**A phase II/III, double-blind, randomised trial comparing maintenance lapatinib versus placebo after first line chemotherapy in HER1/2 positive metastatic bladder cancer patients.**

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**Purpose:** The purpose of this trial was to establish if maintenance lapatinib after first-line chemotherapy is beneficial in HER1/HER2 positive metastatic urothelial bladder cancer (UBC) patients.

**Method:** Patients with metastatic UBC were screened for HER1/HER2 status by centralised immunohistochemistry (IHC). HER1/2 positive screened patients, who did not have progressive disease during chemotherapy (4-8 cycles) were randomised (1:1) to lapatinib (L) or placebo (P) after completion of first line chemotherapy. The primary endpoint was progression free survival (PFS).

**Results:** Between 2007-2013, 446 UBC patients were screened and 232 HER 1 or 2 positive patients were randomised. The median PFS for L and P was 4.5 months (95% CI: 3.3 – 5.4) and 5.1 months (95% CI: 3.0 – 5.8) respectively [HR: 1.08 (95% CI: ≤1.43) p = 0.62]. The overall survival for L and P was 12.6 months (95% CI: 9.0 – 16.2) and 12.0 months (95% CI: 10.6 – 15.8) respectively [HR = 0.96 (95% CI: ≤1.31) p = 0.79]. Discontinuation due to AEs were similar in both arms (6% lapatinib and 5% placebo). The rate of grade 3-4 AEs for L and P was 8.6% vs. 8.1% (p = 0.82). Pre-planned subset analysis of i) HER1/HER2 3+ positive patients (n= 111) ii) HER1 only positive patients (n= 102) iii) HER2 only positive patients (n= 42) showed no significant benefit with lapatinib. A prognostic index from the time of completion of chemotherapy separated patients in 3 discriminatory groups for survival.

**Conclusion:** This is the first personalised randomised phase III trial in metastatic UBC. Maintenance lapatinib does not improve outcomes in HER1 or HER2 positive patients.

**Background.**

The overall survival of patients with metastatic urothelial bladder cancer (UBC), also known as transitional cell cancer (TCC) is short. Treatment for metastatic disease focuses on platinum based combination chemotherapy in the first line setting [1,2]. After chemotherapy is complete, patients have a period of observation. The vast majority of these patients relapse and die from the disease. The activity of further second line chemotherapy remains controversial, with no clear survival advantage [3].

To date, there have been no FDA approved targeted treatments in metastatic UBC, despite a number of molecular targets such as the HER family and VEGF appearing attractive pre-clinically [4-6]. Clinical studies testing these agents in unselected patients have failed to reproduce this in vivo activity [7-9]. There are three possible reasons for these disappointing results. Firstly, combining chemotherapy and targeted therapy in the UBC population, which has multiple co-morbidities, has proven difficult [7,8,10,11]. Secondly, none of the randomised trials to date have selected patients based on expression of molecular targets. Finally, UBC has a high frequency of mutations, therefore targeting only one protein may be inadequate to achieve clinical benefit [12].

To address these three issues, the UK Bladder Cancer Clinical Studies Group embarked on a phase II/III randomised trial testing single lapatinib (a HER 1 and 2 tyrosine kinase inhibitor) against placebo in HER 1 or 2 positive advanced/metastatic UBC. The drug was tested in the period after the completion of first line chemotherapy with the primary aim of delaying the progression free survival (PFS). The goal was to maintain the response to chemotherapy; hence the term maintenance therapy. Placebo was used as the control, allowing for double blinding.

Lapatinib was chosen as the study drug because it targets HER 1 and 2, both of which have been implicated in bladder cancer progression [5,6,13,14]. Preclinical and phase II data support its use in selected HER 1 or 2 positive individuals (on immunohistochemistry [IHC]) [15]. Also, as a single agent it appears well tolerated, which is important in this population where co-morbidites are common.

**MATERIALS AND METHODS**

**Methods**

**Screening phase:** Eligible patients included those with histologically confirmed advanced/metastatic TCC of the urothelial tract. A component of TCC histology was required. Archived paraffin embedded tissue was used for biomarker testing. There was no time limit on the age of the sample. Sites sent the most recent sample for testing when multiple samples were available from the same patient. Screening occurred during or after the completion of first line chemotherapy for advanced metastatic disease. Pathology samples were centrally reviewed and tested for HER 1 and 2. Positive patients were potentially eligible to participate in the trial. Baseline characteristics, treatment and outcome data was collected on the entire screened population. All patients gave informed consent for this trial which has appropriate review and ethical approval (NCT00949455).

**HER 1 and HER 2 testing:** Over expression of HER1 and HER2 was performed using IHC. IHC was performed using the standard Avidin-Biotin Complex (ABC) staining method standardised for both antibodies. The primary antibody was incubated for 1 hour as per the optimised method for each antibody (Novacastra antibodies, HER1 1:20, HER2 1:80). The immunohistochemical scoring was performed independently and blinded by a single pathologist. Expression was scored by staining intensity (0, negative; 1+, weakly positive; 2+, moderately positive; 3+, strongly positive). Only patients with 2+ or 3+ on IHC for HER1 and/or HER2 were considered to be positive and potentially eligible for the study.

**Key Eligibility Criteria:** Patients were required to have completed 4-8 cycles of chemotherapy for advanced metastatic UBC. Randomisation needed to occur at least 4 and at most 10 weeks after the completion of chemotherapy. Any recognised chemotherapy regimen for metastatic UBC was permitted. Prior adjuvant or neoadjuvant chemotherapy was not considered as first line chemotherapy. Patients with radiological progression of disease on first line chemotherapy were excluded. Adequate renal, haematological and liver function were required. Patients with a left ventricular ejection fraction (LVEF) below the normal range were excluded. Patients were required to be at least eighteen years and have resolution of chemotherapy related toxicity prior to randomisation.

**Evaluation on study:** Prior to randomisation, patient history, examination, trial related blood tests and cross sectional imaging occurred. Patients were seen on a 4 weekly basis throughout the trial. Adverse events (AEs) were graded according to version 3.0 of the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAEv3). Disease status and LVEF were assessed every 12 weeks. Response and progression were assessed by Response Evaluation Criteria in Solid Tumors (RECIST; version 1.1). No central review occurred. Patients discontinued study at progression, withdrawal of consent, unacceptable toxicity or death.

**Treatment plan:** Patients were randomly assigned in a double blind manner to lapatinib or placebo (1:1). Stratification by prior response to first-line chemotherapy (SD vs PR/CR) and ECOG performance status occurred. Lapatinib was given continuously at 1500mg once daily (6 x 250mg tablets). In the placebo group 6 visually identical tablets were given instead. Dose reductions to 5 or 4 tablets could occur. A treatment delay of 21 days was permitted due to adverse events.

**Endpoints and statistical consideration:** The primary endpoint was progression free survival (PFS) from the time of randomisation to progression or death. All randomised patients were included in the analysis (Consort diagram figure 1). Secondary endpoints included overall survival (OS), response rates, occurrence of adverse events. Exploratory analysis included outcome of subsets of HER 1 or 2 patients. Additionally, outcomes from the entire screening population was assessed to construct a prognostic index. The baseline time point for the analysis of the screening population was the date of completion of chemotherapy.

The trial followed a phase II/III design. The phase II completed after the 49th event. The subsequent phase III required approximately 221 patients for 196 events and using a single sided design with alpha = 0.025 with a power of 90% to detect an increase of 30% in progression-free survival for the treatment group compared to placebo. The duration of this PFS was assumed to be 6 months, although there was a lack of previous data to guide this estimation. An independent data monitoring committee followed the efficacy and toxicity. The IDMC made the recommendation to continue from phase II to phase III after assessment of the 49th event. Investigators and the study team remained blinded to the results of the trial throughout.

All analyses were conducted on an intention-to-treat basis. PFS and OS was compared between the study arms using the log rank test stratified by the baseline stratification factors and corresponding 95% one-sided CI were presented to align with the one-sided p-values. Significant factors in univariable Cox Proportional hazards regression analysis for OS were included into a multivariable Cox model to identify significant prognostic variables. To construct the prognostic index, significant factors on multivariable analysis were dichotomised and added together to form a prognostic index. Prognostic index was further categorised to indicate patients as low risk, medium risk or high risk depending on the presence of none, one or more than one risk factors.

**Results**

**Screening population:** Between 2007 and 2013, 446 patients were screened for HER 1 and 2 status (Table 1). Overall, 329 (74%) of patients were male and the median age was 71yrs (IQR 64-77) (Table 1). The median number of chemotherapy cycles was 6 (IQR: 4 - 6), 61% received cisplatin based chemotherapy and 48% of patients had visceral metastasis. One hundred and thirty three patients (30%) received second line chemotherapy.

The median duration from the time tissue was taken for diagnosis to screening consent was 5 months (supplementary figure 1). Archived tissue was histologically T1 in 11%, T2-3 in 64%, T4 in 22% and from nodal/metastatic sites in 3%.HER 1 and 2 positivity did not change with increasing T stage (data not shown).15% of screened patients were HER 1 and 2 negative, while 39%, 13% and 33% of patients were HER 1, HER 2 and HER 1+2 positive respectively. There was no significant difference in the PFS or OS of the HER1/2 negative and positive patients in the screened population (HR 0.87 [95% CI: 0.70-1.08] and HR 0.83 [95% CI: 0.66-1.06] respectively) (supplementary figure 2), suggesting it is not a prognostic factor.

The commonest reasons for ineligibility for randomisation were disease progression (n=52 [24%]), patient choice (n=19 [8%]) and reduced LVEF (n=41 [19%]) (see consort diagram: Figure 1).

**Characteristics and outcome of the randomised population.**

There were no significant differences in characteristics in the screened or randomised population, except randomised patients included only HER1/2 +ve patients and excluded those with progression of disease (table 1). Two hundred and thirty-two patients were randomised to lapatinib (n=116) or placebo (n=116). The median follow up was 26.62 (95% CI: 22.08 30.36) months [21]. The progression free survival for lapatinib and placebo were 4.5 months (95% CI: 3.3 – 5.4) and 5.1 months (95% CI: 3.0 – 5.8) respectively [HR: 1.08 (95% CI: ≤1.43) p = 0.62]. The overall survival for lapatinib and placebo were 12.6 months (95% CI: 9.0 – 16.2) and 12.0 months (95% CI: 10.6 – 15.8) respectively [HR = 0.96 (95% CI: ≤1.3) p = 0.79] (Figure 2a and b). The best response rate for lapatinib and placebo were 14% vs 8% (p = 0.14).

Predefined subset analysis of i) HER1/HER2 3+ positive patients on IHC (n= 111: 48%) ii) HER1 only positive patients (n=102: 44%) iii) HER2 only positive patients (n=42; 18%) showed no significant benefit in PFS (HR 0.90 [95% CI: 0.59 – 1.36 ], 0.98 [95% CI: 0.72 – 1.35] and 1.27 [95% CI: 0.87 – 1.85 ] respectively: p > 0.05 for each) or OS (HR 0.77 [95% CI: 0.48 – 1.24 ], 0.90 [95% CI: 0.63 – 1.28 ] and 1.06 [95% CI: 0.69 – 1.62 ] respectively: p > 0.05 for each) for lapatinib. Sub-grouped Forest plot analysis also failed to find a subgroup of patients who benefit from therapy (Supplementary figure 3). Patients treated with cisplatin chemotherapy (as first line treatment) did not have a better OS compared to carboplatin therapies in either the screened (HR 0.83 [95% CI: 0.65 – 1.06] or randomised population (HR = 0.86, 95% CI: 0.61-1.22).

**Dose reduction and adverse event profile:** Lapatinib dose was reduced in 17 patients (7%).Discontinuation due to AEs were similar in both arms (6% lapatinib and 5% placebo). There was no significant difference in the frequency of adverse events (AEs occurring in >10% of patients is shown in table 2). The rate of grade 3-4 AEs for L and P was 8.6% vs. 8.1% (p = 0.82).

**Prognosis of patients at the time of completion of chemotherapy**: The OS for the screened population (n=446) at the time of completion of chemotherapy was 11.7 months [95% CI: 9.9 – 12.8]. Univariable analysis was performed using the screened population at the time of completion of chemotherapy (table 3). Results showed that poor performance status (HR=1.53, 95%CI: 1.28-1.84, p<0.001) and progression with chemotherapy (HR= 4.2, 95% CI: 2.63–6.72, p<0.001) were associated with a poor overall survival. Visceral metastasis (HR=1.32 95% CI: 1.01-1.71, p=0.04) was also significant. A prognostic index incorporating these three factors was generated. Figure 3 shows the survival of the three prognostic groups within this prognostic index. The one year OS for low, medium and high risk patients were 61.2% (95% CI: 52.4-68.9), 49.1% (95% CI: 40.7-57.1) and 21.9% (95% CI: 12.7-32.6) respectively.

**Discussion**

Lapatinib was not associated with clinical benefit in patients with HER 1 and 2 positive UBC tumours. Further analysis of subsets of HER 1 or 2 positive patients did not show any clinical benefit associated with the drug, even in those tumors which expressed the highest level of the biomarker (3+ on IHC), reinforcing the lack of benefit. This study is the first randomised phase III personalised therapy trial in metastatic UBC. The trial design was novel and the phase II results with lapatinib were promising in UBC [15], justifying the study. However, our strategy was unsuccessful. There are a number of potential reasons for this. Firstly, while targeting HER proteins in isolation in breast cancer has been successful, they may not be of key importance in UBC [7,16]. Recent studies investigating trastuzumab (HER-2 antibody) with chemotherapy in UBC were also negative supporting this theory [16]. Secondly, archived paraffin embedded tissue was used to measure biomarker expression, which may not have been representative of the current biomarker status. Also cancer tissue consisted largely of tissue from the bladder which may not be representative of metastatic disease. Nevertheless, all of the subset of analyses were negative, suggesting biomarker positivity may not be the issue.

Levels of grade 3 or 4 adverse events were high in both arms. However drugs discontinuation levels were low, demonstrating that this population, which is recovering from chemotherapy, has high levels of morbidity.

The maintenance trial design in this setting was novel and remains an attractive design in UBC despite our negative result. This is due to the high initial response rates with chemotherapy balanced by the short time to relapse after it is complete (5.5 months). Indeed a new generation of immune therapy studies are using this trial design (NCT02500121).

Results from the screened population showed that HER 1 or 2 status were not prognostic. This is the most robust analysis of this issue to our knowledge, which sheds light on previously contradictory data [17,18]. It also questions the hypothesis that HER 1 or 2 is important in the oncogenic process [13,14].

The trial design allowed us to study the characteristics and outcome of unselected patients after the completion of chemotherapy, which has not been reported previously. Over half the patients received cisplatin (61%) containing regimen, and a high proportion (48%) had visceral metastasis giving some insight into the current population of patients receiving chemotherapy. Survival was short after the completion of chemotherapy, with life median expectancy of under a year. There was no significant difference in outcome when comparing cisplatin and carboplatin (HR 0.83 95% [CI:0.65-1.06]), underlining the modest differences between these agents when compared in prospective series. Also, only 30% of patients received 2nd line chemotherapy demonstrating the need to optimise first line treatment. Together these results show that the UBC population has a poor outcome even if they initially gained clinical benefit from chemotherapy, which underlines the need for new treatments in UBC [18].

Prognostic factors were also assessed in this population. Previous studies looking at prognostic factors have focused on clinical parameters prior to starting first-line therapy [19]. Our trial design allowed us to robustly analyse prognostic factors at the time of completion of chemotherapy. Results showed that radiological progression on chemotherapy, visceral metastasis, and poor performance status were associated with a poor outcome in multivariable analysis. A prognostic model consisting of these factors was constructed and discriminated patients into three clear groups. While further validation is required this information is novel and helpful to patients and their carers.

Overall, this study, with others [16], questions the further exploration of the HER 1 and 2 proteins as targets in UBC.

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**Tables**

**Table 1**. Patients’ demographics and clinical characteristics

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristics** | **Screened but not randomised (N = 214)** | **Randomised (N = 232)** | **Total (N = 446)** |
| **Lapatinib (N = 116)** | **Placebo (N = 116)** |
| **Gender, *n (%)*** | Female | 57 (26.6) | 28 (24.1) | 32 (27.6) | 117 (26.2) |
|  | Male | 157 (73.4) | 88 (75.9) | 84 (72.4) | 329 (73.8) |
| **Age (Years), *median (IQR)*** |  | 70.4 (64.7 - 77.2) | 70.7 (63.9 - 77.2) | 71.1 (63.8 - 76.3) | 70.7 (64.2 - 77.1) |
| **Performance status** | 0 | 30 (22.6) | 53 (45.7) | 52 (44.8) | 125 (35.2) |
|  | 1 | 79 (59.4) | 52 (44.8) | 51 (44.0) | 187 (52.7) |
|  | >1 | 24 (18.1) | 11 (9.5) | 13 (11.5) | 43 (12.1) |
| **Response to previous chemotherapy, *n (%)*** | CR or PR | 92 (51.1) | 80 (69.0) | 78 (67.2) | 250 (60.7) |
| SD | 36 (20.0) | 36 (31.0) | 38 (32.8) | 110 (26.7) |
| PD | 52 (28.9) | 0 (0.0) | 0 (0.0) | 52 (12.6) |
| **Tumour grade, *n (%)*** | Grade 1 or 2 | 16 (9.3) | 4 (4.0) | 4 (4.0) | 24 (6.4) |
|  | Grade 3 or 4 | 156 (90.7) | 98 (96.0) | 98 (96.1) | 352 (93.7) |
| **Visceral metastasis, *n (%)*** | Yes | 77 (46.1) | 60 (53.6) | 47 (43.1) | 214 (48.0) |
|  | No | 90 (53.9) | 52 (46.4) | 62 (56.9) | 232 (52.0) |
| **HER status, *n (%)*** | HER1 positive | 73 (34.1) | 53 (45.7) | 49 (42.2) | 175 (39.2) |
|  | HER2 positive | 18 (8.4) | 21 (18.1) | 21 (18.1) | 60 (13.5) |
|  | Both positive | 57 (26.6) | 42 (36.2) | 46 (39.7) | 145 (32.5) |
|  | HER negative | 66 (30.8) | 0 (0.0) | 0 (0.0) | 66 (14.8) |
| **Previous Cisplatin based chemotherapy, *n (%)*** | Yes | 114 (57.3) | 71 (64.0) | 73 (65.2) | 258 (61.4) |
| No | 85 (42.7) | 40 (36.0) | 39 (34.8) | 164 (38.9) |
| **Haemoglobin (g/dL)\*, *n (%)*** | Normal | 17 (9.2) | 31 (28.4) | 26 (22.4) | 74 (18.1) |
| Low | 168 (90.8) | 78 (71.6) | 90 (77.6) | 336 (81.9) |
| **Albumin (g/L)\*, *n (%)*** | Normal | 157 (88.7) | 108 (99.1) | 111 (97.4) | 376 (94.0) |
| Low | 20 (11.3) | 1 (0.9) | 3 (2.6) | 24 (6.0) |
| **Creatinine (umol/L)\*, *n (%)*** | Normal | 77 (41.9) | 49 (45.0) | 36 (31.6) | 162 (39.8) |
| High | 107 (58.1) | 60 (55.0) | 78 (68.4) | 245 (60.2) |

**Table 2**. Adverse Events

|  |  |  |
| --- | --- | --- |
| **AE type, *n(%)*** | **Lapatinib (N =97)** | **Placebo (N = 99)** |
|  | **Grade 1 - 2** | **Grade 3 - 4** | **Grade 1 - 2** | **Grade 3 - 4** |
| Anorexia | 12 (12.4) | 0 (0.0) | 7 (7.1) | 0 (0.0) |
| Constipation | 14 (14.4) | 2 (2.1) | 17 (17.2) | 1 (1.0) |
| Cough | 8 (8.2) | 0 (0.0) | 9 (9.1) | 1 (1.0) |
| Diarrhoea | 59 (60.8) | 6 (6.2) | 22 (22.2) | 1 (1.0) |
| Fatigue | 34 (35.1) | 4 (4.1) | 41 (41.4) | 1 (1.0) |
| Infection | 26 (26.8) | 5 (5.2) | 14 (14.1) | 4 (4.0) |
| Itch | 12 (12.4) | 0 (0.0) | 11 (11.1) | 1 (1.0) |
| Nausea | 22 (22.7) | 1 (1.0) | 19 (19.2) | 1 (1.0) |
| Neuropathy | 7 (7.2) | 0 (0.0) | 13 (13.1) | 1 (1.0) |
| Pain | 37 (38.1) | 10 (10.3) | 41 (41.4) | 6 (6.1) |
| Rash | 43 (44.3) | 2 (2.1) | 21 (21.2) | 0 (0.0) |
| Shortness of breath | 12 (12.4) | 0 (0.0) | 7 (7.1) | 3 (3.0) |
| Vomiting | 15 (15.5) | 3 (3.1) | 15 (15.2) | 1 (1.0) |

**Table 2. Number of Patients by treatment arm, AE type and grade.** Most common adverse events graded according to CTCAE v3.0. Data was inadequately recorded or missing on 36 patients, equally balanced from both arms.

**Table 3**. Univariable analysis for prognostic factors at the time of completion of chemotherapy.

**Table 3:** Univariable Analysis

|  |  |  |  |
| --- | --- | --- | --- |
|   | **PFS**  |  | **OS** |
| **N** | **Events** | **HR** | **95% CI** | **P-value** |  | **N** | **Events** | **HR** | **95% CI** | **P-value** |
| **Age (Years)** | 353 | 313 | 0.99 | 0.98 - 1.01 | 0.31 |   | 393 | 313 | 1.00 | 0.99 - 1.01 | 0.87 |
| **Gender** |   |   |   |   |   |   |   |   |   |   |   |
|  Female | 101 | 92 | 1 | - | - |   | 106 | 93 | 1 | - | - |
|  Male | 252 | 221 | 0.82 | 0.64 - 1.05 | 0.12 |   | 287 | 220 | 0.82 | 0.65 - 1.05 | 0.12 |
| **ECOG Performance status** | 310 | 274 | 1.25 | 1.06 - 1.48 | 0.01 |   | 336 | 261 | 1.55 | 1.32 - 1.83 | <0.001 |
| **HER status** |   |   |   |   |   |   |   |   |   |   |   |
|  HER negative | 44 | 41 | 1 | - | - |   | 47 | 43 | 1 |   |   |
|  HER1 positive | 141 | 121 | 1.21 | 0.85 - 1.72 | 0.30 |   | 158 | 125 | 1.07 | 0.75 - 1.51 | 0.72 |
|  HER2 positive | 53 | 48 | 1.25 | 0.82 - 1.90 | 0.29 |   | 58 | 48 | 0.90 | 0.59 - 1.36 | 0.62 |
|  Both positive | 115 | 103 | 1.00 | 0.70 - 1.44 | 0.99 |   | 130 | 97 | 0.84 | 0.59 - 1.21 | 0.36 |
| **Visceral metastasis** |   |   |   |   |   |   |   |   |   |   |   |
|  No | 176 | 151 | 1 | - | - |   | 184 | 137 | 1 | - | - |
|  Yes | 146 | 133 | 1.27 | 1.01 - 1.61 | 0.044 |   | 169 | 140 | 1.44 | 1.14 - 1.83 | 0.002 |
| **Response to previous chemotherapy** |   |   |   |   |   |   |   |   |   |   |   |
|  CR or PR | 235 | 209 | 1 | - | - |   | 230 | 184 | 1 | - | - |
|  SD | 110 | 98 | 1.03 | 0.81 - 1.31 | 0.83 |   | 109 | 78 | 0.94 | 0.72 - 1.23 | 0.67 |
|  PD | - | - | - | - | - |  | 47 | 46 | 3.06 | 2.20 - 4.26 | <0.001 |
| **Tumour grade** |   |   |   |   |   |   |   |   |   |   |   |
|  1 and 2 | 16 | 13 | 1 | - | - |   | 21 | 15 | 1 | - | - |
|  3 and 4 | 290 | 257 | 1.10 | 0.63 - 1.92 | 0.75 |   | 318 | 253 | 1.31 | 0.78 - 2.20 | 0.32 |
| **Previous Cisplatin based chemotherapy** |   |   |   |   |   |   |   |   |   |   |   |
|  No | 137 | 126 | 1 | - | - |   | 148 | 122 | 1 | - | - |
|  Yes | 206 | 177 | 0.81 | 0.65 - 1.02 | 0.07 |   | 235 | 183 | 0.81 | 0.64 - 1.02 | 0.07 |
| **Haemoglobin (g/dL)** | 337 | 298 | 1.00 | 0.99 - 1.01 | 0.75 |   | 374 | 296 | 1.00 | 0.99 - 1.01 | 0.64 |
| **Albumin (g/L)** | 331 | 293 | 0.97 | 0.94 - 0.99 | 0.01 |   | 366 | 289 | 0.92 | 0.89 - 0.94 | <0.001 |
| **Creatinine (umol/L)** | 334 | 295 | 0.998 | 0.996 - 1.001 | 0.153 |   | 371 | 293 | 0.998 | 0.996 - 1.001 | 0.158 |

**Figures:**

**Figure 1.** Consort diagram: Overview of screened and randomised patients.

Allocated to lapatinib (n=116)

Excluded (n=214)

* Disease progression (n=52)
* Declined to participate (n=19)
* HER1/HER2 negative (n=42)
* Reduced LVEF (n=41)
* Other reasons (n=37)
* Unknown (n=23)

Screened (n=446)

## Analysis

## Follow-Up

## Enrollment

Randomised (n=232)

## Allocation

Allocated to placebo (n=116)

Analysed (n=116)

* Lost to follow-up (n=0)

Discontinued intervention

* Progression (n=83)
* Adverse events (n=5)
* Death (n=5)
* Patient choice (n=5)
* Other (n=18)
* Lost to follow-up (n=0)

Discontinued intervention

* Progression (n=82)
* Adverse events (n=7)
* Death (n=3)
* Patient choice (n=7)
* Other (n=17)

Analysed (n=116)

**Figure 2.** Comparison of outcomes for the randomised population using the Kaplan Meier method

a)



**Figure 2a**. Kaplan-Meier analysis for PFS: the primary endpoint [HR: 1.07 (95% CI: 0.81-1.43), p=0.63

b)



**Figure 2b**. Kaplan-Meier analysis for OS: the secondary endpoint [HR: 0.96 (95% CI: 0.70-1.31), p=0.79]

**Figure 3.** Prognostic index predicting outcome from the time of chemotherapy completion.



**Figure 3.** The last day of chemotherapy was considered the start date for data analysis. OS was the chosen endpoint. Factors associated with a poor outcome on Multivariable analysis were included in the prognostic model: low PS, progression of disease on chemotherapy and presence of visceral metastasis were all allocated 1 point. Three groups (low risk =none, medium risk= 1 factor, and high risk= more than one factor were formed).

**Supplementary data:**

**Supplementary Figure 1.**



**Supplementary Figure 1.** Time from tissue collection (archived FPPE tissue) to screening.

**Supplementary Figure 2.** Kaplan-Meier overall survival curve by HER status from completion of chemotherapy.



**Supplementary Figure 3**. Sub-grouped Forest plot analysis for PFS.



**Favouring Placebo**

**Favouring Lapatinib**

**Supplementary Figure 3**. Results on the left of the curve favour Lapatinib. Results on the right favour placebo.