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Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Baselga J, Bradbury I, Eidtmann H, et al, on behalf of the NeoALTTO Study Team. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2012; published online Jan 17. DOI:10.1016/S0140-6736(11)61847-3.

Supplementary Appendix (Baselga et al. for the NeoALTTO Study Team)

Section 1: Neo-ALTTO Collaborative Group Participants (in alphabetic order)

BrEAST (Breast European Adjuvant Studies Team); FNCLCC (Fédération Nationale des Centres de Lutte Contre le Cancer); GBECAM (Grupo Brasileiro de Estudos do Câncer de Mama); GBG (German Breast Group); GECO PERU (Grupo de Estudios Clínicos Oncológicos del Perú); German ALTTO (AGO BREAST (Arbeitsgemeinschaft Gynäkologische Onkologie); IBCSG (International Breast Cancer Study Group); KCSG (Korean Cancer Study Group)

NBCG (Norsk Bryst Cancer Gruppe); NCIC-CTG (National Cancer Institute of Canada - Clinical Trials Group); NOGGO (Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie); SOLTI (Solid Tumor Intensification); SUCCESS; TCOG (Taiwan Cooperative Oncology Group); WSG (West German Study Group) and Independent sites.

Section 2.: NeoALTTO Study design (Figure A1)

Doses and schedules of pre-surgery lapatinib, trastuzumab and paclitaxel are described in the text. Post-surgery chemotherapy consisted of three 21-day cycles of FEC chemotherapy [5-fluorouracil (500 mg/m^2 given on day 1), epirubicin (100 mg/m^2 given on day 1) and cyclophosphamide (500 mg/m^2 given on day 1)]. Doses and schedules of anti-HER2 therapy administered for 34 weeks following chemotherapy were 1500 mg per day for lapatinib alone, a loading dose of 8 mg/kg infused over a 90 minute period with subsequent doses of 6 mg/kg infused over a 30 minute period every three weeks for trastuzumab alone, and the same schedule of trastuzumab as described above plus 1000 mg daily of lapatinib for the combination arm.

Section 3: Study Agents' Dose Modification Algorithms

During the administration of lapatinib if non haematological grade 3-4 toxic effects occurred and it was deemed consistent with previously observed lapatinib adverse events, lapatinib could be withheld for a maximum of 14 days and until recovery to grade 1 or lower. In patients receiving paclitaxel and lapatinib in combination, if diarrhoea grade 3-4 occurred, supportive measures were implemented and both therapies were withheld until recovery to grade 2. If grade 2 toxicity persisted the dose of paclitaxel was reduced by 20% and if it persisted further, lapatinib (and paclitaxel if toxicity ≥3) administration was discontinued. In case of abnormal liver function, grade ≥3 ALT/AST or bilirubin, or grade 2 for both ALT and bilirubin, lapatinib was permanently discontinued. Lapatinib was also discontinued in cases with persistent grade 2 ALT or bilirubin and dose was reduced for patients with persistent grade 1 ALT /AST or bilirubin. The criteria for abnormal liver function were not applied to trastuzumab. If non haematological grade 3 or 4 toxic effects occurred, trastuzumab was temporarily held until recovery to grade 2 or lower. If non haematological grade 3 or 4 toxic effects occurred upon re-challenge, then trastuzumab was permanently discontinued.

Treatment with trastuzumab, lapatinib or both was to be permanently stopped if a patient developed severe symptomatic congestive heart failure and a drop in left ventricular ejection fraction (LVEF) of more than 10 points from baseline and to below 50% or in cases of a drop in LVEF of more than 10 points from baseline and to below 50, confirmed by a second LVEF assessment after holding treatment for approximately three weeks. An algorithm for discontinuation of lapatinib and/or trastuzumab based on interval LVEF assessments was implemented.

Section 4:: Table A1. Characteristics of Cardiac Adverse Events, including Decreased Left Ventricular Ejection Fraction, occurring during Neoadjuvant Treatment

	Lapatinib (N=154)	Trastuzumab (N=149)	Lapatinib + Trastuzumab (N = 152)
Cardiac Adverse Events of Special Interest[a]			
Subjects with Events, n (%)	1 (0.6%)	2 (1.3%)	4 (2.6%)
Number of Events	1	2	4
Event Characteristics, n			
Serious	0	0	0
Considered to be treatment related	1	2	3
Leading to withdrawal of study medication	0	0	0
Fatal	0	0	0
Maximum Severity, n (%)			
Grade 1	1 (0.6%)	1 (0.7%)	2 (1.3%)
Grade 2	0	1 (0.7%)	1 (0.6%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Missing	0	0	1
Outcome, n			
Recovered/resolved	1	2	2
Recovering/resolving	0	0	0
Recovered/resolved with sequelae	0	0	1
Not recovered/resolved	0	0	0
Fatal	0	0	0
Missing	0	0	1
Action Taken, n			
Study treatment withdrawn	0	0	0
Dose reduced	1	0	0
Dose not changed	0	1	1
Dose delayed/interrupted	0	1	2
Missing	0	0	1
Time of Onset (Days since start of treatment)			
Mean (standard deviation)	81.0 (-)	84.0 (59.4)	81.3 (40.3)
Median (range)	81 (-)	84 (42, 126)	77 (39, 133)
Duration Days			
Mean (standard deviation)	12.0 (-)	105.5 (67.2)	105.0 (152.6)
Median (range)	12 (-)	106 (58, 153)	25 (9, 281)

Other Cardiac Adverse Events[b]			
Subjects with Events, n (%)	8 (5.2%)	6 (4.0%)	8 (5.3%)
Number of Events	8	6	10
Event Characteristics, n			
Serious	0	0	0
Considered to be treatment related	5	4	6
Leading to withdrawal of study medication	0	0	0
Fatal	0	0	0
Maximum Severity, n (%)			
Grade 1	4 (2.6%)	4 (2.7%)	7 (4.6%)
Grade 2	4 (2.6%)	2 (1.3%)	1 (0.7%)
Grade 3	0	0	0
Grade 4	0	0	0
Grade 5	0	0	0
Missing	0	0	0
Outcome, n			
Recovered/resolved	7	5	8
Recovering/resolving	0	0	0
Recovered/resolved with sequelae	0	0	0
Not recovered/resolved	0	0	0
Fatal	0	0	0
Missing	1	1	2
Action Taken, n			
Study treatment withdrawn	0	0	0
Dose reduced	0	0	0
Dose not changed	7	5	10
Dose delayed/interrupted	0	1	0
Missing	1	0	0
Time of Onset (Days since start of treatment)			
Mean (standard deviation)	69.1 (48.3)	74.7 (62.6)	80.2 (15.4)
Median (range)	64 (4, 140))	83 (1, 146)	74 (60, 105)
Duration Days			
Mean (standard deviation)	20.3 (24.4)	43.6 (61.9)	25.4 (35.4)
Median (range)	8 (2, 64)	11 (1, 146)	11 (1, 96)

Notes:

i) Percentages are of numbers in the arm. ITT population used.

a) Includes Adverse Events with the following preferred terms: 'ejection fraction decreased', 'cardiac failure congestive', 'myocardial ischaemia'

b) Includes all other Adverse Events with body system class 'cardiac disorders'

Section 5: Dose Reductions of Study Agents

One-hundred and nine patients (70·8%) in the lapatinib-alone arm and 65 patients (42·8%) in the combination arm completed lapatinib without dose reductions. The majority of the remaining patients had one dose reduction (26 (16·9%) vs. 81 (53·3%) in lapatinib-alone and lapatinib plus trastuzumab, respectively). Eighty-six patients (55·8%) in the lapatinib-alone arm and 94 patients (61·8%) in the lapatinib plus trastuzumab arm experienced no delays in dosing with lapatinib.

There were no reductions in paclitaxel dose. Sixty-seven patients (43·5%) in the lapatinib-alone arm, 103 (69·1%) in the trastuzumab-alone arm, and 84 (55·3%) in the combination arm completed paclitaxel treatment without any dose delays. The majority of patients experienced only one delay: 47 (30·5%) in the lapatinib-alone arm, 29 (19·5%) in the trastuzumab-alone arm, and 35 (23·0%) in the combination arm. The median dose of paclitaxel received per patient (mg/m2) was 880 in the lapatinib arm, 960 in the trastuzumab-alone arm and 960 in the combination arm

Ninety-eight patients (65·8%) in the trastuzumab-alone arm and 90 (59·2%) in the combination arm completed trastuzumab dosing with no delays. Disease progression while on therapy resulted in treatment discontinuation for eight patients; three in the lapatinib-alone arm, four in the trastuzumab-alone arm, and one in the lapatinib plus trastuzumab arm. Of these eight patients, one in the lapatinib-alone arm received no paclitaxel, one each in the trastuzumab-alone and in the lapatinib plus trastuzumab arms received one dose of paclitaxel, and the remaining five patients received two or more doses of paclitaxel.

Section 6: Pathological Complete Response (pCR) Rates for Subgroups

Table A2: Proportion of Patients in ITT Population with Pathological Complete Response (pCR) at the Time of Surgery, Split by Clinical Lymph Node Status at Baseline

Lymph Node status N0/1 at Baseline	Lapatinib	Trastuzumab	Lapatinib + Trastuzumab
Number of Patients [N]	129	126	128
Number of Patients with pCR [r]	31	36	64
Rate of pCR [r/N]	24·03%	28·57%	50·00%
Exact 95% CI for pCR Rate	(16·95%, 32·34%)	(20·88%, 37·30%)	(41·04%, 58·96%)
Binomial p-value: comparisons vs.trastuzumab	0·4102		0·0005
Difference vs. trastuzumab and Exact 97·5% CI	-4·54% (-18·6%, 9·35%)		21·43% (7·67%, 35·01%)

Lymph Node status N2+, Nx or missing at Baseline	Lapatinib	Trastuzumab	Lapatinib + Trastuzumab
Number of Patients [N]	25	23	24
Number of Patients with pCR [r]	7	8	14
Rate of pCR [r/N]	28·00%	34·78%	58·33%
Exact 95% CI for pCR Rate	(12·07%, 49·39%)	(16·38%, 57·27%)	(36·64%, 77·89%)
Binomial p-value: comparisons vs. trastuzumab	0·6125		0·1058
Difference vs.trastuzumab and Exact 97·5% CI	-6·78% (-37·3%, 25·72%)		23·55% (-9·98%, 53·86%)

Table A3: Proportion of Patients in ITT Population with Pathological Complete Response (pCR) at the Time of Surgery, Split by Surgery Planned at Baseline

Non-conservative surgery planned (or non-operable) at baseline	Lapatinib	Trastuzumab	Lapatinib + Trastuzumab
Number of Patients [N]	107	112	106
Number of Patients with pCR [r]	28	33	52
Rate of pCR [r/N]	26·17%	29·46%	49·06%
Exact 95% CI for pCR Rate	(18·15%, 35·55%)	(21·23%, 38·82%)	(39·22%, 58·95%)
Binomial p-value: comparisons vs. trastuzumab	0·5865		0·0030
Difference vs.trastuzumab and Exact 97·5% CI	-3·30% (-18·4%, 11·89%)		19·59% (4·43%, 34·17%)

Conservative surgery planned at baseline	Lapatinib	Trastuzumab	Lapatinib + Trastuzumab
Number of Patients [N]	47	37	46
Number of Patients with pCR [r]	10	11	26
Rate of pCR [r/N]	21·28%	29·73%	56·52%
Exact 95% CI for pCR Rate	(10·70%, 35·66%)	(15·87%, 46·98%)	(41·11%, 71·07%)
Binomial p-value: comparisons vs. trastuzumab	0·3744		0·0147
Difference vs. trastuzumab and Exact 97·5% CI	-8·45% (-32·3%, 15·94%)		26·79% (1·90%, 49·06%)

NeoALTTO Study Design