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## STATE-OF-THE-ART IN THE MANAGEMENT OF CANCER

# BREAST CANCER — PART IV CURRENT TREATMENT MODALITIES

### BREAST CANCER STAGING AND PROGNOSIS

Treatment of breast cancer is based on tumor histologic type and disease stage, and the patient's age, menopausal status, and general health. Once a histopathologic diagnosis of breast cancer is established, disease stage is determined in order to plan suitable therapy. The two most common breast cancer staging methods used today are clinical and pathological (see Exhibit 1). Although stage and pathology form the evaluation/end-point basis for most modern clinical trials and determine treatment options, the goal of investigators is to define the biologic activity of the tumor in order to identify biologic markers that may further predict the tumor's behavior and more accurately guide therapy.

Breast cancer incidence at first diagnosis by stage in the USA and elsewhere is estimated in Exhibit 2. Incidence by hormonal status by stage in the USA and elsewhere is estimated in Exhibit 3 and 5-year survival by stage in Exhibit 4. There are major racial differences in disease stage at time of first diagnosis and in survival rates (see Exhibits 5 and 6). From 1986-91, the overall 5-year relative survival rate was 84.4% for white American women and 69.4% for African-American women (see Exhibit 6). In terms of stage of disease at time of diagnosis, localized disease was diagnosed in 59% of white women but in 48% of African-American women (see Exhibit 5). In comparison, 6% of cases were distant metastases in whites compared to 9% in African-Americans. Racial differences of cancer stage at diagnosis probably reflect differences in attitudes between the races regarding screening, stemming from socioeconomic and cultural influences, rather than an inherent racial predisposition to more aggressive disease.

Staging, in conjunction with histologic information about tumor type and other patient variables, is employed in a complex decision tree to arrive at optimal treatment. Recently published oncology practice guidelines (Oncology, 10 (11), suppl, November 1996, pp 47-75) developed by the National Comprehensive Cancer Network (NCCN) co-ordinate the collective experience of 15 major institutions with active oncology centers, regarding the state-of-the-art in the treatment of breast and other cancers. These practice guidelines combine information on staging, diagnostic work-up, and primary, adjuvant and neoadjuvant treatment protocols to arrive at a specific regimen for each patient.

Variability in disease progression, treatment response, and survival among patients with similar disease stage and tumor histology, administered similar treatment regimens, points to other factors that need to be defined to identify those with distinct disease types. Generally, prognosis and evolution of primary breast cancer vary considerably among patients despite similar tumor stage and histology. In some patients disease is indolent and is either cured by local therapy or progresses very slowly allowing patients to survive for many years even after developing metastases. Also, a small percent of patients will survive more than 10 years without any treatment. In other patients, however, disease follows an aggressive, rapidly progressive course that is refractory to treatment. Different clinical outcome is usually the result of variability in tumor doubling time as well as other cellular attributes. When compared to other tumors, breast cancer exhibits a low growth fraction (proportion of cells in the cell cycle), with estimated values ranging from 5%-30%, depending on the method used to calculate it. This implies that the majority of cells in a clinically detectable breast tumor are in G0-phase of the cell cycle and do not contribute to tumor growth; on average, only 5% of cells are in S-phase, which is related to proliferative rate. In contrast, in rapidly growing tumors such as testicular cancer or high-grade lymphomas, the S-phase fraction may exceed 50%.

Tumor volume doubling times in primary breast cancer are also prolonged. Various studies found doubling times ranging from 44 to more than 1,800 days (average doubling time is estimated at 200 days). This slow doubling time would require that elapsed time between malignant transformation of a cell to the development of a 1 cm to 2 cm tumor exceeds 20 years. Even if doubling time was 100 days, it would still require 10 years for a tumor to develop to a detectable size. However, truly fast-growing tumors (doubling time of 20 days) may take only 2 years to become detectable. These calculations are based on logarithmic growth that assumes rates are constant throughout tumor development. A more accurate growth model is based on the Gompertzian model of breast cancer proliferation that postulates that tumor cell growth may vary at various tumor stages; for instance, on the average, tumors may grow faster in later stages or metastatic lesions may grow at a faster rate than primary tumors. Generally, however, as is the case with prostate cancer, there seems to be a long period of growth before detection of most breast cancers. It is, therefore, likely that the poorer prognosis associated with breast cancer in younger women (<35 years old) is attributable to more aggressive faster growing tumors because, had they been growing at a slower rate, they would have probably not reached detectable stage so early in the patient's life. Another aspect of slow growing tumors is the fact that delays in diagnosis of a few months from the first symptoms of primary breast cancer do not have a major impact on the presence or absence of metastases or ultimate patient survival. However, although it has been estimated that a three-month or longer delay in diagnosis would adversely affect only 5% of patients, diagnosis and treatment of primary tumors a full year earlier would reduce by 30% the number of patients presenting with

**Exhibit 1**
**Breast Cancer Staging and Populations by Stage**

| Stage (American Joint Committee Classification) | Description | TNM Classification System[1] |
|---|---|---|
| Breast carcer *in situ* | About 13%-20% of breast cancers are early cancers, or carcinoma *in situ;* it is often difficult to distinguish carcinoma *in situ* from invasive breast cancer; Paget's* disease with no associated tumor mass | |
| | Ductal carcinoma *in situ* (DCIS), also known as intraductal carcinoma involves premalignant growth in ducts | $T_{is}, N_0, M_0$ |
| Stage 0 | Lobular carcinoma *in situ* (LCIS) which is not clinically cancer, but it is classified as carcinoma *in situ*, or Stage 0 breast cancer; women with LCIS have a 25% chance of developing breast cancer over the next 25 years of life | |
| Stage I | Tumor is < 2 cm and limited to the breast; 5-year crude survival rate is estimated at 85% (range 82%-94%) | $T_1, N_0, M_0$ |
| Stage II | Stage II is associated with a 5-year crude survival rate of 66% (range 47%-74%) and is defined by any of the following: | |
| Stage IIA | Tumor is > 2 but <5 cm and may or may not have spread to the axillary lymph nodes | $T_0, N_1, M_0; T_1, N_1, M_0; T_2, N_0, M_0$ |
| Stage IIA | Tumor is > 5 cm but has not spread to the axillary lymph nodes | $T_2, N_0, M_0$ |
| Stage IIB | Tumor is less than 2 centimeters but has spread to the axillary lymph nodes | $T_2, N_1, M_0; T_3, N_0, M_0$ |
| Stage III | Stage III is associated with a 5-year crude survival rate of 41% (range 7%-80%) | |
| Stage IIIA | Tumor is <5 cm and has spread to the axillary lymph nodes, which have grown into each other or into other attached structures; or tumor is > 5 cm and has spread to the axillary lymph nodes; operable | $T_0, N_2, M_0; T_3, N_1, M_0; T_{0-3}, N_2, M_0$ |
| Stage IIIB | Tumor has spread to tissues near the breast (skin, chest wall, including the ribs and muscles in the chest); or tumor has spread to lymph nodes inside the chest wall along the breast bone; inoperable or inflammatory (inflammatory breast cancer is rare and spreads rapidly; the breast appears inflamed because of its red appearance and warmth; the skin may show signs of ridges and wheals or it may have a pitted appearance; inoperable | $T_4$, any N, $M_0$; any T, $N_3, M_0$ |
| Stage IV | Tumor has spread to other organs of the body, most often bone, lungs, liver, or brain, or locally to the skin and lymph nodes inside the neck, near the collarbone; crude 5-year survival rate is only 10% | Any T, any N, $M_1$ |
| Recurrent breast cancer | In recurrent disease cancer reappears after "successful" treatment; it may recur in the breast, the chest wall, or elsewhere in the body | |

***Legend:***

***Primary tumor (T):***

*TX: Primary tumor cannot be assessed*
*$T_0$: No evidence of primary tumor*
*$T_{is}$: Carcinoma in situ*
*$T_1$: Tumor 2.0 cm or less in greatest dimension***
*$T_{1a}$: 0.5 cm or less in greatest dimension*
*$T_{1b}$: > 0.5 cm but not <1.0 cm in greatest dimension*
*$T_{1c}$: > 1.0 cm but <2.0 cm in greatest dimension*
*$T_2$: Tumor >2.0 cm but <5.0 cm in greatest dimension***
*$T_3$: Tumor >5.0 cm in greatest dimension***
*$T_4$: Tumor of any size with direct extension to chest wall or skin; chest wall includes ribs, intercostal muscles, and serratus anterior muscle but not pectoral muscle*
*$T_{4a}$: Extension to chest wall*
*$T_{4b}$: Edema (including peau d'orange), ulceration of the skin of the breast, or satellite skin nodules confined to the same breast*
*$T_{4c}$: Both of the above ($T_{4a}$ and $T_{4b}$)*
*$T_{4d}$: Inflammatory carcinoma*

***Regional lymph nodes (N):***

*$N_X$: Regional lymph nodes cannot be assessed (e.g., previously removed)*
*$N_0$: No regional lymph node metastasis*
*$N_1$: Metastasis to movable ipsilateral axillary lymph node(s)*
*$N_2$: Metastasis to ipsilateral lymph node(s) fixed to one another or to other structures*
*$N_3$: Metastasis to ipsilateral internal mammary lymph node(s)*

***Distant metastasis (M):***

*$M_X$: Presence of distant metastasis cannot be assessed*
*$M_0$: No distant metastasis*
*$M_1$: Distant metastasis present (includes metastasis to ipsilateral supraclavicular lymph nodes)*

**Paget's disease associated with tumor mass is classified according to the size of the tumor.*

metastases. These findings somewhat confirm the notion of biological predetermination that sets forth the theory that only certain tumors are predetermined by biological attributes to metastasize.

Heterogeneity of breast cancer complicates patient management. Tumor biology and growth rate factors dictate different treatment protocols. However, these factors do not always adequately predict prognosis. One

**Exhibit 2**
**Estimated Stage Distribution of Female Breast Cancer at Time of Diagnosis in Selected World Regions**

| | USA | | North America | | Europe | | Former USSR | | Japan | | Triad* | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Stage | Cases (#) | % | Cases (#) | % | Cases (#) | % | Cases (#) | % | Cases (#) | % | Cases (#) | % |
| Localized | 107,631 | 58.4 | 118,494 | 58.4 | 170,069 | 55.6 | 54,143 | 54.6 | 14,493 | 58.2 | 303,056 | 56.8 |
| Regional | 59,345 | 32.2 | 65,334 | 32.2 | 102,470 | 33.5 | 31,831 | 32.1 | 8,043 | 32.3 | 175,847 | 32.9 |
| Distant | 11,058 | 6.0 | 12,174 | 6.0 | 21,717 | 7.1 | 8,726 | 8.8 | 1,519 | 6.1 | 35,411 | 6.6 |
| Unstaged | 6,266 | 3.4 | 6,899 | 3.4 | 11,623 | 3.8 | 4,462 | 4.5 | 847 | 3.4 | 19,369 | 3.6 |
| All Stages | 184,300 | 100.0 | 202,900 | 100.0 | 305,880 | 100.0 | 99,163 | 100.0 | 24,902 | 100.0 | 533,682 | 100.0 |

**Triad includes North America, Europe (excluding the former USSR) and Japan.*

would assume that fast-growing tumors would require aggressive treatment because of their poor prognosis, while indolent disease that is unlikely to compromise survival may be managed more conservatively sparing the patient the morbidity and cost associated with certain interventions, but this is not the case and it is speculated that many additional tumor or host factors need to be identified to more accurately predict patient outcome.

Among currently employed prognostic factors are degree of tumor nuclear differentiation, tumor necrosis, tumor size (tumors < 2.0 cm are associated with poor prognosis), tumor aggressiveness or metastatic potential, tumor growth rate and proliferative capacity (thymidine labeling index, S-phase and ploidy), and tumor sensitivity/resistance to planned regimens. Newer prognostic candidates under scrutiny include oncogenes and tumor suppressor genes implicated in breast cancer via various mechanisms such as inhibition (bcl-2) or inducement (p53) of apoptosis, and growth factors implicated in angiogenesis, among others. However, as of today, the role of these markers in any aspect of the management of breast cancer remains undetermined with contradictory or conflicting information emanating from numerous studies. For instance, an 8-year study of the influence of bcl-2 and p53 on the therapeutic value of tamoxifen in women with ER+ tumors, found that high bcl-2 expression was associated with a relatively indolent tumor phenotype that responded to treatment resulting in longer patient survival (Elledge R, etal, ASCO96, Abs. 159:123).



## STANDARD TREATMENT BY STAGE

Most strategies in the anticancer armentarium are employed against breast cancer with regimens selected based on disease stage and tumor histology. Although early disease is managed by either mastectomy or lumpectomy with radiation therapy, numerous combination chemotherapies, monotherapies and multimodality approaches, including transplantation of autologous hematopoietic cells, are employed to combat locally advanced or metastatic disease (see Exhibit 7). Drugs marketed worldwide for the treatment of breast cancer are listed in Exhibit 8.

### Carcinoma *in situ*

About 13%-20% of breast cancers are early cancers, or carcinomas *in situ.* There are two types of breast cancer *in situ,* ductal carcinoma *in situ* (DCIS), also known as intraductal carcinoma, and lobular carcinoma *in situ* (LCIS). LCIS is not actually cancer, but for classification purposes it is referred to as carcinoma *in situ*, or Stage 0 breast cancer. Women with this condition have a 1% chance per annum of developing breast cancer in either breast within 25 years after diagnosis. Carcinoma *in situ* is difficult to distinguish from either LCIS or invasive breast cancer.

***DCIS*** is a proliferation of a subgroup of epithelial cells that are confined to the mammary ducts, not having extended through the basement membrane and invaded the stroma. Among the various types of DCIS (comedo, cribriform, solid, papillary, and micropapillary), comedo DCIS is associated with increased rates of local recurrence, and may progress to invasive breast cancer more rapidly than other types. It has also been observed that neu is overexpressed in solid or comedo types of DCIS but not in small-cell papillary or cribriform types, although there is no proven correlation between neu overexpression and tumor size. Also, the significance of ER and progesterone receptor (PgR) status in DCIS has not been established.

Controversy surrounds the diagnosis, prognosis and treatment of DCIS. Epidemiology cannot be used to assess this lesion's likelihood of evolving into full-fledged cancer because many DCIS lesions are removed during biopsy and others are misdiagnosed as benign. Many recommend aggressive treatment of DCIS, basing their opinion on the premise that breast cancer is a progressive disease and DCIS is an early manifestation that will eventually evolve into invasive mode. Others, however, cite the many problems arising from a DCIS diagnosis which is most commonly made in women under the age of 50:

- may stigmatize women for life because, for the purposes of obtaining employment, loans, health and life insurance, DCIS is considered in the same vein as invasive cancer
- may unnecessarily mutilate women because the

**Exhibit 3**
**Estimated Stage Distribution of Breast Cancer by Hormonal Status at Time of Diagnosis in Selected World Regions**

| | USA | | North America | | Europe | | Japan | | Triad | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Stage** | **Cases (#)** | **%** | **Cases (#)** | **%** | **Cases (#)** | **%** | **Cases (#)** | **%** | **Cases (#)** | **%** |
| Carcinoma *in situ* | 28,290 | 13.3 | 31,152 | 13.3 | 46,830 | 13.3 | 3,825 | 13.3 | 81,808 | 13.3 |
| DCIS | 22,542 | 10.6 | 24,821 | 10.6 | 37,347 | 10.6 | 3,047 | 10.6 | 65,215 | 10.6 |
| LCIS | 5,748 | 2.7 | 6,331 | 2.7 | 9,483 | 2.7 | 778 | 2.7 | 16,592 | 2.7 |
| Stage I | 84,630 | 39.8 | 93,176 | 39.8 | 135,794 | 38.5 | 11,347 | 39.5 | 240,317 | 39.0 |
| ER + | 59,241 | 27.9 | 65,223 | 27.9 | 95,056 | 27.0 | 7,943 | 27.7 | 168,222 | 27.3 |
| ER - | 25,389 | 11.9 | 27,953 | 11.9 | 40,738 | 11.6 | 3,404 | 11.9 | 72,095 | 11.7 |
| Stage II | 62,565 | 29.4 | 68,882 | 29.4 | 105,499 | 29.9 | 8,503 | 29.6 | 182,884 | 29.7 |
| ER + | 43,796 | 20.6 | 48,217 | 20.6 | 73,850 | 20.9 | 5,952 | 20.7 | 128,019 | 20.8 |
| ER - | 18,770 | 8.8 | 20,664 | 8.8 | 31,650 | 9.0 | 2,551 | 8.9 | 54,865 | 8.9 |
| Stage III | 12,147 | 5.7 | 13,364 | 5.7 | 21,204 | 6.0 | 1,637 | 5.7 | 36,205 | 5.9 |
| ER + | 8,503 | 4.0 | 9,355 | 4.0 | 14,843 | 4.2 | 1,146 | 4.0 | 25,344 | 4.1 |
| ER - | 3,644 | 1.7 | 4,009 | 1.7 | 6,361 | 1.8 | 491 | 1.7 | 10,862 | 1.8 |
| Stage IV | 8,113 | 3.8 | 8,941 | 3.8 | 14,461 | 4.1 | 1,120 | 3.9 | 24,522 | 4.0 |
| ER + | 5,679 | 2.7 | 6,259 | 2.7 | 10,123 | 2.9 | 784 | 2.7 | 17,166 | 2.8 |
| ER - | 2,434 | 1.1 | 2,682 | 1.1 | 4,338 | 1.2 | 336 | 1.2 | 7,357 | 1.2 |
| Unknown | 16,845 | 7.9 | 18,537 | 7.9 | 28,922 | 8.2 | 2,294 | 8.0 | 49,753 | 8.1 |
| All Stages | 212,590 | 100.0 | 234,052 | 100.0 | 352,711 | 100.0 | 28,727 | 100.0 | 615,490 | 100.0 |
| Excluding CIS | 184,300 | 86.7 | 202,900 | 86.7 | 305,880 | 86.7 | 24,902 | 86.7 | 533,682 | 86.7 |
| ER + | 129,010 | 60.7 | 142,030 | 60.7 | 214,116 | 60.7 | 17,432 | 60.7 | 373,577 | 60.7 |
| ER - | 55,290 | 26.0 | 60,870 | 26.0 | 91,764 | 26.0 | 7,471 | 26.0 | 160,105 | 26.0 |



recommended treatment, i.e. mastectomy rather than lumpectomy with/without radiation therapy, may be too aggressive for a lesion that may never develop into an invasive malignancy in a woman's lifetime

Additional diagnostic and prognostic tests are necessary to decide whether mammography-detected DCIS is a lesion that may evolve into invasive malignancy and should be treated or if it is truly indolent and should be left alone. It is possible that in the patient presenting with DCIS certain other biologic markers are in evidence that are more reliable predictors of the eventual emergence of invasive disease. In the absence of these markers DCIS would be preferably given a different name and considered a benign condition.

Even with treatment, breast cancer recurs in of 9%-21% of DCIS cases, but only one half of these are invasive carcinomas. Total mastectomy, the standard treatment for DCIS currently used in 50% all detected cases, results in a combined local and distant recurrence rate of 1%-2% per year. The other alternative approach is conservative surgery (lumpectomy) combined with radiotherapy. Salvage mastectomy is also used after recurrences with survival rates comparable to primary mastectomy. No randomized comparisons of mastectomy versus conservative surgery plus radiation therapy have been undertaken. However, study B-17 of the National Surgical Adjuvant Breast and Bowel Project (NSABP) randomly assigned 790 women with localized DCIS and negative margins, following excisional biopsy, to breast irradiation (50 Gy) or no further therapy; 80% of all enrolled patients were diagnosed by mammography and 70% had lesions ≥ 1.0 cm. Addition of radiation therapy improved 5-year event-free survival that was attributed entirely to a decrease in ipsilateral breast cancers. Also, cumulative incidence of recurrent DCIS at 5 years, was reduced by radiation from 10.4% to 7.5%, and occurrence of invasive cancer decreased from 10.5% to 2.9%. The only risk factors identified in the DCIS patients, namely absence of clear tumor margins and moderate to significant comedo necrosis, did not sufficiently alter rate of recurrence in the radiation arm to make mastectomy the preferable option. Also, mortality was not appreciably different from that encountered in patients treated by mastectomy. Lumpectomy with radiotherapy and tamoxifen for the treatment of DCIS is currently under evaluation. The NSABP is currently conducting a trial (B-24) of 1,800 women with DICS randomly assigned, following local excision, to either radiation therapy plus tamoxifen or radiation therapy plus placebo.

**Exhibit 4**
**Estimated Five-Year Survival of Female Breast Cancer by Stage in Selected World Regions**

| | USA | | North America | | Europe | | Triad | |
|---|---|---|---|---|---|---|---|---|
| **Stage** | **(#)** | **(%)** | **(#)** | **(%)** | **(#)** | **(#)** | **(#)** | **(%)** |
| Localized | 103,380 | 96.1 | 113,872 | 96.1 | 147,068 | 85.5 | 266,997 | 87.3 |
| Regional | 44,419 | 74.9 | 48,935 | 74.9 | 65,721 | 64.9 | 120,238 | 68.8 |
| Distant | 2,184 | 19.8 | 2,410 | 19.8 | 3,267 | 15.3 | 6,002 | 17.6 |
| Unstaged | 3,387 | 54.1 | 3,732 | 54.1 | 4,471 | 43.1 | 9,042 | 49.9 |
| All Stages | 153,370 | 83.2 | 168,949 | 83.3 | 220,527 | 72.3 | 402,279 | 75.5 |

***LCIS*** which arises from the small end ducts (lobules) of the breast, is characterized by clusters within lobules of anaplastic small cells of good nuclear grade. LCIS is usually discovered incidentally at biopsy. When the lesion extends beyond the boundary of the lobule from which it arises, it is known as invasive lobular carcinoma and may be indistinguishable from the conventional infiltrating duct carcinoma. LCIS, also referred to as lobular neoplasia, is considered a marker for the subsequent development of invasive disease rather than a premalignant lesion. LCIS is generally widely distributed throughout the breast and is frequently bilateral. A patient with LCIS has a 1% chance per annum of developing invasive cancer (either lobular or, more commonly, infiltrating duct cancer) in either breast. The true incidence of lobular carcinoma is unknown.



Like DCIS, the clinical management of LCIS is also controversial; options include no treatment after biopsy with careful follow-up (physical examination and mammography) or bilateral prophylactic mastectomies. Axillary lymph node dissection is not necessary for the *in situ* lesion. Many physicians favor periodic examination and mammography without therapy, provided patients are aware of the risk of developing invasive cancer and of the possibility of developing metastatic cancer before a clinical diagnosis is established. Patients with locally excised LCIS are eligible for a large multicenter clinical trial of tamoxifen to prevent development of invasive cancer.

## Stage I Breast Cancer

Stage I breast cancer is often curable using various surgical options such as mastectomy, mastectomy with reconstruction, or conservative surgery (i.e., lumpectomy) plus radiotherapy. However, patients managed with surgery alone experience a relapse rate of about 21% within a 10 to 20-year follow-up. Survival is equivalent with any of these options as documented in prospective randomized trials. Surgical procedures that conserve a major portion of the involved breast, followed by radiotherapy, have been shown to provide tumor control equivalent to more extensive surgical procedures. Axillary lymph node dissection is also performed because histologic involvement is found in approximately one third of patients with clinically negative nodes. In the node-negative patient, ER and PR status, tumor size, and measures of proliferative capacity are highly predictive for risk of relapse. Those considered at low risk of relapse may not require post-operative adjuvant hormonal therapy or chemotherapy. High histologic grade and high rate of mitosis may identify a high-risk subset of patients with $T_1$ lesions less than 1.0 cm in size.

Meta-analysis of randomized clinical studies involving over 75,000 pre- or post-menopausal women with Stage I or II breast cancer who were treated by systemic hormonal, cytotoxic, or biologic therapy methods, was performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) to assess treatment effectiveness. The analysis found that hormonal therapy with tamoxifen (20 mg daily for at least 2 years or perhaps longer) in post-menopausal ER+ women, prevented recurrent disease and increased survival, with the benefits of initial treatment persisting for up to 10 years; in view of these findings, it is suggested that ER- women may also benefit from tamoxifen treatment. Additionally, there was a decreased incidence of carcinoma in the contralateral breast and decreased cardiovascular mortality in women treated with tamoxifen. Cytotoxic chemotherapy, usually with CMF for 6-12 months, was also shown to decrease recurrence and increase survival in all patients with Stages I and II disease. Ovarian ablation in women under the age of 50 produced a survival benefit comparable to that seen with chemotherapy in pre-menopausal women, suggesting that a portion of the impact of systemic chemotherapy is through an endocrine mechanism similar to ovarian ablation. For instance, in one study, a 12-week chemotherapy regimen that induced menopause less frequently than a 36-week regimen, was associated with poorer survival. Also, treatment with ovarian ablation and chemotherapy may have an additive effect, as would tamoxifen and cytotoxic chemotherapy in post-menopausal women. Adjuvant chemotherapy with a proven effective regimen may be suitable for certain ER- patients. Although routine use of adjuvant chemotherapy in all patients with ER-, node- cancer remains controversial, it may prove appropriate in patients with a poor prognosis.

## Stage II Breast Cancer

Stage II breast cancer, similarly to Stage I disease, is curable with surgical intervention. Axillary lymph node dissection is also done for staging purposes and, when clinically positive nodes are present, such dissection may have a localized therapeutic benefit.

***Post-operative chest wall radiotherapy*** is considered in selected patients with residual tumor after surgery or at a high-risk for locoregional failure, including those with four or more involved axillary nodes. In these patients radiotherapy may decrease locoregional recurrence even in those treated by adjuvant chemotherapy.

***Adjuvant combination chemotherapy*** administered to positive-node breast cancer patients results in prolonged disease-free interval and survival for both pre- and post-menopausal patients. Standard duration of administration of such chemotherapy must not exceed one year. Adjuvant hormonal therapy with tamoxifen, administered for at least two years, prolongs disease-free interval and perhaps overall survival of node+, post-menopausal women with hormone-receptor-positive tumors. CA and CMF regimens (see Exhibit 8) seem to produce similar results in terms of disease-free survival in both pre- and post-menopausal patients; choice of regimen depends on the combination's toxicity profile. In a trial by the NSABP (B-16), node+, PR+ women between the ages of 50-59 years and women 60 years of age and older irrespective of receptor status, experienced an improvement in disease-free and overall survival when treated with tamoxifen and chemotherapy (CA) compared to those treated with tamoxifen alone. A study by the Eastern Cooperative Oncology Group (ECOG; Denver, CO), comparing CMFP and CMFPT to surgery alone in node+ post-menopausal patients, reported a disease-free survival benefit with CMFP in ER- patients, but overall survival was not prolonged. In contrast, CMFPT, administered for 1 year, failed to improve either disease-free or overall survival. ER+ women experienced no benefit on either regimen. A trial comparing tamoxifen alone to CMFVP alone or CMFVP plus tamoxifen, conducted by the Southwest Oncology Group (SWOG; San Antonio, TX) in 966 node+, post-menopausal, ER+ women, demonstrated that CMFVP alone or in combination with tamoxifen was not superior to tamoxifen alone. The 5-year survival rate is 77% for the tamoxifen arm, 78% for CMFVP, and 75% for the combination. Severe or worse toxicity was experienced by 56% of patients on CMFVP and 61% on CMFVP plus tamoxifen, compared with 5% on tamoxifen alone. CMFVP chemotherapy, either alone or in combination with tamoxifen, has not been shown to be superior to tamoxifen alone in the treatment of ER+, node+, post-menopausal women with operable breast



**Exhibit 5**
**Stage Distribution of Breast Cancer by Race in the USA at Time of Diagnosis**

| | Overall Distribution | | Others Distribution | | Blacks Distribution | |
|---|---|---|---|---|---|---|
| **Stage** | **(#)** | **(%)** | **(#)** | **(%)** | **(#)** | **(%)** |
| ***In Situ*** | 28,290 | 13.3 | 25,726 | 13.3 | 2,564 | 13.4 |
| Stage I | 84,630 | 39.8 | 79,498 | 41.1 | 5,132 | 26.8 |
| Stage II | 62,565 | 29.4 | 55,900 | 28.9 | 6,665 | 34.8 |
| Stage III | 12,147 | 5.7 | 10,445 | 5.4 | 1,702 | 8.9 |
| Stage IV | 8,113 | 3.8 | 6,963 | 3.6 | 1,150 | 6.0 |
| Unknown | 16,845 | 7.9 | 14,894 | 7.7 | 1,951 | 10.2 |
| All Stages | 212,590 | 100.0 | 193,426 | 100.0 | 19,164 | 100.0 |

**Exhibit 6**
**Stage Distribution and Five-Year Survival of Female Breast Cancer in the USA by Race**

| | DISTRIBUTION | | | | FIVE-YEAR SURVIVAL | | | |
|---|---|---|---|---|---|---|---|---|
| | Other | | Blacks | | Other | | Blacks | |
| **Stage** | **(#)** | **(%)** | **(#)** | **(%)** | **(#)** | **(#)** | **(#)** | **(%)** |
| Localized | 98,943 | 59.0 | 7,968 | 48.0 | 95,717 | 96.7 | 7,095 | 89.0 |
| Regional | 53,664 | 32.0 | 6,308 | 38.0 | 41,021 | 76.4 | 3,806 | 60.3 |
| Distant | 10,062 | 6.0 | 1,494 | 9.0 | 2,037 | 20.2 | 241 | 16.1 |
| Unstaged | 5,031 | 3.0 | 830 | 5.0 | 2,799 | 55.6 | 385 | 46.3 |
| All Stages | 167,700 | 100.0 | 16,600 | 100.0 | 141,574 | 84.4 | 11,527 | 69.4 |

**Exhibit 7**
**Drugs on the Market Worldwide for the Treatment of Breast Cancer**

| Brand Name/Generic Name/ Number/Developer and Affiliates/Market | Description/Mechanism of Action/Indication | Delivery/Dosage/Average Wholesale Price (AWP) | Market Status/Comments |
|---|---|---|---|
| Adriamycin PFS/doxorubicin/ Pharmacia & Upjohn/ WW market is estimated at $134 million in 1995 and $110 million in 1996 | Cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius* var. *Caesius*; DNA topoisomerase I and II inhibitor/ binds nucleic acid by intercalation with the DNA base pairs | Injectable/60-75 mg/m$^2$ (monotherapy), single injection, every 21 days; 40-60 mg/m$^2$ (in combination) single injection, every 21-28 days/$241.56 for 50 mg | Multisource (Rubex; Bristol-Myers Squibb); widely used anticancer agent; maximum cumulative lifetime dose of doxorubicin and daunorubicin is 550 mg/m$^2$ |
| Adriamycin RDF/doxorubicin/ Pharmacia & Upjohn | See above | Injectable/same as above/ $230.00 for 50 mg | Same as above |
| Afema/fadrozole (CGS-16949a, CGS-20287)/Ciba-Geigy (Novartis) | Aromatase inhibitor/ post-menopausal breast cancer | PO | L (96)/Japan; phase III (94)/ USA, Europe |
| Android/methyltestosterone/ ICN | Synthetic androgen/secondary treatment of post-menopausal women (1 to 5 years) with advanced inoperable metastatic (skeletal) breast cancer | PO/50-200 mg daily/ $1.12 for 10 mg | |
| Anzatax/paclitaxel/Faulding; NaPro Bio Therapeutics (licensor) | Paclitaxel formulation | Injectable | A (1/95)/Australia/advanced breast and ovarian cancer |
| Aredia/pamidronate disodium/ Ciba-Geigy; Chiron (exclusive USA rights)/sales are estimated at $40 million in the USA in 1996 | Bisphosphonate/bone resorption inhibitor/bone pain in advanced or metastatic breast cancer | Injectable/initial single dose of 60 mg (4-hour infusion) to 90 mg (24-hour infusion)/ $383.36 for 60 mg | A (7/96) and L(96)/USA, UK |
| Arimidex/anastrozole (ZD-1033, ICI-D-1033)/ Zeneca Group | Aromatase inhibitor/blocks enzyme responsible for estrogen synthesis/advanced breast cancer in postmenopausal women with disease progression after tamoxifen therapy | PO/1 mg once daily/$6.00 for 1 mg | L/UK (9/95), USA (3/96), Ireland, Luxembourg, A (1/96)/Europe and other major markets outside Japan |
| Bondronat or Bonviva/ ibandronate/Boehringer Mannheim | Bisphosphonate/tumor-induced hypercalcemia | IV/2-hour infusion of 2-4 mg/$1,330 for 5 mg/ml in Germany | A (6/96)/Europe; L (12/96)/Germany and Austria |
| Cyclophosphamide | Alkylating agent/cross-links tumor cell DNA/treatment of breast cancer alone or in combination with other cyctotoxic agents | PO/1-5 mg/kg/day; IV/40-50 mg/kg in divided doses over 2-5 days; 10-15 mg/kg every 7-10 days; 3-5 mg/kg twice weekly/$2.91 for 50 mg | Multisource (Cytoxan; Mead Johnson Oncology, Neosar; Pharmacia & Upjohn); broad anticancer indications |
| Decapeptyl/triptorelin (AY-25650, BIM-21003, BN-52104, WY-42422)/Debio Recherche Pharmaceutique; Tulane U (licensor), Pharmacia & Upjohn (licensee, NA) | Gonadorelin analog, polypeptide analog of LHRH | PO (CR, SR) and depot | Launched in over 85 countries outside North America; NDA (6/96) pending in the USA; see FO, V2 #2/3, p 304 |
| Doridamina/lonidamine (AF-1890, KN-228)/Angelini and various licensees | Derivative of indazole carboxylic acid, radio/chemosensitizer, potentiates anticancer drug activity | | Launched outside the USA, in Europe (Italy 86, Portugal 90), phase II in Japan; also indicated for prostate cancer; see FO, V2 #2/3, p 304 |
| Estrace/17b-estradiol/ Mead Johnson | Induces gene transcription by binding to and activating nuclear estrogen receptors/palliative treatment of breast cancer | PO/10 mg three times daily for at least three months/ $0.44 for 2 mg | |
| Estratab/esterified estrogens/ Solvay | Palliative treatment of metastatic breast cancer | PO/10 mg three times daily for at least three months | |
| Fareston/toremifene (FC-1157, FC-1157a, NK-622)/ Orion Pharma (Farmos), Schering-Plough (USA); Nippon Kayaku | Anti-hormonal agent; antiestrogen/advanced breast cancer | PO/$1.7 for one 60 mg tablet in Ireland | Approvable (10/96)/USA; launched outside the USA, UK (7/96) |

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| | | | |
|---|---|---|---|
| Femara/letrozole (CGS-20267)/ Chugai and Ciba-Geigy (Novartis) | Aromatase inhibitor/selective non-steoidal aromatase inhibitor/ second-line treatment of advanced breast cancer in post-menopausal patients after antiestrogen therapy | PO/2.5 mg daily ($7 for one 2.5 mg tablet in the UK) | L (12/96)/UK; A (7/96)/France; approvable (12/16; NDA f7/96)/USA; phase II (3/96)/Japan |
| Fluorouracil (5-FU) Systemic | Antimetabolite; thymidine synthetase inhibitor/inhibits formation of DNA-specific nucleoside base thymidine/ management of symptoms of breast cancer | IV/12 mg/kg/day for 4 consecutive days (up to 800 mg daily); if no toxicity is observed, 6 mg/kg on days 6, 8, 10 & 12/$1.54 for 500 mg (Adrucil) | Multisource (Adrucil; Pharmacia & Upjohn) |
| Fluorouracil (5-FU) Topical | | Topical/cream 5%, 25 gm at $36.90; solution 5%, 10 ml at $32.57 (Roche); cream 1%, 30gm at $34.83; solution 1%, 30 ml at $34.83 (Allergan) | Multisource (Efudex; Roche, Fluroplex; Allergan) |
| Formestane/Lentaron/ Ciba-Geigy (Novartis) | Selective aromatase inhibitor/ advanced breast cancer | IM injection/ 250 mg q 2 weeks | A (95)/UK, Germany, France; when evaluated at 250 and 500 mg IM fornightly, objective RR was 24.7% (8 CR, 10 PR) and 34.2% (12 CR, 15 PR), respectively (Bajetta, E, etal, ASCO96, Abs. 106:110) |
| Frone/Ares Serono | Fibroblast-derived IFN-β/ adjuvant therapy for breast cancer | | Approved outside the USA since 1982 for various indications including adjuvant therapy for breast cancer |
| Furtulan/doxifluoridine/Roche | | | Marketed in Japan and Korea; also used in ovarian cancer |
| Halotestin/fluoxymesterone/ Pharmacia & Upjohn | Androgenic hormone/palliative treatment of androgen-responsive recurrent mammary cancer in women who are >1 but <5 years postmenopausal or have hormone-dependent tumors | PO/10-40 mg daily/ $0.46 for 2 mg | L/USA |
| Lupron, Lupron Depot, Leuplin/leuprorelin leuprolide acetate (TAP-144SR)/TAP Pharmaceuticals (Abbott Laboratories and Takeda jv)/ 1995 global sales (prostate cancer and gynecological diseases) for all formulations are estimated at $667 million | Leuteinizing hormone-releasing hormone (LHRH) agonist/potent inhibitor of gonadotropin/ palliative treatment of advanced breast cancer in peri-menopausal women | Subcutaneous injection/1 mg (0.2 ml) daily/ $278.12 for 5 mg/ml for 2 weeks<br><br>Depot suspension/7.5 mg monthly/$496.25 for 7.5 mg | Launched in the USA (85) and in over 30 countries worldwide; marketed by TAP in the USA, Abbott in Canada, Latin America and Europe (Enantone) and Takeda (Leuplin, launched in Japan in 1992) elsewhere; patent expired in 1996; also approved in a three-month (84-day) 22.5 mg formulation in December 1995, based on an ANDA filed in December 1994; TAP will conduct phase IV to compare the two dosage forms |
| Megace/megestrol acetate/ Mead Johnson Oncology (Bristol-Myers Squibb) | Synthetic antineoplastic and progestational drug/pallative treatment of advanced breast cancer | PO/160 mg/day (40 mg four times daily)/$1.30 for 40 mg | Multisource (Barr Laboratories, Par Pharmaceuticals) |
| Methotrexate | Antimetabolite/inhibits dihydrofolic acid reductase; interferes with DNA synthesis, repair and cellular replication/used alone or in combination with other cytotoxics | Injectable/$4.75 for 50 mg | Multisource (Immunex, Pharmacia & Upjohn) |
| Miltefosin, Miltex, Navoban/ hexadecylphosphocholine, miltefosine (D-18506, HPC)/ Asta Medica Kayaku (Asta Medica jv with Nippon Kayaku) | Phospholipid derivative/ cutaneous metastatic breast cancer | PO | L/Germany (93), France, Brazil |



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| | | | |
|---|---|---|---|
| Navelbine/vinorelbine tertrate, NVB (KW-2307)/Pierre Fabre; Kyowa Hakko; Glaxo Wellcome (North America) | Semi-synthetic vinca alkaloid; norvinblastine derivative/interferes with microtubule assembly; inhibits mitosis at metaphase/advanced breast cancer | IV, PO/$49.18 for 10 mg | L (91)/France and elsewhere in Europe and in French speaking Africa; prereg (95)/Japan; L (USA)/nsclc (see FO,V1 #6, p 94) |
| Nilandron (USA), Anandron/nilutamide (RU-23908)/Roussel Uclaf (Hoechst) | Antiandrogen with a long duration of action | PO/50 mg tablet | Launched outside the USA in South America, France (87); prereg/Canada/breast cancer; A (11/96)/USA/prostate cancer |
| Nolvadex/tamoxifen citrate/Zeneca, NCI/WW market is estimated at $580 million in 1995 | Nonsteroidal antiestrogen/binds estrogen receptors/metastatic breast cancer and delay of recurrence of tumors following a mastectomy | PO/one or two 10 mg dose administered twice daily (morning and evening)/$1.53 for 10 mg | Launched WW; patent expired outside the USA where it expires in 2002; sales of Barr's tamoxifen were about $143 million in fiscal 1995 and $171 million in 1996 |
| Novantrone/mitoxantrone HCL/Immunex; Wyeth-Ayerst (Canadian rights) | Synthetic anthrecenedione; DBA-reactive agent/DNA intercalator; inhibits topoisomerase II; cytocidal effect on both proliferating and nonproliferating cultured cells/breast cancer in postmenopausal women after surgery and irradiation and metastatic breast cancer | Injectable/$720.04 for 20 mg | A (3/96)/Canada/various indications including advanced breast cancer; L/USA /ANLL (see FO, p 299 and 316) |
| Taxol/paclitaxel (BMS-181339)/Bristol-Myers Squibb/NCI | Taxane, antimicrotubule agent; tubulin-active agent/enhances tubulin polymerization and stabilizes microtubules/2nd line treatment for metastatic breast cancer | IV/administered to premedicated patients at 175 mg/m$^2$ over 3 hours every three weeks/$182.63 for 30 mg | A (4/94)/USA and globally; WW sales were $340 million in 1994, $580 million in 1995, and are expected to to exceed $800 million in 1996 (they were $604 million in the first nine months of 1996) and $1 billion annually by the end of the decade (see FO, V1 #7/8) |
| Taxotere/docetaxel (NSC-628503, RP-56976)/Rhône-Poulenc Rorer; Chugai (co-develoment and marketing, Japan), NCI | Taxane/acts on cellular microtubules, promoting their assembly and blocking their breakdown/anthracycline-resistant locally advanced or metastatic breast cancer | IV/100 mg/m$^2$, over 1 hour repeated every 3 weeks/$1,587 per cycle | Available in 36 countries; A/Europe; (5/96)/USA and (10/96)/Japan |
| Teslac/testolactone/Bristol-Myers Squibb | Aromatase inhibitor/adjunct treatment for palliation of advanced or disseminated breast cancer | PO/250 mg qid/$1.29 for 50 mg | |
| Testred/methyltestosterone/ICN Pharmaceuticals | Synthetic derivative of testosterone/second-line hormonal treatment of advanced breast cancer | PO/50-200 mg daily/$1.37 for 10 mg | |
| Thioplex/lyophilized thiotepa/Immunex; American Home Products (Canadian rights); also Thiotepa/Immunex; Lederle Laboratories (American Home Products); WW sales for Thioplex and Thiotepa were $20 million in 1995 | Alkylating agent; nitrogen mustard-derived; ethylenimine-type compound/selectively reacts with DNA phosphate groups to produce chromosomal cross-linking; blocks nucleoprotein synthesis, releases ethylenimine radicals disrupting DNA bonds/palliative treatment of breast adenocarcinomas | IV/rapid administration of 0.3-0.4 mg/kg at 1-4 week intervals/$78.45 for 15 mg | L (2/95)/USA; used as a palliative for various late stage cancers, has a more stable and longer shelf life than Thiotepa |
| UFT/tegafur + uracil (BMS-200604-01)/Taiho, Bristol-Myers Squibb (licensee; North and Latin America and European rights) | Fluoropyrimidine | PO | Approved for breast cancer in Japan, Spain and Asia; may be pursued for breast cancer in other countries; see FO, p 55 |



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| | | | |
|---|---|---|---|
| Velban/vinblastine sulfate/ Eli Lilly | Vincalekoblastine sulfate/inhibits microtubule formation in the mitotic spindle; arrests cell division at metaphase/palliative treatment of breast cancer unresponsive to surgery and hormonal therapy | Injectable/initial dose of 3.7 mg/m$^2$; second, third, fourth and fifth dose schedule of 5.5, 7.4, 9.25, or 11.1 mg/m$^2$; maximum dose is 18.5 mg/m$^2$/$38.92 for 10 mg | Recommended for administration not more than once every seven days |
| Zinecard/dexrazoxane/ Pharmacia & Upjohn | Potent intracellular chelating agent derivative of EDTA/reduces anthracycline-induced cardiac toxicity associated with DOX in metastatic breast cancer | Injectable/recommended dosage ratio of Zinecard: DOX is 10:1 (e.g., 500 mg/m$^2$ Zinecard:50 mg/m$^2$ DOX)/$268.75 for 500 mg | Approved for use in women with metastatic breast cancer previously treated with at least 300 mg/m$^2$ DOX; L (1/96)/USA, Canada |
| Zoladex/goserelin acetate (CI-118630)/Zeneca; Zeneca Yakuhin KK (Zeneca & Sumitomo jv; Japan) | Gonadotropin-releasing hormone agonist; LHRH analog/lowers estrogen serum levels to typical postmenopausal levels/palliative treatment of advanced breast cancer in pre- and peri-menopausal women | Implant/3.6 mg implant administered by subcutaneous injection into the upper abdominal wall every 28 days/$383.65 at 3.6 mg | Approved (1/96)/USA and 36 other countries; L/Sweden, A(95)/UK/France, Finland, the Netherlands (see FO,V2 #2/3, p 305) |

cancer (Rivkin SE, etal, Journal of Clinical Oncology, 1994 Oct, 12(10):2078-85). Similarly, a multicenter study comparing CMF with CEF (which replaces doxorubicin with epirubicin) in pre-menopausal women did not show any difference in overall survival or in relapse-free survival between the two treatment groups at 4.5 years. Early (before 6 weeks after surgery) initiation of adjuvant chemotherapy in node+ patients does not seem to influence disease-free survival. Also, the 10-year survival rate for both pre-and post-menopausal women treated with 6 or 12 cycles of CMF has been shown to be identical.

### Node-Negative Breast Cancer

Treatment of patients with primary breast cancer and negative axillary nodes remains controversial. Although it has been assumed that because of a good prognosis such cancers need only be treated with surgery, findings from two NSABP trials in which no treatment other than surgery was used, showed an unacceptable rate of tumor recurrence and death from breast cancer. In one of the trials, treatment failed in approximately 25% of patients and 15% died within 5 years of follow-up. The 1985 NIH consensus conference on early-stage breast cancer did not recommend adjuvant therapy in node+ patients but the 1990 NIH consensus conference considered the fact that adjuvant chemotherapy with six cycles of CMFP is effective in improving 5-year disease-free survival among high-risk patients with operable axillary node- breast cancer. The greatest impact of chemotherapy appears to be in ER+ and post-menopausal patients. Meta-analysis of trials involving 75,000 women reported that for those between the ages of 50 and 69 years old with early breast cancer, chemotherapy plus tamoxifen is better than chemotherapy alone for delaying recurrence or death and better than tamoxifen alone for delaying recurrence (Lancet, 1992 Jan 4, 339(8784):1-15).

It would be desirable to identify markers that would predict the likelihood of relapse in node- patients so only those at risk are treated with adjuvant chemotherapy. In 1,800 patients treated with locoregional procedures until relapse, only cell proliferation measurements predicted incidence of both locoregional and distant metastases and survival, regardless of the status of such other prognostic factors as patient age, tumor size or ER or PgR status. Hormone receptor status was a significant indicator of distant metastasis and overall survival (Silvestrini R, etal, J Clin Oncol, March 1995, 13:697-704).



### Stage IIIA (Operable) Breast Cancer

Operable cases are initially treated by either modified radical or radical mastectomy. Because of the high risk of local recurrence, radiotherapy such as external-beam irradiation to the chest wall is included in the standard protocol. A boost may also be indicated in patients with positive or close margins. Adjuvant and neoadjuvant chemotherapy with or without hormonal therapy are also indicated. Commonly used combination chemotherapy regimens that were shown to be equally effective, are listed in Exhibit 8.

Clinical trials evaluating combination chemotherapy with or without hormonal manipulation are ongoing (see Exhibit 11). Preliminary data indicate that neoadjuvant chemotherapy may allow breast conservation in previously unsuited candidates. High-dose chemotherapy with hematopoietic cell support is also indicated in suitable patients.

### Stage IIIB (Inoperable) Breast Cancer

In Stage IIIB breast cancer, including inflammatory cancer, surgery is generally limited to the initial biopsy. Radiotherapy is used to treat locoregional disease and systemic chemotherapy to treat occult metastases. For

patients with Stage IIIB breast cancers, neoadjuvant chemotherapy after biopsy and prior to local therapy with surgery or radiotherapy, may result in tumor shrinkage and early systemic control. A recent preliminary report observed biopsy-confirmed complete responses following combination chemotherapy prior to local treatment. Surgical removal of residual tumor may be performed if a good response is achieved with the other therapies employed.

If the response with preoperative chemotherapy is good, local therapy with surgery and/or irradiation is recommended. If the response is poor, palliative radiotherapy is recommended. If combination chemotherapy is contraindicated, pretreatment with tamoxifen may be used in patients with ER+ and PR+ tumors. Phase II studies are evaluating newly developed chemotherapeutic or biologic agents which may be considered for patients whose local disease is not controllable with standard regimens. High-dose chemotherapy with hematopoietic stem cell support is also an option.

ECOG is currently conducting a multi-center phase II clinical trial (E-4195) to determine the effectiveness and cardiotoxicity of doxorubicin (DOX)-based induction therapy, followed by paclitaxel, in women aged between 18-70 with Stage IIB/IV breast cancer who have not been previously treated systemically with either anthracyclines or taxanes. The protocol involves induction with DOX (60 mg/m$^2$) administered as a 5-minute infusion on day one, followed by a 3-hour infusion of paclitaxel (200 mg/m$^2$), 10 minutes after DOX, with daily G-CSF (5 μg/kg) support from days 2 until post-nadir ANC ≥ 10,000, repeated every three weeks for four to six courses. Responding patients and those with stable disease are then placed on maintenance therapy with paclitaxel with or without G-CSF, repeated every three weeks for another two or more courses.



### Stage IV Breast Cancer

Stage IV breast cancer is often responsive to treatment with durable complete remissions attainable in 10%-20% of patients, although cure, manifested by long disease-free survival, is rare. Surgery is limited to biopsy procedures to determine histology and ER and PR status and to control local disease (hygienic mastectomy) as an alternative to radiotherapy. External-beam irradiation is also used for palliation of symptoms, particularly pain caused by bone metastases. Patients with Stage IV breast cancer are considered candidates for ongoing clinical trials as described in Exhibit 11. For patients with recurrence after an anthracycline-containing regimen, paclitaxel has been approved by the FDA for second-line therapy.

### Inflammatory Breast Cancer

Inflammatory breast cancer is treated by a combination of chemotherapy, hormonal therapy, and radiation therapy, which may be combined with mastectomy. Treatment is usually similar to that for Stage IIIB or IV breast cancer.

### Recurrent Breast Cancer

Recurrent breast cancer is often responsive to therapy although treatment is rarely curative in metastatic disease. Radiotherapy is used as palliation of locally recurrent disease and symptoms such as pain from bone metastases. Results from long-term follow-up indicate that between 10% and 20% of patients with carcinoma *in situ* will have locally recurrent disease in the breast between 1 and 9 years after lumpectomy plus radiotherapy. For patients with local recurrence, surgery and/or radiotherapy may be curative. ER and PR levels at the time of recurrence and previous treatment are considered in selecting therapy. If ER and PR status is unknown or positive, then the site of recurrence, disease-free interval, response to previous treatment, and menopausal status, are useful in choosing between chemotherapy or hormonal therapy. Prognosis of patients with recurrent breast cancer after lumpectomy plus radiotherapy is much better than for those with chest-wall recurrence after mastectomy. About 9%-25% of patients who opt for lumpectomy plus radiotherapy are diagnosed with distant metastases or locally extensive disease that may prevent mastectomy at the time of recurrence.

### Breast Tumor Histology

Breast tumors are classified under a variety of histologic types (see Exhibit 9). The most common ductal tumors, infiltrating duct carcinomas not otherwise specified (NOS) that exhibit no specific histologic structure, account for about 80% of breast cancers; 52.6% of breast cancers are pure infiltrating duct lesions (NOS). Tumors arising from duct epithelium commonly found only within the lumen of these ducts, are intraductal and do not invade surrounding stroma (non-infiltrating). These tumors usually arise from large ducts and may be of different types. One such type, papillary carcinoma, that grows into the ducts accounts for about 1% of breast cancers. Such carcinomas rarely become infiltrating and survival rate after local excision is almost 100%.

### Staging by Hormonal Status

Hormonal status is an important determinant of treatment choice. Incidence of breast cancer by hormonal status and by stage is estimated in Exhibit 3. Nearly all ER- and about 40% of ER+ tumors are resistant to endocrine therapy.

## SURGERY

Surgery is the treatment of choice for early breast cancer and is performed for disease control in all stages of breast cancer. Approximately 600,000 surgical procedures (see Exhibit 10) are performed annually in North America, Europe and Japan, almost equally split between mastectomies and breast conserving procedures (lumpectomies).

### Standard Surgical Interventions

***Mastectomy*** represents the gold standard in curative intervention in early breast cancer. Radical mastectomy

**Exhibit 8**
**Treatment of Breast Cancer by Disease Stage and Hormonal Status**

| Stage | Standard Treatment | Recurrence % | New Approaches in Late Clinical Trials |
|---|---|---|---|
| **Carcinoma *in Situ*** | | | |
| DCIS | Mastectomy or CS+ radiation; rarely, some of the axillary lymph nodes may also be removed during surgery | 1-2 per year; 7.5 at five years; 2.9 at five years invasive | CS + radiation + TAM |
| LCIS | Observation (biopsy, annual follow up) or bilateral mastectomy | | TAM |
| **Stage I** | | | |
| Stage I | CS + radiation or total mastectomy/MRM with separate axillary node dissection | 10-20 at 10 years; 21 (surgery alone) at 10 years | |
| Stage I; more favorable histologic types of tumors > 1.0 cm in size, and diploid tumors with less than a 10% fraction of cells in S phase | As Stage I (probably would not benefit from adjuvant chemotherapy) | | |
| Stage I; node-, poor prognosis (poor nuclear differentiation, tumor necrosis, and tumor size <2.0 cm) | As Stage I+ adjuvant chemotherapy | | TAM or CMF or a combination of methotrexate, 5-FU and leucovorin |
| Stage I; ER+ | As Stage I + TAM | | Ovarian ablation (women >50 years of age) |
| Stage I; ER- | Routine use of adjuvant chemotherapy in patients with ER-, node- cancer remains controversial; however, it may prove appropriate in patients with poor prognosis | | TAM |
| **Stage II** | | | |
| Stage II | CS + radiation or total mastectomy/MRM | 33-44 at 20 years | Neoadjuvant and adjuvant chemotherapy |
| Stage II; negative-node (stage IIA, T2N0M0) | | 33-44 at 20 years | CMF, ovarian ablation; TAM in post-menopausal women |
| Stage II; at high risk of loco-regional recurrence, including those with known residual disease or four or more involved nodes | As Stage II + radiotherapy to the chest wall and regional nodes | | High-dose chemotherapy with hematopoietic cell transplantation in women with four to nine positive lymph nodes |
| Stage II; ER- | As Stage II + chemotherapy for < 1 year | . | >10 nodes-HDC/BMT |
| Stage II; ER+ | As Stage II + TAM | | + adjuvant chemotherapy |
| Stage II; ER+, n+ | Stage II + TAM | | + adjuvant chemotherapy (CA) |
| Stage II; ER+, n+, post-menopausal | As Stage II + adjuvant hormonal therapy with tamoxifen, administered for at least two years prolongs disease-free interval and perhaps survival | | |
| **Stage III** | | | |
| Stage IIIA, ER± | RM/MRM + radiation + combination of adjuvant chemotherapy (CMF, CAF, CA ± TAM, CMFVP, CMFP) | 50-70 at 10 years | Neoadjuvant pre-operative chemotherapy; HDC with hematopoietic cell transplantation combination; cytotoxic chemotherapy and hormonal therapy (HT) |

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| | | | |
|---|---|---|---|
| Stage IIIB; locoregional disease | Radiotherapy; surgical removal of residual tumor may be performed if a good response is achieved with neoaduvant therapy | | HDC with hematopoietic cell transplantation; new agents |
| Stage IIIB; metastatic disease | Systemic chemotherapy for occult metastases; surgical removal of residual tumor (as above) | | |
| **Stage IV** | | | |
| Stage IV | Surgery + radiation + chemotherapy + hormonal therapy | 80-90 at 5 years | New agents; HDC with hematopoietic cell transplantation |
| Stage IV; ER+, PgR+, no visceral disease | As Stage IV + chemotherapy + TAM or oophorectomy for pre-menopausal patients; TAM and progestational agents for post-menopausal patients | | HT |
| Stage IV; ER- | As Stage IV + combination chemotherapy | | |
| Stage IV; ER-, PgR-, or visceral disease | Combination chemotherapy with CMF, or CAF or CA or CMFP or CMFVP | | Combination chemotherapy with/without HT as first-line treatment |
| Inflammatory breast cancer | As Stage IV | | |
| Recurrent breast cancer | Radiotherapy | 15-20 at 10 years | New chemotherapeutic and biologic agents in clinical trials |
| ER+, PgR+, or unknown and no visceral disease | TAM or oophorectomy (or chemical castration with LHRH agonists if surgery cannot be performed) for pre-menopausal patients; TAM or progesterone with megestrol acetate (160 mg daily) for post-menopausal patients; aminoglutethimide | | HT |
| ER-, PgR+, or visceral disease | As Stage IV; also vinorelbine has demonstrated activity in patients who relapse after treatment with an anthracycline-containing regimen and has been effective as first- and second-line treatment in advanced breast cancer | | For metastatic disease, HDC with autologous bone marrow/peripheral stem cell transplantation has been associated with a high response rate, although responses are generally not of long duration |
| Relapse after response to additive HT | As above or androgen therapy for pre- and postmenopausal patients or corticosteroids | | |
| Recurrence after an anthracycline-containing regimen | Paclitaxel or docetaxel as second-line therapy | | |
| Recurrent breast cancer-locoregional or visceral recurrence | Radiotherapy and/or salvage mastectomy | | |
| Recurrent breast cancer-locoregional recurrence | Salvage mastectomy | 50 at 10 years | |

*CS: conservative surgery (lumpectomy, wide excision, quadrantectomy, segmental mastectomy), RM: radical mastectomy; MRM: modified radical mastectomy, HT: hormonal therapy, HDC: high-dose chemotherapy, TAM: tamoxifen, CMF:: cyclophosphamide + methotrexate + fluorouracil, CAF: cyclophosphamide + doxorubicin + fluorouracil, CA: cyclophosphamide + doxorubicin, CMFP: cyclophosphamide + methotrexate + fluorouracil + prednisone, CMFVP: cyclophosphamide + methotrexate + fluorouracil + vincristine + prednisone*

was based on the premise that breast cancer spread through local lymphatic channels and, as a result, the largest the area removed the most likely that most of the tumor was removed, preventing its dissemination. However, in the late 1980s, several randomized clinical trials demonstrated that a more conservative approach, such as simple mastectomy (limited to the breast alone) or lumpectomy produced similar results as more radical approaches. This empirical observation enforced the theory that breast cancer was spread systemically via the circulation and that more conservative surgery with or without radiation was as effective as a more radical approach.

With advances in surgical technique mastectomies have become routine so that it has been suggested that they could be performed on an outpatient basis. Needless to say this brought on an onslaught of objections and the idea has been shelved. Another finding about breast cancer surgery regarding the timing it is performed, may improve its effectiveness. William J. Hrushesky, MD, of Albany Medical College in New York has shown in animal and human studies that performing surgery during the middle of the menstrual cycle results in a four-fold better chance of survival. Retrospective and multivariate analysis confirmed that surgical timing is an independent predictor of cancer recurrence and death.

***Lumpectomy*** (removal of the tumor and immediately surrounding tissue), usually in conjunction with radiation therapy, has gained ground worldwide. In the USA alone, it is estimated that there were about 97,000 lumpectomies in 1995, which still represents a somewhat lower rate than in Europe where lumpectomies are more common than mastectomies in concert with organ conservation practices of European oncologists.

## Novel Surgical Approaches

Research to improve surgical removal of soft tissues such as tumors, including breast cancer, centers on interventions that are minimally invasive or even noninvasive.

***Interstitial laser photocoagulation*** guided by magnetic resonance imaging (MRI) is being used by investigators at the National Medical Laser Centre, University College London Medical School in the UK, to treat primary breast cancer. In interstitial laser photocoagulation a small-diameter single-fiber probe is inserted into the tumor. Laser energy delivered through the probe coagulates tissue adjacent to the probe which may need to be inserted several times for adequate tissue destruction. Twenty female breast cancer patients underwent interstitial laser photocoagulation prior to surgical excision. Gadolinium-enhanced T1-weighted three-dimensional fast low-angle shot (FLASH) MRI was performed before and after laser therapy (median, 48 hours; range, 24-96 hours). Following resection, tumors were mapped in detail histopathologically. The extent of disease, size of laser burn, and extent of residual tumor were correlated with MRI findings. Twenty-seven tumors were detected at histopathologic examination. Twenty-five of the 27 tumors were identified by MRI. Early (4-hour) follow-up images failed to depict the laser effect but later (24-96 hours) images depicted the laser-induced necrosis as a zone of nonenhancement within the residual enhancing tumor (Mumtaz H, etal, Radiology, 1996 Sep, 200(3):651-8).

***Cryosurgery*** may also provide a minimally invasive approach to tissue destruction in breast cancer. UROS (San Diego, CA), announced in August 1996 that it received FDA approval to market the UROSProbe Model 1000 cryosurgical system that may be employed to destroy diseased tissue of the breast, prostate, liver, and kidney. UROS has developed a cryosurgery system that combines the benefits of precise localization of diseased tissue and a minimally invasive procedure. UROSProbe has the potential to allow the precise visualization of both the target and the cryosurgical probe, using a proprietary "chip at the tip" detector as a targeting mechanism.

***Ultrasound***, currently used to localize diseased tissue to facilitate biopsies, may also be used in breast cancer treatment. In focused ultrasound, short exposure times are used to produce tissue destruction with sharp well-defined margins. Focused ultrasound works best when tissues are accessible without interference from gas-filled spaces and bone. Researchers at GE Medical Systems (Milwaukee, WI) in collaboration with Brigham and Women's Hospital and Harvard Medical School (Boston, MA) have combined focused ultrasound surgery and MRI thermometry/guidance to obtain on-line temperature measurements and for accurate targeting of the tissue slated for removal. This system is being currently evaluated for removal of fibroadenomas of the breast.

## RADIATION THERAPY

Radiotherapy is a common treatment modality for almost all stages of breast cancer. Used in combination with lumpectomy as a curative intervention, it allows satisfactory cosmesis in early breast cancer. Radiotherapy consists of external-beam radiation to the entire breast. If a boost is used, it can be given either with an interstitial radioactive implant or by external-beam radiation, generally with electrons.

Radiation side effects that include myocardial damage for left-sided breast lesions, radiation pneumonitis, arm edema, brachial plexopathy, and the risk of second malignancies, may be minimized with careful attention to technique. Techniques are also in place to minimize radiation dose to the contralateral breast to reduce absolute risk of contralateral breast cancer in women under the age of 45. Secondary cancer such as sarcomas in the treatment field and leukemias are very rare. With proper dosimetry risk of lung cancer is minimal in nonsmokers but smokers may run an increased risk of lung cancer in the ipsilateral lung. Also, an increase in non-breast cancer deaths was observed in patients treated by radiation, par-

**Exhibit 9**
**Incidence of Invasive Breast Cancer by Histologic Types at First Diagnosis in the USA**

| Histologic Type | # Cases | % Total | Extrapolated Incidence | Comments |
|---|---|---|---|---|
| **Pure Tumor Groups** | 681 | 68.1 | 125,508 | |
| Infiltrating duct NOS[2] | 526 | 52.6 | 96,942 | Do not exhibit a specific histologic structure |
| Medullary | 62 | 6.2 | 11,427 | Histopathologically distinct invasive carcinomas that arise from large ducts; survival outlook of patients with medullary carcinoma is better than with infiltrating duct carcinoma |
| Lobular invasive | 49 | 4.9 | 9,031 | |
| Mucinous | 24 | 2.4 | 4,423 | Mucinous, or colloid carcinomas are bulky, indolent tumors; prognosis tends to be good in predominantly mucinous tumors |
| Tubular | 12 | 1.2 | 2,212 | Tubular carcinoma with evident tubule formation, is associated with a better prognosis than infiltrating duct cancer, but less favorable than that of medullary carcinoma, despite the fact that the medullary cancer cells are less differentiated |
| Other pure tumor groups | 8 | 0.8 | 1,474 | |
| **Paget's Disease** | 23 | 2.3 | 4,239 | Associated with a relatively long history of changes in the nipple such as itching, burning, oozing, and/or bleeding; underlying tumor in the breast is palpable in about two thirds of cases; histologically, the nipple epithelium contains nests of tumor cells; prognosis depends on whether the tumor is intraductal or invasive |
| **Combinations With Infiltrating Duct (NOS)** | 280 | 28.0 | 51,604 | |
| + Tubular | 165 | 16.5 | 30,410 | |
| + Lobular invasive | 33 | 3.3 | 6,082 | |
| + Mucinous | 16 | 1.6 | 2.949 | |
| + Lobular invasive + tubular | 16 | 1.6 | 2,949 | |
| + Papillary | 12 | 1.2 | 2,212 | |
| + Adenocystic | 10 | 1.0 | 1,843 | |
| Other combinations with infiltrating duct NOS | 28 | 2.8 | 5,160 | |
| **Other Combinations of Tumor Types (exclusive of NOS)** | 16 | 1.6 | 2,949 | |
| **Total** | 1,000 | 100.0 | 184,300 | |

*[1]Rates based on 1,000 cases of breast cancer from the NSABP B-04 trial and extrapolated to incidence of breast cancer in the USA in 1996*
*[2]NOS - not otherwise specified*



ticularly older women, that may be related to an increase in cardiac mortality.

## ADJUVANT, NEOADJUVANT, SALVAGE AND PALLIATIVE TREATMENT APPROACHES

Standard adjuvant, neoadjuvant, salvage and palliative chemotherapy protocols are being evaluated using a variety of approved anticancer drugs in a plethora of regimens based on different drug combinations, dose levels and drug sequence and treatment duration. Thousands of breast cancer patients, those presenting with advanced disease, those with early cancer but a poorer prognosis and relapsed patients, become candidates for drug therapy every year. These patients are usually offered a variety of chemotherapy treatment options or are entered into clinical trials evaluating new approaches. In the USA alone, there are approximately 1.5 million women who have been diagnosed with breast cancer; every year a portion of these women relapse and re-enter various treatment programs targeting recurrent disease. Although it is extremely difficult to estimate how many chemotherapeutic regimens are performed annually, it is estimated that approximately one million women with breast cancer (newly diagnosed and recur-

rent) are treated by chemotherapy in the North America, Europe and Japan (see Exhibit 12).

There is no consensus as to the impact of chemotherapy treatment on disease-free and overall survival. Comparisons of death rates indicate a significant drop in those in the 1990s which many attribute not so much to early detection but to more aggressive treatment regimens using hormonal therapy and chemotherapy. More aggressive treatment regimens are also extending survival among breast cancer patients with advanced disease. A retrospective review of outcomes of 1,581 women with metastatic breast cancer treated by a standard combination regimen between 1973 and 1982, found that 17% experienced CR with a median survival of 42 months. However, 3% remained in CR for at least 5 years, 53% of them remained in CR after 11 to 21 years and 8% survived 10 to 20 years before dying from other causes (Greenberg PAC, etal, J Clin Oncol, 1996 Aug, 14:2197-205).

**Exhibit 10**
**Estimated Surgical Procedures for Breast Cancer in Selected World Regions in 1995**

| Surgical Procedure | USA | North America | Europe[3] | Japan | Triad |
|---|---|---|---|---|---|
| Conservative Surgery[1] | 96,840 | 107,360 | 173,480 | 13,580 | 294,420 |
| Mastectomy[2] | 114,480 | 126,180 | 157,830 | 14,290 | 298,300 |
| Total | 211,320 | 233,540 | 331,310 | 27,870 | 592,720 |

*[1]Includes lumpectomy (wide excision, excisional biopsy)*
*[2]Includes total (simple, unilateral simple, unilateral simple extended), modified radical, and radical mastectomy*
*[3]Excludes the former USSR*

Despite these favorable observations, few breast cancer patients with advanced disease benefit from chemotherapy. Obviously, such treatment is effective in a minority of patients who may eventually be singled out as possessing some favorable marker that makes tumors more susceptible to chemotherapy. Some patients appear to respond to almost any regimen as illustrated in Exhibit 11. However, despite the incredible effort to devise an effective regimen, response rates and patient outcomes in advanced disease have remained generally disappointing.

Often, the benefits of adjuvant chemotherapy are questioned in view of its cost. A study undertaken to evaluate the medical and economic impact of adjuvant treatment in the management of breast cancer, compared two types of outlays, the cost of adjuvant treatment and follow-up during a period without recurrence, and costs associated with the management of recurrence. Four different types of treatments were examined, chemotherapy (6 courses), tamoxifen therapy (20 mg/day for 3 years), both treatments or no adjuvant therapy at all. A prospective survey was performed to establish outpatient costs (transportation, physician visits, nursing care, physiotherapy, biological and radiological examinations). Based on 146 medical records, respective costs expressed in 1995 French Francs (FF), at 5 and 10 years, were 43,540 FF and 54,729 FF for tamoxifen therapy, 63,767 FF and 74,956 FF for chemotherapy, 68,891 FF and 80,870 FF for both and 38,416 FF and 49,605 FF for no adjuvant treatment. Medium costs for metastatic recurrence were 175,168 FF, and 287,284 FF and 115,698 FF, respectively, for local recurrence followed or not by metastases. As expected, the analysis revealed that overall costs associated with endocrine therapy are low and comparable to no adjuvant treatment. Use of adjuvant chemotherapy involves a significant incremental cost (16.5% at 5 years) which is expected to rise considerably with use of new drugs. However, considering the high cost of managing recurrence (at least twice as high as any treatment regimen), the incremental cost of adjuvant treatment appears reasonable if shown to prevent such recurrences (Bercez C, etal, Breast Cancer Research and Treatment, 1996, 41(3), Abs 243:258).

## HORMONAL THERAPY



Hormonal therapy is used as maintenance therapy in early disease and in conjunction with various combination regimens in advanced, metastatic breast cancer. In advanced breast cancer the type of hormonal therapy administered is determined by patient menopausal status. Pre-menopausal women may be treated with LHRH agonists, antiestrogens or progestins or undergo oophorectomy. Post-menopausal women are treated with estrogens, androgens, aromatase inhibitors, corticosteroids, or antiestrogens or progestins (see page 445-447 of this issue).

### Antiestrogens

Antiestrogen therapy is effective in both pre- and post-menopausal patients with primary and/or metastatic breast cancer. However, endocrine changes attributed to these drugs vary in these two groups and antiestrogen therapy appears to be most beneficial in ER+ post-menopausal women.

***Tamoxifen*** (Nolvadex; Zeneca) is a widely used oral antiestrogen in the treatment and/or chemoprevention of breast cancer. Tamoxifen, in use over the last 20 years, has revolutionized treatment of all stages of breast cancer. Although adjuvant tamoxifen has been associated with limited toxicity, data from large clinical trials indicate that endometrial cancer occurs at a rate that is 2-7 times greater than that observed in untreated women. A working group of WHO's International Agency for Research on Cancer (IARC) that met on February 13-20,

1996 to review possible carcinogenicity of various pharmaceutical agents including tamoxifen, concluded that there was sufficient evidence that tamoxifen increased the risk of endometrial cancer. On a positive note this group also concluded that tamoxifen reduced the risk of contralateral breast cancers. Studies are underway to assess tamoxifen's causal relationship in the development of endometrial cancer. There is also concern regarding increased risk of gastrointestinal malignancy with tamoxifen therapy which remains unproven.

Before tamoxifen was implicated in the development of endometrial cancer, it was prescribed for at least 5 years and sometimes for life for patients treated for primary breast cancer. Results from the NSABP Protocol B-14, which evaluated 5 years versus 10 years of adjuvant tamoxifen for early-stage breast cancer, indicate no advantage for continuation of tamoxifen beyond 5 years in women with node-negative, ER+ breast cancer. In view of the proven benefits of 5 years of adjuvant tamoxifen, this treatment is recommended whenever appropriate to women with early-stage breast cancer, but because of its association with endometrial cancer, a more conservative tamoxifen regimen that involves a 2-year treatment period at a total daily dose of 20 mg, either once- or twice-a-day in divided dose, is also recommended. One retrospective study found that higher daily doses of 40 mg tamoxifen resulted in endometrial cancer associated with higher grade lesions, more advanced stage and worse outcome than in untreated women.



Nolvadex has been the leading chemotherapeutic in terms of worldwide sales until surpassed by Taxol and UFT in 1996. Recently, Zeneca has been defending its Nolvadex patent (#4,536,516) against various generic versions. In April 1992 a Manhattan federal court declared the Nolvadex patent unenforceable in a patent infringement suit filed by Zeneca against Barr Laboratories (Pomona, NY). Zeneca settled by paying Barr $21 million and entering into a non-exclusive distribution arrangement for tamoxifen. Subsequently, Barr launched a generic version of tamoxifen in November 1993. Sales of Barr's tamoxifen were about $143 million, or 72% of total revenues, in fiscal 1995 and $171 million in fiscal 1996. In contrast, in April 29, 1996, a Baltimore federal court ruled that Zeneca's patent is valid and infringed by Novopharm (Toronto, Ontario, Canada) and awarded Zeneca recovery of its costs. Zeneca initiated patent infringement proceedings against Novopharm in January 1995, following Novopharm's ANDA application. Novopharm can appeal the ruling to the federal circuit appeals court. Zeneca claims that the patent for the breast cancer treatment runs through August 2002. Zeneca faces additional challenges to its patent from Mylan (Pittsburgh, PA), Pharmachemie BV (Haarlem, Netherlands) and Lemmon (Sellersville, PA).

***Toremifene*** [Fareston; Orion (Espoo, Finland)] is an oral antiestrogen agent competitive to tamoxifen indicated for the treatment of advanced breast cancer. The drug was declared approvable (10/96) in the USA and has been launched outside the USA; it was launched in the UK in July 1996. It is licensed to Schering-Plough (Madison, NJ) in the USA and to Nippon Kayaku (Tokyo, Japan) in Japan. Recently, Orion was criticized for promoting toremifene in the UK as a safe alternative to tamoxifen. However, although IARC also considered toremifene as a potential carcinogenic, it did not issue any warnings regarding any risk associated with this agent.

## Aromatase Inhibitors

Aromatase inhibition is used for the treatment of post-menopausal breast cancer (see pages 445-446 of this issue). Aromatase, a cytochrome P450 enzyme, may be inhibited either by non-steroidal inhibitors that interact directly with the prosthetic haem group of the enzyme or by substrate analogs that compete for the enzyme binding site with the normal androgen substrate. Most new aromatase inhibitors are based on the latter approach. Development of the former group has been more problematic with regard to specificity because of the widespread importance of cytochrome P450 enzymes in physiology. NCI researchers have constructed, isolated and produced both inhibitory and non-inhibitory MAbs (Serial #08/559,808) that specifically bind to cytochrome P450 3A3, 3A4, 3A5, and 2E1 which are available for licensing.

Aromatase inhibitors are expected to play an increasingly important role as second-line treatment after tamoxifen or as first-line treatment in advanced disease or as adjuvant therapy in early disease. Anastrozole (Arimidex; Zeneca) was launched as second-line treatment in the USA in 1996, in the UK in 1995 and in Japan. Clinical trials are in progress comparing anas-trozole with tamoxifen as first-line hormonal therapies in advance disease (Tamoxifen versus Arimidex Randomized Group Efficacy and Tolerability or TARGET trial) and either drug alone or in combination for the treatment of early breast cancer.

Formestane (Lentaron; Ciba-Geigy/Novartis), a substrate analog, was approved in Europe in 1995. Formestane is highly selective and of long-lasting effectiveness. In addition to competing for the enzyme binding site, formestane is converted to a reactive intermediate which permanently inactivates the bound enzyme molecule in a mechanism termed suicide inhibition. The recommended dose is 250 mg intramuscularly every 2 weeks.

In December 1996 FDA's Oncologic Drugs Advisory Committee recommended approval of the aromatase inhibitor letrozole (Femara) for the treatment of post-menopausal breast cancer after antiestrogen therapy. An NDA for letrozole had been filed in the USA in July 1996 and the drug has been launched in the UK. Several other aromatase inhibitors are in use and/or in development worldwide.

**Exhibit 11**
**Selected Clinical Trials of Monotherapy/Combination Therapy in the Management of Advanced/Metastatic Breast Cancer**

| Therapy | Results | Status/Location | Reference | Comments |
|---|---|---|---|---|
| **Taxanes, Alone or in Combination** | | | | |
| Paclitaxel (3- or 24-hour IV infusion of 175 mg/m$^2$ or 135 mg/m$^2$ in 2 heavily pretreated patients) q 3 weeks | 2/21 OR with 1 CR and 1 PR (responses lasted 6 and 9 months, respectively); 12/21 (57%) SD; toxicity was mild | Phase II/Regina Elena Cancer Institute (Rome, Italy)/metastatic breast cancer resistant to anthracyclines | Cognetti F, etal, ASCO96, Abs. 227:140 | All patients enrolled in this study were pretreated with anthracyclines |
| Paclitaxel (3-hour infusion of 225 mg/m$^2$) q 3 weeks without G-CSF support | 44% OR with 6/101(6%) CR and 38/101 (37.6%) PR | Phase II/Bristol-Myers Squibb (France), Breast Cancer French Study Group/metastatic breast cancer | Bonneterre J, etal,ASCO96, Abs. 179:128 | |
| Paclitaxel (3-hour IV infusion of 210 mg/m$^2$) q 21 days | 18% OR with 2/74 (2.7%) CR and 10/74 (13.5%) PR; median time to progression and survival were 4 and 11 months, respectively | Phase II/Southwest Oncology Group Study/ refractory metastatic breast cancer | Geyer CE, etal, ASCO96, Abs. 92:107 | |
| Paclitaxel (3-hour IV infusion of 250 mg/m$^2$) with premedication versus paclitaxel (96-hour IV infusion of 140 mg/m$^2$) with no premedication and G-CSF, q 21 days | 96-hour arm has fewer toxic effects but is less convenient | Phase III/MD Anderson (Houston,TX)/ metastatic breast cancer | Holmes FA, etal, ASCO96, Abs. 91:106 | Study to accrue 226 patients |
| Paclitaxel (3-hour IV infusion of 175 mg/m$^2$) q 21 days with standard premedication with diphenhydramine, cimetidine and dexamethasone; dose escalation and reduction allowed | 36% ORR with 1 (4%) CR and 9 (32%) PR | Phase II/Memorial Sloan-Kettering Cancer Center (New York, NY)/ metastatic breast cancer | Riccio L, etal, ASCO96, Abs. 142:119 | Semi-synthetic paclitaxel (Taxol; Bristol-Myers Squibb) |
| Paclitaxel (3-hour IV infusion of 200 mg/m$^2$) for 8 cycles versus standard CMFP for 6 cycles | 31% OR with paclitaxel and 36% with CMFP; 29% SD in each arm; median time to progression and survival were 5.5 and 16.5 months and 6.4 and 11.3 months, respectively | Phase III/Peter MacCallum Cancer Institute (Melbourne,Australia), Bristol-Myers Squibb/ untreated metastatic breast cancer | Bishop JF, etal, ASCO96, Abs. 107:110 | Epirubicin was recommended as second-line treatment for those who progressed/relapsed with this regimen |
| Paclitaxel (3-hour weekly infusion at a starting dose of 45 mg/m$^2$) followed by short-term infusion of CDDP (25 mg/m$^2$) alternately escalated by 5 mg CDDP and 10 mg paclitaxel until DLT (CDDP 35 mg/m$^2$, paclitaxel 65 mg/m$^2$ without G-CSF and 40 mg/m$^2$ and 85 mg/m$^2$, respectively, with G-CSF) | 18/55 (32.7%) PR; 13/30 (43.3%) among the chemotherapy-naive and 5/25 (20%) among those pretreated | Phase I/National Tumor Institute of Naples, Italy/ advanced breast cancer | Frasci G, etal, ASCO96, Abs. 1523:480; Gravina A, etal, Annals of Oncology, V 7 1996, Suppl 5, 637P:132 | Recommended dose is 30 mg/m$^2$ CDDP and 65 mg/m$^2$ paclitaxel; may be safely escalated up to 40 mg/m$^2$ and 85 mg/m$^2$, respectively, with concomitant administration of G-CSF |
| Paclitaxel (3-hour IV infusion starting at 135 mg/m$^2$) after bolus epirubicin at a fixed dose (90 mg/m$^2$) until MDT; cycles repeated q 3 weeks | 83% OR with 17% CR | Dose escalation study/ St. Chiara Hospital (Pisa, Italy), Bristol-Myers Squibb (Italy)/metastatic breast cancer | Conte PF, etal, ASCO96, Abs. 138:118 | |

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| | | | | |
|---|---|---|---|---|
| Paclitaxel (3-hour IV infusion of 175 mg/m$^2$) and mitoxantrone escalated by 2 mg increments (10, 12, 14 mg/m$^2$ IV) both on day 1; cycles repeated q 3 weeks | 4/23 (17%) CR, 11/23 (48%) PR, 6/23 SD, 2/23 PD | Phase I/II/Azienda Ospedaliera "S Maria", Terni, Italy/advanced breast cancer | Di Costanzo F, etal, ASCO96, Abs. 220:139 | 12/23 patients were pretreated |
| Paclitaxel (escalating 3-hour IV infusion of 200-250 mg/m$^2$) and cyclophosphamide (1-hour infusion of 1600-2000 mg/m$^2$) on days 1-2, q 21 days until DLT; treatment sequence alternated with each new patient and successive course; G-CSF (5μg/kg) was initiated SC on day 3 until recovery | Median nadir platelet count was lower for paclitaxel/cyclophosphamide than for the reverse (129 k/ml versus 150 k/ml); ratio of pre/post-treatment platelet count was 44% for paclitaxel/cyclophosphamide versus 52% for the reverse | Phase I/Johns Hopkins Oncology Center (Baltimore, MD)/ metastatic breast cancer | Kennedy MJ, etal, ASCO96, Abs, 1541:484 | 3-hour paclitaxel IV infusion regimen in combination with cyclophosphamide is associated with lower toxicity than infusion regimens of longer duration |
| Paclitaxel (3-hour infusion of 90 mg/m$^2$) followed by CDDP (60 mg/m$^2$ IV) for 8 cycles | 60% RR with 3/25 (12%) CR and 12/25 (48%) PR; median duration of response was 8 months and median survival 11 months | Phase II/Walther Cancer Institute and Indiana University (Indianapolis, IN)/metastatic breast cancer | McCaskill-Stevens W, etal, ACO96, Abs. 144:120 | |
| Paclitaxel (3-hour infusion of 175 mg/m$^2$ on day 1) and ifosfamide (1.8 g/m$^2$ on days 2, 3, 4) and mesna, q 21 days | 11 (50%) OR with 2 (9%) CR and 9 (41%) PR, 5/22 SD; response duration ranges from 4 to 17+ months and median overall survival was 12 months | Phase II/Amorim Hospital das Cl'nicas (Porto Alegre, Brazil) | Murad AM, etal, ASCO96, Abs. 52:97 | Regimen was well tolerated |
| Paclitaxel (3-hour infusion of 175 mg/m$^2$ on day 1) followed by leucovorin (1-hour infusion of 300 mg) prior to 5-FU (350 mg/m$^2$) on days 1-3, q 28 days | 62% ORR with 3/34 (9%) CR and 18 (53%) PR; median survival is 15+ months | Phase II/Vanderbilt Cancer Center (Nashville, TN)/ metastatic breast cancer | Nicholson B, etal, ASCO96, Abs. 72:102 | This regimen was active and well tolerated |
| Paclitaxel (1-hour IV infusion of 135, 175, 200, 225 mg/m$^2$) and epirubicin and cyclophosphamide (TEC regimen) at fixed doses of 50 mg/m$^2$ and 500 mg/m$^2$, respectively; treatment delivered q 3 weeks for a maximum of 10 courses | | Phase I/II/Manitoba Cancer Treatment and Research Foundation (Winnipeg, Manitoba, Canada), Bristol-Myers Squibb/metastatic breast cancer | Nabholtz J-M, etal, ASCO96, Abs. 253:147 | Dose escalation is still being investigated; DLT has not yet been reached |
| Paclitaxel (3-hour IV infusion of 150, 175, 200 mg/m$^2$ on day 1), q 21 days in combination with epirubicin (50 mg/m$^2$) and cyclophosphamide (500 mg/m$^2$) | OR seen in all dose levels; MTD has not yet been reached | Phase I/II/Breast Cancer French Study Group, Bristol-Myers Squibb/ metastatic breast cancer | Tubiana-Hulin, etal, ASCO96, Abs. 265:150 | Enrollment continues for next dose level of paclitaxel of 225 mg/m$^2$ |
| Paclitaxel (3-hour IV infusion of 90 mg/m$^2$) followed by CDDP (3-hour IV infusion of 60 mg/m$^2$), repeated q 2 weeks and continued for a maximum of 8 cycles; treatment with biweekly paclitaxel alone (90 mg/m$^2$) with subsequent dose escalation continued for stable or responding patients without prohibitive toxicity | 3/14 (21%) PR, all responses observed in visceral disease | Phase II/Eastern Cooperative Oncology Group (Brookline, MA)/ advanced breast cancer | Sparano JA, etal, ASCO96, Abs. 121:114 | Enrolled patients had relapsed after treatment with anthracyclines; further investigation of this regimen will not be pursued |

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|---|---|---|---|---|
| Paclitaxel (3-hour IV infusion of 175 mg/m$^2$ on day 1) + folinic acid (15-minute IV infusion of 100 mg/m$^2$), followed by 5-FU (2-hour IV infusion of 350-500 mg/m$^2$ on days 1-3); course repeated q 21 days | 4/10 (40%) PR, 4/10 SD, 2/10 PD; median duration of response was 4+ months, and overall survival was 10+ months | Pilot study/Ser. di Oncologia, Spedali Civili (Brescia, Italy)/advanced breast cancer | Zaniboni A, etal, ASCO96, Abs. 202:134 | |
| Cyclophosphamide (6 g/m$^2$) + mitoxantrone (70 mg/m$^2$) in combination with escalating doses of paclitaxel starting with 250 mg/m$^2$ (400 mg/m$^2$ delivered thus far) | 9/24 (37.5%) CR, 14/24 (58.3%) PR and 1/24 PD; 50% developed neutropenic fever | Phase I/II/NEORCC (Sudbury, Ontario, Canada), Bristol-Myers Squibb (Canada)/ metastatic breast cancer | Glück S, etal, ASCO96, Abs. 212:137 | Study is accruing at 450 mg/m$^2$ paclitaxel |
| Epirubicin (75 mg/m$^2$ push), followed by paclitaxel (3-hour infusion of 135 mg/m$^2$) in combination with G-CSF (5 μg/kg), q 10 days | | Phase I/II/The Netherlands/ metastatic breast cancer in chemotherapy-naive patients | Lalisang R, etal, ASCO96, Abs. 62:99 | This combination regimen was safe |
| Epirubicin (1-hour IV infusion of 60 mg/m$^2$) followed by paclitaxel (3-hour IV infusion of 175 mg/m$^2$) after standard premedication; paclitaxel was escalated to 200 and 225 mg/m$^2$ in the absence of toxicities | 58.7% ORR with 6/46 (13%) CR, 21/46 (45.7%) PR and 17/46 (37%) SD | Phase II/Frauenklinik der Med Hochschule (Hannover, Germany), Bristol-Myers Squibb Oncology (Munich, Germany)/first-line therapy of metastatic breast cancer | Lück LJ, etal, ASCO96, Abs. 147:120 | |
| Epirubicin (75-90 mg/m$^2$ IV bolus) followed by paclitaxel (3-hour IV infusion of 155-200 mg/m$^2$) | 5/24 (20.8%) PR | Phase I/Peter MacCallum Cancer Institute (Melbourne, Australia), Faulding, Pharmacia/ solid tumors | Rischin D, etal, ASCO96, Abs. 1525:480 | MTD appears to be epirubicin at 90 mg/m$^2$ and paclitaxel at 175 mg/m$^2$ |
| Vinorelbine (20 mg/m$^2$) and paclitaxel (3-hour IV infusion of 120 mg/m$^2$) both on day 1 and CDDP (70 mg/m$^2$ on day 2), q 3 weeks; G-CSF (5 μg/kg SC on days 5-15) | 14/25 (54%) PR, 9/25 (35%) SD, 2/25 (8%) PD; 2 deaths occurred in patients with PD; median duration of response was 6+ months and median survival was 7+ months | Clinical/University General Hospital of Heraklion (Heraklion, Crete, Greece)/ anthracycline-resistant advanced breast cancer | Kourousis CH, etal ASCO96, Abs. 258:148 | |
| Vinorelbine (7, 10 and 13 mg/m$^2$ IV daily X 3 days), followed by paclitaxel (3-hour IV infusion of 135 mg/m$^2$ on day 3) repeated q 28 days with G-CSF starting on day 4 | 2/10 (20%) CR, 1/10 (10%) PR | Phase I/North Shore University Hospital (Manhasset, NY), Glaxo Wellcome (Research Triangle Park, NC)/ metastatic breast cancer | Weiselberg L, etal, ASCO96, Abs. 54:97 | Paclitaxel will be escalated to 175 and 200 mg/m$^2$ in phase II |
| DOX (60 mg/m$^2$) + cyclophosphamide (2 g/m$^2$) with G-CSF q 2 weeks X 3, followed by a 96-hour infusion of paclitaxel (140 mg/m$^2$) with G-CSF, q 2 weeks X 3 | Overall weekly dose intensity was DOX at 27 mg/m$^2$, cyclophosphamide at 875 mg/m$^2$ and paclitaxel at 63 mg/m$^2$; 100% overall RR with 4/17 (23.5%) CR, 3/17 (17.6%) PR; 2 too early to evaluate | National Cancer Institute/ high risk primary lymph-node positive breast cancer | Zujewski J, etal ASCO96, Abs. 145:120 | This regimen was active and well tolerated |
| DOX (fixed dose of 50 mg/m$^2$ bolus IV) and paclitaxel (3-hour IV infusion of 130-250 mg/m$^2$ escalated by 30 mg/m$^2$ increments), q 21 days with premedication with dexamethasone, cimetidine and orphenadrine | 78.8% OR with 6/19 (31.6%) CR, 9/19 (47.2%) PR, 3 (15.8%) SD and 1 PD; at dose levels from 190-250 mg/m$^2$ all patients experienced OR (6 CR, 9 PR); median duration of OR and CR were 8+ and 7 months, respectively | Phase I/II/Morgagni-Pierantoni Hospital (Forlì Italy), Bristol-Myers Squibb (Rome, Italy; Bruxelles, Belgium)/ advanced breast cancer | Frassineti GL, etal, ASCO96, Abs. 103:109 | A phase II with fixed doses of DOX 50 mg/m$^2$ and paclitaxel 220 mg/m$^2$ is ongoing |



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| DOX (60 mg/m$^2$ bolus injection), followed by paclitaxel (3-hour infusion of 200 mg/m$^2$) q week; all patients were premedicated with dexametasone, ranitidine and difenhidramine | 1/27 (3.7%) CR, 12/27 (44.4%) PR, 10/27 (37%) SD, 4/27 (14.8%) PD | Clinical/Instituto Dr. Estevez (Buenos Aires, Argentina)/metastatic breast cancer | Cazap E, etal, ASCO96, Abs. 248:146 | |
| DOX (60 mg/m$^2$, 75 mg/m$^2$ or 90 mg/m$^2$ on day 1) with G-CSF (5μg/kg) on days 2-13; paclitaxel (3-hour IV infusion of 175 mg/m$^2$ on day 15 if ANC ≥ 1500) | 7/17 (41.2%) patients with measurable disease achieved CR/PR; symptomatic improvement in bone disease with bone scans improving in 3 patients | Phase I/Shadyside Hospital (Pittsburgh, PA)/advanced breast cancer | Jacobs SA, etal, ASCO96, Abs. 55:97 | Regimen was highly active and manageable; there were 2 deaths |
| DOX (IV infusion of 60 mg/m$^2$), followed by paclitaxel (2-3-hour IV infusion of 250 mg/m$^2$ on day 1) + G-CSF (5 μg/kg SC daily from day 2 until granulocytes reach 1500 cells/mm$^3$); cycles repeated q 21 days for a maximum of 6 courses | 80% ORR with 7/25 (28%) CR, 13/25 (52%) PR and 2 MR | Phase II/Hospital de Clinicas de Porto Alegre (Brazil)/metastatic breast cancer | Schwartsmann G, etal ASCO96, Abs. 168:126 | |
| Docetaxel (100 mg/m$^2$ IV) q 3 weeks | 43% ORR; 1/28 (3.6%) CR and 11/28 (39.3%) PR | Phase II/Sandton Oncology Centre (Johannesburg, South Africa)/advanced breast cancer | Vorobiof DA, etal, ASCO96, Abs. 185:130 | 54% OR among 13 patients treated with only one prior chemotherapy regimen |
| Docetaxel (100 mg/m$^2$ or 70 mg/m$^2$) administered IV with steroids q 3 weeks | 40/210 (19%) PR, 18 (8%) MR, 95 SD (43%), 64 PD (29%); RR by disease site was 19% liver, 5% lung, 6% bone, 24% skin, 14% lymph nodes | Hôpital Brousse (Villejuif, France)/anthracycline-refractory breast cancer | Trandafir L, etal, ASCO96, Abs. 86:105 | |
| Docetaxel (1-hour IV infusion of 100 mg/m$^2$) q 21 days, alternating with epirubicin (120 mg/m$^2$) + cyclophosphamide (830 mg/m$^2$) and lenograstim (150 mg/m$^2$ SC on days 2-100) | 5/5 RR was observed to date was | Phase I/The Netherlands Cancer Institute (Amsterdam, the Netherlands)/advanced breast cancer in chemotherapy-naive patients | Ten Bokkel Huinink W, etal, ASCO96, Abs. 229:141 | |
| Docetaxel (100 mg/m$^2$) q 21 days + dexamethasone (8 mg bid on days -1-4) | 1/26 (3.8%) CR, 2/26 (7.7%) PR, 4/26 MR, 8/26 SD, 11/26 PD | Multicenter pilot study/ University of Texas MD Anderson Cancer Center, Rhône-Poulenc Rorer (Collegeville, PA)/ paclitaxel-resistant metastatic breast cancer | Valero V, etal, ASCO96, Abs. 95:107 | |
| DOX (40-60 mg/m$^2$ IV bolus) followed after a 1-hour interval by docetaxel (1-hour infusion of 50-85 mg/m$^2$ IV) | Among 40 evaluable patients MTD was reached at DOX 50 mg/m$^2$ and docetaxel 85 mg/m$^2$; 16 patients were administered >400 mg/m$^2$ of DOX; ORR was 89% at the highest dose and RR was 89% in liver metastases | Phase I/Institut Curie, Rhône-Poulenc Rorer/ metastatic breast cancer in chemotherapy-naive patients | Bourgeois H, etal, ASCO96, Abs. 259:148; Kalla S, etal, Annals of Oncology, V 7 1996, Suppl 5, 599O:124 | Recommended dose is docetaxel at 75 mg/m$^2$ and DOX 50 mg/m$^2$; phase II and III studies are planned |
| Vinorelbine (20 mg/m$^2$ IV on day 1 and 5), followed immediately by docetaxel (85 mg/m$^2$ on day 1), q 3 weeks | | Phase I/Rhône-Poulenc Rorer (Vitry sur Seine, France) | Bissery MC, etal, ASCO96, Abs. 1550:487 | |

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| Vinorelbine (30-minute IV infusion of 20-22.5 mg/m$^2$ on day 1 and 5) followed by docetaxel (1-hour IV infusion of 60-100 mg/m$^2$ on day 1), q 3 weeks | 8/25 (32%) CR and 11/25 (44%) PR | Phase I/Centre R. Gauducheau (Nantes, France), Rhône-Poulenc Rorer/metastatic breast cancer | Fumoleau P, etal, ASCO96, Abs. 232:142 | Recommended dose for phase II is docetaxel at 85 mg/m$^2$ on day 1 and vinorelbine at 20 mg/m$^2$ on day 1 and 5, q 3 weeks |
| **Aromatase Inhibitors** | | | | |
| Anastrozole (1 and 10 mg PO daily) versus megestrol acetate (4 X 40 mg daily) | Patients with soft tissue lesions had the highest OR (34% for 1 mg and 28% for 10 mg on anastrolzole and 27% on megestrol) | Arimidex International Study Group, Zeneca Pharmaceuticals/advanced breast cancer that progressed on tamoxifen in post-menopausal women | Howell A, etal, ASCO96, Abs. 247:145 | |
| Anastrozole (1 and 10 mg PO once daily) versus megestrol acetate (40 mg X 4 daily) | Serious adverse drug reactions to anastrozole (1 and 10 mg) and megestrol acetate were 16 (6.1%), 12 (4.9%) and 23 (9.1%), respectively | Phase III/Arimidex International Study Group and Zeneca Pharmaceuticals/ advanced breast cancer | Buzdar AU, etal, ASCO96, Abs. 100:109 | Randomized trials confirm the more favorable tolerability profile of anastrozole |
| Letrozole (0.5 mg or 2.5 mg PO) or megestrol acetate (160 mg PO) | RR at dose levels of .5 mg were 1.6% CR and 10.1% PR and at 2.5 mg were 5.7% CR and 17.8% PR; RR with megestrol acetate was 3.7% CR and 12.7% PR | Phase III/Letrozole International Trial Group/ post-menopausal women with advanced breast cancer who failed on anti-estrogens | Dombernowsky P, etal, ASCO96, Abs. 64:100 | 2.5 mgL dose level showed highest RR; 551 patients were randomized to the three regimens |
| Letrozole (0.5 versus 2.5 mg PO daily) | 15% ORR with 2/40 (5%) CR in each dose group and 2 PR on 0.5 mg; sites of responses were soft tissue and viscera; 23% SD | Phase I/Istituto Nazionale per lo Studio e la Cura dei Tumori (Milan, Italy), Ciba/postmenopausal advanced breast cancer | Zilembo N, etal, ASCO96, Abs. 105:110 | |
| **Other Drug Monotherapies/Combinations** | | | | |
| Megestrol acetate (800 mg daily PO) divided in two doses | 15 (34%) PR; 14 (31.8%) MR; highest response was in patients with bone metastases while lowest was in those with liver metastases | Othmer Cancer Center-Long Island College Hospital (Brooklyn, NY)/ metastatic breast cancer recurring after other hormonal therapy | Rosenthal CJ, etal, ASCO96, Abs. 208:136 | |
| Thiotepa (two doses of 7.5 mg) mixed with 0.5 cc 2% xylocaine and dexamethasone (4 mg); endoscopic intratumoral delivery | No recurrence of tumor was observed up until two years post therapy | Phase I/Jafary Medical Clinics & Research Foundation (Beckley, WV)/ recurrence of locoregional solid tumors and lymphomas | Amjad H and Jafary HA, ASCO96, Abs. 1580:494 | |
| Vinorelbine (30 mg/m$^2$ weekly or 25 mg/m$^2$ on days q 21 days | 15/44 (34%) ORR with 3 (6%) CR, 12 (28%) PR, 16 (36%) SD, 13 (30%) PD; medium response duration was 7 months | Instituto de Oncologia Angel H. Roffo (Buenos Aires, Argentina)/heavily pretreated breast cancer | Alverez A, etal, ASCO96, Abs. 250:146 | Vinorelbine monotherapy may be used as standard 2nd- or 3rd-line therapy |
| Epirubicin (120 mg/m$^2$ IV) q 28 days for 6 cycles or until progression | 24/126 (19%) CR, 64/126 (52%) PR, 24% SD, 5% PD; median duration of response and time to progression were 11 and 9 months, respectively | Phase II/Grupo Cooperative Argentino de Cáncer de Mama (Buenos Aires, Argentina)/advanced breast cancer | Bonicatto S, etal, ASCO96, Abs. 251:146 | Randomized phase III clinical trial planned |
| Vinorelbine (30 mg/m$^2$) weekly for 13 weeks and once q two weeks thereafter until disease progression; median weekly dose intensity was 21 mg/m$^2$ | 32% PR lasting > 4 weeks; 46% SD; estimated median time to progression in patients achieving PR was 39 weeks and 32 weeks for all patients | Phase I/advanced breast cancer in patients ≥ 60 years | Vogel C, etal, ASCO96, Abs. 70:101 | |

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| Vinorelbine (escalating incremental dose of 5 mg/m$^2$ daily X 3) starting at 15 mg/m$^2$ daily X 3 repeated q 21 days with/ without filgrastim (5 mg/kg daily beginning on day 5) | DLT observed at 20 mg/m$^2$; 4/5 patients with chest wall disease responded | Phase I/II/Duke University Medical Center (Durham, NC), Glaxo Wellcome (Research Triangle Park, NC), Amgen (Thousand Oaks, CA)/metastatic breast cancer | Havlin K, etal, ASCO96, Abs. 154:122 | Non-hematologic toxicities preclude use of this regimen as a means to increase dose intensity over weekly vinorelbine |
| Idarubicin PO at an initial dose of 20 mg/m$^2$ weekly (mean dose intensity was 17 mg/m$^2$ weekly) | 13 patients were treated ≥ 12 times; 7/19 () PR and 7/19 (36.8%) SD; median duration of response is 12 months | Antwerp University Hospital (Edegem, Belgium), Pharmacia/ advanced breast cancer in the elderly | Provo A, etal, ASCO96, Abs. 177:128 | |
| DOX-SL (1-hour infusion of 60 mg/m$^2$ q 21 days); after the first 13 patients, protocol dose was reduced to 45 mg/m$^2$ q 21 days and later to 45 mg/m$^2$ q 28 days | Of 43 patients completing at least 2 treatment cycles, 3/43 achieved CR, 13/43 PR and 15 PD; 12 SD after 2-4 cycles; 17 patients are too early to evaluate or are not evaluable | Phase II/Christie Hospital (Manchester, UK)/ advanced breast cancer | Ranson M, etal, ASCO96, Abs. 161:124 | Stealth liposomal DOX hydrochloride (Sequus Pharmaceuticals) |
| DOX (1-hour infusion of 135 mg/m$^2$) repeated q 21 days; median dose intensity was 42 mg/m$^2$ weekly (range 20-50 mg/m$^2$ weekly) | 65% ORR with 2/40 (5%) CR, 24/40 (60%) PR, 8/40 (20%) SD and 6/40 (15%) PD | Phase II/Dana-Farber Cancer Institute (Boston, MA), The Liposome Company (Princeton, NJ), Pfizer (New York, NY)/ metastatic breast cancer | Shapiro CL, etal, ASCO96, Abs. 115:112 | Liposome-encapsulated DOX (D-99) |
| DOX (50 mg/m$^2$ IV on day 1) and vinorelbine (25 mg/m$^2$ IV on days 1 and 8) versus DOX (70 mg/m$^2$ IV on day 1); in 16/65 patients, dose was reduced to DOX at 40 mg/m$^2$ on day 1 and vinorelbine to 20 mg/m$^2$ on day 1 and 8 versus DOX at 60 mg/m$^2$ on day 1; regimens repeated q 21 days until a cumulative dose of 450 mg/m$^2$ of DOX or disease progression | No significant differences between DOX/vinorelbine versus DOX alone; RR was 35% versus 30%, respectively | Phase III/Queen's University (Kingston, Canada), Glaxo Wellcome/ metastatic or recurrent breast cancer | Norris BM, etal, ASCO96, Abs. 59:98 | |
| Buserelin (8-week implant inserted SC) and tamoxifen (40 mg/day) versus each drug alone | RR for buserelin alone, tamoxifen alone, and buserelin + tamoxifen are 33%, 29%, 51%, respectively; PD was 31%, 44% and 21%, and median duration of response was 12, 19 and 22 months, respectively | Randomized trial/EORTC Breast Cancer Cooperative Group/premenopausal metastatic breast cancer | Klijin JGM, etal ASCO96, Abs. 132:117 | |
| Epirubicin (100 mg/m$^2$) + cyclophosphamide (800 mg/m$^2$) on days 1-2 and G-CSF SC on days 4-9, repeated q 15 days for 4 cycles | 88% RR [3 (9.4%) CR, 25 (78 %) PR], 3/32 SD, 1/32 PD | Clinical/Hospital Israelita (Buenos Aires, Argentina)/ locally advanced breast cancer | Breier S, etal, ASCO96, Abs. 188:131 | G-CSF support permitted feasibility of 90% dose density and shorter timing to surgery |
| Levo-leucovorin (5 mg/m$^2$ PO) + 5-FU (250 mg/m$^2$) on days 1-14 q 21 days | 5/20 (25%) PR, 7/20 SD, 8/20 PD; median time to progression is 4 months | Castelfranco Veneto, Italy)/ metastatic breast cancer | Colleoni M, etal, ASCO96, Abs. 186:130 | |
| Vinorelbine and DOX (both at 25 mg/m$^2$ IV on days 1 and 8) q 21 days for a maximum of 8 cycles | 82% ORR with 14% CR | Phase II/ELAN do Brazil/ metastatic breast cancer | Costa MA, etal, ASCO96, Abs. 65:100 | Regimen is recommended as first-line treatment for advanced/metastatic breast cancer |

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| Epirubicin (60 mg/m$^2$) followed by CDDP (40 mg/m$^2$) both on day 1 and 2, q 21 days and continuous lonidamine (450 mg PO) for a maximum of 6 cycles | 77.2% overall RR with 31.8% CR and 45.4% PR | Phase II/University of Torino and Sassari (Milan, Italy)/advanced breast cancer | Dogliotti L, etal, ASCO96, Abs. 224:140 | |
| Gemcitabine (30-minute infusion of 1,000 mg/m$^2$ on days 1, 8 and 15) with escalating doses (5 mg/m$^2$ increments) of epirubicin starting at 10 mg/m$^2$ on days 1, 8 and 15 of a 4-week cycle | Preliminary responses of 12 evaluable patients are 25% PR and 50% SD | Phase I/ Universitätsklinikum Charité (Berlin Germany), Lilly Deutschland (Bad Homburg, Germany) | Grunewald R, etal, ASCO96, Abs. 241:144 | |
| Methotrexate (150 mg/m$^2$ IV) followed 23 hours later by IFN-$\alpha$ (60-minute IV infusion of 0-27 MU) and 5-FU (900 mg/m$^2$ IV bolus) one hour after IFN-$\alpha$; leucovorin (12.5 mg) 2 hours after 5-FU for 6-8 doses q 6 hours | 1 CR among breast cancer patients | Phase I/Centro de Estudios Médicos y Bioqu'micos (Comodoro Rivadavia, Argentina)/ solid tumors | Jaremtchuk AV, etal, ASCO96, Abs. 1586:496 | Phase II initiated in colon cancer with IFN-$\alpha$ (9 MU) |
| Vinorelbine (15 mg/m$^2$ IV on day 1) + cyclophosphamide (100 mg/m$^2$ PO on days 1-7) + DOX (40 mg/m$^2$ IV on day 1) + methotrexate (100 mg/m$^2$ IV on day 1) with folinic acid rescue and 5-FU (300 mg/m$^2$ daily continuous IV infusion on days 8 and 9); therapy repeated q 14 days; vinorelbine escalated by 5 mg/m$^2$ increments | 2/9 (22.2%) CR and 4/9 (44.4%) PR | Phase I/Johns Hopkins Oncology Center (Baltimore, MD)/ metastatic breast cancer | Kennedy MJ, etal, ASCO96, Abs. 90:106 | Protocol was later modified to permit further vinorelbine dose escalation by omitting cyclophosphamide and 5-FU and repeating therapy q 3 weeks; at 30 mg/m$^2$ vinorelbine there were 8/16 (50%) RR (2 CR and 4 PR) among evaluable patients; DOX dose escalation, with vinorelbine fixed at 25 mg/m$^2$, is now under study |
| Ifosfamide (1-hour IV infusion of 2 g/m$^2$ on days 1-3) + mesna (400 mg/m$^2$ IV bolus at 0 and 4 hours and 800 mg/m$^2$ PO at 8 hours on days 1-3) + vinorelbine (20-minute IV infusion of 35 mg/m$^2$ on days 1 and 15); courses are repeated q 28 days; during first course, vinorelbine (17.5 mg/m$^2$) was administered on days 8 and 22 | 25/43 (58%) OR with 6 (14%) CR, 19 (44%) PR, 10 (23%) SD and 8 (19%) PD; median time to disease progressionand survival were 12 and 19 months, respectively | Grupo Oncologico Cooperative del Sur (Argentina), Asta Medica AG/metastatic breast cancer | Leone B, etal, ASCO96, Abs. 74:102 | |
| Folinic acid (continuous IV infusion of 500 mg/m$^2$ daily X 5 days) + CDDP (15 mg/m$^2$ IV bolus daily X 5 days), followed by 5-FU (350 mg/m$^2$ IV bolus daily X 5 days) and IFN-$\alpha$ (2 mU/m$^2$ daily X 5 days); cycles repeated q 28 days | 1/34 (3%) CR and 8/34 (23.5%) PR; 5 too early to evaluate and 4 not evaluable | Phase II/City of Hope National Medical Center (Duarte, CA)/advanced or metastatic breast cancer | Leong L, etal, ASCO96, Abs. 175:127 | 28/34 enrollees were pretreated and in 58% breast cancer was refractory to DOX and/or paclitaxel |
| Idarubicin (10 mg/m$^2$ IV) + cyclophosphamide (600 mg/m$^2$ IV) q 3 weeks | 1/20 (5%) CR, 15/20 (75%) PR, 3/20 (15%) MR, 1/20 (5%) PD | Phase II/Clinica Alemana and Fundacion A Lopez Perez (Santiago, Chile)/ Stage IV breast cancer | Majlis A, etal, ASCO96, Abs. 182:129 | |

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| Epirubicin + vinorelbine (both at 25 mg/m$^2$ weekly); G-CSF (300 μg SC daily) starting after first neutropenia | 74% OR with 16/27 (59.2%) PR; 4/27 (14.8%) CR and 7/27 (25.9%) SD; median duration of response is 10 months and time to progression is 9.5 months | Regina Elena Institute (Rome. Italy)/advanced breast cancer | Nisticò C, etal, ASCO96, Abs. 228:141 | |
| 5-FU (1-hour IV infusion of 600 mg/m$^2$ on days 1-3) + DOX (50 mg/m$^2$ IV bolus on day 1) + cyclophosphamide (400 mg/m$^2$ IV bolus on days 1-3) (FAC regimen), q 4 weeks versus 5-FU (continuous infusion of 250 mg/m$^2$ daily on days 1-22) + cyclophosphamide (300 mg/m$^2$ IV bolus on days 1, 8, 15, 22) + DOX (15 mg/m$^2$ IV bolus on days 1, 8, 15, 22) (FULON regimen) q 6 weeks | Median overall survival period for all patients was 22 months and median response duration was 14 months; RR was 54% in the FAC arm and 53% in the FULON arm; response duration and overall survival were 14 and 23 months in FAC compared to 12 and 21 months in FULON, respectively | Randomized trial/Institut Curie (Paris, Cedex, France)/metastatic breast cancer | Pierga J, etal, ASCO96, Abs. 133:117 | The two regimens are equally effective |
| Vinorelbine (25 mg/m$^2$ weekly) with G-CSF (300 μg SC daily 2 X week) support after first neutropenia | 47% ORR with 3/34 (8.8%) CR, 13/34 (38.2%) PR, 14/34 (41.2%) NC and 4/34 (11.8%) PD; median duration of response was 11 months | Regina Elena Institute (Rome, Italy)/advanced breast cancer | Ranuzzi M, etal, ASCO96, Abs. 166:125 | |
| Ifosfamide (1.5 g/m$^2$ on days 1-3) + DOX (60 mg/m$^2$ on day 1) for 3 cycles | 93.3% RR with 2/15 (13.3%) CR, 12/15 (80%) PR and 1 PD; pathological response rate was the same; 12 patients are free of disease and 2 recurrences occurred at median follow-up of 11.4 months | Phase II/Grupo Oncologico Colombiano/locally advanced breast cancer | Restrepo JG, etal, ASCO96, Abs. 190:131 | |
| Cyclophosphamide (600 mg/m$^2$ IV) + methotrexate (40 mg/m$^2$ on day 1) + tegafur (750 mg/m$^2$ PO daily) + folinic acid (45 mg daily on days 2-14), q 3 weeks | 47% ORR with 3/38 (8%) CR and 15/38 (39.5%) PR; median response duration was 3+ months, with 28 patients still on treatment | Hospital Vall d'Hebron (Barcelona, Spain)/ advanced and metastatic breast cancer | Sole LA, etal, ASCO96, Abs. 125:115 | ORR was 52% for chemotherapy-naive patients and 41.5% for anthracycline-resistant breast cancer |
| 5-FU (500 mg/m$^2$) + DOX (50 mg/m$^2$) + cyclophosphamide (500 mg/m$^2$) (FAC regimen) for 4 cycles q 3 weeks followed by 2 cycles of CDDP (120 mg/m$^2$ on day 1) +VP-16 (100 mg/m$^2$ on days 1-5) + mitomycin-C (8 mg/m$^2$ on day 1) (PEM regimen), q 4 weeks | 51.2% OR with FAC with 1 CR and 20 PR; PEM converted SD to 1 CR and 8 PR and PR to CR in 4 patients; combination, therapy resulted in 73.2% ORR with 6 (14.6%) CR and 24 (58.5%) PR | Phase II/Cancer Research Center (Moscow, Russia)/ locally advanced or metastatic breast cancer | Tjulandin S, etal, ASCO96, Abs. 194:132 | |
| Tegafur and uracil (UFT) (350 mg/m$^2$ PO on days 1-14) +DOX (50 mg/m$^2$ IV on day 1) + cyclophosphamide (500 mg/m$^2$ IV on day 1) versus 5-FU (500 mg/m$^2$ IV on days 1 and 8) + DOX (50 mg/m$^2$ IV) + cyclophosphamide (500 mg/m$^2$ IV), both on day 1 | RR for UFT and 5-FU arms was 48.4% and 35.5%, respectively; median response duration was 16 weeks | Phase III/Philippine General Hospital, Cancer Insitute, University of the Philippines (Manila, Philippines)/advanced breast cancer | Villalon AH, etal, ASCO96, Abs. 221:139 | RR and duration of response were comparable between the two regimens |



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| DOX (50-75 mg/m$^2$) and cyclophosphamide (500-750 mg/m$^2$) q 3 weeks as first-line chemotherapy | CR, PR, SD, PD for site specific responses are [Ax lymph node-2/6 (33%), 3 (50%), 1, 0]; [S/C lymph node-14/19 (74%), 4 (21%), 1, 0]; [breast-1/11 (9%), 7 (64%), 2, 1]; [skin -3/6 (50%), 1 (17%), 2, 0]; [lung-7/21 (33%), 4 (19%), 5, 5]; [liver-1/14 (7%), 5 (36%), 6, 2] | Singapore General Hospital (Singapore)/ metastatic breast cancer | Wong K, etal ASCO96, Abs. 223:139 | |
| DOX (20 mg/m$^2$ IV) or mitomycin C (6 mg/m$^2$ IV on day 1 and 8) + cyclophosphamide (100 mg PO daily on days 1-14) + Tamoxifen (20 mg PO daily); cycles repeated q 4 weeks | Response rate is 48% on DOX regimen and 33% on mitomycin-C | Phase III/Japan Clinical Oncology Group (Tokyo, Japan)/metastatic breast cancer | Watanabe T, etal, ASCO96, Abs. 245:145 | Mitomycin C regimen was not as active as DOX regimen when used as first-line therapy |
| **Other Multimodality Therapies** | | | | |
| Cyclophosphamide + DOX + VP16 X 6, followed by regional radiation therapy with Ir-192 implants to chest wall with or without hyperthermia, then methotrexate, 5-FU, CDDP and cyclophosphamide X 2-3 courses | At median follow-up time of 72 months, 19/55 (34.5%) relapsed and 10 (18.2%) died; most common sites of recurrence were brain and bone (36% each); disease-free and overall survival at 6 years are 65% and 81%, respectively | Arlington Cancer Center (Arlington, TX)/advanced primary breast cancer | Blumenschein GR, etal, ASCO96, Abs. 243:144 | 28 patients are alive and relapse-free at 5 years or more |
| 5-FU (500 mg/m$^2$) + cyclophosphamide (500 mg/m$^2$ on day 1) + epirubicin [50 mg/m$^2$ (FEC 50 arm) or 100 mg/m$^2$ (FEC 100 arm) on day 1]; all patients first underwent surgery and were treated by local radiation after chemotherapy; all post-menopausal patients were also treated by daily tamoxifen (30 mg) for 3 years | Mean dose intensity was 94.1% in FEC 50 arm versus 92.2% in FEC 100 arm; 3 year disease-free survival at 30 months follow-up is 62.1% in FEC50 and 70.5% in FEC 100 | Randomized trial/Centre Oscar Lambert (Lille, France)/node-positive operable breast cancer | Bonneterre J, etal, ASCO96, Abs. 82:104 | |
| **Hematopoietic Cell Transplantation** | | | | |
| Cyclophosphamide (6 g mg/m$^2$), etoposide (2.4 g/m$^2$) and carboplatin (1.2 g/m$^2$), followed by rescue with autologous peripheral blood stem cells alone or in combination with bone marrow | Median time to neutrophil engraftment (500 polys/mL) was 11 days; median interval to platelet engraftment (20,000/mL unsupported) was 11.5 days; median follow-up since diagnosis is 456 days | Temple University School of Medicine (Philadelphia, PA)/high-risk non-metastatic breast cancer | Klumpp TR, etal, ASCO96, Abs. 210:136 | Actuarial progression-free survival among patients with Stage IIB, IIIA and IIIB disease is 100%, 64%, and 42%, respectively |
| Mitoxantrone (30 to 50 mg/m$^2$) + fixed doses of carboplatin (1,200 mg/m$^2$) and thiotepa (750 mg/m$^2$ ) with G-CSF-mobilized PBSC support | Among breast cancer patients in the adjuvant setting, 77% were alive and NED with a median follow-up of 15 months; only 5 (22%) Stage IV patients remain alive | Phase I/II/University Hospital Doce de Octubre (Madrid, Spain)/ anthracycline-pretreated Stage II/III breast cancer | Castro IG, etal, ASCO96, Abs. 1032:352 | Recommended dose of mitoxantrone is 40 mg/m$^2$ |

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| Carboplatin (continuous 48-hour IV infusion of 600 mg/m$^2$ ), followed by thiotepa (900 mg/m$^2$) + cyclophosphamide (2-hour IV infusion of 6,840 mg/m$^2$) with autologous hematopoietic stem cell transplant performed 72 hours after therapy | 31/65 (48%) OR with 20/65 (31%) CR and 11/20 (17%) PR post-transplant; 11 (17%) with skeletal metastasis were not evaluable for response, 23 (35%) did not respond to transplantation | Phase II/Baylor University Medical Center (Dallas, TX)/metastatic breast cancer | Fay J, etal, ASCO96, Abs 162:124 | |
| DOX and vinorelbine induction treatment with high-dose combination chemotherapy of 7 g dibromodulcitol, 6.6 g cyclophosphamide, 5 g 5-FU, 1 g methotrexate and 500 mg paclitaxel, followed by peripheral blood stem cell rescue | 13/17 (76.5%) RR in breast cancer, 1/2 ovarian cancer, 2/2 head & neck, 1/1 NHL | The London Oncology and Marrow Transplant Group at the London Clinic (London, UK)/ advanced breast cancer | Price LA, etal, ASCO96, Abs. 995:342 | Higher doses of the seven most effective breast cancer drugs may be given with less toxicity than in some current transplant programs |

*DOX-Doxorubicin* *CR-Complete response* *OR-Objective response* *PR-Partial response*
*CDDP-Cisplatin* *MR-Minor response* *NED-No evidence of disease* *PD-Progressive disease*
*MDT-Maximum tolerated dose* *ORR-Overall response rate* *SD-Stable disease* *ANC-Absolute neutrophil count*
*DLT-Dose limiting toxicity* *RR-Response rate* *PBSC-Peripheral blood stem cells*

## STANDARD CYTOTOXIC CHEMOTHERAPY



Chemotherapy is used in nearly all stages of breast cancer. Adjuvant chemotherapy in addition to surgery or radiation therapy is an established treatment shown to improve both disease-free and overall survival in primary breast cancer in numerous clinical trials worldwide. Neoadjuvant chemotherapy administered prior to surgery and/or radiation to reduce tumor size is also under evaluation. In early studies, tumor size was reduced in about 90% of women treated with neoadjuvant chemotherapy, and about 50% of these women did not require a mastectomy.

Combination chemotherapy is also used as a salvage or palliative approach with numerous regimens under evaluation (see Exhibit 11). Various strategies are used to enhance the effectiveness of these combination regimens, reduce their toxicity or improve their performance in drug-resistant disease.

BioResearch Ireland's (BRI; Dublin, Ireland) National and Cell Tissue Culture Centre has discovered a method for enhancing anticancer activity of certain chemotherapeutic agents, including doxorubicin and vincristine, by adding another class of safe pharmaceuticals already in regular use for another purpose. In *in vitro* tests, the combination worked in many drug-sensitive and also in a subset of drug-resistant human cancer lines. Preliminary data indicate safety and anti tumor efficacy. BRI is seeking investors/collaborators to complete toxicity and clinical trials and to fund further research on mechanism of action.

### Anthracyclines

Anthracyclines which are very active against advanced breast cancer, are routinely used in combination with other agents as first-line and induction therapy. However, their utility is compromised by cardiotoxicity related to cumulative dose. Several anthracycline analogs with a more favorable toxicity profile are in development. Among these are various approved liposomal formulations of doxorubicin, such as Sequus Pharmaceuticals' (Menlo Park, CA) Doxil/Caelyx, and of daunorubicin, such as NexStar Pharmaceuticals' (Boulder, CO) DaunoXome, both approved for Kaposi's sarcoma. These formulations together with TLC D-99, a liposomal formulation of doxorubicin under development by The Liposome Company (Princeton, NJ), are currently in phase III clinical trials in metastatic breast cancer.

### Taxanes

Taxanes, primarily paclitaxel (Taxol; Bristol-Myers Squibb), that were introduced into the global marketplace in this decade, have evolved into blockbuster drugs, a status rarely achieved by anticancer agents. Currently widely available for the treatment of advanced ovarian and breast cancer, they are being investigated alone and in combination with other agents for numerous other indications (see FO, p 176-181). Paclitaxel was approved by the FDA in April 1994 for the treatment of breast cancer that has recurred or progressed despite treatment. Revenues of paclitaxel, currently supplied as Taxol by Bristol-Myers Squibb (BMS), were $340 million in 1994 and $580 million in 1995. Sales were $604 million in the first nine months of 1996 and are expected to

exceed $800 million in 1996 and $1 billion annually by the end of the decade. BMS' exclusivity for Taxol is due to expire in 1997, presenting a very attractive opportunity for generic versions currently pursued by numerous developers (see FO, V1 #7/8 pp 182-183). The company is currently attempting to extend its patent by lobbying Congress. For more information on paclitaxel see FO, pp 172-185, 251, 262, 275 and 368.

As of late 1996, docetaxel (Taxotere; Rhône-Poulenc Rorer) was approved in over 36 countries worldwide as second-line treatment of metastatic breast cancer. It was approved in May 1996 in the USA and in October 1996 in Japan, making it the first taxane to be approved in this country. In two studies of monotherapy with docetaxel (1-hour infusion of 100 mg every three weeks) response rates exceeded 50%. In a study of 45 women who progressed after anthracycline-based chemotherapy, treatment with docetaxel resulted in an overall response of 57% (20 of 35 evaluable patients) with 3 (8.6%) CR and 17 (48.6%) PR. Median response duration was 28 weeks (Ravdin PM, etal, J Clin Oncol, 1995 Dec, 13(12):2879-85). In another study involving 34 evaluable women, 18 (53%) experienced PR. Median time to disease progression and survival duration were 7.5 and 13.5 months, respectively, and median overall survival was 9 months. Nearly all patients (31/35) developed neutropenia which was complicated with fever in 51% (18/35) of patients (Valero V, J Clin Oncol, 1995 Dec, 13(12):2886-94). For more information on docetaxel see FO, pp 172-185, 251, 261-262 and 276.

It is expected that in the near future taxanes will be used alone or in combination as first-line therapy for advanced/metastatic breast and other cancers. Already, off-label use of docetaxel is recommended by certain insurers such as Aetna Health Plan, as first-line therapy for breast and non-small cell lung cancer. In a phase I/II clinical trial involving 40 patients, first-line treatment with a combination of doxorubicin (40-60 mg/m$^2$) and docetaxel (50-85 mg/m$^2$) resulted in an overall response rate of 30/40 (75%); MDT was reached at 50 mg/m$^2$ IV bolus of doxorubicin administered first, followed after one hour by 1-hour infusion of 85 mg/m$^2$ of docetaxel (Kalla S, etal, Annals of Oncology 7 (Suppl 5), 1996, Abs. 599O:124).

## HIGH-DOSE (DENSITY) CHEMOTHERAPY (HDC)

High-dose (or density) chemotherapy (HDC) with growth factor and/or hematopoietic cell support is in routine use in the management of advanced/high risk breast cancer. Rationale of HDC protocols is based on *in vitro*, animal and empirical observations in humans of the effectiveness of this approach in killing cancer cells and inducing responses in patients with advanced disease. For instance, in the *in vitro* setting the log-kill (defined as the fraction of cells killed by exposure to a cytotoxic agent) remains constant irrespective of the number of cells in the tumor but rises in a dose-related manner, so that very high drug doses can kill most tumor cells. Also, in combination regimens, log-kills of the various agents are additive, enhancing their cell killing ability. Such regimens may also combat mutations that render tumor cells resistant to any drug, by simultaneously administering many drugs. However, combination chemotherapy often requires reduction in the dose of the individual component drugs to manage toxicity. Therefore, although clinical trials have demonstrated that tumors often respond better to high levels of chemotherapy, in a dose-response manner, bone marrow toxicity of some HDC regimens limit their feasibility except when performed in conjunction with either protection or regeneration of the bone marrow. Escalating dose levels of certain drugs in combination regimens does not always result in higher response rates; sometimes the results are inferior. Also, even when using doses well below those requiring hematopoietic support, there is evidence of a rising dose-response curve for some drugs used against breast cancer. Another way to enhance the effects of chemotherapy is a protocol that increases dose-density by simultaneously increasing dose-level and shortening the time between treatments.

Although effectiveness of HDC is based on strong scientific evidence, its beneficial impact on patient outcomes has not been categorically established. Attempts to evaluate HDC as an alternative to standard chemotherapy by retrospective analysis of clinical trials have been hampered by the fact that treated populations are not adequately profiled regarding the various prognostic factors that determine disease and treatment outcome, making comparisons difficult. Complex multivariate analysis is necessary in order to establish the value of this approach. Planned prospective studies comparing HDC with standard chemotherapy should produce more definitive information regarding these treatment modalities to help clinicians make more appropriate choices for their patients.

Administration of growth factors that increase production of blood cells to replace those destroyed by chemotherapy has made routine HDC possible. Novel gene therapy approaches to protect the bone marrow or enhance its function are also being pursued by various groups but are still in early stages of development. However, when ablation of the bone marrow is the end result of HDC, it must be restored after therapy for the patient to survive.

### HDC with Hematopoietic Growth Factor Support

HDC with hematopoietic growth factor support is a well established modality in the treatment of cancer. Various regimens under evaluation are described in Exhibit 11. Agents to preserve platelet levels in patients undergoing multiple cycles of chemotherapy are also in development.

## HDC with Hematopoietic Cell Transplantation

Techniques used to restore the bone marrow include autologous bone marrow transplantation (autoBMT) and/or peripheral blood stem cell transplantation (PBSCT). In either of these approaches stem cells extracted from the patient's bone marrow or peripheral blood are re-infused after chemotherapy is completed. Such infusions protect the patient from infections, bleeding and certain death.

**Exhibit 12**
**1995 Estimates of Patients Treated by Chemotherapy and/or Hormonal Therapy in Selected World Regions**

| Region | Induction Chemotherapy (#) | Relapsed Chemotherapy (#) | Chemotherapy Total (#) | Hormonal Therapy (#) |
|---|---|---|---|---|
| EEC | 166,828 | 279,485 | 446,313 | 138,017 |
| non-EEC | 14,864 | 26,847 | 41,711 | 13,768 |
| Eastern Europe | 26,656 | 30,639 | 57,295 | 17,508 |
| **Europe Total** | 208,348 | 336,970 | 545,319 | 168,234 |
| **Former USSR** | 72,300 | 74,372 | 146,672 | 47,598 |
| Japan | 18,051 | 29,882 | 47,934 | 11,953 |
| United States | 125,088 | 211,800 | 336,888 | 103,208 |
| Canada | 12,629 | 23,147 | 35,777 | 10,416 |
| **N. America Total** | 137,717 | 234,947 | 372,665 | 142,030 |
| **Triad** | 364,117 | 601,800 | 965,917 | 322,217 |

Controversy surrounds every aspect of HDC requiring autoBMT and/or PBSCT, from selection of patients, choice of agents/combinations, treatment protocols and cost/benefit considerations. Choice of regimen is still under investigation in numerous clinical trials. Response rates and bone marrow toxicity of HDC vary depending on the combination of the chemotherapeutic agents used. Most HDC regimens incorporate alkylating agents which induce higher response rates but are also associated with hematopoietic toxicity, manifested by granulocyte and platelet suppression. Granulocyte depression with these agents reaches its nadir 8-16 days after treatment with levels returning to normal within 20 days after administration of a single high dose. Cyclophosphamide and ifosfamide are less toxic with blood cell levels returning to normal more rapidly; platelets affected less with these agents and no cumulative damage of hematopoietic components occurs after repeated doses.

One of the original HDC regimens, initiated in the mid-1980s, used in breast cancer is a combination of high-dose cyclophosphamide, cisplatin and BCNU. Combination of these drugs that are associated with steep dose-response curves is synergistically effective against breast cancer. When administered as initial therapy to Stage IV ER- patients with metastatic breast cancer, 54% achieved CR and 16% long-term disease-free survival. Another successful regimen in this population started with 3 or 4 cycles of induction chemotherapy with a combination of doxorubicin, 5-FU and methotrexate, followed by consolidation with high-dose CPA, cisplatin and BCNU. This regimen tested in various clinical trials resulted in CR rates of 44%-68% and 2-year disease-free survival rates of 14%-27%. Most often, overall results reported in the literature are dated because they involve trials conducted over a period of time and completed at least five years ago and sometimes longer in order to report 5-year survival rates. Data from these trials may not reflect newer developments that, in the cancer field, represent small but definitely beneficial improvements in how treatments are delivered and how patients are managed. Results from newer regimens are presented in Exhibit 11 and in the accompanying article of this issue (see page 442).

There are several criteria used in patient selection such as patient age, health status and ability to pay, but there is no consensus regarding patient selection based on disease stage, pre-treatment status and certain prognostic factors. Even when age is considered, age limits set by individual programs vary from as low as 50 or as high as 65. Patient selection is believed to be a key contributor to improved results with HDC with hematopoietic support which may prove most effective when administered earlier to breast cancer patients with a poor prognosis following standard therapy. Candidates for this approach are patients with Stage II/III breast cancer with 4-9 positive axillary lymph nodes and Stage IV breast cancer patients with a single metastatic site that can be resected or encompassed within a single radiation field, or minimal bone marrow involvement. HDC regimens delivered when tumor burden is minimal may eradicate disease in selected breast cancer patients who otherwise have little chance of prolonged disease-free survival following standard treatments.

Preliminary data from prospective randomized clinical trials comparing HDC supported by autoBMT/PBSCT with standard chemotherapy for the treatment of advanced breast cancer point to better response rates and complete remissions, although improved survival in breast cancer has not yet been demonstrated. High initial response rates, including CR, are usually short-lived and overall patient survival is similar to those treated with standard chemotherapy. Lackluster results coupled with patient morbidity and high costs associated with these procedures, has prompted many to recommend that they be used sparingly in the management of breast cancer.

However, despite disappointing clinical outcomes, these procedures, currently being offered outside clinical trials, have proliferated reaching over 8,125 in 1995 in North America, Europe and Japan (see Exhibit 13). In 1996, over 4,000 such procedures for breast cancer are expected to be performed in the USA, a substantial increase from 522 in 1989.

Originally, patients offered HDC supported by autologous cell transplants were those with poor prognosis with unresectable, locally-advanced disease (inflammatory breast cancer or <10 positive lymph nodes), or metastases. Overall five-year survival for these patients after standard treatment is estimated at less than 20%. In these patients high-dose consolidation with cyclophosphamide, cisplatin and carmustine is more effective than standard therapy in the short-term but duration of response and survival are not prolonged when compared with conventional therapy.

Studies using high-dose combinations including alkylating agents in selected chemotherapy-naive patients have demonstrated that between 15% and 25% of these patients can achieve durable remissions extended from 3 to 6 years. Those with limited volume disease and less prior chemotherapy respond better. Durable remissions after a single high-dose therapy and no other intervention extending beyond six years have been observed, and several studies have found extended disease-free survival even in poor prognosis patients. However, toxicity in most early studies was significant, associated with a mortality rate as high as 20% in some trials. However, later series report lower treatment-related death rates, averaging only 6%.

***Autologous bone marrow transplantation*** (autoBMT) involving intravenous infusion of bone marrow cells, restores the bone marrow damaged by high dose regimens by repopulating it. Successful repopulation of the bone marrow requires the infusion of cells capable of producing complete trilineage hematopoietic engraftment. Autologous bone marrow has been the most frequently used source of such cells to date, but other sources of hematopoietic progenitors, such as leukopheresed peripheral blood collections, have overtaken this approach so that currently only about 30% of procedures use autologous bone marrow.

Most pre-transplant induction therapy for advanced breast cancer comprises of one high-dose regimen of cyclophosphamide in combination with one or more other alkylating agents. Marrow is usually infused three days after chemotherapy to allow enough time for the drugs to be excreted, but in time to minimize risk of infection. The time to marrow recovery is about three weeks that are spent in the hospital in isolation. Use of such hematopoietic growth factors as G-CSF (filgrastim, Neupogen; Amgen) or GM-CSF (sargramostim, Leukine; Immunex) or stem cells harvested from the patient's own peripheral blood, or both, can shorten the time to recovery.

Current methods of obtaining cells for bone marrow transplants involve invasive human harvest. Bulk needle aspiration of bone marrow from the posterior or anterior iliac crests is generally performed under regional or general anesthesia with approximately 1-3 x $10^8$ nucleated cells/kg (10-15 ml of marrow/kg body weight) collected from multiple sites. To obtain as many marrow cells with as little peripheral blood contamination as possible, each aspirate site is limited to 3-5 ml. So for a normal female adult, 100 to 200 aspirations are required to collect 600 to 900 ml of marrow needed for the procedure. Collected marrow is processed and cryopreserved to remain viable until re-infused. One of the problems of autoBMT is re-infusion of bone marrow contaminated with cancer cells that results in higher rates of recurrence. *Ex vivo* marrow purging is difficult to accomplish, may remove precursor cells necessary for successful engraftment and is costly. Total body irradiation, used for elimination of tumor cells in acute leukemia and lymphoma, cannot be used for localized solid tumors like breast cancer because the dose required for elimination of macroscopic/microscopic disease often exceeds MDT. Various hematopoietic factors have been approved worldwide to accelerate recovery after autoBMT.

Patient performance status at initiation of therapy appears to be a major predictor of toxicity in autoBMT. Most centers consider autoBMT too toxic for patients over 60 years old and its use in breast cancer has generally been limited to pre-menopausal women. Patients with advanced disease and a history of multiple prior chemotherapy regimens, who are least likely to benefit from this procedure, are most likely to accept its high risk and morbidity

Costs of autoBMT can vary depending on the degree of complications. The General Accounting Office (GAO; Washington, DC) estimates the cost of autoBMT for breast cancer to range between $80,000 and $150,000, averaging about $65,000. In comparison, conventional chemotherapy for breast cancer costs $15,000-$40,000. Although they initially balked, insurers have been forced to cover this procedure in selected patients.

***Peripheral blood stem cell transplantation*** (PBSCT) may be used in the place of bone marrow to restore function destroyed by chemotherapy and radiation. Hematopoietic stem cells circulate in the peripheral blood in very small numbers but they may be expanded by the administration of hematopoietic growth factors such as GM-CSF. Myelosuppressive cancer chemotherapy and administration of hematopoietic growth factors such as GM-CSF or G-CSF increase the number of CD34+ cells circulating in blood. Use of such mobilizing techniques followed by leukapheresis, enables collection of a sufficient number of stem cells from the peripheral blood to permit successful autologous transplantation. Stem cells can be identified by monoclonal antibodies directed against the CD34+ antigen, which is found only

on this population of primitive cells and on vascular endothelial cells. Determination of the CD34+ cell count in peripheral blood is useful in choosing optimal harvest time and, after harvesting, in confirming presence of enough CD34+ cells for engraftment (Passos-Coelho JL, etal, JCO, 13:705, March 1995).

PBSCs are generally collected by one or more leukapheresis procedures, each lasting 3 to 6 hours. Approximately 9-10 liters of peripheral blood are processed on multiple occasions using a continuous flow centrifuge to remove a mononuclear cell fraction, including stem cells, while the rest of the blood is returned to the patient. These cells are subsequently concentrated and cryopreserved. Recent reports have shown that a small volume of cells from peripheral blood collected in a single leukapheresis session and cultivated *ex vivo* with cytokine stimulation may be used successfully to restore bone marrow function. The small amount of CD34+ cells (about 11 million cells representing less that 10% of the required number) may be obtained without leukapheresis. Ease of harvest and adequate availability of autologous progenitor cells may also allow repeat administration of HDC (Brugger W, etal, NEJM, 333:283, Aug 1995).

**Exhibit 13**
**1995 Estimates of Autologous Hematopoietic Cell Transplants for Breast Cancer in Selected World Regions**

| Region | Potential Candidates (#) | Procedures (#) | Penetration (%) |
|---|---|---|---|
| France | 3,507 | 446 | 12.71 |
| Germany | 6,182 | 522 | 8.45 |
| The Netherlands | 1,169 | 141 | 12.06 |
| United Kingdom | 5,304 | 744 | 14.03 |
| **EEC, Total** | 23,414 | 3,037 | 12.97 |
| Finland | 276 | 58 | 20.86 |
| Norway | 229 | 48 | 21.03 |
| Sweden | 501 | 98 | 19.45 |
| Switzerland | 519 | 91 | 17.49 |
| **Non-EEC, Total** | 2,065 | 395 | 19.13 |
| **Eastern Europe, Total** | 4,033 | 111 | 2.75 |
| **Europe, Total** | 29,512 | 3,543 | 12.01 |
| Former USSR | 10,412 | 452 | 4.34 |
| Australia | 832 | 103 | 12.41 |
| Japan | 2,013 | 345 | 17.16 |
| United States | 14,087 | 4,004 | 28.42 |
| Canada | 1,421 | 234 | 16.47 |
| **North America, Total** | 15,508 | 4,238 | 27.33 |
| **Triad, Total** | 47,032 | 8,126 | 17.28 |

*Source: Autologous Bone Marrow Transplant Registry, European Group for Blood and Marrow Transplantation and New Medicine*

Originally, PBSCT was indicated for patients who were otherwise candidates for autoBMT but whose bone marrow was unsuitable for the procedure, either because of prior radiotherapy to the marrow or evidence of marrow metastases. However, PBSCT has recently become the procedure of choice in breast cancer indications. Therapeutic advantages of PBSCT over autoBMT include a shorter time to reconstitution of the bone marrow and blood cell counts. In addition, patients treated with PBSCT usually leave the hospital in two instead of three weeks as in the case of autoBMT and some centers perform PBSCT in an outpatient setting. Unlike bone marrow aspiration, peripheral stem cell removal may be performed without anesthesia and is associated with only minor discomfort. Also, PBSCs are less likely than bone marrow to be contaminated with malignant cells. PBSCT usually costs less than autoBMT because of a shorter duration of hospitalization and less need for blood products, antibiotics and other supportive care (Smith TJ, etal, Proc ASCO, 14:314, May 1995). These apparent benefits have led to the increasing the use of PBSCT. An analysis by the Autologous Bone and Marrow Transplant Registry (ABMTR; Milwaukee, WI) estimates that in 1995, 70% of stem cells used in autologous transplants were obtained from peripheral blood compared with 15% from bone marrow alone and 15% from both sources (ABMTR Newsletter, 3(1):6-7, Nov 1996).

## TREATMENT OF COMPLICATIONS OF BREAST CANCER

There are numerous treatment-related complications associated with the management of breast cancer. Because of the size of the affected population and the extensive use of cytotoxic drugs, breast cancer represents a large market for adjunct treatment of such complications as myelosuppression, nausea and vomiting, hypercalcemia, pain, cardiotoxicity, fluid retention, infection and toxicity to normal tissues, among others. Certain protective agents also target toxicities directly associated with certain anticancer agents. For instance, amifostine (Ethyol; U.S. Bioscience) has been approved for reducing toxicities associated with cisplatin and is in phase III clinical trials for reduction of toxicities associated with paclitaxel.

### Hypercalcemia/Bone Pain Palliation

Many patients with advanced breast cancer suffer from hypercalcemia and deep, unremitting bone pain caused

by bone metastases. Although initiation of hormonal therapy usually relieves bone pain, when it fails, palliative options for pain control include analgesics, chemotherapeutics, external-beam radiotherapy and radionuclide therapy. Chemotherapy often results in a moderate, short-term effect. Several agents that treat hypercalcemia have also been shown effective when used in combination with chemotherapy. Radiotherapy is used when all else fails. Intravenously-injected radioisotopes that preferentially localize to bone, offer an effective means of bone pain palliation. One such agent, Metastron (Amersham), using strontium-89, is on the market, and several companies are developing competitive products. For more information on these agents, see FO, pp 310-11.

Recently, a new class of drugs, the bisphosphonates, have been shown to reduce and/or delay complications associated with bone metastasis. Four bisphosphonates, etidronate disodium (Didronel; Procter & Gamble) and pamidronate, are commercially available in the USA and abroad and clodronate (Bonefos; Leiras and Clasteon; Gentili) and ibandronate (Bondronat or Bonviva; Boehringer Mannheim) are available in various markets outside the USA and many others are in development.

***Pamidronate*** (Aredia), developed by Novartis (Ciba Pharmaceuticals) and being marketed by Chiron Therapeutics (Emeryville, CA), a business unit of Chiron, was approved by the FDA in July 1996 as a palliative treatment for osteolytic bone metastases of breast cancer in conjunction with standard antineoplastic therapy. Aredia inhibits osteoclast activation to treat/delay bone pain caused by metastatic breast cancer, reducing the need for narcotic analgesics. Aredia is also approved as a treatment of skeletal osteolytic lesions in multiple myeloma in conjunction with standard chemotherapy (also see FO, p 231).

Recommended regimen of pamidronate for the breast cancer indication is a 2-hour IV infusion of 90 mg, every three to four weeks, for 12 months. Results of clinical trials have confirmed that patients treated with pamidronate experience a significant reduction in skeletal complications (pathologic fractures and spinal cord compression), require less treatment (radiation therapy or surgery to bone) for such complications and report significant relief of bone pain when compared with untreated cohorts. In one double-blind, randomized placebo-controlled trial of a 12-month regimen of pamidronate among 185 Stage IV breast cancer patients with osteolytic metastases of ≥ 1 cm in diameter, treated with pamidronate, 43% experienced incidence of skeletal-related episodes (SRE) compared to 56% among 197 controls. The mean morbidity rate (SRE/year) was lower in the treated group (2.1 versus 3.3) and time to first SRE was longer (median was 13.1 months) in the treated group compared with 7 months in controls (Hortobagyi, GN, etal, ASCO96, Abs. 99:108). In a similar treatment regimen overall skeletal morbidity rate was 2.4 in the pamidronate-treated group compared to 3.6 in the placebo group; time to first SRE was 10.9 versus 6.9 months, respectively (Theriault R, etal, ASCO96, Abs. 152:122).

Results of another multinational, randomized controlled trial carried out by the Aredia Multinational Cooperative Group demonstrated a delay in progression of bone metastases in breast cancer patients treated with intravenous pamidronate. Among breast cancer patients with bone metastases randomly allocated to chemotherapy alone (152 patients) or chemotherapy plus pamidronate (45 mg in 250 ml of saline as a 1-hour intravenous infusion every 3 weeks) (143 patients), median time to disease progression in bone was increased by 48% in patients who received pamidronate (249 versus 168 days). Significant pain relief, defined as a two-point decrease lasting for ≥ 6 weeks, was reported by 44% of pamidronate-treated patients and by 30% of controls. The infusions were well tolerated and no major toxicities were reported (Conte PF, etal, J Clin Oncol, 1996 Sep, 14(9):2552-9).

However, contrary to the results achieved with intravenously-administered pamidronate, supportive treatment with oral pamidronate (300 mg/day) did not prevent nor delay the development of bone metastases in patients with breast cancer, with either locally advanced disease or extraskeletal metastases but no bone metastases. In a clinical trial of 124 patients who were assigned to treatment with oral pamidronate (65 patients) or to a control group (59 patients), actuarial risk of a first skeletal event was similar in both groups. Quality-of-life measurements of bone metastases-related aspects showed no differences between the two groups but 19 patients withdrew from the study because of gastrointestinal complaints attributed to pamidronate (van Holten-Verzantvoort AT, etal, European Journal of Cancer, 1996 Mar, 32A(3):450-4). In contrast, treatment with oral clodronate (1600 mg daily) was shown to reduce the rate of skeletal metastases progression in breast cancer patients with recurrent disease. In a double-blind, randomized placebo-controlled trial of 133 patients with recurrent breast cancer, there were fewer (15 versus 19) skeletal metastases among 66 patients treated with oral clodronate compared to 67 controls. Total number of skeletal metastases was also significantly decreased (32 versus 63), as was the number of hypercalcemic episodes (10 versus 17) and vertebral deformities (35 versus 54); the combined rate of all morbid skeletal events was reduced by 26% (Paterson, AHG, etal, ASCO96, Abs. 81:104).

***Next issue:*** *A database and description of over 100 novel drugs in development for the treatment of breast cancer such as topoisomerase inhibitors; anthrapyrazoles; retinoids, hormonal therapies, immunotherapeutics/vaccines; gene therapy; monoclonal antibodies, immunoconjugates, immunotoxins; agents against multi-drug resistance; drug delivery constructs; etc.*

## MEETING COVERAGE

# MANAGEMENT OF BREAST CANCER

## FROM THE 19TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM, SAN ANTONIO, TX, DECEMBER 12-14, 1996

### NEW APPROACHES IN HIGH-DOSE CHEMOTHERAPY FOR THE TREATMENT OF BREAST CANCER

#### High-Dose Chemotherapy with Stem Cell Support

High-dose chemotherapy with autologous stem cell rescue can result in durable remissions in breast cancer. Patients most likely to benefit from this treatment approach are those with metastatic breast cancer responsive to chemotherapy, either anthracycline-based or other salvage combinations. Because no standard high-dose regimen has been defined for the treatment of breast cancer, a series of phase I/II clinical trials tested various combination regimens including ICE consisting of 10.1 g/m$^2$ ifosfamide (Ifex; Bristol-Myers Squibb), 1.8 g/m$^2$ carboplatin (Paraplatin; Bristol-Myers Squibb), and 3 gm/m$^2$ etoposide (Vepesid, Bristol-Myers Squibb); or MITT combining 90 mg/m$^2$ mitoxantrone (Novantrone; Immunex) and 1000 mg/m$^2$ thiotepa (Thiotepa; Immunex); or TNT consisting of 360 mg/m$^2$ paclitaxel (Taxol, Bristol-Myers Squibb), 46 mg/m$^2$ mitoxantrone, and 900 mg/m$^2$ thiotepa which proved to be an active regimen even in cases of refractory metastatic breast cancer.; or 16 mg/kg busulfan (Myleran; Bristol-Myers Squibb) and 120 mg/kg cyclophosphamide (Cytoxan; Bristol-Myers Squibb) in Stage III breast cancer. Autologous stem cell rescue was primed with either cyclophosphamide or paclitaxel, and the peripheral blood stem cells (PBSC) were further mobilized with 5 µg/kg granulocyte-colony stimulating factor (G-CSF) such as filgrastim (Neupogen; Amgen), starting at 21 hours and continuing until the neutrophil count was normal. A total of 299 women who were diagnosed with Stage II disease and had more than eight positive nodes (25), Stage III disease (32), and inflammatory breast cancer (11) in the adjuvant setting, or with metastatic breast cancer (231), were treated from August 1989 to February 1996.

At four years, event-free survival on all phase I/II protocols was 64% for Stage II patients, 50% for those with Stage III disease, and 27% for women with inflammatory breast cancer. Event-free survival at two years for women with more advanced or metastatic breast cancer being administered ICE with anthracycline-responsive disease, was 25% and with anthracycline-refractory disease, 13%. For patients on MITT, event-free survival at two years for those with anthracycline-responsive disease was 24%, but among those with refractory breast cancer failing anthracyclines and all other salvage therapies, no event-free survival was observed beyond 3.5 years. Event-free survival rate at one year for TNT was 45% for anthracycline-responsive disease and 24% for women refractory to anthracyline-based therapy or all other salvage therapies (Fields KK, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 277:417).

HDC with autologous PBSC support may significantly improve outcome in women with breast cancer, resulting in better objective response rates, increased durations of response, and longer periods of disease-free and overall survival. Ten-year experience has indicated that HDC with autologous stem cell rescue, whether from PBSC support or BMT, confers a prolonged disease-free survival in a subset of patients with metastatic breast cancer. In this study, 102 women with metastatic breast cancer underwent one of three induction regimens between 1986 and 1993. Those with stable or responsive disease were treated by HDC; 79 patients were treated with 7.5 gm/m$^2$ cyclophosphamide and 675 mg/m$^2$ thiotepa and 23 with the same doses of cyclophosphamide and thiotepa plus carmustine (450 mg/m$^2$). The source of stem cell rescue was either BMT alone (44%), BMT plus rhG-CSF-mobilized PBSC (20%), or rhG-CSF-mobilized PBSC alone in patients with metastatic breast cancer involving the bone marrow (36%).

At a median follow-up of 62 months (range 1 to 109 months), initial overall response to induction was 61% with 25% CR and 36% PR and overall response to high-dose chemotherapy among women with stable or responsive disease at induction was 62%, with 27% CR and 35% PR. Median survival from reinfusion was 16 months, with a five-year survival rate of 20%, while the median event-free survival was eight months, with a five-year event-free survival of 11%. At the present time, 19 women are still alive, 11 with no evidence of disease and eight with disease. The longest CR to date in this group of patients is 7.8 years. It should be pointed out, however, that a significant number of women have succumbed to recurrent disease. Clinical trials involving enhanced stem cell manipulation to eradicate tumor cells in the autograft and detection and treatment of minimal residual disease are underway to improve upon these results (Laport GF, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 276:413).

Initial results from a phase I/II study point out that high-dose combination chemotherapy consisting of mitoxantrone, cyclophosphamide, and paclitaxel, coupled with autologous PBSC support, significantly improves survival in women with metastatic breast cancer. Forty-six patients with advanced, chemosensitive breast cancer enrolled in the study, were treated with 6 g/m$^2$ cyclophosphamide, 70 mg/m$^2$ mitoxantrone, and a three-hour infusion of paclitaxel at a starting dose of 250 mg/m$^2$, escalated for the purpose of determining DLT, MTD, and efficacy of the drug combination. Autologous stem cells were mobilized daily with rhG-CSF, and stem cell re-infusion and recovery took place in an outpatient setting. Median duration to recovery for ANC over 0.5/nl was 12 days, as was recovery for platelets over 20/nl. At

the fourth dose level of paclitaxel (400 mg/m$^2$) DLT was noted in three of six patients, which prompted an extended infusion schedule of this dose level lasting six rather than three hours. To date, among 32 women who completed the protocol, there were 10 CRs, 18 PRs, and disease stabilized in two. Median duration of progression-free survival is 12.6 months; median duration of overall survival has not yet been reached. Phase II clinical trials will continue at the MTD level to evaluate efficacy and toxicity (Glück S, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 277:420).

### Tandem High-Dose Chemotherapy with Stem Cell Support

While complete remission rates of around 50% are seen with high-dose chemotherapy, the majority of patients with metastatic breast cancer relapse and ultimately die. In an attempt to increase the proportion of those achieving a CR at the end of therapy, a tandem high-dose chemotherapy regimen was designed which incorporates 24-hour infusion of paclitaxel as the first high-dose cycle of chemotherapy, escalated from 400 to 825 mg/m$^2$. The second intensification was melphalan at 180 mg/m$^2$ at a median 21 days after the first cycle, and the third intensification included cyclophosphamide (6000 mg/m$^2$), thiotepa (500 mg/m$^2$), and carboplatin (800 mg/m$^2$) at a median of 30 days after the second intensification. All cycles were supported with PBSC and rhG-CSF administered on day 0 up to neutrophil recovery, with a minimum of 3 X 10$^6$ CD34+ cells/kg leukapheresed after mobilization. Among 34 women enrolled in the study to date, 24 completed all three cycles. Among 16 evaluable patients, there were three (18.7%) CRs and 13 (81.3%) PRs. The high-dose program was relatively well tolerated, with no deaths from hematologic toxicities. Paclitaxel-related neurotoxicity at grades 2/3 was seen in all patients but appeared and to be unrelated to the extent of pretreatment with paclitaxel or the site of metastases and was reversible (Vahdat LT, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996; Pg 227:419).

Tandem high-dose chemotherapy with mitoxantrone and thiotepa (MiTepa), followed by ICE and combined with PBSC rescue, also results in long-term disease control in high-risk patients and improves survival rates in women with metastatic breast cancer. A total of 58 women were entered in the study; 38 with metastatic breast cancer were treated with tandem therapy and 20 in a high-risk adjuvant setting were treated by a single regimen. Tandem treatment consisted of MiTepa and ICE, while ICE alone was used as single therapy. MiTepa consisted of mitoxantrone (60 mg/m$^2$), administered as a continuous infusion over 72 hours, and thiotepa (300 mg/m$^2$) as a two-hour infusion, both on days one to three. ICE consisted of ifosfamide (12 g/m$^2$), carboplatin (1800 mg/m$^2$) and etoposide (2000 mg/m$^2$), administered as a 96-hour continuous IV infusion on days one to four. A total of 60 PBSC transplants mobilized with rhG-CSF administered daily on day two to 10 or GM-CSF on days two to 10, were performed in those with metastatic breast cancer and 20 transplants mobilized with rhG-CSF were administered to women in a high-risk adjuvant setting. Actuarial survival was calculated from the first PBSC infusion.

For the 38 patients with metastatic breast cancer, median failure-free survival was 17.2 months and median overall survival was 46.6 months, with one-, two-, three-, four-, and five-year failure-free survival rates of 72%, 27%, 19%, 19% and 19%, respectively. In the 20 patients treated in the adjuvant setting, only one woman relapsed at 9.8 months and died at 26 months. Median failure-free survival time and median overall survival time had not been reached for the other 19 patients who remained free of disease 6.5 to 7.8 months after PBSC infusion. In this group, overall survival rate at one-year was 100% and 87% at two years. This method of high-dose chemotherapy and PBSC support was carried out with a low risk of treatment-related deaths. Among women with metastatic breast cancer there were four (10.5%) treatment-related deaths, one from pneumonia at 5.9 months, one from acute myelogenous leukemia at 30.5 months and two other deaths (veno-occlusive disease, aspergillosis) which occurred within the first 100 days of a second transplant (Dillman RO, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996; Pg 278:421).



### Factors Predicting Survival with High-Dose Chemotherapy

The only factor found to be predictive of the length of failure-free or overall survival in high-risk Stage II and III breast cancer, treated by doxorubicin-based adjuvant therapy, and followed by high-dose chemotherapy and stem cell rescue, is the presence of estrogen or progesterone receptors. Patients with Stage II, hormone receptor-positive, high-risk disease, seem to have a better outcome after HDC with autologous stem cell support. In a clinical study, 68 women with Stage II breast cancer and four or more positive nodes or Stage III disease, were treated with standard doxorubicin-based adjuvant therapy, followed by HDC with autologous PBSC support. Twenty-one patients with Stage II disease and four to nine positive nodes were treated with a CVP regimen that combines cyclophosphamide (5.25 g/m$^2$), etoposide (1200 mg/m$^2$), and cisplatin (150 mg/m$^2$), while 18 patients with Stage II breast cancer and 10 or more positive nodes and 29 patients with Stage III disease were treated with a CT regimen of cyclophosphamide (6 g/m$^2$) and thiotepa (600 to 800 mg/m$^2$). After high-dose chemotherapy, all patients were treated with chest wall and axilla radiation and those with hormone receptor-positive tumors were treated with tamoxifen. All Stage II breast cancer patients with four to nine positive nodes were rescued with rhG-CSF and autologous PBSC, while the other two groups were treated with GM-CSF and autoBMT.

The failure-free survival rate for women with Stage II disease treated with CVP and CT was 60% and 81% respectively, with a median follow-up of 334 days and 528 days, respectively. Median failure-free survival of Stage III patients treated with CT was 14 months (nine of 19 Stage IIIA and seven of 10 Stage IIIB patients failed), significantly less than that seen in Stage II patients. Overall survival for the three groups was not significantly different, with a median survival of 36 months. Cox regression model was used to analyze age, time from diagnosis of high-risk breast cancer, dose of doxorubicin, hormone receptor status, S-phase, and dose of thiotepa. Women in the two treatment groups with hormone receptor-negative, high-risk disease, were 2.75 and 2.78 times more likely to relapse or die, respectively, than patients with hormone receptor-positive high-risk disease (Reed EC, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 278:422).

## High-Dose Chemotherapy with Stem Cell Support in Non-metastatic Disease

One of the attractive attributes of HDC with rhG-CSF and PBSC support for patients with non-metastatic breast cancer, is that it may be performed in an outpatient setting. A study was designed to evaluate feasibility of an outpatient regimen of four cycles of high-dose cyclophosphamide and doxorubicin with rhG-CSF and autologous stem cell support in women with non-metastatic breast cancer. Thirty-four patients, 94% of whom were pre-menopausal (median age 45.5 years) and 6% menopausal, were enrolled in the study. Ninety-four percent of the women were diagnosed with ductal carcinoma and 6% with other types of breast cancer. All 34 patients were treated with cyclophosphamide (3000 mg/m$^2$) and doxorubicin (75 mg/m$^2$) in 21-day cycles. Apheresis was performed after the first cycle of chemotherapy (34 patients) and, if necessary, again after the second (9 patients). Support with rhG-CSF (5 µg/kg/day) was started on day three of each cycle and was stopped the day before the last apheresis or when ANC 500/mm$^3$. PBSC was re-infused on day three of cycles three and four. After four cycles of chemotherapy, febrile neutropenia occurred in 25% of the patients, with 15 of the women spending a median of 4.1 days in the hospital. Nausea and vomiting, lack of appetite, and weight loss during treatment were seen in 69%, 52%, and 41% of the patients, respectively.

Local treatment post-chemotherapy included radiotherapy (100%), or surgery and radiotherapy (35%). The first local treatment was performed within a median of 42 days (27-71 days range) after day one of cycle four in the case of surgery and a median of 36 days (24-50 days range) in the case of radiotherapy. Five women were treated with additional hormonotherapy with tamoxifen (20 mg daily). While the physical status of women treated with this protocol was temporarily impaired during the procedure, their overall quality of life was not compromized (Viens P, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 293:534).

## HER-2/neu Overexpression and Relapse

Overexpression of HER-2/neu has been observed in patients with high-risk Stage II and IIIA breast cancer who appear to be at higher risk for relapse even when treated with high-dose chemotherapy and autologous PBSC support. Twenty-five women with high-risk Stage II and IIIA breast cancer (more than 10 involved lymph nodes) were treated with six cycles of standard dose chemotherapy (5-FU, doxorubicin, and cyclophosphamide), followed by high-dose chemotherapy consisting of cyclophosphamide (2.5 gm/m$^2$) and thiotepa (225 mg/m$^2$) both for three days, with autologous PBSC support mobilized by rhG-CSF (5 µg/kg). Actuarial relapse-free survival at three years was 80%, and actuarial overall survival at three years was 56%. Tumors of four patients who relapsed systemically between six and 18 months overexpressed HER-2/neu and nine of the twenty-one women with no or borderline overexpression of HER-2/neu also relapsed (Bitran JD, etal, Breast Cancer Research and Treatment, Vol 4-1, No 3, 1996, Pg 276:415).

Patients with inflammatory breast cancer and HER-2/neu overexpression are also likely to have a poorer outcome despite treatment with multiple cycles of high-dose chemotherapy and stem cell support. Other molecular markers correlated with poor clinical outcome, such as C-erbB-2 expression, p53 accumulation, and S-phase fraction, were also analyzed in a pilot study of 16 patients with inflammatory breast cancer, treated with multiple-cycle HDC. Treatment consisted of six three-weekly cycles of doxorubicin (75 mg/m$^2$) and cyclophosphamide (3 g/m$^2$), followed by rhG-CSF. Peripheral blood progenitor cells mobilized by rhG-CSF were collected after the second chemotherapy course which included a higher dose of cyclophosphamide (6 g/m$^2$). Stem cells were re-infused on day three, following cycles three to six. Mastectomy was performed three weeks after the last cycle of chemotherapy.

Among 15 evaluable cases, there were 11 (73%) CRs and four (27%) PRs, for an overall objective response rate of 100%. Interestingly, a complete pathological response was achieved in four patients (26%) and residual intraductal carcinoma only was present in another five patients (33%). Six patients had residual invasive carcinoma (40%). Five of six patients (40%) who relapsed within a median follow-up of 22 months had a marked HER-2/neu overexpression. Three had experienced a complete or good histological response with only ductal carcinoma *in situ* in the breast, but then relapsed at 12, 15, and 21 months. Three others had a poor response and relapsed at nine, 11, and 13 months. These results, which point to a poorer outcome in inflammatory breast cancer patients with HER-2 overexpression even after multiple high-dose chemotherapy cycles, will need to be confirmed in a larger prospective study (Palangie T, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 277:418).

## NEW AGENTS AND NOVEL REGIMENS FOR ENDOCRINE THERAPY IN BREAST CANCER

### Estrogen Replacement Therapy

Results from a large-scale prospective study of adult American women indicate that use of estrogen replacement therapy does not increase the risk of breast cancer over time and, in fact, is associated with a 16% decrease in breast cancer risk. Overall, 1.2 million adult women nationwide were given a self-administered, four-page, questionnaire soliciting information on estrogen use. After nine years of follow-up, among 422,373 post-menopausal women who were breast cancer-free at study entry, there were 1,469 breast cancer deaths; 884 deaths in women who had never used estrogen (risk reduction 1.00) compared to 585 deaths in those who had used estrogen (risk reduction 0.84). Results from Cox proportional hazards modeling, adjusted for 11 other potential risk factors, showed that use of estrogen replacement therapy was associated with a significantly decreased risk of death from breast cancer.

There was a moderate trend of decreasing risk with younger age at first use of estrogen replacement. For those who used estrogen replacement before 40, relative risk was 0.66 compared to 0.84 in the 40 to 49 years group and 0.89 for those over 50 years of age. In addition, there was increased risk reduction based on estrogen use duration (0.78 in the two to ten years of estrogen use, compared to 0.85 for use of less than one year and 0.93 for more than 11 years). With regard to interaction of co-variates, there was a strong relationship between age at menarche (14 or older), higher risk was documented in women with self-reported cysts, and no link was found with a first-degree family history of breast cancer. Risk of breast cancer death with estrogen replacement therapy was not observed with estrogen use status (baseline/former), age at first use, duration of use, or years since last use. Positive impact of estrogen therapy on breast cancer mortality may be attributed to selection bias, with estrogen users generally being healthier and more likely to undergo annual mammograms. However, estrogen use has been known to prolong the pre-metastatic stage of breast cancer, and has been shown to increase the expression of normal tumor suppressor BRCA1 (Willis DB, etal, Breast Cancer Research and Treatment, Vol 14, No 3, 1996, Pg 219:8).

A prospective clinical trial of 433 post-menopausal women diagnosed with invasive breast cancer found that a larger percent (45% versus 20%) of those who had been treated with estrogen replacement therapy had well-differentiated grade I tumors when compared with their never-treated cohorts; grade II tumors were diagnosed in 44% and 64% and grade III tumors in 10% and 16% of patients, respectively. Tumor size, hormone-receptor status, recurrence rate and incidence of positive nodes was similar between the two groups (Harding C, etal, BMJ, 1996 June 29, 312(7047):1646-7).

### Tamoxifen in the Neoadjuvant Setting

Tamoxifen in the neoadjuvant setting may reduce incidence of relapse and mortality in women with breast cancer. Because the benefit from adjuvant treatment of breast cancer with tamoxifen is overwhelming, a study was set up to evaluate the possible effects on prognosis with use of tamoxifen as a neoadjuvant treatment prior to surgery. Overall, 107 chemotherapy-naive women with non-metastatic breast cancer were treated with tamoxifen (30 mg/day) for three to four weeks, pre-operatively. Ninety-two of the enrollees were matched for age at diagnosis, year of diagnosis, lymph node involvement, and pre-operative radiotherapy, with a control group of 92 women from a hospital-based registry. Mean follow-up was 50 months. There was a definite trend toward a longer relapse-free survival in women treated with pre-operative tamoxifen compared to the control group. Also, this difference in relapse-free survival between the two groups was seen in a subgroup of ER+, PgR+ patients, consistent with the predictive value of response to tamoxifen in hormone receptor-positive breast cancer. Overall survival was also longer in tamoxifen-treated patients than in the controls (Pujol P, etal, Breast Cancer Research and Treatment, Vol 4, No 3, 1996, Pg 292:532).

### Aromatase Inhibitors

***Anastrozole*** (Arimidex; Zeneca), a new potent, oral, once-daily, highly selective, non-steroidal aromatase inhibitor, appears to more effectively inhibit aromatase than formestane, a new steroidal selective aromatase inhibitor administered intramuscularly, every two weeks. In a study comparing the action of anastrozole and formestane, 60 post-menopausal women with advanced breast cancer, all suitable for hormonal therapy, were randomized to anastrozole (1 mg orally, once a day) or formestane (250 mg/m$^2$ intramuscularly, once every two weeks). Treatment was continued until disease progression or withdrawal from the study. Maximal estradiol and estrone suppression were observed by the first week of treatment. At four weeks of treatment with anastrozole, no hormonal recovery was apparent. In contrast, suppression with formestane was less than with anastrozole (mean estradiol concentrations with anastrozole were reduced by 79% and with formestane by 58%) and there was a trend toward recovery with formestane at two and four weeks immediately prior to the next dose. Furthermore, at the doses used in this study, anastrozole inhibited aromatase activity by 96.7% while formestane inhibited aromatase by 84.8%. Consistent estradiol and estrone control was achieved with anastrozole throughout the four weeks of the study which was not possible with formestane (Dowsett M, etal, Breast Cancer Research and Treatment Vol 41, No 3, 1996, Pg 290:522). For additional information, see FO, p 216-17.

***Letrozole*** (Femara; Ciba-Geigy), a fourth generation aromatase inhibitor, appears to be significantly superior to megestrol acetate as second-line treatment for post-

menopausal patients with advanced breast cancer, in terms of objective response rate, duration of response, time to treatment failure, and tolerability. In a large-scale clinical trial involving 551 women with metastatic breast cancer, 188 were treated with oral letrozole (0.5 mg once daily), 174 with oral letrozole (2.5 mg once daily), and 189 patients with oral megestrol acetate (160 mg daily). All responses were confirmed by external, independent peer review. The overall objective response rate (complete and partial) was 12% for letrozole at a dose level of 0.5 mg daily, 23.6% for letrozole at 2.5 mg daily, and 16.4% for megestrol acetate at 160 daily. Median duration of response had not yet been reached for the 2.5 mg letrozole dose, while for 0.5 mg letrozole and megesterol it was 18 months, already a significant difference at this point in time. Median time to treatment failure was significantly longer, with 2.5 mg letrozole at five months (155 days) versus 3 months for 0.5 mg letrozole and four months (118 days) for megestrol acetate. Median survival time was 731 days in the 2.5 mg letrozole arm and 660 days in the megestrol acetate arm. Quality of life evaluations support the contention that women on 2.5 mg letrozole obtain a greater benefit from treatment, with fewer serious side effects (mainly thromboemboli) and less deterioration of performance status. Letrozole may, therefore, replace progestins as a second-line treatment of choice for post-menopausal women with metastatic breast cancer (Leonard R, etal, Breast Cancer Research and Treatment, Vol 4, No 3, 1996, Pg 220:5). For additional information, see FO, p 174.

***Liarozole fumarate*** (R85246, Janssen Research Foundation) is a benzimadazole developed primarily for prostate cancer which blocks $P_{450}$-dependent retinoic acid catabolism and estrogen biosynthesis. In the first clinical study of liarozole in breast cancer, response to treatment was seen in heavily pretreated women refractory to hormonal therapy. To assess the value of this new agent in post-menopausal metastatic breast cancer, 84 women, 13 with ER- disease in first relapse (Group A), 15 with ER+ tamoxifen-refractory disease (Group B), 29 with hormone responsive ER+ or unknown disease which had become resistant to hormonal therapy (Group C), and 27 ER+ or ER- women with metastatic disease refractory to chemotherapy (Group D), were enrolled in a clinical trial of liarozole administered at 150 mg orally, twice a day, until disease progression. To date, validated data from 61 patients (11A, 9B, 27C and 14D) include 10 responders (2A, 1B, 5C, 2D) and 10 with SD. Estradiol suppression occurred within two weeks of treatment and was maintained below assay detection levels throughout the treatment period. There was no blunting of cortisol or aldosterone response to ACTH stimulation. Generally, adverse drug-related events were mild to moderate in severity and appeared to be primarily linked to a hypervitaminosis A syndrome which is consistent with increases in endogenous levels of retinoic acid generated by liarozole intake (Goss PE, etal, Breast Cancer Research and Treatment, Vol 4, No 3, 1996, Pg 290: 521). For additional information, see FO, pp 217 and 307.

## Progesterone Receptor Antagonists

***Onapristone*** (Schering AG), a progesterone receptor antagonist, appears to be an effective endocrine therapy for primary human breast cancer. A study of this agent as first-line endocrine therapy enrolled 19 patients, 12 with locally advanced disease and 7 elderly women with primary breast cancer and poor performance status who were initially treated with hormone therapy. Seventeen of the 19 women were ER+. Patients were treated with oral onapristone (100 mg daily) until disease progression. Overall tumor remission rate in 18 evaluable patients was 67%, with 10 (56%) PRs; stabilization of disease (SD) was reported in two cases (11%) and disease progressed in six, before six months of onapristone therapy. Median duration of remission had not been reached at 50+ weeks (Robertson JFR, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 288:515).

## Combination Endocrine Therapies

***Interferon-β*** (IFN-β, Betaseron; Berlex), retinyl palmitate, and tamoxifen as combination endocrine therapy in pretreated patients with metastatic breast cancer, has demonstrated high activity, with good response rates, increased duration of response, and relatively long-term survival. Over a five-year period ending June 1992, 85 pretreated women with metastatic breast cancer were enrolled into two studies. Among these patients, 76 previously underwent mastectomy, 6 quadrantectomy, and 3 primary radiotherapy. In addition, 21 were treated with adjuvant chemotherapy, 47 with chemotherapy for advanced disease, and 44 with two or more lines of hormonal therapy. In the first study, 49 women with better prognostic variables were treated with a combination of IFN-β ($10^6$ IU/$m^2$) injected subcutaneously thrice weekly, oral tamoxifen (10 mg three times daily), and retinyl palmitate (50,000 IU twice a day). A second group of 36 patients with a shorter disease-free survival were treated with six cycles of an anthracycline-based chemotherapy regimen, two cycles of mitomycin C, mitoxantrone, and methotrexate, and then with the same IFN-β, retinoid, and tamoxifen combination regimen used in the first treatment group. Among 85 evaluable patients, overall objective response rate was 59%, with 23 (27%) CR and 27 (32%) PR; disease stabilized in 17 (20%) and progressed in 18 (21%). ER- patients experienced longer responses than those who were ER+. Median response duration for the total group was 31 months, and median survival, from the start of these salvage treatments was 32 months. Seventeen percent of the patients were still alive at five years (Recchia F, etal, Breast Cancer Research and Treatment, Vol 4, No 3, 1996; Pg 289:520).

***Vinorelbine*** (Navelbine, Glaxo Wellcome) plus high-dose tamoxifen, as well as vinorelbine alone, can produce antitumor responses in heavily pretreated women with extensive metastatic breast cancer. A study was designed to evaluate the safety and efficacy of IV vinorelbine alone in patients with advanced breast cancer who previously failed first-line chemotherapy, and in combination with tamoxifen, in patients who failed to respond or went on to PD with vinorelbine alone. To date, 20 patients have been enrolled in the study, all of whom heavily pretreated (median two regimens with a range of one to five). All patients had previously failed treatment with doxorubicin and paclitaxel. Vinorelbine was administered IV at a dose of 30 mg/m$^2$ on days one and eight of a 21-day cycle. In those who failed to respond, the same dose of vinorelbine was used plus a loading dose of tamoxifen of 150 mg/m$^2$ on day one, followed by a dose of 40 mg/m$^2$ on days two to twelve. Either the tumors of the women in the study were ER- or patients had failed low-dose tamoxifen treatment. Responses were seen in four patients; two (10%) with chest wall disease and liver metastases experienced a PR with vinorelbine alone and two (22%) others among nine who failed to respond to vinorelbine alone, experienced shrinkage (less than 50%) of chest wall and neck lymphadenopathy following treatment with the vinorelbine and tamoxifen combination. The most common toxicity was significant neutropenia with three Grade III and two Grade IV cases (Taylor CW and Albert DS, Breast Cancer Research and Treatment, 4(3), 1996, p 285:504). For additional information, see FO, pp 95, 219 and 262.

### Re-evaluation of Stabilized Disease Associated with Endocrine Therapy

In advanced breast cancer, over the past five years, classification of static disease (SD), previously included with progressive disease (PD) in the "non-responders" category, has been upgraded to the "responders" category which also includes CRs and PRs, as "non-progressive disease". To determine the clinical relevance of SD after six months on endocrine therapy, SD was assessed in 255 breast cancer patients who were treated by both first- and second-line endocrine therapy. Patients were categorized by response (CR, PR, or SD) after six months and those who progressed before six months of therapy were classified as PD. Overall, there was no significant difference in survival between women with SD and either PR or CR after first or second-line treatment. Patients in all three categories survived significantly longer than those with PD, indicating that SD for six months is a clinically useful criterion of remission. Furthermore, this emphasizes that a clinically important distinction exists between non-progressive disease (CR + PR + SD) and progression (PD), with the latter being the clinically relevant indication to institute a change in therapy (Robertson JFR, etal, Breast Cancer Research and Treatment, Vol 41, No 3, 1996, Pg 288:514).

## CORRECTIONS, ADDITIONS AND AMPLIFICATIONS

### CORRECTIONS

### Introgen Therapeutics

In the October issue of FUTURE ONCOLOGY (V2 # 6) it was erroneously reported that Introgen Therapeutics (Austin, TX) is collaborating with RPR Gencell in developing Ad-C-CAM, a construct comprising tumor suppressor gene C-CAM delivered by an adenoviral vector. The company is indeed collaborating with RPR Gencell in developing gene-therapy products based on p53 and K-ras genes but Ad-C-CAM, a prostate cancer treatment in preclinical stage, is being independently developed by Introgen.

### ADDITIONS

### More on Prostate Cancer

***Bone Care International*** (BCI; Madison, WI) is developing improved vitamin D compounds for the treatment of various diseases. The company's second-generation vitamin D compound, LR-103, is expected to enter phase I clinical trials for psoriasis in 1997 and is also being investigated for breast and prostate cancer. A growth rate reduction of prostate or breast cancer cells exposed to certain vitamin D compounds was observed *in vitro* which is probably attributable to the fact that such cancer cells contain intracellular vitamin D receptors. In May 1996, Bone Care was spun off from Lunar (Madison, WI), a firm specialising in osteoporosis diagnosis.



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