

*Helena M Earl (Professor) MBBS^{1,2,3}, Anne-Laure Vallier MSc⁴, Janet Dunn (Professor) PhD⁵, Shrushma Loi BSc⁵, Emma Ogburn PhD⁵, Karen McAdam MBBS^{3,6}, Luke Hughes-Davies BMBCh^{1,3}, Adrian Harnett MBBS^{7,8}, Jean Abraham MBBS^{1,2,3}, Andrew Wardley MD⁹, David A Cameron (Professor) MD¹⁰, David Miles (Professor) MD¹¹, Ioannis Gounaris MD^{12,13}, Chris Plummer PhD¹⁴, Louise Hiller PhD.⁵

1. University of Cambridge, Department of Oncology (Box 193-R4), Addenbrooke's Hospital, Hills Road, Cambridge CB2 0QQ. UK
2. NIHR Cambridge Biomedical Research Centre and Cambridge Experimental Cancer Medicine Centre, Box 277, Hills Road, Cambridge CB2 0QQ. UK
3. Cambridge Breast Unit and Cambridge University Hospitals NHS Foundation Trust, Hills Road, Cambridge CB2 0QQ. UK
4. Cambridge Clinical Trials Unit - Cancer Theme, Cambridge University NHS Foundation Trust, Box 279 (S4), Hills Road, Cambridge CB2 0QQ, UK
5. Warwick Clinical Trials Unit, University of Warwick, Gibbet Hill Road, Coventry CV4 7AL. UK
6. Peterborough and Stamford Hospitals NHS Foundation Trust and Cambridge University Hospital NHS Foundation Trust, Peterborough City Hospital, Edith Cavell Campus, Bretton Gate, Peterborough PE3 9GZ. UK
7. Norfolk & Norwich University Hospital, Colney Lane, Norwich NR4 7UY UK
8. James Paget University Hospital, Lowestoft Rd, Gorleston-on-Sea, Great Yarmouth, Norfolk NR31 6LA. UK
9. The Christie NHS Foundation Trust, 550 Wilmslow Rd, Manchester M20 4BX. UK
10. University of Edinburgh Cancer Research Centre, IGMM, Western General Hospital, Crewe Road South, Edinburgh EH4 2XR, UK
11. Mount Vernon Cancer Centre, Rickmansworth Rd, Northwood, London HA6 2RN. UK
12. Cancer Research UK Cambridge Institute, Li Ka Shing Centre, University of Cambridge, Robinson Way, Cambridge CB2 0RE. UK.

13. The Queen Elizabeth Hospital King's Lynn NHS Foundation Trust, Gayton Rd, King's Lynn, Norfolk PE30 4ET. UK
14. Department of Cardiology, Freeman Hospital, Freeman Rd, Newcastle upon Tyne, Tyne and Wear NE7 7DN. UK

*Presenting author

ABSTRACT

TITLE: Cardiac symptoms, signs, new cardiac medication and left ventricular ejection fraction (LVEF) changes with 6 versus 12 months adjuvant trastuzumab: 2,500 patients in the Persephone Trial.

PURPOSE: We report cardiac events in the Persephone trial which compares six to twelve months adjuvant trastuzumab in women with confirmed HER2 positive, early stage breast cancer.

PATIENTS AND METHODS: Cardiac symptoms, signs and new cardiac medication were recorded and left ventricular ejection fraction (LVEF) was measured at baseline and then 3-monthly for 12 months, in both 6 and 12 month arms.

RESULTS: 2500 patients aged 22-82, were included; 1251 were randomised to 12-months and 1249 to 6-months trastuzumab. 93% (2335/2500) received anthracyclines, 49% of these (1136/2335) with taxanes. Cardiotoxicity delayed treatment in 6% of 12-month and 4% of 6-month patients ($p=0.01$), and stopped treatment early in 8% (96/1214) of 12-month and 4% (45/1216) of 6-month patients ($p<0.0001$). Between 7 and 12 months, more 12-month than 6-month patients had LVEFs $<50\%$ (8% vs 5%; $p=0.004$). LVEFs showed quadratic change over time and 6-month patients had a more rapid recovery ($p=0.02$). Twice as many 12-month patients, who were free of cardiac events at 6 months, had subsequent cardiac problems in months 7 to 12 (6% (60/1015) vs 3% (29/935) of 6-month patients

(p=0.004)). Lower baseline LVEF predicted more cardiac dysfunction in both arms when compared to a reference of $\geq 65\%$ (55-<65% OR 1.64 [95%CI 1.29-2.07]; <55% OR 5.36 [95% CI 3.53-8.14]), and increasing age when compared to <50 years old (50-59 OR 1.56 [95%CI 1.17-2.08], 60-69 OR 1.91[95%CI 1.43-2.5]), 70+ OR 2.63 [95%CI 1.76-3.91]). However, more than 3 cycles of anthracycline predicted a higher risk of cardiac toxicity in the 12-month but not the 6-month arm (OR 1.43 [95% CI 1.06-1.92] and 1.12 [0.81-1.55] respectively).

CONCLUSION: We have demonstrated significantly fewer cardiac events from 6 months adjuvant trastuzumab compared with 12 months. This cardiac signal adds importance to the question of the optimum duration of adjuvant trastuzumab treatment. If 6 months is proven to have non-inferior outcomes to 12 months treatment, these data would support 6 months as the standard of care.