

## National Cancer Medicines Advisory Group (NCMAG) Programme

### NCMAG105 Trastuzumab | Advice Document v1.0 | January 2023

Trastuzumab for treatment of adult patients with human epidermal growth factor receptor 2 (HER2) positive early breast cancer; for patients categorised as lower risk a reduced treatment duration of 6-months, or 9 cycles is proposed.<sup>A</sup>

**NCMAG Decision | Off-label 6-month duration of trastuzumab is supported** as an alternative option to the on-label 12-month duration

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

The generic product available at the lowest acquisition cost should be prescribed.

<sup>A</sup> NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

#### Decision rationale

After consideration of all the available evidence regarding the benefits and risks, the council were satisfied with the clinical- and cost-effectiveness of the 6-month trastuzumab regimen.

#### 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	Breast Cancer systemic anti-cancer therapy subgroup of the Scottish Cancer Network
Medicine Name	Trastuzumab
Cancer type	Early Breast Cancer (EBC)
Proposed off-label use <sup>B</sup>	Reduced treatment duration of 6-months, or 9 cycles for treatment of adult patients with human epidermal growth factor receptor 2 (HER2) positive early breast cancer categorised as lower risk.
Medicine Details	<p><u>Forms</u> 150mg and 420mg powder for concentrate for solution for infusion 600mg solution for subcutaneous injection (Herceptin);</p> <p><u>Dosing</u> IV: 8mg/kg loading dose followed by 6mg/kg every three weeks SC: 600mg every three weeks</p>
Advice eligibility criteria	Patients with EBC considered as lower risk based on their clinicopathological characteristics. These characteristics include: a 10-year mortality benefit from treatment with trastuzumab estimated to be 3-5%, no high-risk features (includes patients with lymph node negative disease, tumour size 5cm or less and age greater than 35 years), or complete pathological response to neoadjuvant treatment.

<sup>B</sup> Trastuzumab has a marketing authorisation for the treatment of adult patients with HER2 positive early breast cancer (EBC) for the following indications:

- following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)
- following adjuvant chemotherapy with doxorubicin and cyclophosphamide, in combination with paclitaxel or docetaxel.
- in combination with adjuvant chemotherapy consisting of docetaxel and carboplatin.
- in combination with neoadjuvant chemotherapy followed by adjuvant trastuzumab therapy, for locally advanced (including inflammatory) disease or tumours > 2 cm in diameter. For this indication the licensed treatment duration is 12-months.

## 1. Current Management Context

Breast Cancer is cancer that begins in the breast; symptoms include a new lump, changes in the skin, nipple, the size, the shape or the feel of the breast. Incidence of breast cancer has increased in recent decades and it is the most commonly diagnosed cancer in the UK with approximately 4,312 case diagnoses in Scotland every year.<sup>2,3</sup>

Stage 1 and 2 (Early Breast Cancer) accounts for approximately 85% of all breast cancer diagnoses. Important pathological features for determining treatment and prognosis include grade of the tumour and its molecular pathology including oestrogen receptor and/or progesterone receptor

(ER/PR) status, human epidermal growth factor receptor 2 (HER2) status and BRAC1/2. HER2 overexpression in breast cancer results in proliferation and survival of cancer cells.

Five-year overall survival for stage 1 and stage 2 breast cancer is 97% and 89%, respectively.<sup>2</sup> HER2 positive breast cancer has been associated with increased risk of recurrence and mortality. Trastuzumab has been shown to reduce the risk of recurrence of, and mortality from, breast cancer by a third.<sup>3</sup> Trastuzumab is a monoclonal antibody that binds to a specific site on the HER2 receptor. Binding of trastuzumab prevents activation of the HER2 receptor by its ligands, prevents HER2 mediated signalling and induces antibody dependent cell-mediated cytotoxicity.<sup>1</sup>

The choice of treatment for HER2 positive cancers depends on tumour grade, the presence of lymph node disease and patient fitness. Adjuvant or neoadjuvant trastuzumab in combination with chemotherapy and/or pertuzumab are treatment options for some patients with stage 1 and stage 2 disease. In patients with early breast cancer who are suitable for trastuzumab, one year of treatment has been the standard of care. Following the publication of recent studies comparing 12-month with 6-month duration, the European Society of Medical Oncology (ESMO) recommends consideration of 6-month trastuzumab as a treatment option for highly selected patients.<sup>4-7</sup>

## 2. Evidence Review Approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE and Embase. The main search concepts were trastuzumab, early breast cancer and HER2. No filters were applied to limit the retrieval by study type. Titles and abstracts were screened by one reviewer with a second opinion sought by another reviewer. The included publications were critically appraised using the following tools: a Measurement Tool to Assess Systematic Reviews-2 (AMSTAR 2) and The Cochrane risk of bias 2.0 tool.

## 3. Clinical Evidence Review Summary

### Clinical Efficacy Evidence

#### **Evidence comparing 6-month treatment with 12-month treatment duration of trastuzumab**

The evidence sources relevant to the proposal of a 6-month treatment duration of trastuzumab are two meta-analyses which pool data from three randomised controlled trials (RCTs) comparing 6-month duration with 12-month treatment duration (the HORG, PERSEPHONE and PHARE trials).<sup>8, 9</sup> The three trials had a similar design; multicentre non-inferiority trials which included women with a histological diagnosis of invasive early breast cancer with overexpression of HER2 receptor.<sup>10-12</sup> The primary outcome was disease-free survival (DFS) and was defined as time from diagnostic biopsy (PERSEPHONE trial) or date of randomisation (PHARE and HORG trials) to the date of first invasive breast cancer relapse or death of any cause. There were slight differences in the population across the trials (Table 1).

**Table 1 | Characteristics of individual trials in the meta-analyses<sup>10-14</sup>**

Study name, year, country	Trastuzumab comparisons	Population				Outcomes (primary in bold)	Median Follow-up (yr)
		ER/PR status +ve (%)	Node Status -ve (%)	HER2 status			
				3+(%)	2+(%)		
<b>HORG 2015, Greece</b>	6-months (n=240)	69	17	93	7.5	<b>DFS</b> , overall survival, toxicity	6-months = 4.3 years; 12-months = 3.9 years
	12-months (n=241)	65	25	91	5.4		
<b>PERSEPHONE 2019, UK</b>	6-months (n=2,043)	69	59	73	24.3	<b>DFS</b> , overall survival, cardiac safety, health resource use, quality of life	5.4 years
	12-months (n=2,045)	69	58	71	26.4		
<b>PHARE 2013, France</b>	6-months (n=1,690)	59	55	92	8.5	<b>DFS</b> , overall survival, cardiac safety	7.5 years
	12-months (n=1,690)	58	55	91	8.8		

ER: oestrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2; DFS: disease-free survival

### Results from meta-analyses and individual RCTs comparing 6-month treatment duration with 12-month treatment duration

The pooled analysis conducted by Wang et al did not show that 6-months of treatment was non-inferior to 12-months of treatment. A similar conclusion is reported by Deng et al (Table 2). In the PERSEPHONE trial, DFS events occurred in 265 (13%) and 247 (12%) in the 6-month and 12-month groups, respectively. The 4-year DFS rates were reported as 89.4% and 89.8% in the respective groups which demonstrated non-inferiority of the 6-month group (Table 2). In the PHARE trial, DFS events occurred in 345 (20%) and 359 (21%) in the 6-month and 12-month groups, respectively which did not demonstrate non-inferiority for the 6-month group.<sup>12</sup> In the HORG trial, DFS events occurred in 28 (12%) and 17 (7.1%) in the 6- and 12-month groups, respectively which did not demonstrate non-inferiority.<sup>11</sup>

**Table 2 | Estimates for pooled analyses and individual trials for 6-months versus 12-months<sup>8-12</sup>**

Study name <sup>a</sup>	DFS HR (95% CI) <i>Adjusted HR (95% CI)<sup>b</sup></i>	Overall survival (95% CI) <i>Adjusted HR (95% CI)</i>	Non-inferiority margin(s)
Wang et al	1.20 (0.96–1.48) <i>1.18 (0.97–1.44)</i>	1.14 (0.92-1.42) <i>1.14 (0.98–1.32)</i>	1.2 for DFS 1.43 for overall survival
Deng et al	1.10 (0.99–1.23)	1.14 (0.99–1.32)	NA
– HORG 2015	1.57 (0.86–2.10)	1.45 (0.57–3.67)	1.53
– PERSEPHONE 2019	1.07 (90% CI 0.93–1.24) <i>1.07 (90% CI 0.93–1.24)</i>	1.14 (90% CI 0.95–1.37) <i>1.13 (90% CI 0.94–1.35)</i>	1.32 for DFS 1.60 for overall survival
– PHARE 2013	1.07 (0.93-1.25) <i>1.08 (0.93–1.25)</i>	<i>1.13 (0.92–1.39)</i>	1.15

<sup>a</sup> random-effects model used in Wang et al; fixed-effects meta-analysis by Deng et al  
<sup>b</sup> adjusted for oestrogen-receptor status, timing of trastuzumab (concurrent or sequential) and chemotherapy (adjuvant or neoadjuvant) chemotherapy in all trials. Adjustment for chemotherapy type was also made in the PERSEPHONE trial. Confidence intervals are 95% unless otherwise stated.  
 DFS = disease-free survival, HR = hazard ratio, NA = not applicable  
 HR>1 favours 12-month group and HR<1 favours 6-month group

### Sub-group analysis results using key prognostic factors

The PERSEPHONE investigators explored differences in outcomes between the 6-month group and the 12-month group according to ER status, chemotherapy type, chemotherapy and trastuzumab timing, age, grade, menopausal status and immunohistochemistry score. Overall, sub-group analysis results indicated that certain groups of patients may respond differently to 6-months of treatment compared to 12-months of treatment. Sub-group differences were detected for chemotherapy type (DFS), trastuzumab timing (both DFS and overall survival) and ER status (overall survival). The sub-group analysis for DFS and overall survival did not reveal any differences for any of the other groups including groups for age ( $\leq 50$  years or  $>50$  years) or tumour size ( $\leq 2$ cm,  $>2-5$ cm and  $>5$ cm [analysis restricted to adjuvant setting only]). It is noted that these sub-group analyses are observational by nature, demonstrate trends but lack statistical power, therefore, results should be interpreted with caution.

### Other evidence sources

An abstract presenting the results of an individual patient data meta-analysis combining individual patient data from two of the three RCTs (PERSEPHONE and HORG) is planned for publication as a full research article in 2023.<sup>15</sup> Preliminary results show that the 5-year invasive disease-free survival rates were 88.56% and 89.26% for the 6-month and 12-month groups, respectively (adjusted HR 1.07, 90% CI: 0.98-1.17).

### Patient-reported outcomes

The PERSEPHONE trial collected data on health-related quality of life in a sub-study consisting of 1,960 patients in the 12-month group and 1,950 patients in the 6-month group. In both groups, reports of 'very good' general health were lower during the first three months of trastuzumab,

remained at similar levels during treatment and then showed signs of improvement after completion of treatment.<sup>10</sup> The EQ-5D-3L data showed a similar steady rise from baseline to six months for both groups with a continued rise for the 6-month group only from six months to 12 months.

### Safety evidence

The two meta-analyses did not use formal statistical techniques to combine the estimates, therefore, the safety data is presented separately for each of the three trials. In summary, there was a lower incidence of cardiac-related events and fewer discontinuations in the 6-month groups in comparison to the 12-month groups for each of the three trials (Table 3).

**Table 3 | Key safety outcomes for the three individual trials<sup>10, 11, 13, 14</sup>**

Event	PERSEPHONE		PHARE		HORG	
	12-months <sup>a</sup>	6-months <sup>a</sup>	12-months n=1,690	6-months n=1,690	12-months n=241	6-months n=240
Serious adverse events	459/1894 (24%)	373/1939 (19%)	20 (1.2%)	20 (1.2%)	NR	NR
Cardiac dysfunction <sup>b</sup>	224/1968 (11%)	155/1994 (8%)	100 (5.9%)	58 (3.4%)	NR	NR
Cardiac death <sup>c</sup>	7/2044 (<1%)	4/2041 (<1%)	0	0	0	0
Low LVEF <sup>d</sup>	228/2040 (11%)	176/2038 (9%)	92 (5.4%)	58 (3.4%)	0	2 (0.8%)

<sup>a</sup> Denominators vary due to patients not receiving trastuzumab, death or withdrawals.  
<sup>b</sup> PERSEPHONE: clinical cardiac dysfunction is defined as symptoms of cardiac disease, signs of congestive heart failure, use of new medication for cardiac disease, or a combination of these factors. PHARE: defined by significant LVEF decrease with asymptomatic or mildly symptomatic (NYHA class I and II) status.  
<sup>c</sup> No cardiac deaths related to trastuzumab.  
<sup>d</sup> LVEF = left ventricular ejection fraction; defined as ejection fraction of less than 50% or unknown ejection fraction but classified on report as not normal.

### Quality assessment of clinical evidence

Overall, the two meta-analyses were well-conducted with comprehensive search techniques and selection processes. The risk of bias of the included trials was appraised using standard quality assessment tools in both meta-analyses which identified some concerns. The trials were sizable and conducted at multiple sites and reported the use of unbiased central randomisation procedures yet the mechanism of allocation concealment was not always provided in the published reports. None of the studies used blinding to allocate patients to treatment groups which may give rise for detection bias especially for the safety outcomes and quality of life outcomes.

### Clinical effectiveness considerations

#### The relative effects of 6-month trastuzumab and 12-month trastuzumab have been well studied

There have been three non-inferiority RCTs and multiple meta-analyses comparing the two durations of trastuzumab. The various trials and analyses have not produced consistent

conclusions, however the hazard ratio across the two biggest RCTs, PERSEPHONE and PHARE which combined included approximately 7,500 patients, were consistent for DFS (1.07) and overall survival (1.14 and 1.13).<sup>10, 12</sup> Furthermore, preliminary results from an individual patient data meta-analysis (using pooled data from the three trials) demonstrates that the absolute difference in 5-year invasive disease-free survival rates between groups is small; 88.56% and 89.26% for the 6-month and 12-month groups, respectively. A key factor affecting the conclusions of the studies was the differences in the pre-specified non-inferiority margin, which was higher for PERSEPHONE. The choice of a non-inferiority margin is based on a combination of statistical reasoning and clinical judgement with the purpose of providing assurance that the new intervention is not substantially inferior to the reference.<sup>17</sup>

### **PERSEPHONE and PHARE study populations had inclusive and pragmatic eligibility criteria**

Both the PERSEPHONE and PHARE trials had a median follow up period of 5.4 and 7.4 years, respectively. HORG median follow up was 4.3 years in the 12-month treatment arm and 3.9 years in the 6-month treatment arm.

Both PERSEPHONE (UK) and PHARE (France) had inclusive and pragmatic eligibility criteria for HER2 positive EBC. The HORG trial recruited patients with lymph node positive disease or lymph node negative 'high-risk' disease with details on high-risk criteria and tumour size not reported. It is uncertain if patients treated in HORG reflect early breast cancer patients treated in the Scottish population.

There are important clinical and pathological differences in the patient populations from the three trials, including proportions with lymph node positive disease (PERSEPHONE 42%, HORG 70%, PHARE 45%). Overall the HORG study population, which was by far the smallest of the three studies, had higher-risk disease than the other two studies. Including these patients in the meta-analysis may affect generalisability of results to the proposed population. The lower risk patient population in the PERSEPHONE and PHARE studies would be expected to derive less absolute survival benefit to trastuzumab therapy.<sup>18</sup>

### **There is no published analysis focused on the proposed low-risk patient group**

There are no available subgroup analyses from the studies aligning with the proposed lower risk population with lymph node negative disease, tumour size 5cm or less, age 35 years or older and pathological complete response in patients treated neo-adjuvantly.

### **Chemotherapy and timing of trastuzumab may affect applicability of results**

In the proposed population trastuzumab can be used in different contexts, that includes in combination with different chemotherapy regimens and concurrently or sequentially. PERSEPHONE, PHARE and HORG included these treatment contexts in varying proportions, however none of the studies were designed to compare 6-month trastuzumab with 12-month trastuzumab across these different context for use. This may affect applicability of results and the absolute overall survival benefit of trastuzumab.

#### 4. Patient group summary

A patient group partner statement from Breast Cancer Now was received and used to inform Council review and decision-making. The group outlined the treatments on offer to EBC patients and detailed the evidence for a 6-month regimen of trastuzumab over the standard 12-month regimen. They understood the evidence to show that 6-months of trastuzumab has similar outcomes to 12-months of trastuzumab with fewer side effects. A shorter course of treatment was viewed to have benefit by reducing time in treatment and thus potentially improving quality of life. The group considered that this option may be suitable for low-risk early breast cancer patients and that patients need to be content that this option is as effective as the standard treatment of a 12-month regimen.

#### 5. Benefit-risk balance

There are conflicting conclusions from large RCTs comparing 6-month of trastuzumab with 12 months. These results may be explained by the non-inferiority margins chosen in the PERSEPHONE and PHARE trials and HORG's higher risk patient population. The efficacy of both regimens are comparable with very small absolute differences between the 12-month and 6-month regimens for disease-free survival. Six-months of trastuzumab offers a shorter treatment duration for patients and has a lower rate of significant adverse effects compared to 12 months of treatment. Use of the 6-month regimen may be most appropriate in the proposed highly selected patient group with lower clinical pathological risk and lower absolute benefit from treatment.

#### 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 a 6-month treatment duration of trastuzumab for patients with HER2 positive EBC categorised as low risk. The off-label 6-month trastuzumab regimen may be considered as an alternative option to the on-label 12-month regimen.

#### 7. Economic Evidence Review Summary

##### Economic Overview

One relevant published cost-utility analysis was identified in the literature search comparing cost and health outcomes of six and 12 months' adjuvant trastuzumab in patients with HER2-positive early breast cancer.<sup>18</sup> This analysis used an NHS perspective and clinical data from the full population of the PERSEPHONE trial. Compared with 12 months of trastuzumab, reducing the treatment duration to 6 months was estimated to produce a cost saving of £9,316 (BNF medicine list prices) and a slight reduction of 0.008 QALYs per individual in a lifetime model. A within-trial analysis estimated a cost saving £9,536 (BNF medicine list prices) and a slight QALY increase of

0.003. The slight difference in QALYs of the lifetime model compared with the within-trial analysis was likely to be due to the non-significant difference in DFS between the two trial arms.

### **Type of Economic Evaluation**

Based on the minimal QALY difference in the published cost-utility analysis, the comparable efficacy from the clinical evidence, and the expected cost savings of a reduced treatment duration, a de-novo cost-minimisation analysis was performed.

### **Population, intervention, comparator and outcomes**

The population used was patients receiving adjuvant trastuzumab following neo-adjuvant or adjuvant cytotoxic chemotherapy for HER2+ve early breast cancer. The intervention was six months of adjuvant trastuzumab, with the comparator being 12 months of adjuvant trastuzumab. As a cost-minimisation analysis was performed, quality-adjusted life-years (QALYS) were not required in the analysis.

### **Costs**

Only trastuzumab acquisition costs were included. Both subcutaneous and intravenous methods of administration were considered. Costs were not discounted.

### **Key results**

Subcutaneous: Compared with 12 months of trastuzumab, reducing the treatment duration to 6 months was estimated to produce a saving of £9,778 per patient. This result was obtained using BNF list prices. When including the PAS discount, reducing the treatment duration to 6 months was estimated to produce per patient cost-savings.

Intravenous infusion (pre-made in sodium chloride 0.9%): When using national framework contract prices, selecting the cheapest available option, reducing the treatment duration to 6 months was estimated to produce per patient cost-savings.

### **Cost-effectiveness considerations**

#### **Generalisability of results**

The dosing schedules of the two considered trastuzumab regimens reflect NHSScotland practice. NHSScotland national framework contract prices were also considered in the analysis to obtain results of greater relevance.

#### **Limitations**

Only trastuzumab acquisition costs were included. This was a simplification. Other costs, such as administration costs and adverse event costs were omitted. However, it can be expected that the shorter treatment duration would reduce the administration frequency and its associated cost. Given the adverse event profiles of the two treatment regimens from the PERSEPHONE results, it can be reasonable to assume these costs would be also similar or lower for the six month regimen. The inclusion of these other costs is therefore unlikely to reverse the cost-saving conclusions.

## Summary

The cost-minimisation analysis provided suitably robust results of high relevance to the proposal. These are likely to be generalisable to NHSScotland. The outlined limitations should be considered when interpreting the cost-saving results.

## 8. Council review | Cost-effectiveness 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 cost effectiveness of a 6-month treatment duration of trastuzumab for patients with HER2 positive EBC categorised as low risk.

## 9. Service Impact

Six-month trastuzumab has been accessible from mid-2020 to March 2023 under COVID-19 NCMAG advice. Continued routine access to 6-month trastuzumab would reduce the number of patient visits for clinic appointments and administration. Appointments for cardiac monitoring using echocardiogram would also be reduced. There would also be an expected reduction in resource demand for the management of adverse events. It is estimated that 150-200 patients would be eligible for six-month trastuzumab.

## 10. Budget Impact

NCMAG is unable to publish the 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 impact with the appropriate confidential pricing information.

## 11. Acknowledgements

NCMAG would like to acknowledge the patient group partner, Breast Cancer Now, for their invaluable input.

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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