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Editorial

Optimising the Duration of Adjuvant Trastuzumab in Early Breast Cancer in the UK

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Adjuvant trastuzumab for patients with HER2-positive early breast cancer showed significant improvements in both disease-free and overall survival with 12 months of treatment [1,2], which was approved by the National Institute for Health and Care Excellence (NICE) in the UK in 2006. When the FinHer trial showed similar results with 9 weeks of trastuzumab [3], there was significant interest in whether shorter durations might be as effective. Additional benefits for patients could be less toxicity, fewer hospital visits and a more rapid return to normal life, with considerable societal benefits of reduced costs. PERSEPHONE was the pragmatic UK duration trial funded by the National Institute for Health Research, Health Technology Assessment Programme (NIHR HTA), which showed that 6 months of adjuvant trastuzumab was non-inferior to 12 months with a 4-year disease-free survival rate of 89.4% compared with 89.8% (non-inferiority $P = 0.01$) [4]. Less toxicity was reported with 6 months, particularly cardiac toxicity, and there were cost savings over the first 2 years [5], which were maintained over an average patient's lifetime when extrapolated using an economic model. After the publication of these results in June 2019, the Optimal Duration of Adjuvant Trastuzumab Working Group was convened, comprising a diverse, multidisciplinary membership. There were representatives from the PERSEPHONE Trial Management Group, including patient advocates, the National Cancer Research Institute (NCRI) Breast Group, the Association of Cancer Physicians, the Royal College of Radiologists and the Independent Cancer Patients' Voice. By November 2019, both dual antibody treatment with trastuzumab and pertuzumab [6] and extended neratinib after single-agent trastuzumab [7] had been approved by NICE, only for those at high risk of recurrence. Therefore, single-agent trastuzumab remained standard of care for those at lower risk of recurrence and recommendations were made for these patients.

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With the aim of assessing current practice and implementation of the PERSEPHONE results, we surveyed breast oncologists in the UK for their views on the recommendations from the Working Group for 6 months of adjuvant trastuzumab. The following three questions were included in the survey:

> Do you agree with the following statement? 'Patients with HER2-positive breast cancer who are receiving adjuvant single-agent trastuzumab with chemotherapy (concurrent or sequential timing) should be considered for 6 months of trastuzumab as standard'
>
> Do you agree with the following statement? 'Patients receiving adjuvant single-agent trastuzumab and suffering severe toxicities, including cardiac toxicity, should be told that receiving only 6 months of treatment will not result in significant loss of benefit from trastuzumab'
>
> Following the results of the PERSEPHONE trial, have you reduced trastuzumab duration for any of your patients?

The survey was hosted by the University of Warwick and used the QUALTRICS online survey tool. It was sent to 330 members of the UK Breast Cancer Group (UKBCG) on 10 January 2020. The Warwick Clinical Trials Unit sent a reminder 1 month later to the principal investigators and recruiting consultants of the PERSEPHONE sites, the majority of whom were in the original mailing.

In total, 117 of 330 contacted, returned completed questionnaires (35%) from 77 sites. Most were consultant oncologists (113/117; 97%), more than half of whom (65/117; 56%) were practising in cancer centres, with 47 (47/117; 40%) in cancer units. Two thirds of respondents (83/117; 71%) were PERSEPHONE investigators or recruiters.

Statement 1

More than three-quarters of respondents (91/117; 78%, see Figure 1) agreed that for patients receiving single-agent trastuzumab, 6 months should be considered as standard. Sixty-eight did not make any qualifying text comments (68/91; 75%), which represents more than half of all respondents (68/117; 58%). Twenty-three of 91 (25%) of those who agreed with statement 1, qualified their response and 11 (48%) considered 6 months of trastuzumab standard for patients with a lower risk of relapse (usually node negative). Of these 11 respondents, three also limited 6 months to patients with oestrogen receptor-positive tumours, two to patients with T1 and one to T1b tumours. Five other comments related to the use of single-agent paclitaxel for patients at low risk of relapse (APT [8]) and whether the PERSEPHONE results could be applied to these patients. One of these five also commented on the use of trastuzumab and pertuzumab in the neoadjuvant setting. Two comments mentioned the need for change in national guidelines before practice changes. Other comments included: (i) a requirement for longer follow-up; (ii) a question about the neratinib treatment pathway; (iii) shared decision-making with patients discussing risks and benefits; and (iv) two confirming their support.

Of respondents who did not agree with the statement (26/117; 22%), half shared comments (13/26: 50%). Three considered that higher risk patients should be excluded, and three felt that longer follow-up and an independent meta-analysis were required before any change in practice. Three respondents expressed concerns about low risk patients who had already de-escalated chemotherapy on the APT regimen [8], with one of these highlighting the predominant use of anthracyclines in the trial. Two respondents referred to the PHARE [9] and HORG [10] trials, which had not shown non-inferiority for 6 months. One respondent discussed the uncertainties of duration with patients, and one said that with the increase of neoadjuvant therapy there was no plan to de-escalate trastuzumab.

Statement 2

Nearly all respondents (114/117; 97%, see Figure 1) agreed with the statement that reassurance should be given to patients who had to stop trastuzumab after 6 months because of severe toxicities that there would not be a significant loss of benefit from trastuzumab. Ten respondents made a comment (10/114: 9%), with four simply confirming their views. Two requested a definition of toxicity and one suggested a minor rewording of the statement. One felt that although 12 months should remain the standard, patients who were frail, elderly or who had comorbidities could be reduced to 6 months. One respondent reported that advice would depend on patient risk profiles and one reported if toxicities were affecting quality of life then 6 months was reasonable. Three respondents who did not agree with the statement made no comments.

Statement 3

Just under half the respondents (53/117: 45%, see Figure 1) said they had reduced trastuzumab for some of their patients since the PERSEPHONE results were published, and of these 25/53 (47%) added a comment. The most frequent (19/25; 76%) related to stopping after 6 months due to cardiac or other toxicity. Three respondents discussed 6 months of treatment with patients, two in a selective way with low risk patients and one as routine. This last respondent also discussed stopping trastuzumab and pertuzumab after 6 months with a pathological complete response to neoadjuvant treatment. One respondent was giving 6 months in T1N0 patients with paclitaxel only chemotherapy (APT) [8], but expressed concern about reducing chemotherapy as well as the duration of trastuzumab in these patients. One respondent excluded patients from 6 months trastuzumab if they had received neoadjuvant therapy or if they had more than 3 axillary nodes containing metastatic cancer. One had switched to 6 months in all lower risk patients, including those receiving weekly taxol and those with concerns about cardiotoxicity.

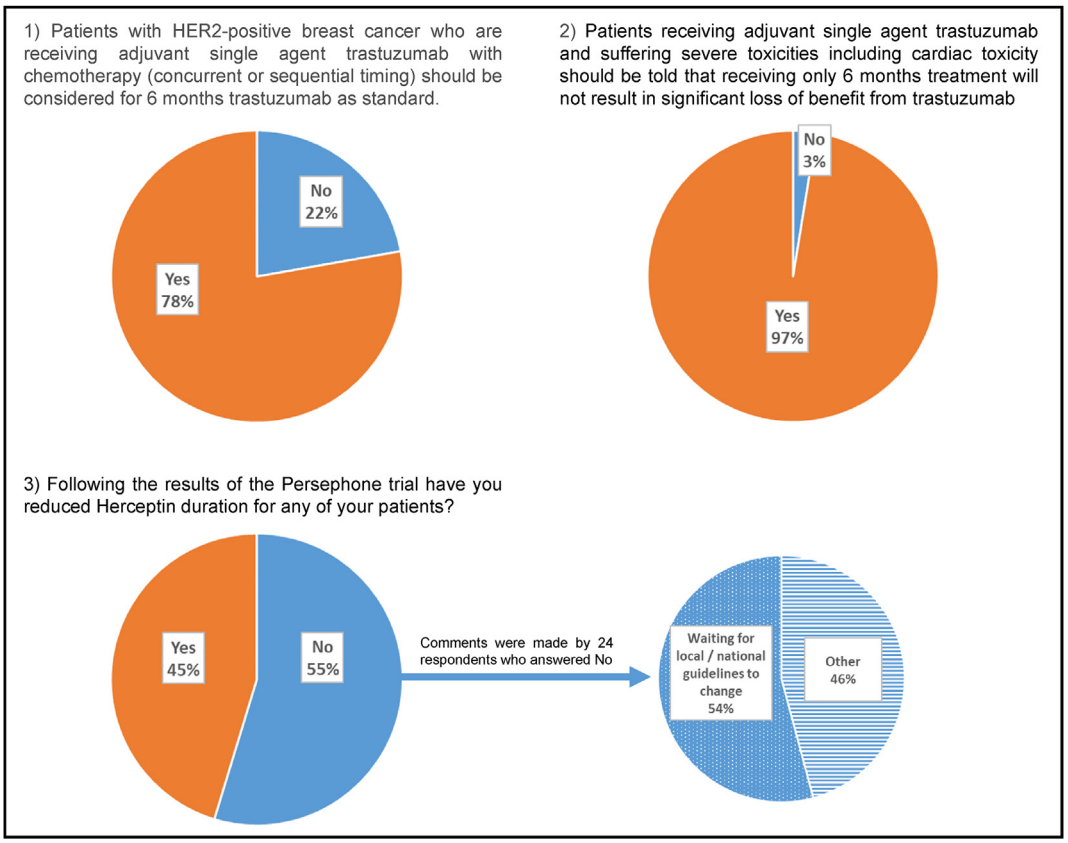

Fig 1. Responses to the three statements within the survey.

Just over half of respondents (64/117; 55%) reported not reducing trastuzumab duration, with 24/64 (37.5%) supplying comments. The most common reason was waiting for local/national guidelines to change (13/24; 54%, see Figure 1). Three other respondents said that for low risk patients they had reduced chemotherapy to paclitaxel only (APT) [8] and for high risk patients had escalated to dual antibodies. Two respondents said they would only reduce trastuzumab duration for toxicity, which one reported they were doing already. Two were not involved in decision-making for these patients. Other comments included: 'not an easy change to sell - not complete consensus with colleagues'; 'not yet'; 'have offered but none have accepted'; 'considering reduction now there are published results'.

Single-agent Taxane Regimens

Nine respondents commented at some point in the questionnaire on low risk patients who are receiving paclitaxel for 12 weeks with concurrent trastuzumab continued for 12 months [8]. The number of patients receiving taxane-only chemotherapy within the PERSEPHONE trial is very small (35, 12 month patients and 38, 6 month patients) [11]. Hence, it is impossible to make any recommendations based on such limited data. However, since the trial results as a whole confirm non-inferiority for 6 months of treatment, it is reasonable to conclude that this can apply to all types of chemotherapy.

Summary

Most respondents (78%) agreed that 6 months of trastuzumab should be a standard option for patients with lower risk disease receiving single-agent treatment. In Scotland, the situation is different and dual therapy is not approved for high risk patients. Hence, we would advise that those in Scotland who elsewhere in the UK would be eligible for dual antibody therapy or extended neratinib, should continue with 12 months of trastuzumab. There was a clear overwhelming consensus (97%) that with severe toxicity patients should be reassured that stopping at 6 months would not result in a significant loss of benefit from trastuzumab. Although the majority agreed with 6 months for patients with lower risk disease, it was notable that over half had not yet introduced this in their clinical practice. This was despite an interval of 19 months and 7 months, respectively, since initial presentation [12] and subsequent full publication [4] of the PERSEPHONE results. This is not unexpected given the well-documented barriers to de-escalation of cancer therapy [13]. Although not specifically explored in our survey, it is likely that the results of PHARE [9] and the HORG [10] study may have led to uncertainty around the strength of the evidence provided by PERSEPHONE. However, it is also crucial to recognise that movement towards de-escalation of therapy is not determined solely by scientific data. Historical, economic, professional and social factors may all favour entrenched

behaviour, even in the face of robust evidence [14]. Consistent with professional and organisational norms being powerful drivers of clinician behaviour, the most common reason given for not reducing trastuzumab duration was waiting for local or national guidelines to change.

The unprecedented crisis of the COVID-19 pandemic has significantly increased the acute risks for cancer patients attending hospital for treatment. The UKBCG has issued prioritisation guidelines for breast cancer treatments [15]. On the strength of the PERSEPHONE data, the UKBCG executive committee has advised that those at low risk of recurrence receiving single-agent trastuzumab should stop at 6 months with immediate effect, as the acute risks of attending hospital clinics are significant and outweigh any minimal loss of long-term benefit. Many hospitals have implemented this prioritisation guidance.

Conflicts of interest

H.M. Earl reports grants from NIHR HTA, during the conduct of the study; grants from Roche and Sanofi, France, personal fees from Prime Oncology, personal fees and expenses from AstraZeneca, Intas Pharmaceuticals and Daiichi-Sankyo, and expenses from Pfizer and Amgen, all outside the submitted work. L. Hiller reports grants from NIHR HTA Clinical Trials (Persephone) during the conduct of the study. J. Dunn reports grants from NIHR HTA Clinical Trials (Persephone) during the conduct of the study. I. Macpherson reports personal fees and non-financial support from Roche Products UK Ltd, Eisai and Eli Lilly; personal fees from Novartis, Pfizer, Daichi Sankyo, Genomic Health, Pierre Fabre, MSD; all outside the submitted work. D. Rea reports personal fees and grants from Roche during the conduct of the study; personal fees from Novartis, Pfizer, Genomic Health and Daiichi-Sankyo, and grants from Celgene, all outside the submitted work. K. McAdam reports grants and personal fees from Roche, personal fees from Novartis, Pfizer, and Eisai, all outside the submitted work. P. Hall reports grants from Roche, Pfizer, AstraZeneca, Novaratis, Eisai and Daiichi-Sankyo, all outside the submitted work. D. Wheatley reports personal fees from Roche, Daichii-Sankyo and Novartis; outside the submitted work. J. E. Abraham reports fees to her institution and expenses from AstraZeneca and Pfizer; outside the submitted work. C. Caldas reports grants from Genentech, Roche, Servier and AstraZeneca all outside the submitted work; and is a Member of AZ iMED External Science Panel. D. Miles reports personal fees from Roche/Genetech, outside the submitted work. Andrew M. Wardley reports personal fees from Roche, Napp Pharmaceuticals Ltd (Cambridge, UK), Amgen, Merck Sharp & Dohme (Hoddesdon, UK), Novartis, Pfizer, AstraZeneca, Laboratoires Pierre Fabre (Paris, France), Accord (Barnstaple, UK), Athenex (Buffalo, NY, USA), Gerson Lehrman Group (New York, NY, USA), Coleman Research Expert Network Group (New York, NY, USA) and Guidepoint Global (New York, NY, USA). He also reports personal fees and other from Eli Lilly and Company (Indianapolis, IN, USA) and Daiichi Sankyo, all outside the submitted work. He is leading the National Cancer Research Institute Breast Group Initiative to develop the next de-escalation trial for HER2-positive breast cancer. David A. Cameron reports funds to his institution from Novartis, Astrazeneca, Pfizer, Roche, Eli Lilly and Company, Puma Biotechnology (Los Angeles, CA, USA), Daiichi Sankyo, Synthon (Nijmegen, the Netherlands), SeaGen International GmbH (Zug, Switzerland), Zymeworks (Vancouver, BC, Canada), Elsevier (Amsterdam, the Netherlands), European Cancer Organisation (Brussels, Belgium), Celgene Corporation, Succinct Medical Communications (Wilmington, DE, USA), Prima Biomed (Sydney, NSW, Australia), Oncolytics Biotech (U.S) Inc. (San Diego, CA, USA), Celldex Therapeutics Inc. (Hampton, NJ, USA), San Antonio Breast Cancer Consortium (TX, USA), Highfield Communication (Oxford, UK), Samsung Bioepis Co. Ltd (Incheon, South Korea), prIME Oncology, Merck Sharp & Dohme Ltd, Prima Biomed Ltd, RTI Health Solutions (Research Triangle, NC, USA) and Eisai, all outside the submitted work. Janet A. Dunn reports that she is a member of the NIHR Efficacy and Mechanism Evaluation funding board and an NIHR senior investigator.

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