OPTIMA: a prospective randomized trial to validate the predictive utility and cost-effectiveness of gene expression test-directed chemotherapy decisions in early breast cancer.

Background: Multi-parameter gene expression assays (MPAs) are widely used to estimate individual patient residual risk in hormone-sensitive HER2-negative node-negative early breast cancer, allowing patients with low risk to safely avoid chemotherapy. Evidence for MPA use in node-positive breast cancer is limited. OPTIMA (Optimal Personalised Treatment of early breast cancer usIng Multi-parameter Analysis) aims to validate MPA's as predictors of chemotherapy sensitivity in a largely node-positive breast cancer population.

Methods: OPTIMA is a partially blinded multi-center, phase 3 randomized controlled trial with an adaptive two-stage design. The main eligibility criteria are women or men aged 40 or older with resected ER-positive, HER2-negative breast cancer and up to 9 involved axillary lymph nodes. Randomization is to standard management (chemotherapy and endocrine therapy) or to MPA-directed treatment. Those with a "high risk" tumor MPA score receive standard management whilst those at "low risk" are treated with endocrine therapy alone. The preliminary phase (OPTIMA prelim) evaluated the performance of several MPAs to select a test to be used in the main efficacy trial based on economic analysis, and assessed the feasibility and acceptability of a large UK trial. OPTIMA prelim used Oncotype DX as the primary discriminator; the main trial will use Prosigna (PAM50) with Prosigna Score ≤60 defined as "low-risk". The co-primary outcomes are (1) Invasive Disease Free Survival (IDFS) and (2) cost-effectiveness of test-directed therapy. Secondary outcomes include IDFS in "low-risk" patients, quality of life and additional survival measures. An integrated qualitative recruitment study will identify and address challenges to recruitment and informed consent. Tumor blocks from all consenting participants will be banked allowing the performance of alternative MPA technologies to be evaluated. Recruitment of 4500 patients will permit demonstration of 3% non-inferiority of test-directed treatment, with 5% significance and 85% power, assuming 3 years follow-up and a control arm 5-year IDFS of at least 85%. The addition of patients from OPTIMA prelim will allow non-inferiority to be assessed with 2.5% significance.

Results: OPTIMA-prelim recruited 412 patients in 23 months from 35 sites with a 47% acceptance rate. The main study opened in January 2017. Early progress indicates that the recruitment target is achievable in the intended 46-month timescale through the participation of >100 sites

Conclusion: OPTIMA, as one of two large scale prospective trials validating the use of test-guided chemotherapy decisions in node-positive early breast cancer, is expected to have a global impact on breast cancer treatment. Experience from OPTIMA prelim showed that patient advocate support and close engagement with sites will aid trial success.

Funding: The project is funded in the UK by the NIHR HTA Programme (10/34/501). Views expressed are those of the authors and not those of the HTA Programme, NIHR, NHS or the DoH.

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