# What is the Optimal Duration of Adjuvant Trastuzumab Therapy in Breast Cancer? The Current Duration Studies

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## INTRODUCTION

Trastuzumab has been shown to improve disease-free and overall survival in patients with HER2 positive breast cancer. All but one of the initial studies gave trastuzumab for one year, either concurrently with, or subsequent to, chemotherapy. Based on these studies the international "standard" duration is one year, but the optimal duration is not known. Whilst toxicity of trastuzumab, as continuing monotherapy, is considered acceptable, a small number of patients develop severe heart failure (Table 1) and, many more, lesser degrees of impaired cardiac function. In the short term this is frequently reversible, but the long term toxicity is unknown. The FinHer study gave trastuzumab for only nine weeks concurrent with docetaxel and prior to the anthracycline regimen. It produced a similar order of benefit to the larger studies, but the small number of patients means that the results are less reliable. There was no increased cardiotoxicity reported in the trastuzumab treated patients. The FinHer study raises the possibility that shorter durations of trastuzumab may be as effective as 12 months therapy and potentially less cardiotoxic. Such therapy would also be more practical for patients and use less resources.

ADJUVANT TRASTUZUMAB BREAST CANCER TRIALS

| Trial (No. of patients) | Schedule | Severe CHF | Systolic Dysfunction |
|---|---|---|---|
| HERA (5102) | | | |
| CT | | | |
| CT → Tras | | 0.6% | 3.0% |
| NSABP B-31 (1736) | | | |
| AC → PTx | | | |
| AC → PTx - Tras | | 3.6% | 15.9% |
| NCCTG N 9831 (1615) | | | |
| AC → PTx | | | |
| AC → PTx + Tras | | 2.5/3.3% | 14/17% |
| BCIRG 006 (3222) | | | |
| AC → Doc | | | |
| AC → Doc + Tras | | 1.9% | 18.1% |
| TC + Tras → Tras | | 0.4% | 8.6% |
| FinHER (232) | | | |
| Doc → +/- Tras | | | |
| Vinblast → +/- Tras | | 0% | 3.5% |

Table 1. Cardiotoxicity in trastuzumab treated patients. All trastuzumab was given for 12 months except in FinHER (trastuzumab given for 9 weeks).

## METHODS

There are currently six studies of alternative durations of trastuzumab (Tables 2 & 3). Trial information was obtained from trial specific websites, clinical trials registries, in particular www.clinicaltrials.gov and from direct communication with trial groups.

## RESULTS

There is no result available from any of the duration studies. Five studies compare shorter duration trastuzumab with 12 months and are accruing. Two of the studies are based on the FinHer protocol comparing that regimen with or without further trastuzumab continuing to 1 year (SOLD) or to a standard sequential anthracycline/ taxane regimen, with trastuzumab given for 12 months starting concurrently with the taxane (Short-HER). In both these studies randomisation occurs before any systemic therapy.

Three studies compare one year with six months of trastuzumab given concurrently with, or sequentially to, a variety of chemotherapy regimens. All of these use anthracyclines before taxanes, but a recent amendment to the UK Persephone study also allows the FinHer regimen of chemotherapy. Randomisation occurs at various times after completion of chemotherapy.

The sixth study is the third arm of the HERA study which gave 24 months of trastuzumab. The HERA study has reported the results of the 12 month trastuzumab and control arms on three occasions[8, 9, 10], but no result is yet available for the 24 month arm. No report is expected before 2011.

## DISCUSSION

There is an obvious advantage in knowing the optimal duration of any therapy. With the other systemic treatments of breast cancer (chemotherapy and endocrine therapy) it took many years after establishing the efficacy of treatment before optimal duration was known. Adjuvant chemotherapy was initially used for 1-2 years, but subsequent trials established that 3-6 months was more effective and less toxic, while shorter durations (single cycle to 3 months) were less effective. In contrast adjuvant endocrine therapy (tamoxifen) was initially given for a year until further trials showed that first 2 years was superior and then 5 years better still. We currently await the results of 10 years compared to 5 years treatment (ATLAS). The optimal duration of aromatase inhibitor therapy is not known.

In our view, the FinHer regimen is an excellent base from which to examine the trastuzumab duration question, because of the biological rationale for its effectiveness. In this regimen trastuzumab is given a) from the beginning of systemic treatment and b) together with docetaxel, with which it is synergistic. One of the primary guiding principles for increasing the effectiveness of chemotherapy, based on the Norton-Simon hypothesis, is to give the most effective drug(s) first. Further, most cardiotoxicity from trastuzumab occurs after about 4 months of treatment, so that shorter durations have the potential to avoid this. Shorter therapies, if shown to be equally effective, would be preferred, as they are more convenient to patients, potentially less toxic and likely to reduce health costs.

In contrast the studies comparing 6 with 12 months of therapy lack a distinct biological rationale and are probably mainly predicated on finding a more practical and less resource intensive regimen.

The results of the 24 month arm of HERA are awaited with interest. Unfortunately the control arm of this study has now been contaminated, by cross-over. Even if the 24 month arm was shown superior to 12 months, those shorter studies using concurrent chemotherapy and trastuzumab (SOLD and Short-HER) remain valid as concurrent treatment is increasingly being considered superior to the sequential therapy, used in the HERA study.

| Trastuzumab Duration | Country | Trial Name | Trial No. | Opened | Closed | Target Accrual | Current Accrual | No. of Sites |
|---|---|---|---|---|---|---|---|---|
| 9 weeks vs 12 months | Belgium, Finland, NZ, Scotland, Serbia, Sweden, Iceland | SOLD: A randomized phase III study comparing trastuzumab plus docetaxel (HT) followed by 5FU, epirubicin, and cyclophosphamide (FEC) to the same regimen followed by single agent trastuzumab as adjuvant treatments for early breast cancer[1] | NCT00593697 | Jan-08 | | 3000 | 594 @ Apr-10 | 38 |
| | Italy | Short-HER: Multicentric Randomised Phase III Trial of Two Different Adjuvant Chemotherapy Regimens plus Three Versus Twelve Months Of Trastuzumab In HER2 Positive Breast Cancer Patients[2, 3] | NCT00629278 | Dec-07 | | 2500 | 457 @ Apr-10 | 67 |
| 6 months vs 12 months | UK | Persephone: Duration of Trastuzumab with Chemotherapy in women with early breast cancer: 6 vs 12 months[4, 5] | ISRCTN52968807 | Feb-07 | | 4000 | 578 @ Mar-10 | 106 |
| | France | Protocol of Herceptin Adjuvant With Reduced Exposure, a Randomised Comparison of 6 Months vs 12 Months in All Women Receiving Adjuvant Herceptin [PHARE][6, 7] | NCT00381901 | May-06 | | 3400 | 3193 @ Mar-10 | 149 |
| | Greece | Six vs 12 Months of Trastuzumab With Docetaxel Following FEC as Adjuvant Treatment in N+ Breast Cancer (Hellenic Oncology Research Group)[8] | NCT00615602 | Oct-04 | Dec-10 | 478 | unknown | 10 |
| 12 months vs 24 months | Global | HERA: A Randomized, Open-Label Study of the Effect of Herceptin On Disease-Free and Overall Survival in Women with HER2-Positive Primary Breast Cancer who have Completed Adjuvant Chemotherapy[9, 10, 11] | NCT00045032 Roche Registry | Jan-01 | Jan-05 | 4482 | 5102 | 395 locations |

Table 2. Summary of trastuzumab duration studies

## CONCLUSION

Establishing the optimal duration of trastuzumab remains one of the most important questions in its use. The SOLD and Short-HER studies are ideally placed to help determine this.

Seven countries are participating in the SOLD study, with an accrual target of 3000. Three New Zealand sites are currently recruiting to the study. There are presently 594 patients in the study, with 41 from New Zealand. The accrual is already twice that in the original FinHer study and exceeds that in three other trastuzumab studies. New Zealand centres and others are encouraged to consider participation.

SCHEDULE OF CURRENT TRASTUZUMAB DURATION STUDIES

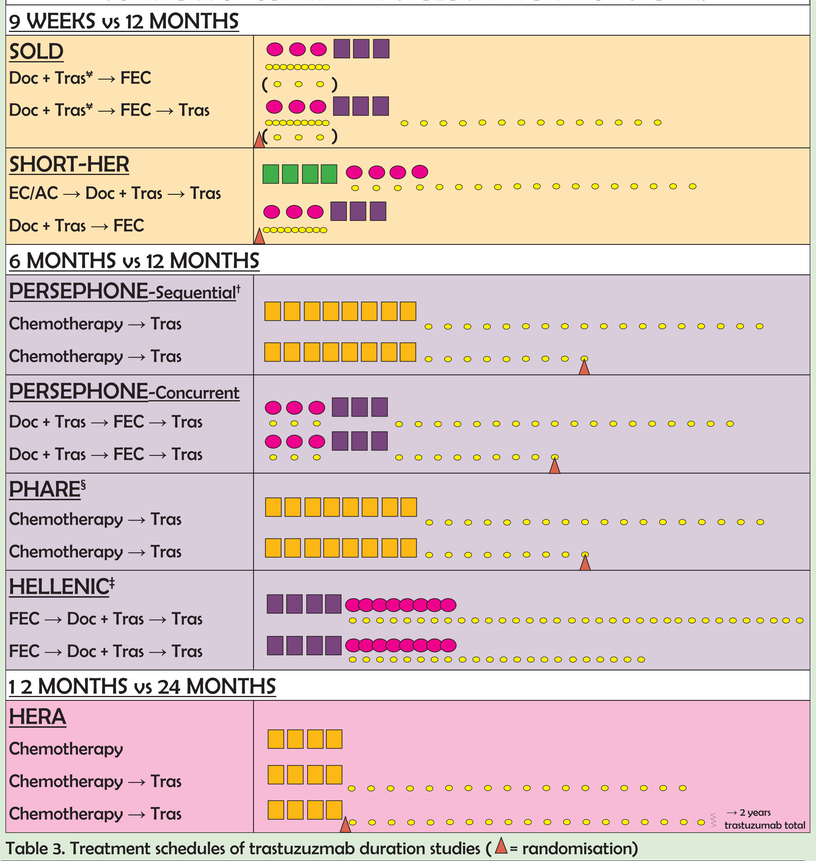


Table 3. Treatment schedules of trastuzumab duration studies (▲= randomisation)

* Trastuzumab weekly or 3-weekly for first 9 weeks. † Chemotherapy type = Anthracycline based (no taxane); Taxane + anthracyclines; Taxane-based (no anthracyclines). 3 or 4 weekly, 6-8 cycles. § Administration modalities of adjuvant chemotherapy = concomitant or sequential. ‡. Time of randomisation unknown.

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