South Western Staffordshire NHS
Primary Care Trust

Enclosure Number: 8
Lead Director: Jan Warren
Lead Officer: Cathy Riley
Meeting Date: 06 December 2005

PROFESSIONAL EXECUTIVE TEAM

For Decision / Ratification

Subject: Position Statement & Guiding Principles for Funding Cases for Trastuzumab -Unlicensed Adjuvant Treatment for HER-2 positive Early Breast Cancer

Key Issues: -

Trastuzumab (Herceptin) is a monoclonal antibody designed to block human epidermal growth factor receptor 2 (HER2), that is on the surface of some breast cancer cells. If the receptors are present, the patient may benefit from Trastuzumab, and this can be determined by two histopathological tests: the HER2 test, and the more specialised Fluorescent Insitu Hybridisation (FISH) test. The latter is only used for borderline cases.

Trastuzumab was originally licensed for use in advanced breast cancer (metastatic) and a NICE TAG (No. 34) published in March 2002 (due for review in April of this year) gave guidance and directed funding for its use in advanced breast cancer, i.e. in patients whose tumours over-express HER-2 as a single agent for second and third-line treatment, or in combination with paclitaxel or in combination with docetaxel as first-line therapy. The pressure now is for this drug to be used in an adjuvant setting at the time of diagnosis and initial chemotherapy, i.e. in early breast cancer.

Trastuzumab (Herceptin) is not yet licensed for the treatment of early stage breast cancer, and is currently in Phase III trials as an adjunct to the standard treatment for early (operable) breast cancer.

Recommendation(s):

The PEC is asked to: -

- Ratify the attached statement and guiding principles (Appendix One)

Standards for Better Health	Issues
Safety	To ensure that this unlicensed treatment when funded is done so under a robust framework to ensure patients safety
Clinical & Cost Effectiveness	To ensure that the funding committee has adequate information on clinical effectiveness and numbers needed to harm
Governance	To ensure consistency when considering applications form adjuvant therapy in early breast cancer
Patient Focus	To ensure patients are aware of risks and have made an informed choice about receiving the therapy
Accessible & Responsive Care	
Public Health	To consider cost effectiveness and the wider need of the population when considering exceptional cases

1. Background to the proposal

1.1 Trastuzumab (Herceptin) is a monoclonal antibody designed to block human epidermal growth factor receptor 2 (HER2), that is on the surface of some breast cancer cells. If the receptors are present, the patient may benefit from Trastuzumab, and this can be determined by two histopathological tests: the HER2 test, and the more specialised Fluorescent Insitu Hybridisation (FISH) test. The latter is only used for borderline cases.

1.2 Trastuzumab was originally licensed for use in advanced breast cancer (metastatic) and a NICE TAG (No. 34) published in March 2002 (due for review in April of this year) gave guidance and directed funding for its use in advanced breast cancer, i.e. in patients whose tumours over-express HER-2 as a single agent for second and third-line treatment, or in combination with paclitaxel or in combination with docetaxel as first-line therapy. The pressure now is for this drug to be used in an adjuvant setting at the time of diagnosis and initial chemotherapy, i.e. in early breast cancer.

1.3 Trastuzumab (Herceptin) is not yet licensed for the treatment of early stage breast cancer, and is currently in Phase III trials as an adjunct to the standard treatment for early (operable) breast cancer.

2. Evidence[1,2]

2.1 Two publications focus on :

2.1.1 **(1) Trastuzumab plus Adjuvant Chemotherapy for Operable HER2-positive Breast Cancer**

2.1.2 This combines the results of two trials (The National Surgical Adjuvant Breast and Bowel Project (NSABP) Trial B-31 and the Intergroup trial NCCTG-N9831) comparing adjuvant chemotherapy with or without concurrent Trastuzumab in women with surgically-removed HER2-positive breast cancer.

2.1.3 *The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 is a phase III randomised trial of chemotherapy with or without adjuvant Trastuzumab, which is underway in the US and Canada. Patients (n=2700) must have axillary (underarm) lymph node involvement (but no other metastatic spread) and must have HER2+ operable breast cancer. B-31 is in two stages. In stage one cardiac safety will be assessed in 1000 patients and, if the combination therapies have acceptable toxicity then a further 1700 patients will be randomised in stage two. Patients are randomised to two arms, standard chemotherapy (doxorubicin and cyclophosphamide, followed by Paclitaxel) or standard chemotherapy plus Trastuzumab.*

2.1.4 *The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-31 is a phase III randomised trial of chemotherapy with or*

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2.1.5 N9831 is a randomised three-arm trial also evaluating the use of Trastuzumab and chemotherapy versus chemotherapy alone. Patients must have operable node-positive HER2+ breast cancer. The dosing regimen is similar to as B31 above, with the addition of a sequentially dosed Trastuzumab arm.

NB: N9831 and B31 results are presented as combined analysis in the publication[1]

2.2 **(2) Trastuzumab after Adjuvant Chemotherapy in HER2-Positive Breast Cancer**

2.2.1 A multi-centre, international RCT (HERA trial) compares one or two years of Trastuzumab given every three weeks with observation in patients with HER-2 positive and either node-negative or node-positive breast cancer who had completed locoregional therapy and at least four cycles of neoadjuvant or adjuvant chemotherapy.

2.2.2 The HERA trial[2] is a phase III, open label, multi-centre, three-arm Roche sponsored international study. The study enrolled patients who had previously undergone a standard chemotherapy regimen recognised as best practice within the host country, patients were then divided into 3arms; one year of Trastuzumab versus two years Trastuzumab versus no Trastuzumab in the final arm. The trial enrolled over 5000 patients. It is planned to run for approximately 6 yrs.

2.2.3 **NB: Unlike the other trials, HERA interim results don't show statistically significant increase in overall survival, although data very immature and not definitive by any means.**

3. Trial characteristics and potential benefits and risks

3.1 These are detailed in Tables 1 & 2 to allow comparison between the trials. In summary Trastuzumab appears from this interim analysis to be effective as an adjuvant in early breast cancer, which is HER-2 positive and may be differentially effective where nodes are present. This benefit comes however at a significant risk of Cardiac toxicity, especially congestive heart failure.

4. Implications

4.1 The editorial that accompanies these papers[3] says, "on the basis of these results, our care of patients with HER2-positive breast cancer must change today. Certainly, patients with lymph-node-positive, HER2-positive breast cancer should receive trastuzumab as part of optimal adjuvant systemic therapy, unless the antibody is clearly contraindicated."

4.2 The drug costs for a year of trastuzumab are in the range of £15–20,000, dependant on body weight. In addition, there will be the cost of testing for HER2 (Roche will sponsor in 2005/06), administering the drug, and monitoring cardiac function (LVEF)- with capacity issues.

5.0 Position Statement

5.1 The PCT has a policy to not fund drugs that have either not been approved by NICE, or are not being used in a manner approved by NICE. In addition, Trastuzumab is currently unlicensed for this indication in the UK.

5.2 However, in line with the majority of other PCTs, and following both regional and local advice, there appears to be no choice but to fund requests for Trastuzumab, providing the following guiding principles are met.

6.0 Guiding Principles

6.1 The PCT has developed a process to consider exceptional cases, and below are some guiding principles:

6.1.1 1) Any patient to be considered as an exceptional case must be clinically appropriate to receive Trastuzumab in early breast cancer, and they meet the clinical criteria laid out in the trials[1,2], e.g.

- Histologically confirmed, completely excised invasive breast cancer with HER-2 over-expression, in the range of IHC 3+. For patients assessed as IHC 2+, a further FISH test must be done and this must be FISH-positive

- Node-positive (irrespective of tumour size) or node-negative disease (if tumour greater than 1cm)
- Adequate hepatic, renal and bone marrow function
- LVEF that meets or exceeds the lower limit of normal and decrease of less than 16% points from baseline (baseline is measured before start of chemotherapy)
- No evidence of metastasis or a previous invasive breast carcinoma or a neoplasm not involving the breast
- No congestive heart failure, coronary artery disease with previous Q-wave MI, angina pectoris requiring medication, poorly controlled hypertension, clinically significant valvular disease, unstable angina, arrythmia requiring medication, severe conduction abnormality, cardiomegaly on chest X-ray, or cardiomyopathy.

6.1.2 (2) The patient will be able to have LVEF regularly monitored by the specialist centre (initially and at least every three months).

6.1.3 (3) The patient has had chemotherapy courses in line with trials[,2]

6.1.4 (4) The patient is having/has had radiotherapy in line with trials[1,2]

6.1.5 (5) Anastrozole/ Tamoxifen treatment is in line with trials[1,2] in patients with hormone-receptor-positive disease, as appropriate.

6.1.6 (6) The patient is aware that the treatment is unlicensed and there is only limited experience of its use for this indication. The patient has had possible efficacy and potential for harm (especially CHF and cardiac death) explained in terms of NNT and NNH, and therefore has made an informed decision about desiring this treatment.

Recommendation(s):

The PEC is asked to: -

- Ratify the attached statement and guiding principles (Appendix One)

Table 1

Summary of trial characteristics and benefits

*The 2 trials, N9831 and B31, despite different protocols, were combined for analysis.

Trial	Planned duration	Primary outcome(s)	Secondary outcomes	Interim analysis median follow-up	Projected Survival rates (death)		Disease free survival (proj)	
NCCTG-N9831 & B-31*	8 yrs approx	DFS**	Overall survival Time to distant recurrence, death from breast cancer, contralateral breast cancer, and other second primary cancers.	2.0yrs	**3yr** 94% vs. 92% ARR 2%, NNT 50	**4yr** 91% vs. 87% ARR 4%, NNT 25	**3yr** 87% vs75% ARR 12% NNT 8	**4yr** 85% vs 67% ARR 18% NNT 6
HERA	6 years approx	DFS**	Cardiac safety, overall survival, site of first disease-free-survival event, time to distant recurrence	2yr (1yr of trastuzumab)	**2 yr survival** 96% vs. 95%, ARR 1%, NNT 100		**2yr** 85.8% vs. 77.4% ARR 8.4 NNT 12	No longer timescale available

**DFS = Disease Free Survival

NNT- numbers needed to treat, i.e. number of patients that you need to treat to get one futher patient surviving compared to control

ARR- absolute risk reduction

[1] N Eng J Med 2005; 353:1673-84

[2] N Eng J Med 2005; 353:1659-72

[3] N Eng J Med 2005; 353;1734-36

Table 2

Summary of risks

Trial	CHF	LVEF reduction Below normal level LVEF or LVEF decrease ≤15% from baseline	Cardiac events (including death and CHF), 3 years	Comments
NCCTG-N9831	3-4%, NNH 25-33	_	ARH 2.9% NNH 35	Adverse cardiac outcomes appear to be more likely when Herceptin is used in concurrent combination with Paclitaxel. A sequential use of Herceptin appears to have fewer cardiac problems, but a poorer survival outcome.
NSABP-B31	3.4%, NNH 29	_	ARH 3.3% NNH 30	
HERA	1.67% NNH 60	7.1% vs. 2.2% ARH 4.9%, NNH 20	2.27 vs 0.12 ARH 2.15% NNH 47	

Other safety concerns: - In the HERA trial, 7% vs. 4.7% (NNH 43) experienced at least 1 serious adverse effect (infection), and 7.9% vs. 4.3% (NNH 28) experienced at least one grade 3 or 4 Adverse event (Infection & vascular disorder).

NNH- numbers needed to harm, i.e. number of patients that are treated before one further harmful event (specified) happens than would happen in control group

[1] N Eng J Med 2005; 353:1673-84
[2] N Eng J Med 2005; 353:1659-72
[3] N Eng J Med 2005; 353;1734-36