Appendix Nine: Updated* trastuzumab (Herceptin) clinical trial summaries**

	Sequential treatment trials, long duration (12 month)[1] regimens			Concurrent treatment trials, long duration (12 month) regimens			Concurrent treatment trials with short duration regimens[2]
	HERA	**N9831 Arm B**	**PACS04[3]**	**B31[4]**	**N9831 Arm C[4]**	**BCIRG006[5]**	**FinHer**
Patient Numbers	Observation: 1,693 Trastuzumab (1 yr): 1,694 Trastuzumab (2 yr):[1] 1,694	Observation: 979 Trastuzumab: 985	Observation: 268 FEC100 – n/a ED – n/a Trastuzumab: 260 FEC100 – n/a ED – n/a	Observation: 1,024 Trastuzumab: 1,019	Observation: 979 Trastuzumab: 840	Observation: 1,073 Trastuzumab: 1,074	Observation: (116) vinorelbine – 58 docetaxel – 58 Trastuzumab: (116) docetaxel - 54 vinorelbine - 62
Intervention	1 loading dose (8mg/kg) trastuzumab, then 6mg/kg every 3 weeks for one year or two years	1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks	1 loading dose (8mg/kg) trastuzumab, then 6mg/kg every 3 weeks for one year	1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks[4]	1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks[4]	1 loading dose (4mg/kg) trastuzumab, then 2mg/kg every week for 52 weeks	9 trastuzumab infusions at 1 week intervals. First dose 4mg/kg, remaining doses 2mg/kg
Timing of treatment	Sequential (after completion of all chemotherapy – anthracycline chemotherapy[6] and taxane treatment[7])			Concurrent with taxane (paclitaxel), after completion of anthracycline chemotherapy			Concurrent with taxane (docetaxel) treatment, before anthracycline chemotherapy[2]
Disease free survival (DFS) hazard ratio (HR) (95% confidence interval)	12-mth median follow-up (mfu): 0.54 (0.43-0.67) 23-mth mfu: 0.64 (0.54-0.76)	1.5-yr mfu: 0.87 (0.67-1.13)	4-yr mfu: 0.86 (0.61-1.22)	2.4-yr mfu: 0.45 (0.35-0.58) 3.3-yr mfu: Not reported (joint analysis with N9831 = 0.49 (0.40-0.58) at 2.9-yr mfu[4])	1.5-yr mfu: 0.55 (0.38-0.76) 2.4-yr mfu: Not reported (joint analysis with B31 = 0.49 (0.40-0.58) at 2.9-yr mfu[4])	23-mth mfu: 0.49 (0.37-0.79) 36-mth mfu: 0.61 (0.48-0.76)	36-mth mfu: 0.42 (0.21-0.83)
Overall DFS HR (95% CI)	0.72 (0.67-0.78) (2-yr HERA f/u)			0.53 (0.46-0.60) (3-yr BCIRG006 f/u, 2.9-yr joint B31/N9831 f/u)			0.42 (0.21.0.83)
Overall survival (OS) HR (95% CI)	12-mth mfu: 0.76 (0.47-1.23) 23-mth mfu: 0.66 (0.47-0.91)	1.5-yr mfu: 0.85 (0.55-1.33)	4-yr mfu: 2.06 (0.61-6.99)	Not reported (joint analysis with N9831= 0.67 (0.48-0.93) at 2.0-yr mfu, 0.63 (0.49-0.81) at 2.9-yr mfu[4])	Not reported (joint analysis with B31= 0.67 (0.48-0.93) at 2.0-yr mfu, 0.63 (0.49-0.81) at 2.9-yr mfu[4])	36-mth mfu: 0.59 (0.42-0.85)	36-mth mfu: 0.41 (0.16-1.08)
Overall OS HR (95% CI)	0.76 (0.65-0.88)			0.63 (0.51-0.77)			0.41 (0.16-1.08)

*Updates to this table since TAR 75 (August 2006) and TAR 75b (April 2007) are indicated by red text.

**The six RCTs reporting disease outcomes for adjuvant trastuzumab compared with standard chemotherapy treatment alone in HER2-positive early breast cancer

[1] No data have yet been reported for the outcomes of the 2 year trastuzumab treatment arm in the HERA trial.

[2] A seventh study, ECOG E2198, which compared 12 months with 10 weeks trastuzumab given concurrently with paclitaxel, was presented as a poster at the San Antonio Breast Cancer Symposium in 2006 (Sledge et al, http://www.abstracts2view.com/sabcs06/view.php?nu=SABCS06L_561). However, this was a pilot study not designed to test efficacy nor powered to determine equivalence and has not reported outcomes against standard chemotherapy treatment.

[3] The randomisation of patients to trastuzumab in PACS04 was a second randomisation applied specifically to the HER2 positive subpopulation (n=528 randomised). All patients in this trial (total n=3010) were initially randomised to receive either Arm A: 6 cycles of adjuvant 5-fluorouracil-epirubicin-cyclophosphamide (FEC100: F and C 500 mg/m^2, E 100 mg/m^2), or Arm B: 6 cycles of concomitant ED (E and D 75 mg/m^2) every 3 weeks. As soon as HER2 status was available, patients with HER2 positive tumours were randomised to Arm C: additional observation only, or Arm D: additional 1 year of trastuzumab (T) (8 mg/kg loading dose, 6 mg/kg 3qw). The primary endpoint was 3-yea DFS for the C and D arms. The distribution of patients between the other chemotherapy treatments (FEC100, ED) in the HER2 positive subpopulation is not available.

[4] Although reported jointly, the NSABP-B31 and NCCTG- N9831 trials of concurrent regimens differed in patient eligibility (high risk negative node status); methods of randomisation allocation; taxane regimens, anthracycline regimens, sequencing with radiotherapy, sequencing with hormonal therapy, aromatase inhibitor types, and when they started to be used in the trials; recommendations for post surgical radiotherapy; and primary endpoints (disease free survival (DFS) for N9831, overall survival for B31).

[5] Note that there was also an arm to BCIRG006 ('arm TCH') that consisted of 6 cycles of docetaxel and carboplatin with concurrent trastuzumab (i.e. no anthracycline chemotherapy). However, because this regimen is not comparable to the other regimens, these results are not presented in this table. For further information regarding BCIRG006 see TAR 75 Appendix One: Minutes of the relevant clinical advisory committee meetings.

[6] Anthracycline containing chemotherapy regimens (FEC or FAC).

[7] The HERA trial allowed several different chemotherapy regimens.