surgery for breast cancer are relevant: "I am pleased that I was able to cope and that I did get a choice, but I should not have had to fight for this . . .". Approaches to breast cancer should not vary so much from one hospital to another, nor should treatment be dependent on the opinion of one surgeon. It should not be, as one doctor put it, "a kind of lucky dip . . . I hope that in future all women will be given the opportunity to choose the most appropriate form of treatment on the basis of clearly presented information. Until there is a clear consensus that one form of treatment is better than all others in terms of survival the patient must be able to participate in any decision about what is to be done with her body" [17].

The statement from the King's Fund Forum on the treatment of primary breast cancer included a recommendation that ". . . if the woman is fully involved in decisions about her own care without feeling patronised she is most likely to feel positive about the treatment she elects, however distasteful it may be; if she is free to refuse treatment, frank discussion of her reasons for refusal will minimise resentment on either side and a relationship of trust will be established, making it easier for both parties should problems occur" [18].

It is hoped that this paper will encourage further work to be undertaken in this area so that standards can be set and guidelines written for managing patients with early breast cancer so that they can be offered a choice of treatment. Within the context of the purchaser–provider division, it is important that contract specifications are developed to allow consideration of issues other than those relating to cost-effectiveness.

1. Cancer Research Campaign. Fact Sheet 6.1: Breast Cancer. 1991.
2. Fisher B, Redmond C, Poisson R, *et al.* Eight-year results of a randomised clinical trial comparing total mastectomy and lumpectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1989, **312**, 665–673.
3. Morris J, Farmer A, Royle G. Recent changes in the surgical management of early breast cancer in England. *Eur J Cancer* 1992, **28A**, 1709–1712.
4. McCarthy M, Bore J. Treatment of breast cancer in two teaching hospitals: a comparison with consensus guidelines. *Eur J Cancer* 1991, **27**, 579–582.
5. Gazet JC, Rainsbury R, Ford H, Powles T, Coombers R. Survey of treatment of primary breast cancer in Great Britain. *Br Med J* 1989, **290**, 1793–1795.
6. NIH Consensus Conference. Treatment of early-stage breast cancer. *JAMA* 1991, **265**, 391–395.
7. Ganz P, Schag A, Lee J, Polinsky M, Tan S. Breast conservation versus mastectomy. Is there a difference in psychological adjustment or quality of life in the year after surgery? *Cancer* 1992, **69**, 1729–1738.
8. Fallowfield L, Hall A, Maguire GP, Baum M. Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. *Br Med J* 1990, **301**, 575–580.
9. Morris J, Royle G. Offering patients a choice of surgery for early breast cancer: a reduction in anxiety and depression in patients and their husbands. *Soc Sci Med* 1985, **26**, 583–585.
10. Wilson R, Hart A, Dawes P. Mastectomy or conservation: the patient's choice. *Br Med J* 1988, **297**, 1167–1169.
11. Wolberg W, Tanner M, Romsaas E, Trump D, Malec J. Factors influencing options in primary breast cancer treatment. *J Clin Oncol* 1987, **5**, 68–74.
12. Nattinger A, Gottlieb M, Veum J, Yahnke D, Goodwin J. Geographic variation in the use of breast conserving treatment for breast cancer. *N Engl J Med* 1992, **326**, 1102–1107.
13. Morris J, Ingham R. Choice of surgery for early breast cancer: psychosocial considerations. *Soc Sci Med* 1988, **27**, 1257–1262.
14. Lasry JC, Margolese R. Fear of recurrence, breast-conserving surgery and the trade-off hypothesis. *Cancer* 1992, **69**, 2111–2115.
15. Forrest P. *Breast Cancer Screening.* London, HMSO, 1986.
16. Tabar L, Gad A, Holmberg L, *et al.* Reduction in mortality from breast cancer after mass screening with mammography. *The Lancet* 1985, **i**, 829–832.
17. Prior A. Personal view. *Br Med J* 1987, **295**, 920.
18. King's Fund Forum. Consensus development conference: treatment of primary breast cancer. *Br Med J* 1986, **293**, 946–947.

Eur J Cancer, Vol. 29A, No. 13, pp. 1803–1804, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00
Pergamon Press Ltd

Facilitating Phase I Trials of Products of Recombinant DNA Technology

RECOMBINANT DNA technology has opened the way for the investigation of a vast range of new proteins and peptides with potential for cancer therapy. The initial use of this technology to produce human hormones and cytokines has been greatly extended by advances in protein engineering which make it possible to design and produce proteins and peptides which do not occur naturally. Improved knowledge of cancer biology creates many opportunities for exploiting this technology.

The novel engineered molecules are being exploited to control growth of cancer cells, to target cancer-related antigens, for catalytic activity and to activate or avoid recognition by the immune system. Fusion proteins in which two or more functions are combined in the same recombinant molecule provide remarkable opportunities for the design of novel therapeutic agents. Molecules which combine antitumour antibody with cytokine or enzyme functions are early examples of applications of fusion proteins to tumour targeting of the cytokine or enzyme.

The ability to genetically engineer proteins combined with the practicality of producing useful quantities of the novel agents in eukaryotic or prokaryotic cells is established. Many are being produced in universities and research institutes without direct involvement of the pharmaceutical industry. How are these products which present new questions about safety, quality and efficacy to be exploited in the diagnosis and therapy of cancer?

It is recognised that the requirements of the licensing authority with regard to physicians undertaking a limited trial of a drug on their own responsibility, are less demanding than those required of a drug company seeking a clinical trial certificate, for which requirements have already been defined. Careful preclinical testing is still essential but it is appropriate that the costs of production and toxicology are not prohibitive and destructive to the venture. The value of animal testing is limited

Received 16 June 1993; accepted 29 June 1993.

as far as cancer is concerned because human cancers are unique and not accurately mimicked by animal models. Thus the effects on tumour and on normal tissues cannot be predicted in more than general terms from animal studies. There is, therefore, a need to define appropriate preclinical testing for phase I trials. Information from such clinical studies is a suitable test for many of the new products of recombinant DNA technology because they are designed specifically for actions in man which are not accurately reproduced in animal models.

The Cancer Research Campaign Phase I/II Trials Committee has addressed similar problems in development of cytotoxic drugs and monoclonal antibodies, producing operation manuals of control recommendations for products prepared for investigational administration to patients with cancer in phase I trials. This group, together with the National Institute for Biological Standards and Control and the EORTC Group for Biological Agents has now produced an operation manual for products of recombinant DNA technology which is published in this issue (pp. 1907–1910). This defines suitable preclinical testing which is within the scope of academic departments or capable of being contracted out at a moderate cost.

With the route for phase I studies facilitated in this way, clinical investigators can more easily address the challenging problems of characterisation of the biological effects of these exciting new agents in man.

R. Begent
Department of Clinical Oncology
Royal Free Hospital School of Medicine
Rowland Hill Street
London NW3 2PF
U.K.

Eur J Cancer, Vol. 29A, No. 13, pp. 1804–1805, 1993.
Printed in Great Britain

0959–8049/93 $6.00 + 0.00

Firmer Evidence on the Value of Breast Screening—the Swedish Overview

Jocelyn Chamberlain

MORE HAS been done in Sweden to evaluate breast cancer screening than in any other country. No fewer than five randomised controlled trials have been carried out between 1976 and 1990, in Kopparberg, Ostergotland, Malmo, Stockholm and Gothenburg. The Kopparberg and Ostergotland trials, together known as the Two Counties Study, published their first results in 1985, showing a 31% reduction in breast cancer deaths 7 years after women were first invited for screening [1]. This positive outcome, together with similar findings from the original screening trial conducted 10 years earlier in New York [2], and three retrospective studies also indicating a reduction in risk of breast cancer death in screened women [3–5], led many authorities to conclude that breast cancer screening had been adequately tried and tested and was now ready for widespread implementation [6].

But several months later, consternation was caused by publication of Malmo results which showed only a 4% non-significant mortality reduction, appearing only *after* the scheduled 'end' of the trial, 10 calendar years from its start, equivalent to an average period of follow-up for each woman of 8.8 years [7]. Much emphasis was placed in this report on validation of the cause of death among patients with breast cancer. An independent death review committee found that for 15 out of 193 deaths in patients with breast cancer there was a possibility of biased classification, and with a difference of only three deaths between the invited and control groups such a level of misclassification could have led to biased conclusions about the effectiveness of screening.

Recognising that the Malmo study lacked statistical power because of its small sample size, and that this problem could to a lesser extent also constrain the Stockholm and Gothenburg studies, the Swedish Cancer Society initiated an independent review of combined data from all five trials in order to reach a more definitive answer on the extent to which screening could reduce breast cancer mortality in Swedish women [8].

A team was appointed to conduct the overview headed by a senior oncologist, and comprising epidemiologists and clinicians who had not been involved in any of the trials. Unlike meta-analyses which aggregate 'raw' ungrouped data from a number of trials, or overviews which sum up already published data, this team chose a different approach. Their method was specifically designed to ensure consistency between the five trials (a) in the completeness of ascertainment of the main end-point — death from breast cancer; (b) in its classification by an independent committee; and (c) in the method of analysis. The only data from the original trials submitted to the overview was a register of every woman in the trials, including identification details, date of birth, date of randomisation, and randomisation group — invited or control. These registers were then merged into one and matched against the Swedish national death register (100% complete) and cancer registry (98% complete). From these sources all 1301 women who had been diagnosed with breast cancer after their date of entry to the trial, and who had died of any cause before 1 January 1990, were selected for special study.

Copies of their death certificates, autopsy reports, pathology reports and medical records were obtained; some clinical information about the period leading up to death was available for 99% of cases. The relevant records, blinded as to identity and randomisation group, were then reviewed by an end-point committee consisting of the pathologist, surgeon, oncologist and radiologist from the overview team. The deaths were classified as follows: (i) breast cancer was the underlying cause of death; (ii) active breast cancer was present at death although not necessarily the underlying cause; or (iii) active breast cancer was not present at the time of death. Each member of the end-point committee assessed each case independently and their

Correspondence to J. Chamberlain at the DH Cancer Screening Evaluation Unit, The Institute of Cancer Research, Section of Epidemiology, 15 Cotswold Road, Sutton, Surrey SM2 5NG, U.K.
Received 18 June 1993; accepted 29 June 1993.