press BC growth. Contralateral BC rates were reduced in randomised trials by adjuvant goserelin added to other adjuvant therapies including tamoxifen and by adjuvant anastrozole compared to tamoxifen with short term follow-up. A new international trial, IBIS II, will be launched in 2002 comparing anastrozole to tamoxifen or placebo in postmenopausal women at increased risk. The NSABP STAR trial is comparing tamoxifen with raloxifene. The "RAZOR" pilot trial is investigating the use of goserelin and raloxifene in premenopausal women at very high risk.

Outside of trials, strategies may vary with personal circumstance (age and risks of uterine cancer, thrombosis and osteoporosis) and preferences (attitude to surgery and importance of continued ovarian function. Population strategies however aim to optimise risk-benefit and cost-benefit ratios and are not necessarily relevant to individual women.

20 INVITED

Update on new studies in Europe

J. Cuzick. *Imperial Cancer Research Fund, Mathematics, Statistics & Epidemiology, London WC2A 3PX, UK*

Three European prevention studies using tamoxifen are now maturing and should provide definitive evidence on the role of tamoxifen in prevention in the next few years. New studies are focusing on the value of directly reducing oestrogen levels. The IBIS-II study will randomise 10,000 high risk post-menopausal women between anastrozole, tamoxifen and placebo, and another 4000 women between anastrozole and tamoxifen. The recent ATAC data have shown that anastrozole can reduce recurrence by 27% in receptor positive women compared to tamoxifen and new contralateral tumours have been reduced by 58% compared to tamoxifen, suggesting a 70–80% reduction compared to no treatment. The side effect profile appears to be more favourable, with fewer hot flushes, endometrial cancers, thromboembolic events, and strokes. However, fracture rates are increased.

In premenopausal women, pilot studies with zoladex are being undertaken. The key question here is the most effective 'add-back' agent or agents in terms of bone preservation and menopausal studies. These different pilot studies are exploring the use of raloxifene, tibolone, and bisphosphonates as add-back.

An Italian study – HoT is evaluating the role of low-dose tamoxifen (5 mg/day) in reducing breast cancers associated with HRT.

Wednesday, 20 March 2002 14:45–16:15

SYMPOSIUM

New standards of care in adjuvant endocrine therapy

21 INVITED

The rationale of the new endocrine agents

M. Dowsett. *Royal Marsden Hospital - NHS Trust, Professor of Biochemical Endocrinology, London, United Kingdom*

The rationale for the most widely used medical endocrine therapies is invariably based around the antagonism or withdrawal of oestrogen stimuli to oestrogen receptor and/or progesterone receptor positive breast cancer. The methods of withdrawal differ according to the menopausal status of the patient. In premenopausal women the aim is to block ovarian stimulation using GnRH agonists. There are now GnRH antagonists in late stage development which have the advantage of no initial gonadal stimulation and in contrast to GnRH agonists achieve persistent FSH suppression which may yield more complete ovarian ablation. In postmenopausal women, third generation aromatase inhibitors have been shown to achieve near complete oestrogen deprivation. Cell-line data indicate that increased sensitivity to residual oestrogens occurs after long-term oestrogen deprivation, and there are clinical data consistent with this. This observation suggests that the completeness of oestrogen withdrawal with aromatase inhibitors may be important. Recent data have demonstrated that in post-menopausal women such oestrogen deprivation is more effective than the selective oestrogen receptor modulator (SERM) tamoxifen. This may be due to significant agonist activity of tamoxifen which is more pronounced at low oestrogen levels. Some preclinical and clinical data indicate that the differential effectiveness of oestrogen deprivation and tamoxifen is greater in the presence of HER-2 and/or EGFr. These observations enhance the need for a SERM with no breast agonist activity and provide a rationale for the pure anti-oestrogen ICI 182780 which has a double effect on reducing oestrogen stimulation: antagonism at the level of ER and destabilisation of ER leading to reduced ER levels.

22 INVITED

LHRH agonists

R. Jakesz. *Vienna University, Dept. of Surgery, Vienna, Austria*

Ovarian ablation in the adjuvant treatment of premenopausal patients has shown to improve recurrence-free and overall survival over untreated controls.

In premenopausal women with hormone-responsive tumors, ovarian ablation and CMF chemotherapy produce identical longterm effects with respect to recurrence-free and overall survival.

Patients who develop amenorrhea upon chemotherapy show a significantly better longterm outcome than those retaining their mensis. These results clearly demonstrate that ovarian ablation is an important tool to improve the prognosis of premenopausal patients with hormone-responsive tumors.

LHRH agonists serve to produce reversible ovarian supression and, in premenopausal women with estrogen receptor-positive disease, have resulted in 5-year recurrence-free survival rates that are identical to those achieved with CMF.

A trial conducted by the Austrian Breast and Colorectal Cancer Study Group randomized patients to receive either a combination of LHRH analog (goserelin) and tamoxifen or adjuvant CMF chemotherapy. After a median survival of 5 years, patients undergoing endocrine treatment experienced significantly superior relapse-free survival over those treated with CMF.

In turn, Intergroup Trial 0101 in premenopausal women with hormone receptor-positive tumors allocated patients to either anthracycline-containing chemotherapy alone, to a combination with goserelin, or to a combination with goserelin and tamoxifen. The addition of combined endocrine treatment to chemotherapy yielded significantly superior recurrence-free survival benefits not achieved by the chemotherapy-goserelin combination.

In summary, LHRH analogs are to be considered an important tool in the treatment of premenopausal patients with hormone-responsive breast cancer. Goserelin and CMF are shown to be equally effective modalities. Finally, goserelin-tamoxifen combination treatment is superior to CMF, and this combination added to FAC is significantly more effective than FAC alone.

23 INVITED

Current status of aromatase inhibitors

M. Baum. *The Portland Hospital, Department of Oncology, London, United Kingdom*

Aromatase inhibitors prevent oestrogen biosynthesis in tissues by inhibiting the enzyme aromatase, which catalyses the conversion of adrenal androgens (androstenedione and testosterone) to oestrogens (oestrone and oestradiol). Aromatase activity is present in many tissues, but the main sources of circulating oestrogens are the ovaries in premenopausal women and the adipose tissue in postmenopausal women. Furthermore, unlike most other hormonal pathways, oestrogen concentrations in postmenopausal women are not under feedback control. Aromatase inhibitors can therefore reduce circulating oestrogen concentrations to below the limit of detection.

Aminoglutethimide was the first aromatase inhibitor to be approved for the treatment of breast cancer, but this drug lacked specificity and had troublesome side effects. A new generation of both steroidal and non-steroidal aromatase inhibitors which are highly selective, are well tolerated and have demonstrated clinical effectiveness in the treatment of advanced breast cancer are currently under investigation in the adjuvant setting for postmenopausal women.

The new generation of oral specific aromatase inhibitors, such as Anastrazole, make a very attractive option for adjuvant therapy in ER positive postmenopausal women. In fact the largest and most rapidly recruited trial in the history of the subject (ATAC)involving over 9,000 patients has just been reported.This study compares Anastrozole with Tamoxifen alone or in combination. Other trials making use of alternative aromatase inhibitors,cross over or sequencing with tamoxifen or as perioperative therapy are also in progress.

24 INVITED

Faslodex, a new pure antagonist for endocrine therapy of breast cancer.

C.K. Osborne, R. Schiff. *Breast Center Baylor College of Medicine, Houston, Texas, USA*

Although many breast cancer patients whose tumors are estrogen receptor (ER) positive benefit from endocrine therapy, most will eventually develop acquired resistance over time. Tamoxifen is a selective estrogen receptor modulator that demonstrates both estrogen agonist and antagonist qualities when bound to ER depending on the tissue and gene. Faslodex was developed as a new steroidal antiestrogen with more complete estrogen antagonist properties. The drug inhibits both transcription activating functions of ER and induces ER degradation and loss from the cell. Faslodex binds ER with an affinity similar to estradiol. In a pre-clinical in vivo model of human breast cancer, Faslodex was more potent than either estrogen withdrawal or tamoxifen. The time from start of treatment to the development of resistance was twice as long with Faslodex. Furthermore, tumors that eventually developed acquired resistance to prolonged estrogen withdrawal or to tamoxifen were both inhibited by Faslodex suggesting that this class of antiestrogens could reverse resistance developing to SERM therapy. Clinical trials of Faslodex confirmed this hypothesis. In a small study it was shown to be effective in tamoxifen-resistant patients, and in two large Phase III trials Faslodex was found to be at least as effective as Arimidex in patients with tamoxifen-resistance. Side effects are minimal in patients with breast cancer. In conclusion, Faslodex is the first of a new class of endocrine therapy that works by completely antagonizing ER-induced gene transactivation, and by reducing ER levels in the cell. It is effective in tamoxifen-resistant patients and offers a new alternative for the endocrine therapy of breast cancer.

25 INVITED

New standards of care in adjuvant endocrine therapy. How do we integrate these new drugs in daily practice?

C. Rose. *Department of Oncology, University Hospital, Lund, Sweden*

Cytotoxic and endocrine therapy are important parts in the management of most women with breast cancer both in the adjuvant and metastatic settings. Until recently oophorectomy and Tamoxifen have been considered the treatment of choice for first line endocrine therapy in pre- and postmenopausal women with metastatic breast cancer. In the past few years newer forms of endocrine therapy have been introduced and based upon available evidence first line endocrine therapy in the metastatic setting for premenopausal women is now a combined approach with an LH-RH agonist and Tamoxifen. Likewise, 3 generation aromatase inhibitors are considered the drugs of choice for first line endocrine therapy in postmenopausal women. Fulvestrant (Faslodex) has demonstrated comparable activity to Anastrozole and can be considered for second line endocrine therapy like progestins and aromatase inhibitors in previously Tamoxifen treated patients.

Although, the first data regarding aromatase inhibitors in the adjuvant setting is encouraging, they still have to be used in the context of control trials whereas LH-RH agonists already now are considered safe substitutes for surgical castration. So far, the role of Fulvestrant in the adjuvant setting is unclear. Important remaining questions are the role of combined chemo-endocrine therapy including the specific aromatase inhibitors and a proper sequence of the various forms of endocrine therapy when we consider treatment in the adjuvant and metastatic setting as a continuum.

Wednesday, 20 March 2002 14:45–16:15

SYMPOSIUM

Long term results of early breast cancer

26 INVITED

Is breast cancer curable?

S. Hellman[1], R. Heimann[2]. *[1] University of Chicago, Dept of Rad & Cell Onc, Chicago, USA; [2] University of Chicago, Dept of Rad & Cell Onc, Chicago, USA*

The title suggested by the conference organizers "Is Breast Cancer Curable?" suggests that breast cancer may not be a curable disease since recurrence continues to occur and those who die without recurrence would have eventually recurred had they not succumbed to another disease. These views derive from past studies of patients with seemingly localized disease in which there continued to be recurrences long after treatment. Further, some investigators suggest that those patients apparently cured of their cancer have a tumor with the appearance of a cancer but with no malignant potential. Using a large series of patients treated with curative intent for seemingly localized disease, we present evidence supporting the cure of breast cancer in a significant proportion of breast cancer patients. The force of recurrence decreases with time with a plateau eventually reached. There are still occasional patients recurring but this is uncommon. Only 3.7% of our 20yr recurrence-free survivors eventually had a recurrence comprising 1.3% of our total recurrences. We describe two characteristics of the recurrence-free curves for the various clinical patient groupings: V or virulence, the initial rate of recurrence; M or metastagenicity, 1-M is the proportion of patients on the plateau or 'cured'. Virulence increases with size and axillary nodal involvement. 1-M decreases with size and node involvement but in all groups a plateau is reached. Large tumors with many involved axillary nodes are more likely to recur and these recurrences appear sooner. Identification of the likelihood of cure can be determined earlier in advanced disease although the probability of cure decreases with advancing stage. A similar analysis of a recent series of patients treated with lumpectomy and radiation was performed. V varies depending on the method of diagnosis (mammography or physical examination), size, nodal involvement, and adjuvant treatment. In each patient group V is lower than in the older study. The 8-year median survival of this recent series is too short to determine M.

The results are most consistent with breast cancer being a curable disease although one cannot assure any individual patient of their being free of their cancer. Rather, the likelihood of being cured increases with time.

27 INVITED

Local recurrences after conserving therapy

L. Cataliotti. *University of Florence, Surgery Department, Florence, Italy*

Conservative surgery is now the usual therapy for small invasive tumours. The surgeon must combine the width of the excision with the cosmetic result carrying out as large an excision as possible with the smallest cosmetic damage or doing the smallest possible excision with minor oncological risk. Conservative surgery is always followed by radiotherapy and therefore the role the latter can play in the local control of the disease should not be forgotten. Tumour radiosensitivity evaluation is an important parameter to consider. The primary role of surgery is local control. In many cases, local control also means general control of the disease. There are many risk factors for a local recurrence after conservative surgery. Some of these can be evaluated before surgery and must be taken into account by the surgeon's operative plan. Particularly, the surgeon should know the patient's age, tumour size, the presence or not of multifocality and the radiological pattern. If available, he should have cytological or histological results too. This information often leads to a larger or smaller excision because his aim is to obtain a free margin. Margin's status is one of the most important factors in as much as it is a variable the surgeon can control, while the biological characteristics are not affected by treatment. The difficulty is to define which is an adequate margin and this varies according to the tumour aggressiveness. The histological factors associated with an increase risk of local recurrence after conservative treatment are particularly the high grade extension of intraductal component (E.I.C.) adjacent to the primary tumour and macroscopic margin involvement in the presence of vascular invasion. From a technical point of view the surgeon has to choose the best procedure to obtain free margins not forgetting, however, the cosmetic results.