Healthcare Improvement Scotland | SMC Advice on new medicines

SMC2284

pertuzumab 420mg concentrate solution for infusion (Perjeta®)

Roche Products Ltd

07 August 2020

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

ADVICE: following a resubmission assessed under the orphan medicine process

pertuzumab (Perjeta®) is accepted for restricted use within NHSScotland.

Indication under review: for use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.

SMC restriction: for use in patients with lymph node-positive disease

The addition of pertuzumab to trastuzumab and chemotherapy improved invasive disease-free survival in patients with HER2-positive early breast cancer at high risk of recurrence.

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

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

Chairman
Scottish Medicines Consortium

Indication

For use in combination with trastuzumab and chemotherapy in the adjuvant treatment of adult patients with HER2-positive early breast cancer at high risk of recurrence.[1]

Dosing Information

The recommended initial loading dose of pertuzumab is 840mg administered as a 60 minute intravenous infusion, followed every three weeks thereafter by a maintenance dose of 420mg administered over a period of 30 to 60 minutes. An observation period of 30 to 60 minutes is recommended after completion of each infusion. The observation period should be completed prior to any subsequent infusion of trastuzumab or chemotherapy.

Pertuzumab should be administered in combination with trastuzumab for a total of one year (up to 18 cycles or until disease recurrence, or unmanageable toxicity, whichever occurs first) as part of a complete regimen for early breast cancer and regardless of the timing of surgery. Treatment should include standard anthracycline- and/or taxane-based chemotherapy. Pertuzumab and trastuzumab should start on Day 1 of the first taxane-containing cycle and should continue even if chemotherapy is discontinued.

Patients must have HER2-positive tumour status, defined as a score of 3+ by immunohistochemistry (IHC) and/or a ratio of ≥2.0 by in situ hybridisation (ISH) assessed by a validated test.

Pertuzumab should only be initiated under the supervision of a physician experienced in the administration of anti-cancer agents. Pertuzumab should be administered by a healthcare professional prepared to manage anaphylaxis and in an environment where full resuscitation facilities are immediately available.

See summary of product characteristics for additional information including doses of trastuzumab and chemotherapy.[1]

Product availability date

31 May 2018

Pertuzumab meets SMC orphan equivalent criteria for this indication.

Summary of evidence on comparative efficacy

Pertuzumab is a recombinant, humanised immunoglobulin (Ig) G1κ monoclonal antibody, which targets human epidermal growth factor receptor 2 (HER2), a transmembrane glycoprotein with intrinsic tyrosine kinase activity. By binding to extracellular subdomain 2, pertuzumab prevents dimerization of HER2 with other HER family receptors, resulting in the blockage of ligand-activated downstream signalling.[1] It is also licensed for use as part of combination therapy in patients with

metastatic breast cancer and the neoadjuvant treatment of locally advanced, inflammatory or early stage breast cancer at high risk of recurrence, and has been accepted for use by SMC for these indications (SMC2120 and SMC2119). The submitting company has requested that SMC considers pertuzumab when positioned for use in patients with lymph node-positive disease.

The key evidence for this indication is APHINITY, an ongoing, randomised, multicentre, double-blind, Phase III study. Pertuzumab was compared with placebo, both added to standard adjuvant chemotherapy plus one year of treatment with trastuzumab in patients with HER2-positive early stage breast cancer who have had surgery. Patients had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, known hormone receptor status, confirmed HER2-positive status and baseline left ventricular ejection fraction (LVEF) ≥55%. Initially patients with node-positive disease or high risk node-negative disease were included however a protocol amendment stopped the inclusion of any further patients with node-negative disease due to a higher than expected recruitment of these patients.[2]

Patients were randomised equally, to receive pertuzumab (n=2,400), or matching placebo (n=2,404) as follows:

- pertuzumab or placebo: loading dose 840mg IV infusion, followed by 420mg every three weeks for a maximum of 18 cycles within a year, and
- trastuzumab: loading dose of 8mg/kg IV infusion then 6mg/kg every three weeks for a maximum of 18 cycles within a year, and
- chemotherapy according to one the following schedules: three or four cycles (every 3 weeks) of 5-fluorouracil plus either epirubicin or doxorubicin plus cyclophosphamide, followed by 3 or 4 cycles (every 3 weeks) of docetaxel or 12 weekly cycles of paclitaxel; 4 cycles (every 3 weeks or every 2 weeks) of cyclophosphamide plus either doxorubicin or epirubicin, followed by either 4 cycles (every 3 weeks) of docetaxel or 12 weekly cycles of paclitaxel; or 6 cycles (every 3 weeks) of docetaxel plus carboplatin.

All patients were allowed to receive concomitant radiotherapy and/or adjuvant hormone therapy, if indicated, according to standard therapy.[2, 3]

The primary outcome was invasive disease-free survival (IDFS), measured in the intention to treat population and defined as the time from randomisation until the date of the first occurrence of one of the following events:

- ipsilateral invasive breast tumour recurrence (an invasive breast cancer involving the same breast parenchyma as the original primary lesion);
- ipsilateral local-regional invasive breast cancer recurrence (an invasive breast cancer in the axilla, regional lymph nodes, chest wall, and/or skin of the ipsilateral breast);
- distant recurrence (evidence of breast cancer in any anatomic site – other than the two above mentioned sites—that was either histologically confirmed or clinically diagnosed as recurrent invasive breast cancer);
- death attributable to any cause including breast cancer, non-breast cancer, or unknown cause (but cause of death was specified if at all possible);
- contralateral invasive breast cancer.[2, 3]

At the primary analysis, after median follow up of 45.4 months, the 3-year rate of IDFS was 94.1% in the pertuzumab group and 93.2% in the placebo group (HR = 0.81, 95% confidence interval [CI]: 0.66 to 1.00, p=0.045).[2] At a calendar-driven interim analysis, after a median of 74.1 months follow up, the 6-year rate of IDFS was 90.6% and 87.8% in the pertuzumab and placebo groups, respectively (HR: 0.76 [95% CI: 0.64 to 0.91]).[4] The 3-year and 6-year IDFS results in the subgroup of patients with lymph node-positive disease (the proposed positioning) are in table 1.

Table 1. Invasive disease-free survival in subgroup of patients with lymph node-positive disease [2, 4]

	Pertuzumab (n=1,503)	Placebo (n=1,502)	HR (95% CI)
3-year rate of IDFS	92.0%	90.2%	0.77 (0.62 to 0.96)
6-year rate of IDFS	87.9%	83.4%	0.72 (0.59 to 0.87)

IDFS: invasive disease-free survival, HR: hazard ratio, CI: confidence interval

Key secondary outcomes were IDFS including second primary non-breast cancer (IDFS-SPNBC), disease-free survival (DFS) and overall survival. The results are presented in table 2. At the interim analysis there was no significant difference in survival between the groups in the intention-to-treat population; 6-year overall survival estimates of 94.8% and 93.9% in the pertuzumab and placebo groups respectively, (HR 0.85 [95% CI: 0.67 to 1.07], p=0.17).[4]

Table 2. Key secondary efficacy outcomes in APHINITY study, intention-to-treat population at the primary analysis[3]

Secondary Endpoint	3-year event-free rate		HR (95% CI)	p-value
	Pertuzumab (n=2,400)	Placebo (n=2,404)		
IDFS-SPNBC	93.5%	92.5%	0.82 (0.68 to 0.99)	0.043
DFS	93.4%	92.3%	0.81 (0.67 to 0.98)	0.033
Overall survival*	97.7%	97.7%	0.89 (0.66 to 1.21)	0.467

CI: confidence interval, DFS: Disease-free survival, HR: Hazard ratio, IDFS-SPNBC: Invasive disease-free survival including second primary non-breast cancer. *First interim overall survival analysis performed after 26% of planned deaths occurred.

Health related quality of life (HRQoL) was assessed using the European Organisation for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30), its breast cancer module (QLQ-BR23), and the EuroQol group European quality of life five dimensions (EQ-5D) questionnaires. Of the nine EORTC QLQ-C30 symptom scales, diarrhoea was the only symptom that showed a clinically meaningful worsening from baseline in the pertuzumab group compared with the control group. There were no major differences (≥ 5 percentage points) between treatment arms in the five EQ-5D domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).[3]

Summary of evidence on comparative safety

Generally, the overall safety profile of pertuzumab plus trastuzumab and chemotherapy in the APHINITY study was consistent with the known safety profile of pertuzumab. No new toxicities were reported.[3]

Any treatment-related adverse event (AE) was reported by almost all patients (99.9% and 99.5%) in the pertuzumab (n= 2,364) and placebo (n=2,405) groups, respectively. Patients reporting a grade 3 or higher AE were 64% versus 57%, patients with a reported serious AE were 29% and 24%, the overall number of AE leading to pertuzumab/placebo interruption/modification were 31% and 26%. The overall number of AE leading to treatment withdrawal were 13% and 12% and the number of AE leading to pertuzumab/placebo withdrawal were 7.0% and 5.8%.[3]

The most common AE (any grade) in either the pertuzumab or placebo group were nausea (69% versus 65%), alopecia (67% versus 67%), diarrhoea (71% versus 45%), fatigue (49% versus 44%), vomiting (32% versus 30%), arthralgia (29% versus 33%), constipation (29% versus 32%), myalgia (26% versus 30%), stomatitis (28% versus 24%).[3]

Decreases in LVEF have been reported with medicines that block HER2 activity, including pertuzumab and incidence of symptomatic left ventricular systolic dysfunction (LVD) was higher in patients treated with pertuzumab in combination with trastuzumab and chemotherapy compared with trastuzumab and chemotherapy. Patients who have received prior anthracyclines or prior radiotherapy to the chest area may be at higher risk of LVEF declines.[1] No new cardiac emerged at the interim analysis, following 74.1 months of follow up.[4]

Summary of clinical effectiveness issues

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related deaths in women worldwide. The HER2 receptor has been identified as an important target for the treatment of breast cancer due to its involvement in regulating cell growth, survival, and differentiation. Amplification and/or overexpression of HER2 occurs in around 15% to 20% of breast cancers and is associated with increased tumour aggressiveness, higher rates of recurrence, and increased mortality.[3]

The submitting company has requested that SMC considers pertuzumab when positioned for use in patients with lymph node-positive disease. These patients are considered at high risk of recurrence of disease.

Currently in Scotland, in the adjuvant setting, patients with HER2 positive early breast cancer are treated with six to eight cycles of chemotherapy, usually including an anthracycline and a taxane, in addition to one year of trastuzumab. Despite the current available adjuvant treatment, up to one in four women with HER2-positive early breast cancer will experience recurrence or death

within 10 to 11 years of diagnosis.[3] Pertuzumab meets SMC orphan equivalent criteria for this indication.

In the APHINITY study, the addition of pertuzumab to trastuzumab and chemotherapy yielded a small, statistically significant reduction in the risk of disease recurrence. The European Medicines Agency (EMA) considered these results to be clinically relevant in the patient population with a high risk of recurrence. The EMA noted that the results from the primary analysis of the APHINITY study were after only 4 years of follow-up and this is relatively short for an adjuvant study of early breast cancer. Consequently, there were few events at this point in time; 7.1% of patients in the pertuzumab group and 8.7% of the placebo group have had an IDFS event so far. In particular, limited conclusions can be drawn regarding overall survival and many of the secondary endpoints due to the low number of events at this point. The results following a median of 6 years of follow up are reassuring; pertuzumab continued to be associated with a benefit over placebo in patients with lymph node-positive disease measured by IDFS, although there was still no significant difference in overall survival. Due the number of available treatments for patients with relapsed disease, overall survival analyses are likely to be affected by subsequent treatments.

The study included patients who were node negative until a protocol amendment, these patients are at a lower risk of recurrence of disease. The proposed positioning is represented by the subgroup of 63% (3,005/4,804) of patients who had lymph node-positive disease at baseline. Results in this group were consistent with the overall study population. All included patients had ECOG performance status 0 or 1 so there is no evidence in patients with a poorer performance status. Only 13% and 12% of patients in the pertuzumab and placebo groups, respectively, were aged 65 years or older, therefore, evidence of efficacy in the age group is limited.[3]

While the EMA advises the use of overall survival and DFS as clinically relevant outcomes in cancer studies, the primary outcome IDFS, is a valid composite outcome. Although the definition of IDFS used in APHINITY excluded the occurrence of second primary non-breast invasive cancer, IDFS including second primary non-breast invasive cancer was assessed as a secondary outcome in addition to overall survival and DFS.

The addition of pertuzumab to trastuzumab and standard chemotherapy is well-tolerated, but is associated with increased incidence of diarrhoea, cardiac events, mucositis, and infusion-related reactions. Most toxicities appear manageable and related to chemotherapy. Long-term follow-up is considered especially relevant regarding cardiac toxicity, in order to allow a better assessment of the long-term outcome.[3] At the second interim analysis of overall survival, after more than 6 years of follow up, there were no new cardiac safety concerns.[4]

Clinical experts consulted by SMC considered pertuzumab as a therapeutic advance, providing the opportunity for dual HER2 blockade and improved disease-free survival in patients with node positive HER2-positive early breast cancer.

The addition of pertuzumab to current standard of care would require additional IV infusions so may impact on patients and the service.

Patient and clinician engagement (PACE)

A patient and clinician engagement (PACE) meeting with patient group representatives and clinical specialists was held to consider the added value of pertuzumab, as an orphan-equivalent medicine, in the context of treatments currently available in NHSScotland.

The key points expressed by the group were:

- A diagnosis of breast cancer is devastating for patients and their families. HER2-positive breast cancer is aggressive and often diagnosed in younger women.
- The fear of recurrence has a massive impact on patients and their families causing anxiety, stress and fear about the future.
- Patients with lymph node-positive disease are at a higher risk of disease recurrence and are most likely to benefit from additional treatment.
- The addition of pertuzumab to trastuzumab and chemotherapy further decreases the risk of cancer returning which is highly valued by patients with breast cancer and their families. Reducing recurrence of disease could lessen the burden of the management of metastatic breast cancer.
- Patients may need to spend longer in hospital to receive this treatment regimen. The reduced risk of recurrence may outweigh this potential inconvenience.
- Pertuzumab is generally well tolerated by patients and no additional monitoring is required.

Additional Patient and Carer Involvement
We received a patient group submission from Breast Cancer Care and Breast Cancer Now (a new charity formed from a merger between Breast Cancer Care and Breast Cancer Now), which is a registered charity. In the past two years, Breast Cancer Care has received 0.69% pharmaceutical company funding and Breast Cancer Now has received 10% pharmaceutical company funding, both including from the submitting company. A representative from the merged organisation participated in the PACE meeting. The key points of their submission have been included in the full PACE statement considered by SMC.

Summary of comparative health economic evidence

The company submitted a cost-utility analysis of the addition of pertuzumab to trastuzumab and chemotherapy for the adjuvant treatment of patients with HER2-positive early breast cancer at high

risk of recurrence. The analysis focused on patients with lymph-node positive disease only. SMC clinical experts confirmed no treatments would be displaced and the comparator is appropriate.

A Markov model was used with seven health states: IDFS on treatment, IDFS off treatment, non-metastatic recurrence, remission, first-line treatment for metastatic breast cancer (mBC), subsequent treatment lines for mBC, and death. Patients enter the model in the IDFS health state and remain there until recurrence or death. The time horizon of the model was 52 years. Sensitivity analysis reducing the time horizon to 60, 50, 40, 30, 20 and 10 years was also provided. The clinical data used in the economic model were largely based on patient-level data from the IDFS outcome in the lymph-node positive subgroup of the APHINITY study.[2] Where data from APHINITY were not available, data from published studies, expert opinion and assumptions were used.

Parametric functions were used to extrapolate beyond the clinical study period. The approach to modelling IDFS was broken down into 3 discrete periods: 0-3 years, 3-10 years, and 10-52 years. In the initial period, examination of the IDFS data indicated the proportional hazard assumption did not hold and therefore parametric models for each treatment arm were modelled independently. In the base case analysis the log-normal function was used and alternative models were tested in the sensitivity analysis. The company referenced published evidence from two trastuzumab studies (HERA and BCIRG-006)[4, 5] showing a patient's risk of recurrence in the first few years is not representative of their risk over time and argued that to extrapolate based only on the risk observed in the study period would overestimate the rate of recurrence. On this basis, the extrapolations were adjusted based on longer term data from two published trastuzumab studies (HERA and BCIRG-006) such that the proportion of patients 'cured' (ie no longer at risk of recurrence and only subject to background mortality) increased linearly over time from 0% at 36 months to a maximum of 95% at 10 years. For the final time period in the model, it was assumed that 95% of patients are no longer at risk of recurrence beyond 10 years and only the age-adjusted background mortality rate is applied.

Additional assumptions were made regarding the duration of the pertuzumab treatment effect. In the base case analysis the company assumed the treatment benefit with pertuzumab observed from the APHINITY study would continue until 7 years followed by a waning of the treatment effect (linear decrease) until 10 years when no additional benefit was assumed. The company argued that the long-term follow-up in trastuzumab studies have shown maintenance of treatment effect and the complementary mechanism of action of pertuzumab is expected to further enhance this. The assumption in the base case analysis of the original submission (treatment benefit to 4 years, waning to 7 years and no benefit thereafter) was stated by the company to be overly conservative and clinically implausible given the new data available.

EQ-5D data were collected in the APHINITY study with responses collected at baseline, end of the anthracycline treatment period, week 13, week 25, end of study treatment, 18 months, 24 months and 36 months after randomisation. EQ-5D data from the lymph-node positive population were used in the model. No statistically significant differences were observed between the two treatment arms in the APHINITY study which meant the data were pooled for the base case analysis. Utility values in the IDFS health state were 0.756 for patients on chemotherapy, 0.785 for

patients on treatment/off chemotherapy, and 0.822 for patients off treatment. No EQ-5D data were collected when patients progressed and therefore assumptions were made that non-metastatic recurrence and remission utilities would be equivalent to IDFS on chemotherapy and IDFS off treatment respectively. For metastatic disease, utility values were taken from a published study resulting in utility values of 0.773 for first-line mBC and 0.52 for second-line mBC. Disutilities associated with adverse events were not included separately on the basis that any quality of life impact would be captured in the EQ-5D responses.

Resource use included medicine acquisition and administration costs of initial and subsequent treatments, health state costs, supportive care costs and costs associated with treating adverse events. A range of sources were used including expert clinical opinion, clinical guidelines and assumptions. Costs of cardiac monitoring were included. Medicines costs for up to 18 cycles (1 year) of pertuzumab and trastuzumab were included, plus chemotherapy costs based on the regimens used in the APHINTY study. On request, a revised base case analysis was provided by the company to reflect a 20% higher treatment administration cost in the pertuzumab arm due to the additional chair time required and is reflected in the cost-effectiveness results presented in tables 3 and 4.

A PAS was proposed by the company and assessed by PASAG as acceptable for implementation in NHS Scotland. Under the PAS a discount is offered on the list price for pertuzumab.

Table 3: Base case results with PAS

Treatment	**Incremental LYG**	**ICER (cost per QALY)**
Pertuzumab + trastuzumab + chemotherapy	0.544	£31,412
Trastuzumab + chemotherapy		
QALY- quality adjusted life year LYG- life year gained		

Table 4: Sensitivity analysis with PAS

	Scenario		ICER (cost per QALY)
	Revised base case with additional administration cost for pertuzumab arm		£31,412
1	IDFS parametric distribution – Gompertz		£31,268
2	Proportion of recurrences that are metastatic varied between 0% and 50% (base case 81%)	0%	£59,081
3		10%	£53,470
4		20%	£48,767
5		30%	£44,767
6		40%	£41,323
7		50%	£38,328
8	Maximum 'cure' proportion varied between 0% and 80% (base case 95%)	0%	£23,650
9		20%	£24,921
10		40%	£26,354
11		60%	£27,980
12		80%	£29,838
13	Time horizon reduced to 30 years		£36,367
14	Time horizon reduced to 20 years		£53,324
15	Treatment effect duration maintained over time		£28,215

The following limitations were noted:

- The clinical data from the APHINITY study, updated since the previous submission (median follow-up of around 73.5 months), were extrapolated over a long time horizon (52 years) meaning predictions of cost-effectiveness are uncertain. Results show some sensitivity to the choice of parametric distribution and reducing the time horizon to 20 or 30 years.
- Results are also sensitive to assumption made about the proportion of patients who would be considered cured and the timing of any cure assumption. The base case analysis assumes the point at which a proportion of patients can be assumed cured is 3 years and the maximum 'cured' proportion is assumed to be 95% and is reached at 10 years in the model.
- There is inherent uncertainty in the assumptions made about the duration of the treatment benefit with pertuzumab. Base case analysis assumes benefit continues until year 7 following by a waning of the treatment effect until year 10. Beyond this period there is no additional treatment benefit assumed in the pertuzumab arm. The company argued the assumptions given in the original submission can now be said to be overly conservative and even clinically implausible. The trend shown up to six years does suggest there is increased benefit for a period beyond six years, but given the immaturity of the data the duration of benefit is unknown.

The benefits of pertuzumab were considered in the context of the SMC decision modifiers that can be applied when encountering high cost-effectiveness ratios. As pertuzumab is an orphan equivalent medicine, SMC can accept greater uncertainty in the economic case.

After considering all the available evidence and the output from the PACE process, pertuzumab was accepted for restricted use in NHSScotland.

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

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) updated its guideline "Early and locally advanced breast cancer: diagnosis and management" in July 2018.[7] With respect to patients with HER2-positive early breast cancer at risk of recurrence, the guideline made the following recommendations:

- For people with breast cancer of sufficient risk that chemotherapy is indicated, offer a regimen that contains both a taxane and an anthracycline.
- Offer adjuvant trastuzumab for people with T1c and above HER2-positive invasive breast cancer, given at 3-week intervals for 1 year in combination with surgery, chemotherapy and radiotherapy as appropriate.
- Consider adjuvant trastuzumab for people with T1a/T1b HER2-positive invasive breast cancer, taking into account any comorbidities, prognostic features and possible toxicity of chemotherapy.
- Assess cardiac function before starting treatment with trastuzumab.
- Offer bisphosphonates (zoledronic acid or sodium clodronate) as adjuvant therapy to postmenopausal women with node-positive invasive breast cancer.
- Following surgery, Radiotherapy be given but may be delayed if there are complications from the mastectomy or reconstruction. Immediate reconstructions using implants may be more affected by radiotherapy than immediate flap reconstructions.

The European Society of Medical Oncology (ESMO) Clinical Practice Guidelines on Primary Breast Cancer: Guidelines for diagnosis, treatment and follow-up were updated in 2019.[8] These guidelines indicate that the decision on systemic adjuvant treatment should be based on the predicted sensitivity to particular treatment types, the benefit from their use and an individual's risk of relapse. These guidelines made the following annotations:

- HER2-positive (non-luminal) cancers should be treated with chemotherapy plus trastuzumab unless very low risk
- Trastuzumab combined with chemotherapy in patients with HER2 overexpression/ amplification approximately halves the recurrence risk and improves overall survival, compared with chemotherapy alone

- Chemotherapy usually consists of four to eight cycles of anthracycline- and/or taxane-

based regimen. Sequential use of anthracyclines and taxanes, instead of concomitant, is recommended

- Due to its cardiotoxicity, trastuzumab should not be routinely administered concomitantly with anthracyclines. Combination with taxanes is safe and has been demonstrated to be more effective than sequential treatment
- Dual treatment with trastuzumab and pertuzumab can be considered in patients with high risk disease

The Scottish Intercollegiate Guidelines Network published SIGN 134: Treatment of primary breast cancer in 2013.[9] With regard the population for the indication under review, the following recommendations were made:

- Adjuvant chemotherapy with an anthracycline and a taxane should be considered for all patients with breast cancer where benefit outweighs risk.
- Adjuvant trastuzumab should be considered in all patients with HER-2 positive breast cancer who receive adjuvant chemotherapy.
- Adjuvant trastuzumab should not be given concurrently with anthracyclines but may be given either concurrently with taxane based regimens or sequentially.
- Cardiac function should be monitored in patients being treated with anthracyclines and/or trastuzumab.
- Trastuzumab should be used with caution in patients with significant cardiac comorbidity. The benefits of adjuvant chemotherapy with or without trastuzumab may be outweighed by the potential harms in these patients, and treatment should only be recommended after careful consideration.

Additional information: comparators

Pertuzumab is used in combination with current standard of care.

Additional information: list price of medicine under review

Medicine	Dose Regimen	Cost per course (£)
pertuzumab	**840mg IV on day 1, then 420mg every 21 days for 1 year (18 cycles)**	**45,505**

Costs from BNF online on 29 May 2020. Costs do not take patient access schemes into consideration.

Additional information: budget impact

The company estimated there would be 202 patients eligible for treatment in year 1 and 205 in year 5. The company estimated a market share of 60% (121 patients) in year 1 rising to 90% (184 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.

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

References

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3. The European Medicines Agency (EMA) European Public Assessment Report. Pertuzumab (Perjeta®). 26 April 2018, EMEA/H/C/002547/II/0034. www.ema.europa.eu.
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7. National Institute for Health and Care Excellence. Early and locally advanced breast cancer: diagnosis and management. July 2018. Available at: https://www.nice.org.uk/guidance/ng101/resources/early-and-locally-advanced-breast-cancer-diagnosis-and-management-pdf-66141532913605.
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9. Scottish Intercollegiate Guidelines Network. SIGN 134: Treatment of primary breast cancer. September 2013. Available at: https://www.sign.ac.uk/assets/sign134.pdf.

This assessment is based on data submitted by the applicant company up to and including 27 July 2020.

**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/media/3572/20180710-release-of-company-data.pdf*

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.