Professional organisation statement template

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation

ASSOC. OF BREAST SURGERY AT BASO.
ROYAL COLLEGE OF SURGEONS
35-43, LINCOLN'S INN FIELDS,
LONDON WC2A. 3PE.

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? **yes**
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? **yes**
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? **yes**
- other? (please specify)

Professional organisation statement template

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?. Is there significant geographical variation in current practice? Are there differences of opinion between professionals as to what current practice should be? What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient? Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics? Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?

Please tell us about any relevant **clinical guidelines** and comment on the **appropriateness** of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.

Answer:

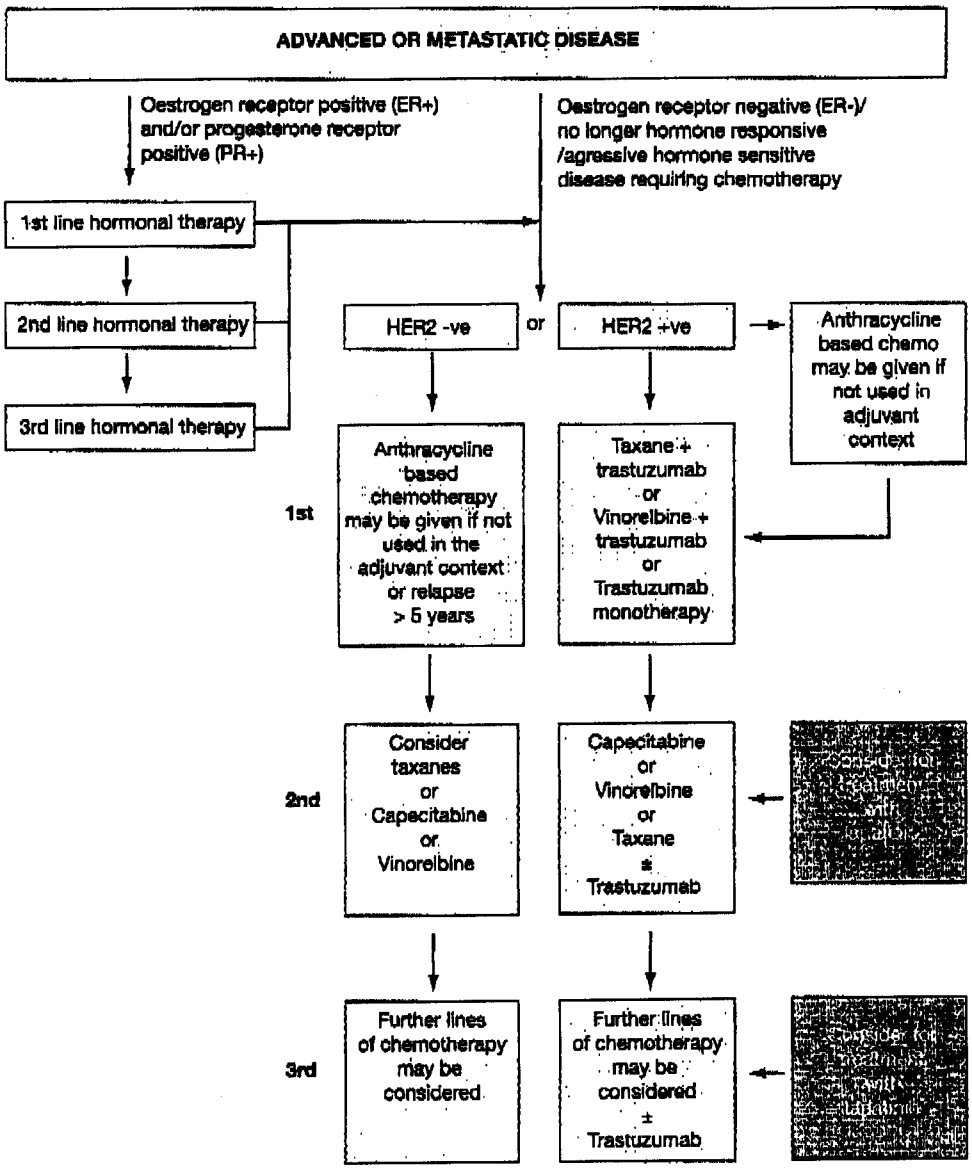
Metastatic breast cancer is currently treated with chemo-endocrine therapy (see following page).

Because of large randomised phase 3 studies in this setting, comparing a new treatment with the standard of care, we are able to rely on level 1α evidence to make our treatment decisions. As such, there are few variations in care although the decision to treat or not treat is made between the doctor and the patient. Patients at this stage are not considered to have curable disease, and the toxicity of any treatment is therefore particularly important..

This new drug, an oral once daily therapy, will be used following EMEA approval, in the following patients with histologically proven breast cancer (both criteria required):

1. Progressive HER2+ metastatic or locally advanced breast cancer.
2. Previously treated with anthracycline, taxane and trastuzumab (Herceptin) and no prior capecitabine.

Professional organisation statement template



- This algorithm includes systemic therapies only and attempts to describe treatment options for the majority of patients; a single algorithm cannot describe the appropriate management of all patients
- At any stage in treatment patients may be eligible for a clinical trial
- At any stage in treatment no further therapy may be the correct option
- Following chemotherapy, maintenance hormonal therapies may be considered for ER+ and/or PR+ patients
- The algorithm may include drugs used outside of their marketing authorisation; for prescribing information refer to the appropriate Summary of Product Characteristics

National Institute for Health and Clinical Excellence
Professional organisation statement template
Single Technology Appraisal of Lapatinib for the treatment of previously treated, advanced or metastatic breast cancer

Estimated Patient Numbers

The following figures may act as a guide for local calculations:

Assumption	Rate
The incidence of breast cancer in the UK*	74/100,000
Around 50% of women diagnosed with primary breast cancer will eventually relapse and 42/100,000 develop metastatic disease.3 In addition, around 14% of patients present with locally advanced or metastatic disease at first diagnosis	42/100,000
Assume 68% of patients receive first line chemotherapy†	29/100,000
Assume 22% of patients over-express HER2 and are suitable for treatment with trastuzumab††	6/100,000
Assume 50% of patients receive second line chemotherapy†**	3/100,000
Assume 43% of patients receive third line chemotherapy†**	1/100,000

* Crude incidence rate per 100,000 population.

† Data provided by Guy's and St Thomas' NHS Foundation Trust.

†† Some patients will not receive trastuzumab in combination with first-line chemotherapy; it is assumed that such patients will receive trastuzumab in combination with second-line chemotherapy.

** Patients will be eligible for treatment with lapatinib if they have previously received trastuzumab for metastatic disease.

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?

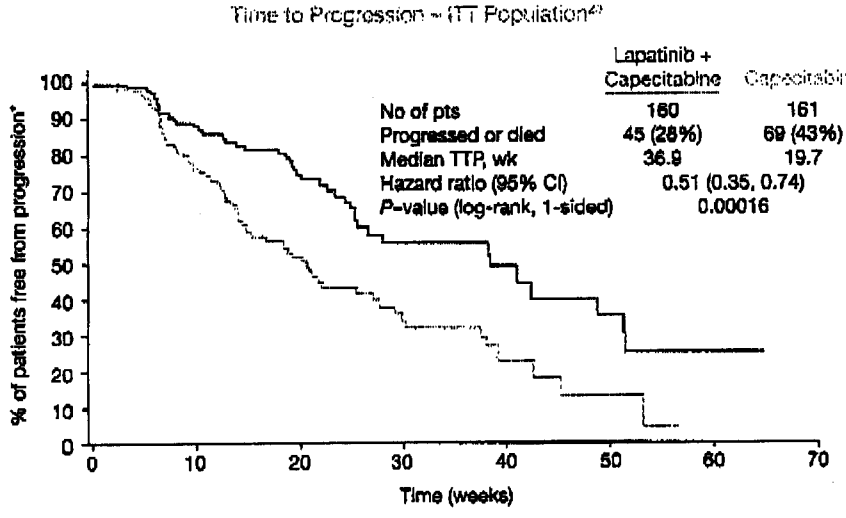
Advantages: Lapatinib will be prescribed, according to local protocol, under the supervision of an oncologist with experience of managing patients with breast cancer, based on results of a randomised controlled trial.

As an orally administered drug, there should be none of the additional service costs associated with a new intravenous drug.

Lapatinib in combination with capecitabine is administered in 21-day cycles. There should be no additional hospital visits compared to the administration of capecitabine monotherapy.

Use of this oral combination may benefit chemotherapy service capacity; existing alternative intravenous regimens require specialist preparation and administration.

The main advantage is as follows:



* Censors four patients who died due to causes other than breast cancer

This phase 3 trial was stopped at its first interim analysis because of the survival advantage observed.

Disadvantages:

There is only one phase 3 trial that has been undertaken to support its use, and a difference in overall survival has not yet been shown, only a difference in time to progression above. All patients require an ECHO or MUGA to assess left ventricular ejection fraction prior to treatment. Adverse events were similar in both arms of the study, although diarrhoea, hand-foot syndrome and rashes were more common with the combination regimen.

In the phase 3 trial, five cardiac events were reported: four in patients who had received the lapatinib and capecitabine combination (all treatment related) and one in a patient receiving capecitabine monotherapy, which was considered treatment unrelated. All were considered asymptomatic (< grade 2) and reversible. There were no withdrawals due to a decrease in LVEF although monitoring in clinical practice will be less stringent. The final disadvantage is the likely cost, in the few patients for whom it will be eligible.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

The main evidence is derived from Geyer CE, et al.
Lapatanib plus capectibaine for HER2 positive advanced breast cancer. N Engl J Med 2006 Dec 28th;355:2733-43.

In this trial, women with HER2-positive, locally advanced or metastatic breast cancer that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab were randomly assigned to receive either combination therapy (lapatinib at a dose of 1250 mg per day continuously plus capecitabine at a dose of 2000 mg per square meter of body-surface area on days 1 through 14 of a 21-day cycle) or monotherapy (capecitabine alone at a dose of 2500 mg per square meter on days 1 through 14 of a 21-day cycle). The primary end point was time to progression, based on an evaluation by independent reviewers under blinded conditions. The interim analysis of time to progression met specified criteria for early reporting on the basis of superiority in the combination-therapy group. The hazard ratio for the independently assessed time to progression was 0.49 (95% confidence interval, 0.34 to 0.71; P<0.001), with 49 events in the combination-therapy group and 72 events in the monotherapy group. The median time to progression was 8.4 months in the combination-therapy group as compared with 4.4 months in the monotherapy group. This improvement was achieved without an increase in serious toxic effects or symptomatic cardiac events. In conclusion, Lapatinib plus capecitabine is superior to capecitabine alone in women with HER2-positive advanced breast cancer that has progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab.

All other published studies are phase 2 trials or mechanistic studies of the tyrosine kinase blocking activity (EGFR and HER2) of this drug and a selected list of these is shown on the following page:

References

1. Nelson MH, Dolder CR. Lapatinib: a novel dual tyrosine kinase inhibitor with activity in solid tumors. Ann Pharmacother 2006; 40: 261–269.
2. Rusnak DW, Affleck K, Cockerill SG et al. The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: potential therapy for cancer. Cancer Res 2001; 61: 7196–7203.
3. Burris HA, 3rd. Dual kinase inhibition in the treatment of breast cancer: initial experience with the EGFR/ErbB-2 inhibitor lapatinib. Oncologist 2004; 9 (Suppl 3): 10–15.
4. Olayioye MA, Neve RM, Lane HA et al. The ErbB signaling network: receptor heterodimerization in development and cancer. EMBO J 2000; 19: 3159–3167.
5. Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001; 2: 127–137.
6. Johnson SRD, Leary A. Lapatinib—a novel EGFR/HER2 tyrosine kinase inhibitor for cancer. Drugs for Today 2006; 42: 441–453.
7. Nicholson RI, Gee JM, Harper ME. EGFR and cancer prognosis. Eur J Cancer 2001; 37 (Suppl 4): 59–15.
8. Holbro T, Civenni G, Hynes NE. The ErbB receptors and their role in cancer progression. Exp Cell Res 2003; 284: 99–110.
9. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 1987; 235: 177–182.
10. Rusnak DW, Lackey K, Affleck K et al. The effects of the novel, reversible epidermal growth factor receptor/ErbB-2 tyrosine kinase inhibitor, GW2016, on the growth of human normal and tumor-derived cell lines in vitro and in vivo. Mol Cancer Ther 2001; 1: 85–94.
11. Xia W, Liu LH, Ho P, Spector NL. Truncated ErbB2 receptor (p95ErbB2) is regulated by heregulin through heterodimer formation with ErbB3 yet remains sensitive to the dual EGFR/ErbB2 kinase inhibitor GW572016. Oncogene 2004; 23: 646–653.
12. Fujita T, Doihara H, Kawasaki K et al. PTEN activity could be a predictive marker of trastuzumab efficacy in the treatment of ErbB2-overexpressing breast cancer. Br J Cancer 2006; 94: 247–252.
13. Budman DR, Calabro AR. Synergistic combinations of ErbB tyrosine kinase inhibitors and conventional chemotherapy: in vitro median effect analysis in cell lines. Proceedings of San Antonio Breast Cancer Conference (SABCS) 2002; Abs 521.
14. Magne N, Fischel JL, Dubreil A, et al. ZD1839 modifies the activity of key enzymes linked to fluoropyrimidine activity : rational basis for a new combination therapy with capecitabine. Clin Cancer res 2003; 9: 4735–4742.
15. Johnston SRD. Clinical efforts to combine endocrine agents with targeted therapies against epidermal growth factor receptor/human epidermal growth factor receptor 2 and mammalian target of rapamycin in breast cancer. Cin Cancer Res 2006; 12: 1061–1068s.
16. Chu I, Blackwell K, Chen S, Slingerland J. The dual ErbB1/ErbB2 inhibitor, lapatinib (GW572016), cooperates with tamoxifen to inhibit both cell proliferation- and estrogen-dependent gene expression in antiestrogen-resistant breast cancer. Cancer Res 2005; 65: 18–25.
17. Zhou H, Kim YS, Peletier A et al. Effects of the EGFR/HER2 kinase inhibitor GW572016 on EGFR- and HER2-overexpressing breast cancer cell line proliferation, radiosensitization, and resistance. Int J Radiat Oncol Biol Phys 2004; 58: 344–352.
18. Grana TM, Sartor CI, Cox AD. Epidermal growth factor receptor autocrine signaling in RIE-1 cells transformed by the Ras oncogene enhances radiation resistance. Cancer Res 2003; 63: 7807–7814.
19. Geyer G, Cameron D, Lindquist D et al. A Phase II randomised, open-label international study comparing Lapatinib and Capecitabine versus Capecitabine in women with refractory advanced or metastatic breast cancer (EGF100151). Late breaking abstract. American Society of Clinical Oncology Annual Meeting 2006
20. Geyer G, Cameron D, Lindquist D et al. A Phase II randomised, open-label international study comparing Lapatinib and Capecitabine versus Capecitabine in women with refractory advanced or metastatic breast cancer (EGF100151). Late breaking clinical trial data presented orally at American Society of Clinical Oncology Annual Meeting 2006.
21. Therasse P, Arbuck SG, Eisenhauer EA et al. New Guidelines to Evaluate the Response to Treatment in Solid Tumours. J Natl Cancer Inst 2000; 92: 205–216.
22. Perez EA, Byrne JA, Hammond IW et al. Results of an analysis of cardiac function in 2,812 patients treated with lapatinib. J Clin Onc 2006 ASCO Annual Meeting Proceedings Part I Volume 24 (June 20 Suppl): 583.
23. Perez EA, Byrne JA, Hammond IW et al. Results of an analysis of cardiac function in 3,127 patients treated with lapatinib. Oral presentation at American Society of Clinical Oncology Annual Meeting 2006.
24. Lin NU, Bellon JR, Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004; 22: 3608–3617.
25. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003; 97: 2972–2977.
26. Lin NU, Carey LA, Liu MC et al. Phase II trial of lapatinib for brain metastases in patients with HER2+ breast cancer. J Clin Oncol 2006; ASCO Annual Meeting Proceedings Part I Volume 24 (June 20 Suppl): 503.

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

The difficulty with lapatanib is that it is likely to be expensive, and suitable only for a very small minority of patients who have a limited life expectancy (median survival < 40 weeks in patients who received the combination regimen). The license is not for lapatanib monotherapy, but for lapatanib plus capecitabine. Patients with advanced or metastatic breast cancer who are HER2+, and have progressed on anthracycline, taxane and trastuzumab and who are ineligible for any ongoing lapatinib study may receive lapatinib, through an expanded access programme, involving approximately 30 UK centres.

The expanded access programme is registered as a clinical trial and run in accordance with local standard operating procedures. Patients will receive lapatinib until disease progression. The study endpoints are PFS, OS and safety. Patients will also be asked to enrol in an optional pharmacogenetics study.

The expanded access programme will close to new patients when lapatinib receives marketing authorisation; however, lapatinib will continue to be provided, free of charge, for those patients already enrolled in the expanded access programme prior to marketing authorisation, until the point of disease progression.

Anticipated Licence Developments

There are a number of ongoing clinical trials investigating the role of lapatinib in breast cancer. These include trials in both HER2+ and HER2– breast cancer, and of lapatinib both as a single agent and in combination with other therapeutic agents, including:

- First-line HER2+ advanced or metastatic breast cancer.
- First-line hormone sensitive advanced or metastatic breast cancer.
- Adjuvant management of early breast cancer.

An anticipated future indication for lapatinib is for the first-line treatment of hormone-responsive advanced or metastatic breast cancer in combination with letrozole. A phase III trial to support this indication is near to completion and expected to be presented during 2007. There are ongoing trials of lapatinib in other EGFR+

tumours, including renal cell carcinoma, carcinoma of the bladder, squamous cell carcinoma of the head and neck, non-small cell lung cancer and pancreatic carcinoma.