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Clinical Trial

Health related quality of life of women in TEACH, a randomised placebo controlled adjuvant trial of lapatinib in early stage Human Epidermal Growth Factor Receptor (HER2) overexpressing breast cancer ☆,☆☆

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[1] The TEACH investigators are listed in Appendix 4.

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SF-36

Summary ***Background:*** To evaluate health related quality of life (HRQOL) in TEACH, a phase III randomized placebo controlled trial of 12 months of adjuvant lapatinib in HER2 positive (HER2+) early breast cancer which demonstrated marginal benefit in disease-free survival.

Methods: Women on TEACH completed the Short Form 36-item health survey (version2; SF-36v2) at the baseline, six and 12 months after therapy initiation and six monthly thereafter. Mean changes were compared between treatment groups for two summary measures (Physical and Mental Component Summary scores; PCS and MCS) and eight domain measures (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health), and in patients discontinuing therapy. A five-point change was deemed a Minimally Clinically Important Difference (MCID). Response analysis compared the proportion of patients demonstrating a MCID in HRQOL, and a regression analysis identified predictors of worsening HRQOL.

Findings: 3074 (97%) subjects completed baseline SF-36v2. During the initial 12 months, summary SF-36v2 scores decreased in both arms but did not reach Minimally Clinically Important Difference (MCID) despite significant incidences of diarrhoea and rash in lapatinib treated patients. At six months, women receiving lapatinib had more significant reductions ($p < 0.01$ versus placebo) in social functioning. Early treatment discontinuations were more frequent on lapatinib (32% versus 18%), and were associated with more substantial decrements of HRQOL in both arms. For those discontinuing primarily due to adverse events, decrements in HRQOL reached MCID in Mental Summary scores (MCS) only. Lower baseline HRQOL was a significant predictor of worsening HRQOL ($p < 0.05$).

Interpretation: Despite frequent but usually mild toxicities, adjuvant lapatinib is not associated with clinically significant decreases in overall HRQOL. These placebo-controlled results may also help to inform physicians and patients using lapatinib in metastatic HER2 positive breast cancer.

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1. Introduction

Standard initial adjuvant treatment of Human Epidermal Growth Factor Receptor overexpressing (HER2+) breast cancer is chemotherapy, and one year of intravenous trastuzumab [1]. Without these treatments, patients with HER2+ disease have an increased risk of a disease free survival (DFS) event (relative risk RR = 2.0) and mortality (RR = 2.7) as compared to those without HER2+ disease [2,3].

Globally, many women with HER2+ tumours cannot receive trastuzumab for economic or logistic reasons [4–6] and remain at chronically elevated risk of recurrence. The TEACH trial (Tykerb®/Tyverb® Evaluation After CHemotherapy) examined the efficacy and safety of lapatinib, an oral, small molecule TKI inhibitor of EGFR and HER2, in this patient population [7,8]. In the metastatic setting lapatinib is approved for use in combination with chemotherapy, hormonal therapy and trastuzumab. Toxicities include diarrhoea, skin rash, fatigue, transient elevations of transaminases and rarely symptomatic cardiac toxicity [9,10].

In TEACH, outcomes of breast cancer showed a trend in favour of lapatinib, particularly in those with centrally confirmed HER2 positivity (Hazard Ratio (HR) for disease-free survival (DFS): 0.82; 95% confidence interval (CI): 0.67, 1.00; $p = 0.04$) and in those with hormone receptor negative disease (HR 0.68; 95% CI: 0.52, 0.89; $p = 0.006$). No additional toxicities were encountered beyond those encountered in the metastatic setting [8]. These potential benefits need to be weighed against the burden of treatment, which is potentially different with an oral agent versus injectables. We therefore compared health related quality of life (HRQOL) of lapatinib versus placebo, with the hypothesis that a mild decrement in HRQOL would be observed, due to lapatinib toxicities, particularly during the first 12 months of therapy; and that this would be reversible on cessation of therapy (Fig. 1).

2. Methods

2.1. Study design and participants

TEACH was a multi-national phase III, randomised, double blind, placebo-controlled trial of adjuvant lapatinib in clinically disease free women in follow-up for early stage HER2+ breast cancer, who had received