Appendix A: Summary of evidence from surveillance

2020 exceptional surveillance of early and locally advanced breast cancer (2018) NICE guideline NG101

Summary of evidence from surveillance

As part of this exceptional review, feedback from topic experts was considered alongside the evidence to reach a view on the need to update guideline recommendations on biological therapy.

Only recommendations relevant to the exceptional review are listed below concerning adjuvant biological therapy for invasive breast cancer.

1.8 Adjuvant chemotherapy for invasive breast cancer

Biological therapy

1.8.4 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. [2009, amended 2018]

1.8.5 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. [2018]

1.8.6 Assess cardiac function before starting treatment with trastuzumab. [2009]

1.8.7 Use trastuzumab with caution in people with HER2-positive invasive breast cancer who have any of the following:

- a baseline left ventricular ejection fraction (LVEF) of 55% or less
- a history of, or current, congestive heart failure
- a history of myocardial infarction
- angina pectoris needing medication
- cardiomyopathy
- cardiac arrhythmias needing medical treatment
- clinically significant valvular heart disease
- haemodynamic effective pericardial effusion
- poorly controlled hypertension. [2009, amended 2018]

Surveillance decision

These recommendations should not be updated.

2020 surveillance summary

Longer versus shorter durations of adjuvant trastuzumab treatment in people with human epidermal growth receptor 2 (HER2)-positive early breast cancer were assessed in 2 systematic reviews and in 12 publications originating from 9 individual randomised controlled trials (RCTs).

Survival outcomes

Data for survival outcomes are reported in table 1.

A systematic review and meta-analysis (1) included 6 RCTs (2–7), all of which have also been assessed in this exceptional review. The review found that versus the standard 12 months of trastuzumab, shorter trastuzumab treatment was associated with significantly worse disease-free survival, which was not influenced by oestrogen receptor status (p=0.23), nodal involvement (p=0.44), or the different durations of trastuzumab in the experimental arm (p=0.09). A second systematic review (8) included the same 6 RCTs and produced very similar results.

Of the 9 individual RCTs identified by the surveillance review, 6 were set up as non-inferiority studies (2–6,9). Among these 6 RCTs, only 1 (the PERSEPHONE trial, based on a non-inferiority hazard ratio margin of 1.32) was able to conclude that a shorter duration of trastuzumab (6 months) was non-inferior to the standard duration of 12 months in terms of disease-free survival (2). A second RCT (the PHARE trial) with a very similar size and design to the PERSEPHONE trial found an almost identical point hazard ratio and confidence interval when comparing disease-free survival with 6 and 12 months trastuzumab (3). However, it defined non-inferiority differently (including a lower hazard ratio margin of 1.15) and concluded that 6 months treatment was not non-inferior to 12 months. If the same non-inferiority margin of 1.15 had been used by the PERSEPHONE trial, non-inferiority would not have been shown. The other 4 non-inferiority studies used a variety of approaches to analyse non-inferiority and were also unable to claim non-inferiority across a range of short-duration treatments (9 weeks up to 6 months) versus 12 months treatment.

Two RCTs (7,10) set up as simple comparison studies found no significant difference in disease-free or recurrence-free survival between standard and shorter (9 or 12-week) trastuzumab regimens.

An RCT (11) comparing 12 months trastuzumab with either 24 months trastuzumab or with observation found that 12 months treatment significantly improved disease-free survival versus observation, but 24 months trastuzumab had no additional survival benefit over 12 months.

An unplanned subgroup analysis of the PHARE trial (12) (not included in table 1) compared the magnitude of benefit of shorter and longer duration of trastuzumab treatment in

subgroups of patients with differing risks of metastasis. Four risk categories were created: very low (node negative and tumour size ≤2 cm), low (1–3 positive nodes and tumour size ≤2 cm, or node negative and tumour size >2 cm), intermediate (1–3 positive nodes and tumour size >2 cm, or >3 positive nodes and tumour size ≤2 cm), or high (>3 positive nodes and tumour size >2 cm). A total of 261 metastatic events were observed. In the 6-months trastuzumab arm, the 3-year metastasis-free survival (MFS) rates in the very-low, low, intermediate and high-risk groups were 98.3%, 94.2%, 85.7% and 74.8% respectively. In the 12-months arm, the MFS rates were 98.3%, 95.8%, 90.4% and 78.4% respectively. Namely, in the very low-risk group, 6 months of trastuzumab appeared to be similarly effective as 12 months, whereas in higher-risk groups, longer trastuzumab treatment may be more effective.

Table 1 Survival outcomes

Study reference/ trial name	No. of studies / n	Intervention*	Comparator*	Outcome	Median follow up	Result	Non-inferiority
Systematic reviews							
(1)	6 RCTs (n=11,603)	12 months trastuzumab	Shorter durations of trastuzumab (9 weeks in 2 trials, 12 weeks in 1 trial, 6 months in 3 trials)	Disease-free survival	47 to 90 months	HR 1.14 (95% CI 1.05 to 1.25, p=0.002) – favours 12 months	N/A
(8)	6 RCTs (n=11,603)	12 months trastuzumab	Shorter durations of trastuzumab (9 weeks in 2 trials, 12 weeks in 1 trial, 6 months in 3 trials)	Disease-free survival	47 to 90 months	HR 1.13 (95% CI 1.03 to 1.25, p=0.01) – favours 12 months	N/A
RCTs							
PERSEPHONE (2)	n=4,089	12 months trastuzumab	6 months trastuzumab	Disease-free survival	64.8 months	12 months: 89.8% 6 months: 89.4% HR 1.07 (90% confidence interval 0.93 to 1.24)	6 months WAS non-inferior to 12 months [a]
PHARE (3)	n=3,384	12 months trastuzumab	6 months trastuzumab	Disease-free survival events	90 months	12 months: 345/1691 (20.4%) 6 months: 359/1693 (21.2%) HR 1.08 (95% CI 0.93 to 1.25)	6 months WAS NOT non-inferior to 12 months [b, c]
SOLD (4)	n=2,176	12 months trastuzumab	9 weeks trastuzumab	Disease-free survival	62.4 months	12 months: 90.5% 9 weeks: 88.0% HR 1.39 (90% CI 1.12 to 1.72)	9 weeks WAS NOT non-inferior to 12 months [d]

Study reference/ trial name	No. of studies / n	Intervention*	Comparator*	Outcome	Median follow up	Result	Non-inferiority
Short-HER (5)	n=1,254	12 months trastuzumab	9 weeks trastuzumab	Disease-free survival	72 months	12 months: 88% 9 weeks: 85% HR 1.13 (90% CI 0.89 to 1.42)	9 weeks WAS NOT non-inferior to 12 months [e]
HORG (6)	n=481	12 months trastuzumab	6 months trastuzumab	Disease-free survival	47 to 51 months	12 months: 95.7% 6 months: 93.3% HR 1.57 (95% CI 0.86 to 2.10)	6 months WAS NOT non-inferior to 12 months [f]
ALTTO (9)	n=8,381 (of which only 4,188 patients were relevant to the analyses reported here)	12 months trastuzumab	12 weeks trastuzumab	Disease-free survival	54 months	12 months: 86% 12 weeks: 87% HR 0.93 (97.5% CI 0.76 to 1.13)	12 weeks WAS NOT non-inferior to 12 months [g]
E2198 (7)	n=227	12 months trastuzumab	12 weeks trastuzumab	Disease-free survival	77 months	12 months: 73% 12 weeks: 76% HR 1.3 (95% CI 0.8 to 2.1, p=0.3)	N/A [h]
FinXX (10)	n=1,500 (of which 176 HER-2 positive patients received trastuzumab)	12 months trastuzumab	9 weeks trastuzumab	Recurrence-free survival	80.4 months	12 months: 89.3% 9 weeks: 88.9% HR 0.98 (95% CI 0.36 to 2.71, p=0.976)	N/A [h]
HERA (11)	n=3,399	12 months trastuzumab	Observation	Disease-free survival	132 months	12 months: 69% Observation: 63% HR 0.76 (95% CI 0.68 to 0.86) – favours 12 months	N/A [h, i]
HERA (11)	n=3,402	12 months trastuzumab	24 months trastuzumab	Disease-free survival	132 months	12 months: 69% 24 months: 69% HR 1.02 (95% CI 0.89 to 1.17)	N/A [h, i]

CI – Confidence interval

HR – Hazard ratio

* NOTE: All studies gave trastuzumab alongside various chemotherapy regimens. See individual publications for details.

a The non-inferiority margin was prespecified as no worse than an absolute value of 3% below the 12-month group's 4-year disease-free survival (i.e. an HR of less than 1·32). The CI excluded 1.32 therefore non-inferiority of 6 months trastuzumab was demonstrated.

b The non-inferiority margin was prespecified at 15% in relative terms (i.e. an HR of 1·15), corresponding to a 2% difference in absolute terms. The CI included 1.15 therefore non-inferiority of 6 months trastuzumab was not demonstrated.

Study reference/ trial name	No. of studies / n	Intervention*	Comparator*	Outcome	Median follow up	Result	Non-inferiority
c A 3.5-year follow up of the PHARE trial (13) had similar findings to this study. d Non-inferiority was prespecified as shown if the upper limit of the CI was less than or equal to an HR corresponding to a 4% absolute difference (i.e. an HR of 1.39). This did not occur therefore non-inferiority of 9 weeks trastuzumab was not demonstrated. e The upper limit of the CI crossed the prespecified non-inferiority margin set at 1.29, therefore non-inferiority of 9 weeks trastuzumab was not demonstrated. f The upper limit of the CI was greater than the prespecified non-inferiority margin set at 1.53 (derived from an estimated absolute difference in 3-year disease-free survival of 8%, based on an expected disease-free survival in the 12-month group of 85%) therefore non-inferiority of 6 months trastuzumab was not demonstrated. g Non-inferiority was tested for based on the null hypothesis HR of 1.11. The CI included 1.11 therefore non-inferiority of 12 weeks trastuzumab was not demonstrated. h This trial was not set up as a non-inferiority study. i An 8-year follow up of the HERA trial (14) had similar findings to this study.							

Cardiotoxicity outcomes

Data for cardiotoxicity outcomes are reported in table 2.

A systematic review and meta-analysis (1) found that versus the standard 12 months of trastuzumab, shorter trastuzumab treatment (ranging from 9 weeks to 6 months) was associated with significantly less cardiac dysfunction. A second systematic review (8) including the same 6 RCTs produced very similar results.

All 9 individual RCTs identified by the surveillance review reported cardiotoxicity data but only 5 reported statistical analysis (2,4,5,7,13). Among these 5 trials, 4 showed that a shorter duration of trastuzumab (9 weeks or 6 months) was significantly less cardiotoxic than the standard duration of 12 months.

Table 2 Cardiotoxicity outcomes

Study reference/ trial name	No. of studies / n	Intervention*	Comparator*	Outcome	Median follow up	Result
Systematic reviews						
(1)	6 RCTs (n=11,603)	12 months trastuzumab	Shorter durations of trastuzumab (9 weeks in 2 trials, 12 weeks in 1 trial, 6 months in 3 trials)	Cardiac dysfunction	47 to 90 months	OR 0.67 (95% CI 0.55 to 0.81, p<0.001) – favours shorter durations
(8)	6 RCTs (n=11,603)	12 months trastuzumab	Shorter durations of trastuzumab (9 weeks in 2 trials, 12 weeks in 1 trial, 6 months in 3 trials)	Cardiac event	47 to 90 months	OR 0.52 (95% CI 0.43 to 0.62, p<0.00001) – favours shorter durations
RCTs						
PERSEPHONE (2)	n=4,089	12 months trastuzumab	6 months trastuzumab	Clinical cardiac dysfunction	64.8 months	12 months: 224 of 1968 patients (11%) 6 months: 155 of 1994 patients (8%) – p=0.00014 in favour of 6 months
PHARE (13)	n=3,384	12 months trastuzumab	6 months trastuzumab	Cardiac event	90 months	12 months: 96 of 1690 patients (6%) 6 months: 32 of 1690 patients (2%) – p<0.0001 in favour of 6 months
PHARE (3)	n=3,384	12 months trastuzumab	6 months trastuzumab	Cardiac event	90 months	The abstract stated: '…the safety analysis remained similar to the previously published report [of the PHARE trial] (13) […] no change in the cardiac safety comparison'
SOLD (4)	n=2,176	12 months trastuzumab	9 weeks trastuzumab	Cardiac adverse event	62.4 months	12 months: 42 of 1089 patients (4%) 9 weeks: 22 of 1085 patients (2%) – p=0.01 in favour of 9 weeks
Short-HER (5)	n=1,254	12 months trastuzumab	9 weeks trastuzumab	Cardiac event	72 months	RR 0.33 (95% CI 0.22 to 0.50) – p< 0.0001 in favour of 9 weeks
HORG (6)	n=481	12 months trastuzumab	6 months trastuzumab	Cardiotoxicity	47 to 51 months	12 months: no patients (0%) 6 months: 2 patients (0.8%) – p value not reported†
ALTTO (9)	n=8,381 (of which only 4,188 patients were relevant to the analyses reported here)	12 months trastuzumab	12 weeks trastuzumab	Primary cardiac end point	54 months	12 months: 18 patients (<1%) 12 weeks: 5 patients (<1%) – p value not reported†

Study reference/ trial name	No. of studies / n	Intervention*	Comparator*	Outcome	Median follow up	Result
E2198 (7)	n=227	12 months trastuzumab	12 weeks trastuzumab	Post-trastuzumab left ventricular ejection fraction decline >10%	77 months	12 months: 9 of 111 patients (8%) 12 weeks: 12 of 112 patients (11%) – p=0.6
FinXX (10)	n=1,500 (of which 176 HER-2 positive patients received trastuzumab)	12 months trastuzumab	9 weeks trastuzumab	Left ventricular dysfunction	80.4 months	12 months: 3 patients 9 weeks: 1 patient – p value not reported†
HERA (14)	n=3,399	12 months trastuzumab	Observation	No data reported	132 months	No data reported
HERA (14)	n=3,402	12 months trastuzumab	24 months trastuzumab	Decrease in left ventricular ejection fraction	132 months	12 months: 69 patients (4.1%) 24 months: 120 patients (7.2%) – p value not reported†
HERA (11)	n=3,399	12 months trastuzumab	Observation	Primary cardiac endpoint	132 months	12 months: 18 events (1%) Observation: 2 events (0.1%) – p value not reported†
HERA (11)	n=3,402	12 months trastuzumab	24 months trastuzumab	Primary cardiac endpoint	132 months	12 months: 18 events (1%) 24 months: 17 events (1%) – p value not reported†

CI – Confidence interval

OR – Odds ratio

RR – Risk ratio

* NOTE: All studies gave trastuzumab alongside various chemotherapy regimens. See individual publications for details.

† p value not reported in abstract (or full text if freely available)

Intelligence gathering

Initial intelligence noted completion of the PERSEPHONE trial (2), a National Institute for Health Research funded study (HTA 06/303/98). The published paper referenced several other studies comparing shorter and longer treatment durations, therefore a search was performed for RCTs and systematic reviews to examine this area in detail. We also contacted topic experts to ask for feedback on the potential impact of the new evidence.

One topic expert believed that current NICE recommendations on trastuzumab in early breast cancer are still valid, and it remains uncertain what the optimal duration of trastuzumab should be, noting that trials give similar results but come to different conclusions, and that longer follow-up data are needed. The systematic reviews are also

publication-based meta-analyses rather than individual patient level meta-analysis, and the latter is ideally needed to help draw clearer conclusions. The expert highlighted that this is being planned by the Early Breast Cancer Trialists Collaborative Group and will hopefully provide more robust evidence.

A second expert noted that the benefits of any systemic treatment segregate with baseline risk of recurrence and there will be patients with low-risk HER2-positive disease where the incremental benefits of 12 months treatment are very small and outweighed by adverse effects. They noted the PERSEPHONE trial was a large well-conducted UK study, and that it is difficult to show non-inferiority in such studies. They thought that it should be possible to define a low-risk group where the 'risk of harm from undertreatment' is minimal.

A third expert noted this is a complex issue. From the headline result of meta-analyses, it appears there is insufficient evidence to change current NICE recommendations. However, there is an issue for low-risk HER2-positive patients. The latest update of NICE guideline NG101 found a benefit for treatment of all HER2-positive patients. Previously, most clinicians avoided chemotherapy with HER2 therapy for women with small, node negative cancers. The expert therefore felt there is a question about duration of trastuzumab in the low-risk group, and noted more elderly low-risk patients are being treated. But they further noted that the evidence is not conclusive, though the cardiac toxicity data is compelling.

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