10 and <20, and was less for patients with a PD-L1 CPS≥1 compared with <1. As a benefit with pembrolizumab was observed across PD-L1 subgroups, there is no restriction included in the indication based on PD-L1 expression.[2, 7, 8]

2.2. Health related quality of life outcomes

Health Related Quality of Life (HRQoL) was assessed as a secondary outcome using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Core 30 (QLQ-C30) and EORTC Breast Cancer–Specific QoL (QLQ-B23) questionnaires and as an exploratory outcome using the EuroQol-5 Dimension 5 level (EQ-5D-5L) visual analogue scale (VAS). For all instruments, the changes in scores in both groups during the neoadjuvant and adjuvant treatment phases were generally similar; HRQoL was generally poorer in the neoadjuvant phase compared with the adjuvant phase in both groups, which is not unexpected given the higher treatment burden. For the EQ-5D VAS, there was a decrease (worsening) from baseline in both groups in the neoadjuvant phase and adjuvant phase. The EQ-5D-5L questionnaire in KEYNOTE 522 was mapped to the EQ 5D-3 level utility value set for the UK for use in the economic analysis.[2, 9]

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

3. Summary of Safety Evidence

The regulator noted that no new safety concerns had been identified during KEYNOTE-522, overall higher rates of adverse events (AEs), including serious and fatal AEs were reported in the pembrolizumab group compared with placebo. This was particularly evident during the neoadjuvant phase, which highlights the increased toxicity associated with the addition of pembrolizumab to chemotherapy. In the KEYNOTE-522 study at the March 2021 data cut-off, the median duration of treatment in the pembrolizumab group was 13.3 months and in the placebo

group was 13.6 months. Any treatment-emergent AE was reported by 99% (777/783) of patients in the pembrolizumab group and 100% (389/389) in the placebo group and these were considered treatment-related in 99% and 100% respectively. In the pembrolizumab and placebo groups respectively, patients reporting a grade 3 or higher treatment-related AE were 77% versus 73%, patients with a reported serious treatment-related AE were 34% versus 20%, and patients discontinuing pembrolizumab or placebo therapy due to a treatment-related AE was 28% versus 14%.[2]

The most frequently reported treatment-related AEs of any grade with an incidence >25% in the pembrolizumab group versus the placebo group were: nausea (63% in both groups), alopecia (60% versus 57%), anaemia (55% in both groups), neutropenia (47% versus 48%), fatigue (42% versus 39%), diarrhoea (30% versus 25%), alanine aminotransferase increased (26% versus 25%), vomiting (26% versus 22%), asthenia (25% versus 26%), rash (25% versus 17%), neutrophil count decreased (24% versus 29%). Immune-related AEs of special interest were observed more frequently in the pembrolizumab group including infusion reactions, hypothyroidism, severe skin reactions and hyperthyroidism, these mainly occurred during the neoadjuvant treatment phase. No new immune-related AEs associated with pembrolizumab were identified in KEYNOTE-522. There were three deaths due to AEs that were considered by the investigator to be treatment-related in the pembrolizumab group. These were due to one pneumonitis and pulmonary embolism in the neoadjuvant phase and one autoimmune hepatitis in the adjuvant phase.[2]

4. Summary of Clinical Effectiveness Considerations

4.1. Key strengths

- KEYNOTE-522 was a randomised, placebo controlled phase III study. As pembrolizumab is an additional treatment in the neoadjuvant and adjuvant setting, placebo plus neoadjuvant chemotherapy followed by adjuvant placebo alone is an appropriate comparator.
- The addition of pembrolizumab to neoadjuvant chemotherapy followed by adjuvant chemotherapy was associated with a statistically significant improvement in pCR rate, with a between group difference of 9.2% (95% CI: 2.8% to 15.6%) and EFS, HR 0.63 (95% CI: 0.48 to 0.82). At the most recent interim analysis in March 2021, all patients had completed or discontinued treatment and had been followed-up for at least 1 year.[2, 7, 8]

4.2. Key uncertainties

- Overall survival data are immature as only 12% of study patients had died at the March 2021 data cut-off after a median follow up of approximately 37 months, therefore the long-term survival benefit of the addition of pembrolizumab is uncertain. The final analysis for all outcomes has yet to be conducted, however it is unlikely that the pre-planned threshold of 297 events for the final overall survival analysis will have been reached and results may be confounded by subsequent treatments.[2]

- At the final pCR analysis, the between group difference was lower than the target of point estimate of 15% in the power calculation and was minimally exceeded by the upper bound

of the 95% confidence interval. The regulator also noted that the lower bound of 2.8% was disappointing. Non-responders were typically older, post-menopausal, had more advanced tumours and tended to have a PD-L1 expression below a certain cut-off. For EFS, although statistical significance was reached, the results were based on a relatively low number of events and median time to event had not been reached in either treatment group. At the interim analysis the median follow up was 37.6 months, this is beyond the highest risk time period for recurrence of TNBC which is 2 to 3 years post diagnosis. Data from previous interim analyses are consistent which is reassuring and it is unlikely that the results from subsequent interim analysis will significantly change the overall result.[2, 7, 8]

- There is no direct or indirect evidence comparing pembrolizumab with adjuvant capecitabine in patients with TNBC that did not achieve a pCR. Guidelines and clinical experts consulted by SMC noted that the value of adjuvant capecitabine after neoadjuvant platinum chemotherapy is uncertain and that use in this setting in clinical practice may vary. The regulatory report indicates that the use of adjuvant capecitabine was not common practice when KEYNOTE-522 was started. Olaparib has also been licensed in the adjuvant setting for patients with a germline BRCA1/2 mutation however a comparison with pembrolizumab is not expected as SMC has not yet issued advice for this indication (SMC2518).[2, 4, 6]

- In KEYNOTE-522, all patients received platinum chemotherapy with carboplatin in the neoadjuvant setting and there is limited evidence for the addition of pembrolizumab to neoadjuvant regimens that do not contain a platinum agent. Although the addition of a platinum to standard neoadjuvant taxane and anthracycline chemotherapy may increase the pCR rate in TNBC, guidelines do not make strong recommendations regarding the selection of patients that may receive the most benefit.[4, 5] Clinical experts consulted by SMC confirmed that in Scottish clinical practice, most patients with high risk locally advanced or early TNBC receive carboplatin as part of their neoadjuvant chemotherapy regimen as standard.

- In KEYNOTE-522, no crossover was permitted and patients remained in the same randomised treatment groups during the neoadjuvant and adjuvant treatment phases. This means it is not possible to separate the contributing effect of pembrolizumab in the neoadjuvant setting or adjuvant setting to longer-term outcomes such as EFS or overall survival and it is uncertain if both are required. Therefore because of this study design, the licensed indication specifies pembrolizumab as neoadjuvant and adjuvant treatment.[2]

- The indication under review is for patients with early stage and locally advanced TNBC. However, KEYNOTE-522 excluded patients with stage I and IIa disease where adjuvant therapy is recommended. Therefore there is no evidence for the use of pembrolizumab in this patient population. Details regarding exact tumour size and nodal status of patients included in the study are available in the SPC.[1, 2]

- The discontinuation rate was higher in the pembrolizumab group during the neoadjuvant phase (24% versus 15%) mainly because of adverse events (14% versus 5%), and there were also higher rates of AEs, serious AEs and fatal AEs compared with placebo.[2] This highlights the additional toxicity associated with adding pembrolizumab in the neoadjuvant setting where patients are already receiving a treatment regimen including four systemic anticancer therapies.

- The SPC states that pembrolizumab may be given as an alternative dosing regimen of 400mg every 6 weeks (up to a total of nine cycles in the neoadjuvant and adjuvant setting combined); this is different than the dosing regimen used in KEYNOTE-522. The regulatory report notes that the 400mg every 6 weeks regimen is considered a suitable dosing option based on pharmacokinetic and safety data which are similar to the 200mg every 3 weeks dose.[1, 2]

4.3. Clinical expert input

Clinical experts considered that the introduction of pembrolizumab in the neoadjuvant and adjuvant early TNBC setting would fill an unmet need because of the aggressive nature of the disease, the lack of responsiveness to treatment and the young fit patient population. They considered that the addition of pembrolizumab in this setting is a therapeutic advance due to the results of KEYNOTE-522, namely the improved response and survival outcomes, and considered that it would be used in high risk patients including those who are young with larger and more advanced tumours.

4.4. Service implications

Pembrolizumab is an additional treatment in the neoadjuvant and adjuvant setting. Therefore, longer oncology day unit admissions will be required in the neoadjuvant setting and additional visits will be required in the adjuvant setting to complete treatment. Additional pharmacy and oncology clinical resources will be required to prepare and administer the medicine and to monitor and treat AEs.

5. Summary of Patient and Carer Involvement

The following information reflects the views of the specified Patient Group.

- We received a patient group submission from Breast Cancer Now, which is a registered charity.
- Breast Cancer Now has received 0.65% pharmaceutical company funding in the past two years, with none from the submitting company.
- A diagnosis of primary triple negative breast cancer (TNBC) can cause considerable anxiety to patients as well as their family and friends, including fear of recurrence or fear of it spreading to other parts of the body where it becomes incurable. This fear and anxiety can be heightened for patients diagnosed with TNBC as generally treatment options for this type of breast cancer remain limited, and it tends to be more aggressive and is associated

with an initial high risk of recurrence and poorer prognosis than other types of breast cancer.

- Patients with this type of breast cancer generally feel that there have been fewer advances in the treatment options available to them on the NHS to reduce the risk of recurrence and breast cancer spreading to other parts of the body. They desperately want to see new effective treatments which could significantly reduce the risk of recurrence and provide them with reassurance.
- Pembrolizumab could be an important new milestone and advancement in the treatment of certain patients with primary TNBC by reducing the risk of recurrence. Increasing the time until a patient's disease progresses is also likely to bring some comfort to their relatives and friends.

6. Summary of Comparative Health Economic Evidence

6.1. Economic case

A summary description of the economic analysis performed is provided in Table 6.1

Table 6.1 Description of economic analysis

Criteria	Overview
Analysis type	Cost-utility analysis (CUA)
Time horizon	Lifetime (51 years)
Population	Adults with locally advanced, or early stage, TNBC at high risk of recurrence.
Comparators	Pembrolizumab plus chemotherapy (neoadjuvant phase) followed by pembrolizumab monotherapy (adjuvant phase) was compared to chemotherapy alone (in the neoadjuvant phase only). The chemotherapy in both arms consisted of carboplatin and paclitaxel (for 4 cycles of 21 days), followed by doxorubicin or epirubicin and cyclophosphamide (for 4 cycles of 21 days).
Model description	A Markov model consisting of four health states: Event Free (EF), Locoregional recurrence (LR), Distant metastasis (DM) and death. Patients started in the EF state and could transition to LR, DM or death. From the LR state patients could transition to DM or death. The only transition from DM was to death.
Clinical data	The primary clinical data source used for transitions from the EF state, for the pembrolizumab plus chemotherapy and the chemotherapy alone arms, was KEYNOTE-522 study.[7, 8] Further, combined data from both arms of the same study were used for estimation of transition probabilities from the LR to DM or death states. Overall survival data from the KEYNOTE-522 study were considered immature, and so several other sources were used to estimate mean survival in the DM state for a range of subsequent treatments. These sources included the KEYNOTE-355[10] and a network meta-analysis conducted by the company. A US database study was used to estimate mean OS in the DM state for patients who did not receive first line subsequent therapy.[11]
Extrapolation	Extrapolation of EFS for the pembrolizumab plus chemotherapy and chemotherapy alone arms used 2 stage piecewise modelling, in which the observed data were used up to a cut-off of 68 weeks and then a parametric function fitted. The log-normal function was selected based on clinical opinion. For estimating transition probabilities from LR to DM or death an exponential function was chosen based on goodness of fit statistics and visual fit. For transitions from DM to death, constant weekly mortality rates were estimated based on the weighted mean overall survival for each treatment arm.

Quality of life	EQ-5D-5L data were collected as part of the KEYNOTE-522 study. These were mapped to the EQ-5D-3L utility value set for the UK, and used to estimate health state utility values and AE disutilities. Age adjustment was applied.
Costs and resource use	Medicine acquisition, administration costs and AE costs were included for both arms of the model. Additional costs for subsequent lines of therapy were also applied. Time on treatment for each therapy used in the EF state was estimated using observed data from KEYNOTE-522. A lump sum cost was included for each subsequent line therapies assumed to be used in the DM state. Health state costs for disease management were estimated based on evidence from a previous HTA submission. The model also included costs of surgery and terminal care.
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 NHSScotland. Under the PAS, a simple discount was offered on the list price of pembrolizumab. The results presented do not take account of the PAS discounts for atezolizumab and nab-paclitaxel, which were used in subsequent treatment lines, but these were considered in the results used for decision-making. SMC is unable to present the results provided by the company which used an estimate of the PAS prices for atezolizumab and nab-paclitaxel due to commercial confidentiality and competition law issues.

6.2. Results

The base case incremental cost effectiveness ratio (ICER), when the PAS on pembrolizumab is applied but not those discounts on subsequent treatments, was estimated to be £10,402 per quality adjusted life year (QALY) gained. The inclusion of the PAS for subsequent therapies acted to increase the ICER.

Disaggregated results demonstrated that the main driver of incremental costs are additional medicine acquisition (plus administration) costs in the neoadjuvant and adjuvant phases. Costs were partly offset by lower costs associated with the DM stage for the pembrolizumab plus chemoetherapy arm due to less use of immunotherapy therapy than the comparator chemotherapy arm.

The estimated QALY difference was primarily related to EFS benefit in the pembrolizumab arm. Those gains were partly offset by a loss of QALYs in the DM state from a greater use of more effective immunotherapies for metastatic TNBC in the comparator chemotherapy arm.

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

6.3. Sensitivity analyses

The company provided a variety of analysis to help explore areas of uncertainty in the economic model. One-way sensitivity analysis indicated that the ICER was sensitive to changes in the assumptions underlying the EFS extrapolations.

Additionally, the company provided a range of scenario analyses, a selection of which are shown in Table 6.4. The scenario results are inclusive of the PAS discount on pembrolizumab, but not those on subsequent treatments.

Table 6.4 Key scenario analyses results (inclusive of PAS discount on pembrolizumab)

#	Scenario description	Base Case description	ICER (£/QALY)
1	EFS extrapolation: Log-logistic (second best-fitting curve) fitted to observed data from week 68	EFS extrapolation: Log-normal fitted to observed data from week 68	£9,400
2	EFS extrapolation: Log-normal fitted to observed data from week 50		£17,126
3	EFS extrapolation: Log-normal fitted to observed data from week 43		£7,491
4	EFS Extrapolation: Log-normal fitted to observed data from week 109		£25,396
5	Time horizon (20 years)	Time horizon (51 years)	£17,508
6	Use of KEYNOTE-522 data to estimate OS in DM state	Use of KEYNOTE-355 and network meta-analysis results to estimate OS in DM state	£10,295
7	Treatments in metastatic TNBC assumed to have same efficacy	Treatments in metastatic TNBC assumed to different efficacy based on available evidence	£10,516
8	Time to immunotherapy eligibility in the DM state post neoadjuvant pembrolizumab initiation: ≥1.5 years	Time to immunotherapy eligibility in the DM state post neoadjuvant pembrolizumab initiation: ≥2 years	£10,934
9	Exclude costs of 2nd line plus subsequent therapies	Include costs of 2nd line plus subsequent therapies	£10,576
10	Pembrolizumab dosing - 400mg every 6 weeks	Pembrolizumab dosing - 200mg every 3 weeks	£9,211

Abbreviations: EFS, Event Free Survival; OS, overall survival; HTA, Health Technology Assessment; DM, distant metastases; mg, milligram

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

6.4. Key strengths

The key strengths of the economic analysis were assessed as being:

- The model structure was simple, easy to follow and avoided unnecessary complexity.
- The company provided a clear explanation for the modelling approach and assumptions used. Where there was remaining uncertainty, this was adequately explored through sensitivity and scenario analysis.
- The KEYNOTE-522 study provided patient level data which was used to inform model efficacy estimates and utility values. These estimates had good face validity.

6.5. Key uncertainties

The key weaknesses of the economic analysis were assessed as being:

- There are some uncertainties with the comparator regimen used in the economic analysis, in particular whether capecitabine used in the adjuvant phase of treatment should be considered within the comparator regimen. Feedback from SMC clinical experts indicated this was not frequently used in Scottish practice.

- There was some uncertainty associated with the extrapolation of EFS, particularly the point of switching from observed data to the parametric function. The company selected 68 weeks as the base case, with several other potential data cut points were also identified (43, 50, 93 and 109 weeks). These alternative points led to shifts in the ICER, some of which were upward (see Scenarios 2, 3 and 4 in Table 6.4).
- Due to immaturity of the overall survival data in KEYNOTE-522, several other indirect sources were used to estimate overall survival for patients in the DM state. The use of external sources and a network meta-analysis may have introduced some error. However, scenarios exploring alternative overall survival assumptions and data sources had only a small impact on the ICER (see Scenarios 6 and 7).
- There was uncertainty associated the costs of subsequent therapies in the DM state. Patients were assumed to wait 2 years after neoadjuvant pembrolizumab immunotherapy in order to be eligible for further immunotherapy. This led to greater use of atezolizumab plus nab-paclitaxel in the comparator arm, increasing costs in that arm. However, a scenario reducing the time between immunotherapy treatments (Scenario 9) and exclusion of subsequent treatment costs all together (Scenario 10) led to only small changes in the ICER.

7. Conclusion

After considering all the available evidence, the Committee accepted pembrolizumab for use in NHSScotland.

8. Guidelines and Protocols

The European Society for Medical Oncology (ESMO) published 'Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up' in 2003 and these were updated in 2019. See here

The National Institute for Health and Care Excellence (NICE) updated its national guideline (NG) 101: Early and locally advanced breast cancer: diagnosis and management in 2018. See here

The Scottish Intercollegiate Guidelines Network (SIGN) published guideline 134 'Treatment of primary breast cancer: a national clinical guideline' in 2013. See here

9. Additional Information

9.1. Product availability date

26 May 2022

9.2. Summary of product characteristics

Pembrolizumab concentrate for solution for infusion SPC

Table 9.1 List price of medicine under review

Medicine	Dose regimen	Cost per cycle (£)
Pembrolizumab	**200mg intravenously every 3 weeks or 400mg intravenously every 6 weeks**	**3 week cycle 5,260** **6 week cycle 10,520**

Costs from BNF online 07/03/23. Costs do not take any patient access schemes into consideration.

10. Company Estimate of Eligible Population and Estimated Budget Impact

The submitting company estimated there would be 89 patients eligible for treatment with pembrolizumab in year 1 and 92 patients in year 5. The estimated uptake rate was 20% in year 1 and 50% in year 5. A discontinuation rate was not applied, but instead was accounted for in the mean number of doses received in the neoadjuvant and adjuvant phases. This resulted in 18 patients estimated to receive treatment in year 1 rising to 46 patients in year 5.

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 subsequent treatment lines.

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

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This assessment is based on data submitted by the applicant company up to and including 08 April 2023.

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.