Healthcare Improvement Scotland

National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG125 Paclitaxel (weekly) in combination with trastuzumab plus pertuzumab | Advice Document v1.0 | January 2026

Paclitaxel (weekly) in combination with trastuzumab plus pertuzumab for the first-line treatment of adults with HER2-positive metastatic or locally recurrent unresectable breast cancer who are considered fit for treatment with pertuzumab plus trastuzumab plus a taxane [A]

NCMAG Decision | this off-label use is **supported** as an alternative option to on-label treatments

This advice applies only in the context of the confidential pricing agreements in NHSScotland, upon which the decision was based, or confidential pricing agreements or list prices that are equivalent or lower.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith Scottish Medicines Consortium remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of the available evidence regarding the clinical benefits and harms, the Council were **satisfied** with the clinical effectiveness case for paclitaxel (weekly) in combination with trastuzumab plus pertuzumab in the proposed population. After consideration of all relevant information under the Decision-making Framework for Value Judgements the Council made a decision to **support** this use.

Governance Arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	NHSScotland oncologists treating breast cancer
Medicine Name(s)	Paclitaxel in combination with pertuzumab plus trastuzumab
Cancer type	Breast Cancer

Proposed off-label-use[B]	For the first-line treatment of adults with HER2-positive metastatic or locally recurrent unresectable breast cancer who are considered fit for treatment with pertuzumab plus trastuzumab plus a taxane
Medicine Details	Form: Concentrate for solution for infusion Dose: Paclitaxel[C] 80mg/m^2 body surface area (BSA) intravenous (IV) weekly for up to 12 to 18 weeks in combination with: Loading dose pertuzumab 1,200mg plus trastuzumab 600mg subcutaneously (SC) (combination product) followed by pertuzumab 600mg plus trastuzumab 600mg SC (combination product) every 3 weeks. Treatment may continue until disease progression or unmanageable toxicity, even if taxane is discontinued Or Loading dose pertuzumab 840mg IV plus trastuzumab 8mg/kg IV followed by maintenance dose pertuzumab 420mg IV plus trastuzumab 6mg/kg IV every 3 weeks. Treatment may continue until disease progression or unmanageable toxicity, even if taxane is discontinued

Advice eligibility criteria	Patients who meet the criteria for treatment with pertuzumab, trastuzumab plus docetaxel (on-label), but for whom paclitaxel (weekly, off-label) is preferred due to docetaxel-related toxicities, comorbidities, or fitness. Inclusion Criteria: • At least 18 years of age • Human epidermal growth factor receptor 2 (HER2) 3+ on immunohistochemistry or ≥2 on FISH • First line of treatment for metastatic disease • Eastern Cooperative Oncology Group Performance Status 0 to 2 • Patients who are not suitable for docetaxel due to docetaxel-related toxicities, comorbidities, or fitness.

[B] Pertuzumab is indicated for use in combination with trastuzumab and docetaxel in adult patients with HER2-positive metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease.

[C] Paclitaxel is indicated for the initial treatment of locally advanced or metastatic breast cancer either in combination with an anthracycline in patients for whom anthracycline therapy is suitable, or in combination with trastuzumab, in patients who over-express human epidermal growth factor receptor 2 (HER-2) at a 3+ level as determined by immunohistochemistry (IHC) and for whom an anthracycline is not suitable.

1. Current Management Context

Metastatic breast cancer symptoms, incidence and prognosis

Metastatic breast cancer (MBC) is where cancer starts in the breast and spreads beyond the breast and nearby lymph nodes to distant organs such as the bones, liver, lungs, or brain. Symptoms can be from the primary cancer (new breast lump, or change in size, shape or feel of breast) or from the effects of the cancer metastases (e.g. pain, fatigue, breathlessness, nausea). In Scotland, there were 4,000 new diagnoses of breast cancer (all stages) and 224 new metastatic breast cancer diagnoses in 2022. Approximately 15% of all breast cancers will be human epidermal growth factor receptor 2 (HER2) positive (HER2+ MBC)[1]. This corresponds to an incidence of fewer than 5 per 10,000 people per year in NHSScotland and meets orphan-equivalent criteria.

Patients with HER2-positive disease tend to be diagnosed at a younger age than the overall breast cancer population, with a median age of approximately 57 years reported in UK registry data. Median overall survival of treated patients is around five years (57 months) from the time of commencing treatment for metastatic disease[2].

Metastatic HER2 positive breast cancer treatment pathway in NHSScotland

Standard first line therapy for HER2+ MBC is docetaxel in combination with pertuzumab plus trastuzumab. This regimen significantly increases progression-free survival and overall survival compared with the previous standard of care, trastuzumab plus docetaxel[3, 4]. Docetaxel is administered every three weeks for up to six cycles, while pertuzumab and trastuzumab are administered 3-weekly and continued until disease progression or unacceptable toxicity. Patients with hormone receptor-positive disease may also receive endocrine therapy after completing chemotherapy. An NHSScotland real world data report: First-line treatment of adults with HER2-positive metastatic breast cancer, found that in recent years, a substantial proportion (approximately 45%) of the relevant population for this proposal have received pertuzumab plus trastuzumab in combination with paclitaxel (weekly), which is the proposed regimen[5]. This has been accessed through individual patient requests where there may be concerns about patient suitability for the combination with docetaxel, and it has not previously been subject to health technology appraisal. Alternative less effective regimens include paclitaxel with trastuzumab or docetaxel combined with cyclophosphamide and trastuzumab although these regimens are used infrequently according to clinical experts and NHSScotland prescribing data[5].

International context for proposed use

The European Society for Medical Oncology (ESMO), the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) support the first line use of pertuzumab in combination with trastuzumab plus docetaxel or paclitaxel[6-8].

Pharmacology of paclitaxel

Paclitaxel, like docetaxel, is a chemotherapy agent belonging to the taxane class. Paclitaxel is used in various doses, combinations and stages for breast cancer treatment. Paclitaxel works by

inhibiting the assembly of microtubules and thereby prevents cell division and leads to cancer cell death[9].

2. Evidence Review Approach

A literature search was conducted to identify clinical and economic evidence on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The search concepts included but were not limited to paclitaxel, trastuzumab, pertuzumab and breast cancer. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer when required. The included key studies were critically appraised using the Risk of bias in non-randomised studies – of interventions tool version 1 (ROBINS-1)[10].

3. Clinical Evidence Review Summary

Clinical Efficacy Evidence

One study was identified as being relevant to this proposal; PERUSE was a global, open label, phase IIIb single arm study with the primary aim of determining the safety and tolerability of pertuzumab in combination with trastuzumab and a taxane in patients with HER2-positive locally recurrent or metastatic breast cancer who are not eligible for curative resection[11, 12]. The study included patients 18 years of age or older with at least one measurable lesion and/or non-measurable disease evaluable according to the modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, patients with an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 2, left ventricular ejection fraction 50% or higher and to have received no prior systemic therapy for locally recurrent or MBC. Patients received pertuzumab 840 mg loading dose, which was then reduced to 420 mg for subsequent cycles every 3 weeks, trastuzumab 8 mg/kg loading dose then 6 mg/kg for subsequent cycles every 3 weeks and a taxane. All medicines were administered intravenously (IV). Taxane choice was determined by the investigator, and the dose was given weekly or every 3 weeks; no data was collected on taxane treatment schedules, although investigators note that around two thirds of patients received two or more doses of paclitaxel per cycle which suggests weekly administration. Taxane selection varied with docetaxel (n=775) being used the most, followed by paclitaxel (n=589) then nab-paclitaxel (n=65).

The primary outcome was to examine the safety and tolerability of pertuzumab, trastuzumab and a taxane. Key secondary outcomes included investigator-assessed progression-free survival (PFS) defined as the interval between enrolment and the first radiographically documented disease progression or death, whichever came first, overall survival (OS) and overall response rate (ORR). The analysis plan included prespecified subgroup analyses of efficacy for selected taxane at enrolment.

The median duration of treatment with an anti-HER2 therapy was 16 months (interquartile range [IQR] 7.7 to 40 months). At the final data cut of 28 August 2019 the median follow-up from the start of treatment with pertuzumab, trastuzumab plus a taxane was 69 months (95% CI 67 to 69). The baseline characteristics for the overall population and subgroups by taxane received is summarised in Table 1.

Table 1| Baseline characteristics of PERUSE[11, 12]

	ITT Population (n=1,436)	Docetaxel (n=775)	Paclitaxel (n=588)
Age median (range)	54 (23 to 87)	53 (23 to 82)	56 (26 to 87)
Older than 65 years, n (%)	269 (19%)	120 (15%)	134 (23%)
ECOG PS 0 to 1 n (%)	1371 (95%)	754 (97%)	547 (93%)
ECOG PS 2	63 (4%)	20 (3%)	40 (7%)

Key: ECOG: eastern cooperative oncology group; PS: performance status. ECOG PS not reported for all patients.

More patients in the paclitaxel group were older than 65 years and had an ECOG PS of 2. Results were presented in the intention to treat population (all patients) and by taxane received with the key results summarised below (Table 2). The median duration of taxane exposure was 6 cycles (range 1 to 94), which equates to 3.8 months (interquartile range [IQR] 3.5 to 5.5) in the docetaxel group and 4.2 months (IQR 3.5 to 5.5) in the paclitaxel group[11, 12].

Table 2 | Key efficacy results of the PERUSE study[a,11, 12]

		Prespecified subgroups by selected taxane	
	ITT Population (n=1,436)	**Docetaxel (n=775)**	**Paclitaxel[c] (n=588)**
Investigator-assessed PFS			
Events, n (%)	872 (61%)	479 (62%)	356 (61%)
Median PFS, months (95% CI)	21 (19 to 23)	19 (17 to 22)	23 (20 to 26)
OS			
Events, n (%)	658 (46%)	351 (45%)	273 (46%)
Median OS, months (95% CI)	65 (61 to 71)	66 (62 to 77)	64 (57 to 72)
Response			
ORR[b], % (95% CI)	79% (77 to 82%)	79% (75 to 82%)	83% (79 to 86%)
Complete response[b], n (%)	175 (15%)	89 (14%)	83 (17%)
Partial response[b], n (%)	784 (65%)	428 (65%)	317 (66%)

[a]Data from the final data cut 26 August 2019

[b]Data from the earlier preliminary analysis, data cut 16 March 2018

[C] Administered weekly for the majority of patients

Key: ITT: intention to treat; PFS: progression-free survival; CI: confidence interval; OS: overall survival; ORR: overall response rate; DoR: duration of response.

Supportive Evidence

Two studies were identified as being supportive of this proposal, a phase II single arm study and a retrospective cohort study[13, 14]. Baseline characteristics for both studies are summarised in Table 3. The Wang et al study examined the safety and efficacy of weekly paclitaxel with trastuzumab and pertuzumab in patients with HER2-overexpressing MBC in the first- and second-line settings[13]. This study included patients 18 years of age or older with measurable or non-measurable disease evaluable according to the modified RECIST version 1.1 and patients with an ECOG performance status score of 0 to 1. The primary outcome was 6-month PFS, and the secondary outcomes included median PFS, 6-month OS and median OS in the full population (n=51). The majority (74%) of patients were treatment naïve and median PFS in the naïve population was 25.7 months (95% CI: 17 to Not reached [NR]), with the median OS not reached in the treatment naïve population. All other results were presented for the entire population irrespective of the line of treatment received[13].

Table 3 | Baseline characteristics of the supportive studies[13, 14]

	Wang et al 2019	Polito et al 2023	
	Paclitaxel (n=69)	**Docetaxel (n=752)**	**Paclitaxel (n=313)**
Age median (range)	53 (26 to 84)	58 (IQR 50 to 66)	62 (IQR 52 to 70)
>65 years, n (%)	NR	229 (30%)	131 (42%)
ECOG PS 0-1, n (%)	99%	418 (56%)[a]	174 (52%)[a]
ECOG PS ≥2, n (%)	1%	34 (5%)[a]	38 (12%)[a]

Key: ECOG: eastern cooperative oncology group; PS: performance status
[a]: missing data in ECOG PS in the Polito study (docetaxel 32% and paclitaxel 40%)

The Polito et al study collected data from the US Flatiron Health Database to examine the effectiveness of first line paclitaxel versus docetaxel, both in combination with pertuzumab and trastuzumab, in patients diagnosed with HER2-positive MBC[14]. Paclitaxel was administered weekly in 77% of patients and docetaxel was administered three weekly in 79% of patients. The outcomes were real world (RW) PFS, RW OS and time to last administration before discontinuation or death (TTLA). Results were presented for the overall population, and by taxane received, and key results are summarised in Table 4[14].

Table 4 | Results from Polito real-world study[14]

	Prespecified subgroups by selected taxane	
	Docetaxel (n=752)	**Paclitaxel (n=313)**
RW PFS		
Median RW PFS, months (95% CI)	15 (13 to 17)	13 (11 to 15)
Adjusted HR (95% CI)	1.09 (0.9 to 1.3)	
RW OS		
Median RW OS, months (95% CI)	49 (44 to 60)	42 (35 to 62)

Adjusted HR (95% CI)	1.23 (0.96 to 1.58)	
TTLA of taxane		
Median TTLA, months (95% CI)	3.5 (3.5 to 3.5)	3.7 (3.3 to 3.9)
Adjusted HR (95% CI	0.85 (0.73 to 1.0)	

Key: RW: real world; PFS: progression free survival; OS: overall survival; CI: confidence interval; HR: hazard ratio; TTLA: time to last administration before discontinuation or death

Safety evidence

The PERUSE study primary outcome was the safety and tolerability of pertuzumab plus trastuzumab and a taxane. Grade 3 or higher adverse events occurred in 61% of patients with 36% considered to be taxane-related[11, 12]. It appears a higher incidence of grade 3 or worse adverse events were reported in the group who received docetaxel compared to paclitaxel (estimate of 55% versus 46%, based on visual inspection of published figure). Higher proportions of grade 3 or greater neutropenia (15% compared to 5%) and febrile neutropenia (11% compared to 1%) were found in patients who received docetaxel and higher rates of hypertension (4% versus 2%, based on visual inspection) and peripheral neuropathy (3% versus 2%, based on visual inspection) in patients who received paclitaxel[11, 12]. Grade 3 or higher diarrhoea was reported at similar incidence for patients receiving docetaxel and paclitaxel (8% and 9%). Adverse events led to the discontinuation of taxanes in 20% of patients, with neuropathy being the most common reason[11, 12]. Fatal adverse events were reported in 16 and 19 patients who received docetaxel and paclitaxel respectively[11].

Patient Reported Outcomes

The PERUSE study collected patient reported outcomes using the Functional Assessment of Cancer Therapy – Breast (FACT-B) questionnaire, which were reported in the final analysis (Data-cut 26 August 2019). Only 10% of patients completed the FACT-B questionnaire; while the study reports minimal change from baseline in total FACT-B score, this result should be interpreted with caution due to the low response rate[11, 12].

Quality assessment of clinical evidence

The quality of the PERUSE study was assessed using the Risk of bias in non-randomised studies of interventions (ROBINS-I) tool. Overall, the study was judged to have a serious risk of bias; mainly due to the trial being a non-randomised, single arm trial with lack of adjustment for confounders. The remaining domains were scored as either moderate to low risk, with the main concerns coming from the taxane selection, which was investigators choice and outcome measurement, which was unblinded and investigator-assessed with no independent assessment.

Clinical effectiveness considerations

The non-randomised PERUSE study reported similar median overall survival and progression-free survival for the prespecified subgroups receiving either docetaxel or paclitaxel, in combination with pertuzumab and trastuzumab.

The PFS and OS reported for the PERUSE study appear consistent with those reported for on-label pertuzumab plus trastuzumab with docetaxel regimen in the CLEOPATRA study. There are

important differences between the studies which mean cross-trial comparisons should be interpreted with caution. These include differences in study designs and patient characteristics which impact on efficacy outcomes, such as prior trastuzumab exposure (PERUSE 28%, CLEOPATRA 12%), presence of visceral disease (PERUSE 70%, CLEOPATRA 78%) and the use of endocrine therapy (permitted in PERUSE only).

The study was single arm, however a subgroup analysis based on different investigator-choice taxanes suggest similar PFS, OS and ORR (similar central estimates and overlapping 95% confidence intervals) for regimens including either docetaxel or paclitaxel. This is consistent with a meta-analysis which indicated that weekly paclitaxel has similar PFS and OS compared to 3-weekly docetaxel in advanced breast cancer[15].

The reliability of the PERUSE study analysis of treatment effects across subgroups receiving paclitaxel or docetaxel is uncertain.

In the PERUSE study taxane selection (paclitaxel, docetaxel, or nab-paclitaxel) and frequency (3-weekly or weekly) were at the investigator's discretion. In the absence of randomisation and stratification there is a risk of important differences between groups, other than their assigned treatments, which may affect patient outcomes. This makes reported results challenging to interpret as they are very uncertain[11, 12].

Compared to the group that received docetaxel, those who received paclitaxel were older and had poorer performance status. Other baseline characteristics such as oestrogen status, progesterone receptor status, visceral disease, and prior trastuzumab use were generally well balanced between paclitaxel and docetaxel groups.

The primary endpoint in PERUSE was safety in the overall study population. It was not designed or powered to compare cancer outcomes between taxanes. The clinical differences that may have influenced the initial choice of taxane may also impact overall survival. It may be reassuring that the study included a substantial number of patients, including in the groups receiving docetaxel (n=775) and paclitaxel (n=588)[11, 12].

The lack of blinded or central assessment of disease response adds to the risk of bias in outcome assessment and further uncertainty around interpreting subjective outcomes including those based on disease progression, response or patient reported outcomes. The consistent use of RECIST v1.1 for monitoring disease provides some reassurance.

An analysis of a real-world study, with adjustment for differences in prognostic factors, may provide reassurance on the impact of confounding factors in the PERUSE study

The Polito et al real-world study examined the differences in baseline characteristics and efficacy between patients treated with docetaxel (n=752) and those treated with paclitaxel (n=291) or nab-paclitaxel (n=22), which were combined for analysis. It found that docetaxel was associated with better PFS and OS. However, after adjusting for differences in baseline characteristics and prognostic factors, the efficacy outcomes appeared comparable. It is important to note that

residual confounding due to unaccounted variables and the weighting applied to the specified adjustments may have introduced bias, potentially leading to spurious results[14].

The large patient population treated with paclitaxel and docetaxel in the PERUSE study, along with supportive evidence from the phase II trial and the Polito et al real-world study demonstrates a consistent treatment effect for PFS and overall survival for the combination of paclitaxel, pertuzumab plus trastuzumab, which may provide some reassurance[11-14].

Evidence supporting weekly administration of paclitaxel is reassuring

In the PERUSE study, the paclitaxel dosing schedule (weekly or three-weekly) was not explicitly recorded, however, the number of administrations suggests that weekly dosing was used in two thirds of patients. The Polito et al real-world study in which 77% of patients received weekly paclitaxel and the Wang et al Phase II study where 100% of patients received paclitaxel with weekly dosing may provide further reassurance on the proposed weekly dosing of paclitaxel[11-14].

The PERUSE study findings are likely generalisable to NHSScotland although there are some uncertainties

In the PERUSE study, compared to the docetaxel group, the paclitaxel group included slightly older patients and a greater number with poorer performance status (ECOG PS 2). An NHSScotland real world data report on the use of weekly paclitaxel or 3-weekly docetaxel in combination with pertuzumab plus trastuzumab found that a substantial proportion (approximately 45%) of the relevant population have received the paclitaxel regimen in recent years. Patients treated with paclitaxel were older (median 60.5 years of age compared to 55) and more had poorer performance status and higher comorbidity score (Charlson score) than those treated with docetaxel. The older age, greater comorbidities and poorer performance status aligns with proposed use of paclitaxel in combination with pertuzumab plus trastuzumab[5, 11, 12].

In the PERUSE study the choice of taxane was significantly influenced by treatment location, with some countries almost exclusively using docetaxel. Of the 1,436 participants, 1,009 were enrolled in Europe, including 142 from the United Kingdom[11, 12]. Differences in healthcare systems may limit the generalisability of the results[11, 12].

Subsequent treatments profiles are not published

Details on subsequent treatment based on the taxane chosen were not provided in the PERUSE study publication; if these were unbalanced, they may have affected the overall survival results. [11, 12].

Paclitaxel may have a preferable safety profile for certain patients

In the PERUSE study a detailed breakdown of all types of grade 3 adverse event rates by taxane was not provided. However, paclitaxel was associated with lower rates of grade 3 or higher adverse events for febrile neutropenia (1% compared to 11% for docetaxel) and neutropenia (5% compared to 15%). Conversely, paclitaxel was associated with higher rates of all-grade peripheral neuropathy (31% versus 16%). A detailed breakdown of grade 3 or worse adverse events by taxane choice was not reported. Visual inspection of a graph of grade 3 or worse adverse events

occurring in more than 2% of patients suggest overall rates were approximately 45% for paclitaxel compared to 55% for docetaxel. Rates of grade 3 or worse peripheral neuropathy were estimated at 2% for docetaxel and 3% for paclitaxel. Within the limitations of visual estimation, this may provide some reassurance regarding the toxicity profile of paclitaxel relative to docetaxel[11, 12].

Given these differing toxicity profiles, paclitaxel may be the preferred option in cases where there is concern about the risk of life-threatening neutropenic sepsis, and where the risk of peripheral neuropathy is considered more acceptable.

Both paclitaxel and docetaxel are widely used in breast cancer treatment, and their respective harmful effect profiles are well understood among breast cancer clinicians.

4. Patient Group Summary

We received statements from Breast Cancer Now, Make 2nds Count and METUP UK who are all registered charities. Breast Cancer Now reported 0.5% of their annual funding came from the pharmaceutical industry in 2025. Make 2nds Count reported 17% of their annual funding came from the pharmaceutical industry in 2025 and METUP UK reported that 23% of their annual funding came from the pharmaceutical industry in 2025. A representative from all three patient groups attended the NCMAG council meeting. The key points from the submissions are:

Secondary or metastatic breast cancer severely disrupts daily living through persistent symptoms, frequent hospital visits, and “scan-to-scan” anxiety. The pPertuzumab, trastuzumab plus docetaxel regimen can be difficult to tolerate, particularly in less fit patients, impacting quality of life. Patients and clinicians emphasise the need for alternatives, such as paclitaxel, to provide more options that balance longevity and quality of life.

Paclitaxel offers comparable efficacy with a different side-effect profile, potentially improving tolerability. Paclitaxel may include a higher risk of peripheral neuropathy, and the weekly infusions increases time in hospital, but it has lower rates of neutropenia and febrile neutropenia. Patient groups stress the importance of individualised care and access to both options.

5. Benefit-Risk Balance

The proposed use of paclitaxel in combination with trastuzumab plus pertuzumab is off-label. In the non-randomised phase IIIb PERUSE study paclitaxel had similar efficacy to the on-label regimen of docetaxel in combination with trastuzumab plus pertuzumab[11, 12]. Additional supportive studies showed a consistent treatment effect for paclitaxel in the relevant population. Given its differing adverse effect profile compared to docetaxel, including lower rates of neutropenia and febrile neutropenia, the combination of paclitaxel with trastuzumab plus pertuzumab may offer an alternative treatment option for patients who are unsuitable for docetaxel due to docetaxel-related toxicities, comorbidities, or fitness.

6. Council Review |Clinical Benefit-Risk Balance Evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council were **satisfied** that the case had been made for the clinical effectiveness of paclitaxel in combination with trastuzumab plus pertuzumab.

7. Economic Evidence Review Summary

Economic Overview

The literature search for economic evidence returned no cost-effectiveness publications which evaluated paclitaxel in combination with pertuzumab plus trastuzumab for the treatment of metastatic HER-2-positive breast cancer in the proposed population.

Type of economic evaluation

In the absence of a cost-effectiveness analysis, a de-novo cost-comparison analysis has been performed to support this assessment.

Population, intervention, comparator and outcomes

The population used in the study were adult patients with metastatic or locally recurrent unresectable breast cancer, who have not received previous anti-HER2 therapy or chemotherapy and are eligible for pertuzumab plus trastuzumab plus a taxane.

As the economic evaluation sought to compare paclitaxel in combination with pertuzumab and trastuzumab against docetaxel in combination with pertuzumab and trastuzumab, only the differences in treatment were relevant for the cost comparison analysis. Therefore, the intervention consisted of paclitaxel 80mg/m^2 BSA weekly IV, and the comparator was docetaxel 75mg/m^2 BSA every 21 days.

As a cost-comparison analysis has been performed, quality-adjusted life-years (QALYs) were not included in the analysis.

Costs

Costs included were medicine acquisition, administration and adverse event costs for time on treatment. Confidential NHSScotland National Framework prices for off-patent medicines were used (accessed November 2025). The lowest prices were used for each medicine.

Treatment durations for the paclitaxel and docetaxel regimens were informed by the median duration of taxane exposure in the PERUSE study[11, 12]. Paclitaxel was therefore costed for a duration of 4.2 months (6.1 cycles, 18 doses) and docetaxel for 3.8 months (5.5 cycles, 5 doses).

The administration cost for paclitaxel and docetaxel was based on delivery of simple parenteral chemotherapy given an estimated nurse and chair time of between 30 to 60 minutes (NHS National Reference costs 2024-25). The costs associated with febrile neutropenia were calculated using adverse event rates from the PERUSE study and NICE TA1042 per event costs[11, 12]. No other costs for adverse events were included as these were not expected to significantly increase costs.

Costs were not discounted as the treatment duration did not exceed one year.

Results

All figures in the cost-comparison exclude VAT.

Based on medicine acquisition cost alone, paclitaxel (weekly) costs more per patient compared with docetaxel (NHSScotland confidential prices, accessed November 2025). Overall, including medicine administration and adverse event costs, treatment with the paclitaxel (weekly) regimen is estimated to increase per patient costs compared to NHSScotland SOC. The cost-comparison results are presented in Table 5.

The Council considered results using confidential NHSScotland medicine pricing agreements in decision making. NCMAG is unable to publish the results using confidential pricing due to commercial in confidence issues.

Table 5 | Summary of cost-comparison results (confidential price, excluding VAT)

Cost category	Medicine acquisition (£)	Medicine administration[B] (£)	Adverse event[C] (£)	Total costs per-patient (£)
Paclitaxel[A]	CIC	7,957	62	CIC
Docetaxel[A]	CIC	2,400	681	CIC
Cost difference	CIC	5,557	619	CIC (cost increasing)

CIC = commercial in confidence

[A] Paclitaxel and docetaxel dosing and duration data from the PERUSE study have been used in these cost calculations. Paclitaxel duration of 4.2 months (6.1 cycles, 18 doses) and docetaxel for 3.8 months (5.5 cycles, 5 doses). Both paclitaxel and docetaxel are available as generic medicines and confidential NHSScotland National Framework prices for off-patent medicines were used (accessed November 2025).[B] Administration costs are based on weekly paclitaxel and 3-weekly docetaxel.

[C] Rates of grade 3 or higher febrile neutropenia from the PERUSE study have been used to inform adverse event costs (11% docetaxel versus 1% paclitaxel)

Generalisability of the cost comparison

The dosing schedule of paclitaxel reflects the proposed dosing in NHSScotland. NHSScotland national framework prices for medicines were considered in confidence to increase the generalisability of the net costs.

Limitations of the cost comparison

Pertuzumab plus trastuzumab regimen was assumed to be the same route and duration when used in combination with both treatments

As the cost comparison included a direct comparison between paclitaxel and docetaxel only, it was assumed that the same regimen for pertuzumab and trastuzumab was taken for both treatments and costs were therefore equal. This was a simplifying assumption given the complexity of modelling all variations in pertuzumab plus trastuzumab, and the different costs associated with the subcutaneous and intravenous form of pertuzumab plus trastuzumab.

The use of paclitaxel in place of docetaxel is therefore assumed to have no impact on the route of administration of pertuzumab plus trastuzumab. This has been validated by clinicians.

The duration of treatment with pertuzumab plus trastuzumab by taxane was uncertain, but similar between patients treated with paclitaxel and patients treated with docetaxel. Therefore, in the cost-comparison analysis, it was assumed that the duration of treatment was equal, for simplicity.

The cost of supportive medicines, including primary prophylaxis of neutropenia with granulocyte-colony stimulating factor (GCSF) have not been included in the analysis.

Use of GCSF in this setting is not uniform across NHS Scotland and clinical experts estimate that only around 20% of the eligible population may receive this. In addition, low-cost generic versions of GCSF are available and its inclusion in the cost-comparison analysis is likely to have limited effect on the results. Endocrine therapy, which has a low cost, would also be given to patients with both regimen and has not been included in the analysis.

Most adverse events associated with the treatment were not costed in the analysis

Grade 3 adverse events in the PERUSE study, that were similar between the paclitaxel and docetaxel treatment regimen or that were not considered likely to require a hospital stay were not costed in the model. This includes adverse events such as neutropenia, fatigue, hypertension and peripheral neuropathy, which were identified from clinical data.

The cost-comparison excluded dosing adjustments

The dosing was not adjusted to account for dose reductions or treatment interruptions. The duration and dosing may vary in real-world setting due to multiple factors like comorbidities, tolerability etc. Due to issues of data paucity, adjusting for these factors would likely increase the uncertainty of estimated medicine acquisition costs and were therefore not considered in the calculation.

There was no published cost-effectiveness analysis for the proposed use and cost-effectiveness is not known.

Due to an absence of a cost-utility analysis, the analysis only compared costs. The evidence supporting clinical benefit of paclitaxel given in combination with pertuzumab and trastuzumab in this patient population has been summarised in Section 3. An estimate of cost-effectiveness can be made by modelling the benefits over a longer period and comparing with costs. However, due

to absence of long-term costs and health outcomes, an incremental cost-effectiveness ratio (ICER) is not available, and the cost-effectiveness remains unknown.

Summary

The cost-comparison indicated that paclitaxel (weekly)plus pertuzumab and trastuzumab is a cost-increasing intervention compared to NHSScotland SOC for patients with metastatic breast cancer. However, in the absence of a cost-effectiveness analysis, it is difficult to quantify treatment benefits in relation to costs, and the actual cost-effectiveness remains unknown.

8. Council Review | Cost-Effectiveness Evaluation

After considering all the available evidence, the Council accepted that in the absence of a cost-effectiveness analysis, the cost-effectiveness remained unknown. In this situation Council was able to consider additional relevant information including service impact and estimated net medicines budget impact under the Decision-making Framework for Value Judgements.

9. Service Impact

Compared to three-weekly docetaxel, weekly paclitaxel requires two additional infusions per cycle, resulting in 12 extra infusions over a six-cycle course along with the associated clinical workload of blood tests, prescribing, toxicity review, pharmacy and nursing time for each cycle. Approximately 30 patients per year are expected to receive paclitaxel in combination with trastuzumab plus pertuzumab in NHSScotland. However, data from a CMOP-PHS NHSScotland real-world evidence report suggest that this regimen is already widely used (received by approximately 25 patients per year) and therefore the additional service impact is likely to be limited[5].

10. Budget Impact

Patient uptake

The total estimated number of patients expected to routinely access paclitaxel on an annual basis is 30[5].NHSScotland real world data from the CMOP-PHS report : First-line treatment of adults with HER2- positive metastatic breast cancer, indicates, that on average, approximately 25 patients per year currently receive paclitaxel (weekly) plus pertuzumab and trastuzumab[5]. Access in these instances has been through individual patient requests. Based on clinical opinion, this represents the majority of suitable patients but an estimated additional 5 patients are expected to receive the paclitaxel (weekly) regimen.. As such, the total estimated number of patients annually expected to receive the proposed regimen is 30.

Results

A budget impact was calculated using only medicine acquisition costs with value added tax applied (VAT). This used the same dosing for paclitaxel (80mg/m2 BSA weekly IV) and docetaxel (75mg/m2 BSA every 21 days) as in the cost-comparison analysis.

The results for the total annual patient uptake were presented as the base case in Table 6, which assumes that no patients are receiving paclitaxel (weekly) through routine access. The uptake is assumed to remain constant in subsequent years. A scenario where only 5 patients receive paclitaxel, on the basis that approximately 25 patients annually receive the paclitaxel regimen through individual patient requests, was also explored in Table 6.

Budget impact costs were calculated over a 4-month period as an average of the different times on treatment between the paclitaxel and docetaxel regimens. Discontinuation and mortality rates were not included.

Table 6 | Budget impact base case and scenario analysis results (confidential prices, including VAT)

#	Scenario	Base case	Paclitaxel acquisition cost per patient	Docetaxel acquisition cost per patient	Annual patient uptake	Budget impact – Net medicine costs
	-	Base case	CIC	CIC	30	CIC (budget increase)
1	5 patients[A]	30 patients	CIC	CIC	5	CIC (budget increase)

CIC = commercial in confidence
VAT = value added tax
[A] Assuming that 25 patients each year are currently receiving the paclitaxel regimen via individual patient request, this scenario explores the impact of only an additional 5 patients routinely accessing the treatment if it were NCMAG-supported, offering a comparison to the current real-world context in Scotland.

Limitations

There is uncertainty around the true budget impact given that the patient number expected to receive paclitaxel (weekly) is not known. As the paclitaxel regimen is currently in use across Scotland via individual patient request, the projected number of patients expected to benefit may be overestimated, and therefore the net increase on the budget and service impact may also be overestimated.

Separate information will be supplied by the boards to facilitate budget impact assessment.

11. Council Review | Overall Proposal Evaluation

After consideration of all relevant information under the Decision-making Framework for Value Judgements the Council made a decision to **support** this use.

12. Acknowledgements

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This advice represents the view of the NCMAG Council 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.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by