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EPHOS-B Combined peri-operative lapatinib and trastuzumab in early HER2-positive breast cancer – Long term results of the randomized UK EPHOS-B

Nigel Bundred[1], Nuria Porta[2], Adrian Murray Brunt[3], Angela Cramer[4], Andrew Hanby[5], Abeer M Shaaban[6], Emad A Rakha[7], Anne Armstrong[8], Ramsay I Cutress[9], David Dodwell[10], Marie A Emson[2], Abigail Evans[11], Sue M Hartup[12], Kieran Horgan[12], Stuart A McIntosh[13], Jay Naik[14], Sankaran Narayanan[15], Jane Ooi[16], Anthony I Skene[17], David A Cameron[18]*, Judith M Bliss[2]*

Background

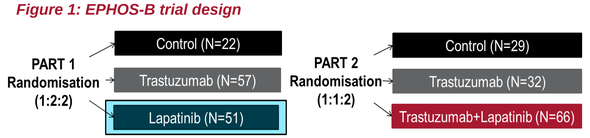
- EPHOS-B is a multi-centre randomized trial designed to investigate whether anti-HER2 therapy given 11 days pre-surgery inhibited proliferation and/or increased apoptosis in HER2-positive early breast cancer.
- Significant differences in Ki67 response (≥30% fall between baseline and surgery) were observed between treatment groups and control, although no significant increases in apoptosis were seen [1].
- We report here 5-year outcomes and their association with peri-operative response, including post-hoc exploratory analyses on stromal tumour infiltrating lymphocytes (TILs).

[1] Bundred N, Cameron D, Amstrong A et al (2016) Effects of perioperative lapatinib and trastuzumab, alone and in combination, in early HER2+ breast cancer − the UK EPHOS-B trial (CRUK/08/002) European Journal of Cancer;57:S1-S8.

Methods

- **Trial design:** In Part 1 patients were randomized (1:2:2) to no perioperative treatment (control), trastuzumab only or lapatinib only. Emerging evidence on the efficacy and safety of combination anti-HER2 therapy led to Part 2 in which patients were allocated to control, perioperative trastuzumab only or lapatinib and trastuzumab (1:1:2). Overall 257 patients were randomised, Part 1=130 (Nov-10 to Jul-13); Part 2=127 (Aug-13 to Sep-15).

Figure 1: EPHOS-B trial design



- **Eligibility: N**ewly diagnosed women with HER2-positive invasive breast cancer due to undergo surgery; LVEF≥55% was required for trial entry.
- **Treatment:** Treatment started 11 days(+2/-1) before scheduled surgery: trastuzumab: iv days 1&8 (6mg/kg) and 15-19 (2mg/kg); lapatinib: orally for 28 days (Part-1: 1500mg/day, Part-2: 1000mg/day). Adjuvant treatment as per local practice.
- **Follow-up:** Every 6 months for 2 years, then annually.

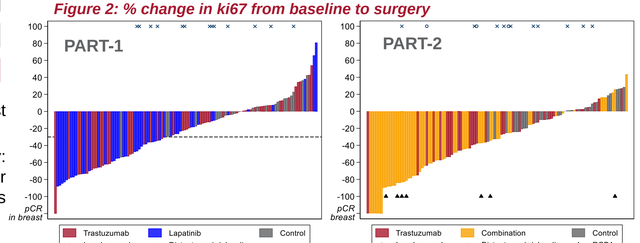
Endpoints and Statistical Analysis

- Central pathology review of cases with evidence of tumour regression calculated Residual Cancer Burden (RCB) class (RCB0[pCR], RCB1 [minimal]; RCB2/3 [moderate or extensive]). Cases without evidence of tumour regression were considered RCB2/3.
- Relapse free survival (RFS) is defined from randomisation to local, regional, or distant tumour recurrence or death from any cause, with second primary cancers censored. Five-year RFS rates were estimated by Kaplan-Meier across groups defined by treatment, and by peri-operative changes in ki67: %reduction (>50%, 10-50% or <10%/no fall); or absolute change (from high[≥10%] or low[<10%] ki67 at baseline to high/low at surgery. For these analysis, patients with pCR were included assuming ki67=0% at surgery.
- Central scoring of TILs on scanned H&E baseline and surgery slides was conducted post-hoc according to the International TILs Working Group. Baseline TILs (bTILS) [low ≤20%, high >20%] were explored across treatment groups, and associated with trial outcomes. Changes in TILS in patients without pathological regression were also correlated with RFS.

Results

- 257 pts randomised, 223/257 for primary endpoint, 231/257 for association ki7 with RFS. 67% ER-positive, median tumour size of 2.2cm
- As previously reported [1], Ki67 response (≥30% fall) was: Part-1 66%L, 37%T, 5%C (P_{LVT}=0.007, P_{LVC}<0.0001), while in Part-2 74%T+L, 45%T, 7%C (P_{T+LVT}=0.02, P_{T+LVC}<0.0001).

Figure 2: % change in ki67 from baseline to surgery



- Central pathology review identified 6 patients achieving complete pathological response (pCR), and 13 RCB1 (as per the Residual Cancer Burden score), all but two in the combination group.
- After median 6 years (IQR 5.2 – 7.4) follow-up, 28 women (11%) had breast cancer recurrence and 19 patients died (all but one due to breast cancer following recurrence). No treatment differences in RFS were found, except for T+L (5y-RFS 92% [95%CI 89-97]) with improved RFS compared to T alone (5y-RFS 87% [67-95%]),but only marginally significant (p=0.046).
- No recurrences observed amongst 6 pCR patients; only 1 local recurrence amongst RCB1 (5y-RFS 92% [67-95%] for 90%[85-93] in RCB2/3).
- For patients with ≥50%ki67 reductions, only 2/72 local recurrences (one followed by distant recurrence) were observed; 17/77 events in the group with 10-50% reductions (15 distant recurrences, 2 local only) and 7/82 events (6 distant, 1 local only) in the group with no relevant reduction; RFS was significantly different between the 3 groups (P=0.002, Figure 3), even in the presence of other prognostic factors. Only treatment seems to drive ki67 ≥50% reductions at surgery (Table 1).
- Most tumours were highly proliferative at baseline (>10% ki67, 98%); those 18% with low values at surgery ("High-Low"+"Low-Low") had better RFS outcome than those with "High" levels still (p=0.04, Figure 3). In RCB2/3 patients, achieving lower TILs at surgery indicated better outcome (Table 2).

Figure 3: RFS Kaplan Meier curves by ki67 perioperative changes

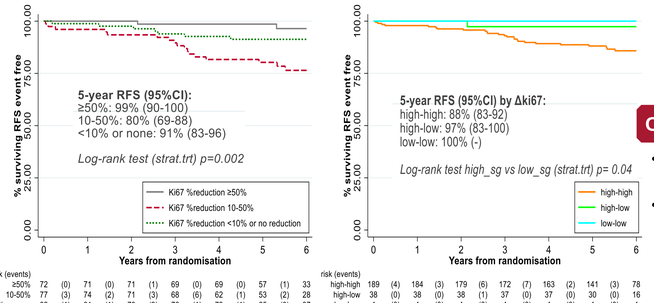


Table 1. Factors associated with Ki67 falls >50%

		Resp / N	Univariate Odds Ratio	Univariate 95% CI	Univariate p-value	Multivariable - full Odds Ratio	Multivariable - full 95% CI	Multivariable - full p-value
Treatment	No treatment	1/48		1 (ref)			1 (ref)	
	Treatment	67/164	32.46	4.37, 241.08	0.001	36.77	4.87, 277.86	<0.001
ER status	-ve	19/66		1 (ref)			1 (ref)	
	+ve	49/146	1.25	0.66, 2.36	0.49	0.88	0.35, 2.19	0.78
PgR status	-ve	28/100		1 (ref)			1 (ref)	
	+ve	27/81	1.29	0.68, 2.43	LR test	1.07	0.43, 2.65	LR test
	Missing	13/31	1.86	0.81, 4.29	0.34	1.44	0.51, 4.11	0.76
Grade*	1-2	38/93		1 (ref)			1 (ref)	
	3	30/119	0.69	0.46, 1.04	0.080	0.45	0.22, 0.91	0.027
Size	≤2cm	40/123		1 (ref)			1 (ref)	
	>2cm	28/89	0.95	0.53, 1.71	0.87	0.81	0.42, 1.54	0.51
Age		68/212	0.99	0.97, 1.02	0.69	1.00	0.97, 1.04	0.88
BL Ki67		68/212	0.99	0.97, 1.01	0.27	1.00	0.98, 1.02	0.99
HER2		68/212	1.04	0.98, 1.12	0.16	1.05	0.98, 1.13	0.19

Table 2. RFS by TILs at baseline and at surgery

	N	RFS event	5-year RFS	95%CI	Log-rank p-value
Baseline TILS					
<=20%	180	23 (13%)	89%	83-93	0.10
>20%	50	2 (4%)	96%	85-99	
Surgery TILS (only RCB2/3)					
<=20%	122	20 (16.4%)	86%	78-91	0.021
>20%	65	3 (4.6%)	95%	86-98	
Change in TILS (only RCB2/3)					
No significant increase	152	21 (13.8%)	88%	81-92	0.16
Increase >20%	35	2 (5.7%)	94%	79-99	

Conclusions

- After 6 years median follow-up, less recurrences were observed in patients with perioperative falls in Ki67% of 50% or more.
- Early response (pCR/RCB1 or Ki67 reductions >50%) after 11 days pre-operative anti-HER2 dual therapy identifies cancers dependent on the HER2 pathway and provides a strategy for individualising treatment, including de-escalation of therapy. .

Contact

Prof. Nigel Bundred
Academic Surgery, Education and Research Centre
Wythenshawe Hospital
Southmoor Road, Manchester, M23 9LT
Email: ephos-b-icrctsu@icr.ac.uk; Twitter: @ICR_CTSU
Web page: http://www.icr.ac.uk/our-research/our-research-centres/clinical-trials-and-statistics-unit

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Affiliations

[1]Manchester University NHS Foundation Trust and University of Manchester, UK; [2]The Institute of Cancer Research, Clinical Trials and Statistics Unit, London, UK; [3]University Hospitals of North Midlands and Keele University, UK; [4]The Christie Pathology Partnership, Manchester, UK; [5]Leeds Institute of Medical Research at St. James's, UK; [6]Queen Elizabeth Hospital Birmingham and University of Birmingham, UK; [7]University of Nottingham, Nottingham UK [8]The Christie NHS Foundation Trust, Manchester, UK; [9]University of Southampton and University Hospital Southampton, UK; [10]Nuffield Department of Population Health, University of Oxford, UK; [11]Poole Hospital NHS Foundation Trust, UK; [12]St James's University Hospital Leeds, UK; [13]Queen's University Belfast, Belfast, United Kingdom; [14]Mid Yorkshire NHS Hospitals Trust, UK; [15]University Hospitals of North Midlands, UK; [16]Royal Bolton Hospital, UK; [17]University of Southampton, UK; [18]University of Edinburgh Cancer Research Centre, Institute of Genetics and Cancer, Western General Hospital, Edinburgh, UK.
*Joint senior authors