

## Supplementary appendix

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

Supplement to: Earl HM, Hiller L, Dunn JA, et al, for the ARTemis Investigators. Efficacy of neoadjuvant bevacizumab added to docetaxel followed by fluorouracil, epirubicin, and cyclophosphamide, for women with HER2-negative early breast cancer (ARTemis): an open-label, randomised, phase 3 trial. *Lancet Oncol* 2015; published online May 12. [http://dx.doi.org/10.1016/S1470-2045\(15\)70137-3](http://dx.doi.org/10.1016/S1470-2045(15)70137-3).

## Earl et al. Web Extra Material.

**Supplementary Table 1: Reasons for 53 patients not having Bev administered for four cycles**

Reasons	N patients
Allergic reaction to Docetaxel. Switched to FEC early.	11
Wound complications /infection.	10
Hypertension	9
Chemotherapy toxicity (withdrew from trial or switched to FEC)	6
Progression / no change – decision to switch to FEC or to surgery	5
Bleeding	5
Veno-Thromboembolism (VTE)	3
Cardiac symptoms	2
MRI head-meningioma; patient withdrew from trial	1
Allergic reaction to bevacizumab	1

**Supplementary Table 2(A): N; Median (IQR) chemotherapy cycle dose intensities**

Cycle	Randomised treatment arm			
	D → FEC		Bev+D → FEC	
	N	Median (IQR)	N	Median (IQR)
1	391	99 (97-101)	384	99 (95-101)
2	385	99 (96-101)	372	99 (94-101)
3	375	99 (94-101)	366	99 (91-101)
4	368	99 (96-101)	363	99 (97-101)
5	363	99 (96-101)	356	99 (96-101)
6	352	99 (97-101)	343	99 (97-101)

**Supplementary Table 2(B): N; Median (IQR) bevacizumab dose intensities**

Cycle	Bev+D → FEC	
	N	Median (IQR)
1	383*	100 (97-101)
2	360	100 (98-102)
3	346	100 (98-102)
4	337	100 (98-101)

\* 1 patient omitted cycle 1 bevacizumab due to dental problems. Continued with protocol stated bevacizumab in cycles 2-4.

**Supplementary Table 3(A): Chemotherapy modifications in the 4418 cycles**

Cycle	Randomised treatment arm			
	D → FEC		Bev+D → FEC	
	N (%) dose reductions	N (%) treatment delays	N (%) dose reductions	N (%) treatment delays
1	6 (2)	18 (5)	4 (1)	11 (3)
2	48 (12)	38 (10)	60 (16)	42 (11)
3	60 (16)	18 (5)	65 (18)	22 (6)
4	9 (2)	21 (6)	15 (4)	18 (5)
5	26 (7)	46 (13)	36 (10)	37 (10)
6	30 (9)	38 (11)	27 (8)	21 (6)

**Supplementary Table 3(B): Bevacizumab modifications in the 1426 cycles**

Cycle	Bev+D → FEC	
	N (%) not given as per protocol	N (%) treatment delays
1	6 (2)	11 (3)
2	7 (2)	31 (9)
3	3 (<1)	17 (5)
4	2 (<1)	14 (4)

**Supplementary Table 4: GCSF administrations in the 4418 cycles**

Cycle	Randomised treatment arm	
	D → FEC N (%)	Bev+D → FEC N (%)
1	195 (50)	209 (54)
2	228 (59)	253 (68)
3	237 (63)	270 (74)
4	195 (53)	238 (66)
5	218 (60)	245 (69)
6	212 (60)	244 (71)

**Supplementary Table 5: Reported Toxicities of grade 1/2 in the 4418 cycles by the 775 patients**

Toxicity	Randomised treatment arm			
	D → FEC		Bev+D → FEC	
	N (%) cycles	N (%) patients	N (%) cycles	N (%) patients
Neutropenia	76 (3%)	62 (16%)	61 (3%)	51 (13%)
Infection	222 (10%)	141 (36%)	208 (10%)	129 (34%)
Fatigue	1464 (66%)	359 (92%)	1409 (65%)	351 (91%)
Diarrhoea	408 (18%)	203 (52%)	396 (18%)	208 (54%)
Nausea	852 (38%)	306 (78%)	731 (33%)	294 (77%)
Vomiting	223 (10%)	129 (33%)	240 (11%)	145 (38%)
Hypertension	60 (3%)	36 (9%)	92 (4%)	50 (13%)
Constipation	560 (25%)	243 (62%)	564 (26%)	231 (60%)
Peripheral Neuropathy	464 (21%)	199 (51%)	497 (23%)	201 (52%)
Proteinuria	11 (<1%)	10 (3%)	83 (4%)	53 (14%)
Alopecia	1758 (79%)	365 (93%)	1726 (79%)	352 (92%)

**Supplementary Table 6: Mastectomy rates across randomised treatment arms**

	D→FEC	Bev+D→FEC	p
Mastectomy	192 (51%)	185 (48%)	0.47
No mastectomy	186 (49%)	201 (52%)	
Overall	378	386	

**Supplementary Table 7: Mastectomy rates split by response to neo-adjuvant therapy**

	Mastectomy	No Mastectomy	p
pCR in all breast tumours AND absence of disease in all removed ax LNs	42 (29%)	104 (71%)	<0.0001
No pCR	335 (54%)	283 (46%)	
Overall	377 (49%)	387 (51%)	
pCR or MRD in all breast tumours	90 (37%)	153 (63%)	<0.0001
No pCR/MRD	287 (55%)	235 (45%)	
Overall	377 (49%)	388 (51%)	

**Supplementary Table 8: Summary of Neoadjuvant Chemotherapy Breast Cancer Trials with Bevacizumab**

STUDY	Treatments	pCR definition	HR+ definition	All patients Bev v No Bev			TN only Bev v No Bev			HR+ only Bev v No Bev			Interaction p
				N	%pCR	OR (p)	N	%pCR	OR (p)	N	%pCR	OR (p)	
GeparQuinto	ECx4-Tx4 +/- Bev 15mg/kg	ypT0 ypN0	10% cells +ve for either ER or PgR	1948	18.4% v 14.9%	1.29 (p=0.04)	633	39.3% v 27.9%	1.67 (p=0.003)	1262	7.8% v 7.7%	0.99 (p=1)	0.07
		ypT0/Tis ypN0			21.7% v 18.3%	(p=0.07)		43.3% v 32.9%	(p=0.007)				
NSABP B-40	Tx4[+/-G or Cap]- ACx4 +/-Bev 15mg/kg x6	ypT0/Tis	>1% cells +ve for either ER or PgR	1186	34.5% v 28.2%	(p=0.02)		51.5% v 47.1%	(p=0.34)		23.2% v 15.1%	(p=0.007)	0.19
		ypT0/Tis			27.6% v 23%	(p=0.08)					16.8% v 11.1%	(p=0.03)	0.25
CALGB 40603 (TN only; Ph II)	wP+/-Carbo x12- ddACx4 +/-Bev 10mg/kg x9	ypT0/Tis	10% cells +ve for either ER or PgR				443	59% v 48%	1.58 (p=0.009)				
		ypT0/Tis ypN0						52% v 44%	1.36 (p=0.057)				
ARTemis	Tx3-FECx3 +/-Bev 15mg/kg x4	ypT0/Tis ypN0	Allred score (0-2=neg; 3-5=wpos; 6-8=strpos)	781	22% v 17%	1.53 (p=0.03)	241	45% v 31%		540	12% v 10%		

**Supplementary Table 9: Investigator list**

Site	Randomising Consultant(s)
Aberdeen Royal Infirmary, Aberdeen	Dr Radha Todd, Dr Ravi Sharma
Addenbrookes Hospital, Cambridge	Dr Helena Earl, Dr Jean Abraham, Dr Luke Hughes-Davies, Dr Karen McAdam, Dr Charles Wilson
Beatson West of Scotland Cancer Centre, Glasgow	Dr Diana Ritchie
Bedford Hospital, Bedford	Dr Sarah Smith, Prof Robert Thomas
Blackpool Victoria Hospital, Blackpool	Dr Shabbir Susnerwala, Dr Andrew Hindley
Castle Hill Hospital, Hull	Prof Michael Lind, Dr Penny O'Neill, Dr Saiqa Spensley
Charing Cross Hospital, London	Dr Rizvana Ahmad, Dr Susan Cleator, Prof Charles Coombes, Dr Matthew Flook, Dr Robert Leonard, Dr Sean O'Cathail, Dr Carlo Palmieri, Dr Pippa Riddle, Prof Justin Stebbing
Cheltenham General Hospital, Cheltenham	Dr Kim Benstead, Dr Radhika Counsell, Dr Sean Elyan
Christie Hospital, Manchester	Dr Anne Armstrong, Dr Sacha Howell, Dr Andrew Wardley
City Hospital, Birmingham	Dr Daniel Rea, Dr David Spooner
Dorset County Hospital, Dorchester	Dr Amitabha Chakrabarti, Dr Perric Crellin
Essex County Hospital, Colchester	Dr Philip Murray
Forth Valley Royal Hospital, Larbert	Dr Judith Fraser, Dr Peter Canney
Furness General Hospital, Barrow-in-Furness	Dr Geraldine Skailes
Glan Clwyd Hospital, Bodelwyddan	Dr Jill Bishop, Dr Cath Bale, Dr Win Soe
Guy's Hospital, London	Dr Janine Mansi
Hairmyres Hospital, East Kilbride	Dr Grainne Dunn
Hinchingbrooke Hospital, Huntingdon	Dr Cheryl Palmer
Kidderminster Hospital, Kidderminster	Dr Mark Churn
King's College Hospital, London	Dr Anne Rigg
Leicester Royal Infirmary, Leicester	Dr Ion Boiangiu, Dr Samreen Ahmed, Dr Kiran Kancherla, Dr Ahmed Osman
Macclesfield District General Hospital, Macclesfield	Dr Lisa Barraclough, Dr Mark Lawrence
Maidstone Hospital, Maidstone	Dr Russell Burcombe, Dr Catherine Harper-Wynne, Dr Rema Jyothirmayi
Medway Maritime Hospital, Gillingham	Dr Charlotte Abson
Nevill Hall Hospital, Abergavenny	Dr Theresa Howe
New Cross Hospital, Wolverhampton	Dr Mark Churn, Dr Rakesh Mehra, Dr Prakash Ramachandra
Newham University Hospital, London	Dr Chris Gallagher, Dr Virginia Wolstenholme
North Middlesex Hospital, London	Dr Jacqueline Newby
Nottingham City Hospital, Nottingham	Dr Stephen Chan
Peterborough City Hospital, Peterborough	Dr Karen McAdam
Poole Hospital, Poole	Dr Amitabha Chakrabarti, Dr Joanne Brady
Prince Charles Hospital, Merthyr Tydfil	Dr Helen Passant
Queen Elizabeth Hospital, Birmingham	Dr Daniel Rea, Dr Suhail Anwar
Queen's Hospital, Burton-on-Trent	Dr Mojca Persic, Dr Anula Chetiyawardana
Queen's Hospital, Romford	Dr Mary Quigley, Dr Emma Staples
Royal Bournemouth Hospital, Bournemouth	Dr Tamas Hickish
Royal Devon and Exeter Hospital, Exeter	Dr Jenny Forrest, Dr Ann Hong, Dr Kate Scatchard
Royal Free Hospital, London	Dr Alison Jones
Royal Glamorgan Hospital, Llantrisant	Dr Jacinta Abraham
Royal Gwent Hospital, Newport	Dr Simon Waters

Royal Hampshire County Hospital, Winchester	Dr Sanjay Raj
Royal Lancaster Infirmary, Lancaster	Dr David Eaton
Royal Liverpool University Hospital, Liverpool	Dr Susan O'Reilly
Royal Surrey County Hospital, Guildford	Dr Robert Laing, Dr Stephen Houston, Dr Anthony Neal
Russells Hall Hospital, Dudley	Dr Rozenn Allerton, Dr Prakash Ramachandra
Sandwell General Hospital, West Bromwich	Dr David Spooner
Southampton General Hospital, Southampton	Dr Peter Simmonds, Dr Clare Crowley
Southend Hospital, Westcliff-on-Sea	Dr Hafiz Algurafi, Dr Anne Robinson
Southport and Formby District General Hospital, Southport	Dr Nasim Ali
St Bartholomew's Hospital, London	Dr Chris Gallagher, Dr Rebecca Roylance, Dr Sarah Slater
St Helens Hospital, St Helens	Dr Helen Innes, Dr Rajaram Sripadam
St James's University Hospital, Leeds	Dr Timothy Perren, Dr Julian Adlard, Dr Sri Kumar, Prof Galina Velikova
St John's Hospital, Livingston	Dr Frances Yuille
St Mary's Hospital, London	Dr Rizvana Ahmad, Dr Susan Cleator, Dr Olivia Hatcher
Torbay Hospital, Torquay	Dr Andrew Goodman, Dr Peter Bliss
Tunbridge Wells Hospital, Tunbridge Wells	Dr Rema Jyothirmayi
University College Hospital, London	Dr Rob Stein, Dr Alison Jones, Dr Grant Stewart
University Hospital Crosshouse, Kilmarnock	Dr Lucy Scott, Dr Graeme Lumsden
University Hospital (UHCW), Coventry	Prof Chris Poole, Prof Robert Grieve
Velindre Cancer Centre, Cardiff	Prof Peter Barrett-Lee, Dr Annabel Borley
Warrington & Halton Hospitals, Warrington	Prof Peter Clark
West Middlesex Hospital, Isleworth	Dr Rizvana Ahmad, Dr Pippa Riddle
Western General Hospital, Edinburgh	Dr Larry Hayward, Dr Angela Bowman, Dr David Cameron
Weston Park Hospital, Sheffield	Dr Matthew Winter
Wishaw General Hospital, Wishaw	Dr Mohammed Rizwanullah, Dr Jonathan Hicks
Ysbyty Gwynedd, Bangor	Dr Cath Bale

**Supplementary Table 10: Participating sites**

Site	Principal Investigator(s) since date of site activation	Total no of patients randomised
Addenbrooke's Hospital, Cambridge	Dr Helena Earl	93
Western General Hospital, Edinburgh	Dr Larry Hayward	53
Peterborough City Hospital, Peterborough	Dr Karen McAdam	44
Nottingham City Hospital, Nottingham	Dr Stephen Chan	41
West Middlesex University Hospital, Isleworth	Dr Rizvana Ahmad	40
Royal Bournemouth Hospital, Bournemouth	Dr Tamas Hickish	31
Royal Surrey County Hospital, Guildford	Dr Robert Laing, Dr Stephen Houston	31
Torbay Hospital, Torquay	Dr Andrew Goodman	23
Charing Cross Hospital, London	Dr Rizvana Ahmad	21
Leicester Royal Infirmary, Leicester	Dr Ion Boiangiu	19
St Helens Hospital, St Helens	Dr Helen Innes	19
Maidstone Hospital, Maidstone	Dr Russell Burcombe	18

New Cross Hospital, Wolverhampton	Dr Laura Pettit, Dr Mark Churn	18
Aberdeen Royal Infirmary, Aberdeen	Dr Ravi Sharma, Dr Radha Todd	17
Christie Hospital, Manchester	Dr Anne Armstrong	17
City Hospital, Birmingham	Dr Daniel Rea	17
St Bartholomew's Hospital, London	Dr Chris Gallagher	17
University College Hospital, London	Dr Rob Stein, Dr Grant Stewart	17
St James's University Hospital, Leeds	Dr Timothy Perren, Dr Julian Adlard	16
Poole Hospital, Poole	Dr Amitabha Chakrabarti	11
Royal Hampshire County Hospital, Winchester	Dr Sanjay Raj	11
Southend Hospital, Westcliff on Sea	Dr Hafiz Algurafi, Dr Anne Robinson	11
University Hospital, Coventry	Prof Christopher Poole	11
Southampton General Hospital, Southampton	Dr Peter Simmonds, Dr Nicholas Murray	10
King's College Hospital, London	Dr Anne Rigg	9
Macclesfield District General Hospital, Macclesfield	Dr Lisa Barraclough	8
Queen's Hospital, Burton Upon Trent	Dr Mojca Persic	8
St Mary's Hospital, London	Dr Rizvana Ahmad	8
Velindre Hospital, Cardiff	Dr Jacinta Abraham	8
Cheltenham General Hospital, Cheltenham	Dr Sam Guglani	7
Glan Clwyd Hospital, Bodelwyddan	Dr Jill Bishop	7
Medway Maritime Hospital, Gillingham	Dr Charlotte Abson	7
Newham University Hospital, London	Dr Chris Gallagher	7
Southport and Formby District General Hospital, Southport	Dr Nasim Ali	7
Dorset County Hospital, Dorchester	Dr Amitabha Chakrabarti	6
Essex County Hospital, Colchester	Dr Mukesh Mukesh, Dr Devyanee Basu, Dr Vivienne Loo, Dr Philip Murray	6
North Middlesex Hospital, London	Dr Jacqueline Newby	6
Bedford Hospital, Bedford	Dr Sarah Smith	5
Castle Hill Hospital, Hull	Prof Michael Lind	5
Hairmyres Hospital, East Kilbride	Dr Grainne Dunn	5
Hinchingsbrooke Hospital, Huntingdon	Dr Cheryl Palmer	5
Queen's Hospital, Romford	Dr Mary Quigley, Dr Emma Staples	5
Royal Devon and Exeter Hospital, Exeter	Dr David Hwang	5
Royal Free Hospital, London	Dr Alison Jones	5
Royal Gwent Hospital, Newport	Dr Simon Waters, Dr Carys Morgan	5
Wishaw General Hospital, Wishaw	Dr Mohammed Rizwanullah	5
Beatson West of Scotland Cancer Centre, Glasgow	Dr Diana Ritchie	4
Blackpool Victoria Hospital, Blackpool	Dr Shabbir Susnerwala	4
Forth Valley Royal Hospital, Larbert	Dr Judith Fraser, Dr Peter Canney	4
Queen Elizabeth Hospital, Birmingham	Dr Daniel Rea	4
Royal Glamorgan Hospital, Llantrisant	Dr Jacinta Abraham	4
Ysbyty Gwynedd, Bangor	Dr Cath Bale	4
Kidderminster Hospital, Kidderminster	Dr Mark Churn	3
Royal Lancaster Infirmary, Lancaster	Dr David Eaton	3
Royal Liverpool University Hospital, Liverpool	Dr Susan O'Reilly	3

Russells Hall Hospital, Dudley	Dr Rozenn Allerton, Dr Prakash Ramachandra	3
Tunbridge Wells Hospital, Tunbridge Wells	Dr Russell Burcombe	3
Weston Park Hospital, Sheffield	Dr Matthew Winter	3
Nevill Hall Hospital, Abergavenny	Dr Theresa Howe, Dr Simon Waters	2
Sandwell General Hospital, West Bromwich	Dr Daniel Rea	2
St John's Hospital, Livingston	Dr Frances Yuille	2
University Hospital Crosshouse, Kilmarnock	Dr Lucy Scott	2
Warrington & Halton Hospitals, Warrington	Prof Peter Clark	2
Furness General Hospital, Barrow-in-Furness	Dr David Eaton	1
Guy's Hospital, London	Dr Janine Mansi	1
Prince Charles Hospital, Merthyr Tydfil	Dr Helen Passant	1
Ayr Hospital, Ayr	Dr Lucy Scott	0*
Basingstoke and North Hampshire Hospital, Basingstoke	Dr Tony Dhillon	0*
Clatterbridge Centre for Oncology, Bebington	Dr Susan O'Reilly	0*
Freeman Hospital, Newcastle upon Tyne	Dr Mark Verrill	0*
Gloucestershire Royal Hospital, Gloucester	Dr Sam Guglani	0*
Hereford County Hospital, Hereford	Dr Sam Guglani	0*
Worcestershire Royal Hospital, Worcester	Dr Radhika Counsell	0*
Yeovil District Hospital, Yeovil	Dr Geoff Sparrow	0*

\*Non-recruiting site but contributed to the ARTemis trial via screening, pharmacy duties etc.