

NSABP Breast Cancer Clinical Trials: Recent Results and Future Directions

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ABSTRACT

Over the past 40 years, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has conducted several large, randomized clinical trials evaluating various aspects of surgical and adjuvant therapy in patients with operable breast cancer. Results from these trials have contributed significantly in reducing the extent of surgical procedures and in improving the outcome of patients with early-stage breast cancer. Furthermore, they have helped to establish standards of care for the surgical management of invasive and non-invasive disease and for the use of adjuvant hormonal therapy and adjuvant chemotherapy for patients with negative as well as for those with positive axillary nodes. More recent trials are evaluating several new classes of promising drugs such as the aromatase inhibitors in postmenopausal women with invasive or intraductal breast cancer, the taxanes for patients with positive nodes and in the neoadjuvant setting and other targeted molecular therapies such as trastuzumab and bisphosphonates. Results from these ongoing and recently completed trials could improve outcomes and quality of life for patients with early-stage breast cancer.

INTRODUCTION

Over the past 40 years, the National Surgical Adjuvant Breast and Bowel Project (NSABP) has made significant contributions toward reducing the extent of surgical procedures and in improving outcomes for patients with early-stage breast cancer through the conduct of large, randomized clinical trials designed to evaluate various aspects of local and systemic therapy. Some of these trials have been instrumental in establishing new standards of care in loco-regional and adjuvant systemic therapy for these patients. Furthermore, as adjuvant therapy for early-stage breast cancer became established, the NSABP along with other major cooperative groups attempted to refine several of its aspects and, more importantly, introduced several new promising drugs into the adjuvant setting.

The rationale, design and updated results from these pivotal and more recent trials will be reviewed in this manuscript. Finally, current and future research directions of the NSABP in the context of other developments in surgical and adjuvant breast cancer therapy will also be discussed.

PIVOTAL LOCO-REGIONAL THERAPY TRIALS FOR INVASIVE AND INTRADUCTAL CARCINOMA

Trials evaluating less radical breast surgery in patients with invasive carcinoma

The NSABP has been instrumental in changing the paradigm of the surgical management of both invasive and non-invasive breast cancer that was based on Halstedian principles of tumor growth and dissemination. Several randomized trials (B-04, B-06, B-17) have demonstrated that the extent of local therapy is not paramount to patient's survival.¹⁻³ As a result of those and other studies conducted at the same time by other groups,^{4,5} such disfiguring operations as radical mastectomy developed a century ago have now been replaced, in the majority of the cases, by the more cosmetically acceptable lumpectomy.

After 25 years of follow-up, the B-04 trial continues to demonstrate no significant differences in long-term outcome between clinically negative-node patients who received radical mastectomy and those who received total mastectomy with or without nodal radiation, or between clinically positive-node patients who received radical mastectomy and those who received total mastectomy with nodal radiation.⁶ Among women with clinically negative nodes, the hazard ratio for death among those who were treated with total mastectomy and radiation as compared with those who underwent radical mastectomy was 1.08 (95% confidence interval, 0.91 to 1.28; $P=0.38$). The hazard ratio for death among those who had total mastectomy without radiation as compared with those who underwent radical mastectomy was 1.03 (95% confidence interval, 0.87 to 1.23; $P=0.72$). Among women with positive nodes, the hazard ratio for death among those who underwent total mastectomy and radiation as compared with those who underwent radical mastectomy was 1.06 (95% confidence interval, 0.89 to 1.27; $P=0.49$).

These findings validate earlier results showing no advantage from radical mastectomy.¹ Although differences in outcome of a few percentage points cannot be excluded, these findings fail to confer a significant survival advantage from removing occult positive nodes at the time of initial surgery or from the addition of loco-regional radiation to total mastectomy. Perhaps more importantly, the initial results of the B-04 trial helped pave the way for the conduct of the NSABP B-06 trial designed to evaluate even less radical surgical procedures for the treatment of early-stage breast cancer.

The NSABP B-06 trial compared lumpectomy and axillary node dissection with or without breast radiation with modified radical mastectomy in patients with tumors 4 cm or less in their greatest diameter. Similar to prior reports,^{2,7} the last update from that trial continues to demonstrate the value of lumpectomy and breast radiation as the preferred treatment in the majority of patients with invasive operable breast cancer. After 20 years of follow-up,⁸ there continue to be no significant differences in overall survival (OS), disease free

survival (DFS), or distant DFS between the group of patients who underwent total mastectomy and the group treated with lumpectomy alone, or with lumpectomy and breast radiation. The hazard ratio for death among the women who underwent lumpectomy alone, as compared with those who underwent total mastectomy, was 1.05 (95% confidence interval, 0.90 to 1.23; $P=0.51$). The hazard ratio for death among the women who underwent lumpectomy and breast radiation, as compared with those who underwent total mastectomy, was 0.97 (95% confidence interval, 0.83 to 1.14; $P=0.74$). Among the lumpectomy-treated women whose surgical specimens had tumor-free margins, the hazard ratio for death among the women who underwent postoperative breast irradiation, as compared with those who did not, was 0.91 (95% confidence interval, 0.77 to 1.06; $P=0.23$). Radiation therapy was associated with a marginally significant decrease in deaths due to breast cancer. However, this decrease was partially offset by an increase in deaths from other causes. The cumulative incidence of recurrent tumor in the ipsilateral breast was 14.3% in the women who underwent lumpectomy and breast radiation, as compared with 39.2% in the women who underwent lumpectomy alone ($P<0.001$).

The NSABP B-06 trial, along with other trials conducted by the Milan group to evaluate quadrantectomy,^{4,5} was instrumental in the establishment of breast conserving surgery plus radiotherapy as the preferred method of local treatment for patients with operable breast cancer.

Effect of radiotherapy and tamoxifen in patients with tumors ≤ 1 cm

One of the unresolved questions following disclosure of the results from the NSABP B-06 trial, as well as the Milan trial, was whether all patients with invasive breast cancer undergoing lumpectomy needed postoperative radiotherapy. It was hypothesized that patients with small tumors (≤ 1 cm) could potentially be spared from radiotherapy because they have lower rates of local recurrence. It was further argued at that time (1990 Consensus Development Conference), that patients with negative nodes and tumors ≤ 1 cm may not even need adjuvant systemic therapy because of their good prognosis. Since the B-06 trial (as well as the B-14 trial, described later in this paper) did not include a sufficient number of patients with tumors ≤ 1 cm, the NSABP designed protocol B-21 to adequately address the radiotherapy and the tamoxifen questions in a randomized prospective trial (figure 1).

The principle objectives of the B-21 study were to examine whether tamoxifen was as effective as radiation in controlling ipsilateral breast tumor recurrence (IBTR) and whether the addition of tamoxifen to radiation was superior to radiation alone in terms of local and systemic control of the disease. Women with node-negative invasive breast cancer ≤ 1 cm in diameter treated with lumpectomy and axillary dissection were randomized to tamoxifen alone, breast radiation plus tamoxifen for 5 years or radiation plus placebo for 5 years. A total of 1,009 patients were randomized (tamoxifen: $n=336$; radiation and placebo: $n=336$; radiation and tamoxifen: $n=337$).

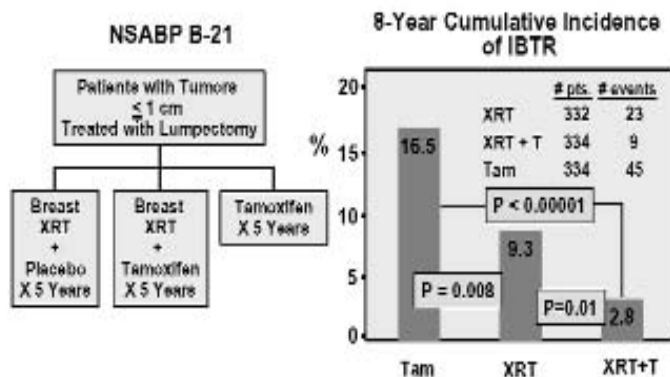


Figure 1. Schema of the NSABP B-21 trial evaluating the role of tamoxifen, breast radiotherapy (XRT) and combination of the two in patients with invasive breast cancer ≤ 1 cm in size treated with lumpectomy and comparison of the 8-year cumulative incidence of ipsilateral breast tumor recurrence (IBTR) rates between the three groups.⁹

Recently published results demonstrated that radiation and placebo resulted in a 49% lower hazard rate of IBTR than did tamoxifen alone; radiation and tamoxifen resulted in a 63% lower rate of IBTR than did radiation and placebo.⁹ When compared with tamoxifen alone and radiation and tamoxifen resulted in an 81% reduction in hazard rate of IBTR.

The cumulative incidence of IBTR over an 8 year period was 16.5% with tamoxifen alone, 9.3% with radiation and placebo, and 2.8% with radiation and tamoxifen (figure 1). Radiation reduced IBTR below the level achieved with tamoxifen alone, regardless of estrogen receptor status. Distant treatment failures were infrequent and not significantly different among the three groups ($P=.28$). When tamoxifen-treated women were compared with those who received radiation and placebo, there was a significant reduction in contralateral breast cancer (hazard ratio, 0.45; $P=.039$). Survival in the three groups was 93%, 94% and 93%, respectively ($P=.93$).

Thus, this trial demonstrated that in the group of node-negative patients with small invasive tumors treated by lumpectomy, tamoxifen was not as effective as breast radiation in controlling the disease in the breast. It further demonstrated that the combination of tamoxifen and breast radiation resulted in better local control of the disease in the breast than either modality alone.

Trial evaluating sentinel node biopsy in patients with invasive, operable breast cancer (NSABP B-32 trial)

Despite several decades of clinical investigations focusing on the prognostic factors for recurrence in patients with operable breast cancer, the status of the axillary lymph nodes has remained the single most important independent factor predicting outcome. Even with the development of several innovative non-invasive, radionuclide imaging modalities (such as Positron Emission Tomography (PET) scan and sestamibi scan), none so far has been shown to be as accurate as pathologic examination of the axillary nodes

in predicting nodal status. Thus, surgical excision of the axillary nodes still represents the gold standard for staging the axilla.

Initial randomized trials evaluating less radical procedures for the surgical treatment of operable breast cancer have demonstrated that elective axillary dissection did not affect survival when compared to delayed axillary dissection (if and when the axillary lymph nodes became clinically palpable).^{1,6} Thus, for several years it has been accepted that elective axillary dissection is mainly performed for staging purposes, to aid in the selection of appropriate adjuvant therapy and for local control of the disease in the axilla. Recent randomized trials however, have demonstrated a small but statistically significant survival advantage by adding loco-regional radiation post-mastectomy in patients with positive axillary nodes who receive adjuvant chemotherapy.^{10,11}

As an alternative to radiotherapy, axillary dissection provides excellent local control of the disease in the axilla in patients with positive axillary nodes. Whether axillary dissection is performed merely for staging purposes or whether it has a small therapeutic benefit in patients with positive nodes, in the majority of patients with operable breast cancer (about 75%) the axillary nodes are found to be histologically negative at the time of surgery. These patients do not derive any therapeutic benefit from the axillary dissection but could experience significant morbidity as a result of the procedure.

The desire to avoid an axillary dissection in these node-negative patients without losing the prognostic information derived from knowledge of the nodal status, has led to the development of lymphatic mapping and sentinel node biopsy. This procedure is currently performed widely in many centers and several non-randomized clinical studies have demonstrated its utility in patients with operable breast cancer (high sentinel node identification rate and low false-negative rate).¹²⁻¹⁸ However, until randomized clinical trials demonstrate an equivalence between sentinel node biopsy and standard axillary dissection in terms of DFS, OS and local control of the disease in the axilla, axillary dissection remains the standard of care.

As a result, after a series of adjuvant therapy trials, the NSABP returned to its surgical roots and is currently about to complete accrual for a large randomized trial to evaluate sentinel node biopsy in patients with operable breast cancer. The NSABP B-32 trial randomizes patients with clinically negative axillary nodes to sentinel node biopsy alone or sentinel node biopsy followed by axillary dissection (figure 2). Patients in the sentinel node biopsy alone group who are found to have positive sentinel node also undergo full axillary dissection.

In addition to its main objective, which is to compare the two procedures in terms of outcome, the study addresses a number of important biological questions including the prognostic significance of immunohistochemically detected tumor cells in lymph nodes when a routine hematoxylin and

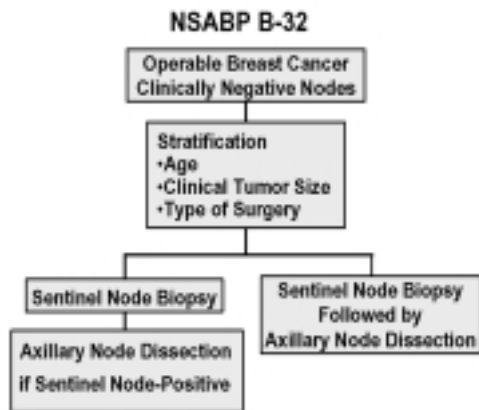


Figure 2. Schema of the NSABP B-32 trial evaluating the safety and efficacy of sentinel node biopsy in patients with operable breast cancer and clinically negative axillary nodes.

tumor cells in lymph nodes when a routine hematoxylin and eosin (H&E) stain is negative. Since June 1999, over 5,000 patients have been accrued into this trial with a target accrual of 5,300 patients (4,000 node-negative patients).

Pivotal NSABP trials in patients with ductal carcinoma in situ

As randomized trials demonstrated the value of breast conserving surgery in patients with invasive breast cancer, an obvious question arose relative to the value of this procedure in patients with non-invasive disease. The introduction and widespread use of mammography has contributed to a dramatic increase in the incidence of small, localized, non-palpable ductal carcinoma *in situ* (DCIS), an entity with excellent prognosis after local therapy alone.

Based on the results of the B-06 and other trials, in the early 1980s there was a paradox in the surgical treatment of early-stage breast cancer with invasive disease being treated progressively more with lumpectomy, whereas mastectomy remained the recommended surgical treatment for non-invasive disease. Thus, it became imperative at the time to test the value of breast conservation in patients with DCIS. The NSABP was the first group to conduct such a prospective randomized trial.

The NSABP B-17 trial compared lumpectomy alone to lumpectomy plus radiation in patients with localized DCIS (figure 3). A mastectomy control group was not included, given the acceptance of lumpectomy based upon the results of the B-06 trial, as well as the excellent prognosis of patients with localized DCIS.

Recently updated results from the B-17 trial after 12 years of follow-up continue to indicate—as previously reported—that radiotherapy significantly decreases the rate of invasive and noninvasive IBTR.^{19,3,20} The cumulative incidence of non-invasive IBTR as a first event was significantly reduced with radiation from 14.6% to 8.0% ($P=0.001$, figure 3). More importantly, the cumulative incidence of invasive ipsilateral recurrence was also significantly reduced from 16.8% to 7.7% ($P=0.00001$, figure 3). However, no difference in OS

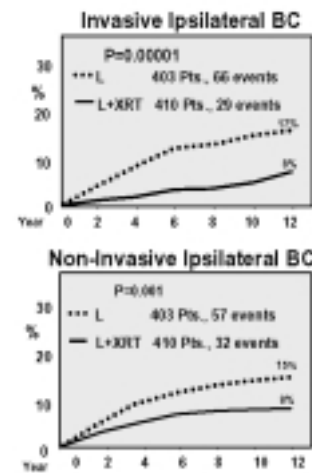
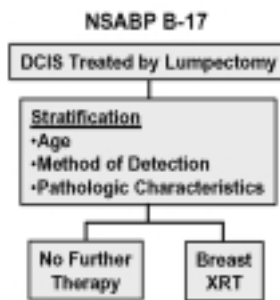


Figure 3. Schema of the NSABP B-17 trial comparing lumpectomy alone to lumpectomy plus breast radiotherapy (XRT) in patients with localized ductal carcinoma in situ (DCIS) and comparison of the 12-year cumulative incidence of invasive and non-invasive breast cancer recurrence between patients receiving lumpectomy alone (L) and those receiving lumpectomy plus breast radiotherapy (L+XRT) (BC: breast cancer).

(Adapted with permission from Fisher B, Land S, Mamounas E, et al. Prevention of Invasive Breast Cancer in Women with Ductal Carcinoma in situ (DCIS): An Update of the NSABP Experience. *Sem Oncol* 2001; 28:400-18.)

has been observed between the two groups (86% vs. 87%, $P=0.80$). In addition, over two-thirds of the deaths occurring in this trial were not breast cancer related.

In a subset of 623 out of 814 evaluable patients from this trial, pathologic features were analyzed relative to their prognostic significance for ipsilateral breast cancer recurrence.²¹ Only the presence of moderate/marked comedo necrosis was a statistically significant independent predictor of risk for ipsilateral breast cancer recurrence in both treatment groups. Radiation markedly reduced the annual hazard rates for ipsilateral breast cancer recurrence in all subgroups of patients.

Following completion of the B-17 trial, another randomized trial was conducted by the NSABP in patients with DCIS to evaluate the role of tamoxifen following lumpectomy and radiation (NSABP B-24, figure 4). At that time, a large body of scientific evidence had accumulated demonstrating benefit from tamoxifen administration in patients with resected early-stage invasive breast cancer.²² In these patients, tamoxifen not only reduced the risk for systemic recurrence but also had a significant impact in reducing the rate of IBTR following lumpectomy and radiation.^{23,24} More importantly, tamoxifen was found to reduce the incidence of second primary breast cancers in the contralateral breast by about 40%.²²⁻²⁸ The latter observation, along with preclinical evidence that tamoxifen inhibits both the initiation and promotion of tumors in experimental animals,^{29,30} made tamoxifen an attractive agent for patients with DCIS treated with lumpectomy and radiation by possibly reducing the rate of development of ipsilateral and contralateral invasive breast cancers.

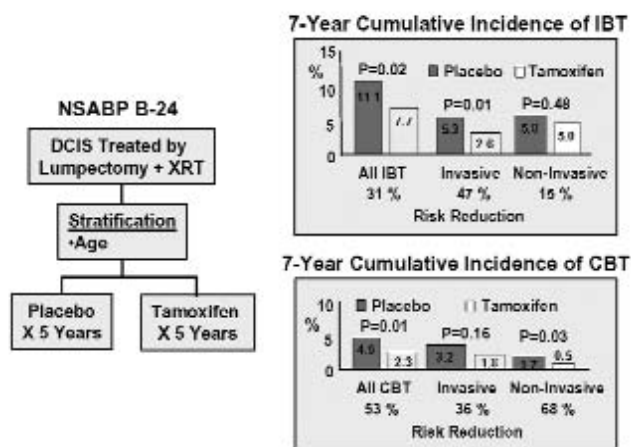


Figure 4. Schema of the NSABP B-24 trial comparing placebo with tamoxifen in patients with DCIS treated with lumpectomy plus breast radiotherapy (XRT) and comparison of the 7-year cumulative incidence of ipsilateral breast cancer events (IBT) and contralateral breast cancer events (CBT) between patients receiving placebo and those receiving tamoxifen.

(Adapted with permission from Fisher B, Land S, Mamounas E, et al. Prevention of Invasive Breast Cancer in Women with Ductal Carcinoma in situ (DCIS): An Update of the NSABP Experience. *Semin Oncol* 2001; 28:400-18.)

Between 1991 and 1994, 1,804 women with DCIS treated with lumpectomy were randomized to receive postoperative radiotherapy and either 20 mg tamoxifen daily for five years or placebo daily for 5 years. In contrast to the B-17 trial, where lumpectomy margins were required to be free of DCIS for eligibility, patients enrolled in the B-24 trial were eligible whether the lumpectomy margins were free, involved, or of unknown status. As a result, about 75% of patients in the B-24 trial had free lumpectomy margins, about 16% had involved margins, and the margins were unknown in 10% of the patients.

Updated results after 7 years of follow-up continue to demonstrate,³¹ that the addition of tamoxifen significantly improved DFS from 77.1% to 83.0% ($P=0.002$). This improvement was mainly the result of a reduction in the incidence of invasive and non-invasive breast cancer events in the ipsilateral as well as in the contralateral breast. The cumulative incidence of all ipsilateral and contralateral breast cancer events was reduced by 39% to 16.0% in the placebo group to 10.0% in the tamoxifen group ($P=0.0003$).¹⁹ When the rate of all invasive breast cancer events was evaluated, tamoxifen resulted in a 45% reduction ($P=0.0009$). When the rate of non-invasive breast cancer events was evaluated, the addition of tamoxifen resulted in a 27% non-significant reduction ($P=0.11$). When the effect of tamoxifen was examined relative to the location of the first event, the cumulative incidence of ipsilateral breast cancers was reduced by 31% (11.1% with tamoxifen vs. 7.7% with placebo, $P=0.02$) and the cumulative incidence of contralateral breast cancers was reduced by 47% (4.9% vs. 2.3%, $P=0.01$) (figure 4).

Several patient and tumor characteristics were found to increase the rate of ipsilateral breast tumor recurrence, such as age under 50, involved/unknown lumpectomy margins, presence of comedo necrosis and DCIS presentation with clinical findings. The effect of tamoxifen in reducing ipsilateral breast cancer was evident irrespective of age, margin status, or presence/absence of comedo necrosis. However, for women with clinically apparent DCIS at study entry, IBTR rates were similar between the tamoxifen and placebo groups even though the number of patients in that category was small.

Results from the B-24 trial indicate a significant benefit from tamoxifen in patients with DCIS. When these results are viewed together with those demonstrating benefit from tamoxifen in women with prior invasive breast cancer,²²⁻²⁸ and in women with atypical hyperplasia and lobular carcinoma *in situ*,³² they support the use of tamoxifen in the entire spectrum of breast neoplasia. However, one outstanding question following disclosure of the B-24 results was whether the observed benefit from tamoxifen was limited to subsets of DCIS patients. Given the strong association between estrogen receptor expression and tamoxifen benefit in patients with invasive breast cancer, presence of a similar association might also be expected in patients with DCIS.

At the 2002 San Antonio Breast Cancer Symposium, Allred et al. presented data from the NSABP B-24 trial assessing the tamoxifen benefit according to the estrogen receptor status of the primary DCIS tumor.³³ Out of the 1804 patients participating in the trial, information on the status of estrogen receptor was available in 628 patients (327 placebo, 301 tamoxifen). Seventy-seven percent of patients had estrogen receptors (ER)-positive tumors. In these patients, the effectiveness of tamoxifen was clear [relative risk (RR) for all breast cancer events: 0.41, $P=0.0002$]. Significant reductions in breast cancer events were seen in both the ipsilateral and the contralateral breast. In patients with ER-negative tumors, little benefit was observed (RR for all breast cancer events: 0.80, $P=0.51$), but the total number of events in this cohort was too small to rule out a small, clinically meaningful benefit. However, when these results are taken together with those evaluating the effect of tamoxifen in patients with invasive breast cancer and negative estrogen receptors, they are consistent with the observation that tamoxifen has no appreciable benefit in reducing rates of recurrence or rates of contralateral breast cancer in patients with ER-negative tumors. Furthermore, these results suggest that routine assessment of estrogen receptor status should now also be performed in patients with DCIS to determine their candidacy for tamoxifen therapy.

In the 1990s significant enthusiasm developed with the demonstration of considerable activity and favorable toxicity profile with third-generation aromatase inhibitors in patients with hormone-responsive advanced breast cancer.³⁴⁻⁴⁰ As a

result, several clinical trials have evaluated or are currently evaluating aromatase inhibitors as adjuvant therapy in patients with early-stage breast cancer.

The first trial to report results in this setting was the Anastrozole Tamoxifen Against Combination (ATAC) trial.⁴¹ This trial compared 5 years of adjuvant tamoxifen with 5 years of adjuvant anastrozole and 5 years of the combination of anastrozole plus tamoxifen in patients with stage I-II breast cancer. It demonstrated significant DFS superiority for anastrozole when compared to tamoxifen.

An important finding in this trial was the observation that the incidence of contralateral breast cancer was significantly decreased in patients treated with anastrozole compared to those treated with tamoxifen (odds ratio 0.42, $P=0.007$). The majority of the contralateral breast cancers were invasive (83%), and when the analysis was restricted to these events, the difference between the treatment groups was somewhat larger (odds ratio 0.30, $P=0.001$).

This observation has major implications relative to the potential use of aromatase inhibitors for patients with DCIS and for those at high-risk for developing invasive breast cancer. This rationale was further strengthened by the favorable side-effect profile of anastrozole when compared to tamoxifen. When compared to tamoxifen, anastrozole-treated patients experienced a reduction in endometrial cancer, vaginal bleeding and discharge, cerebrovascular events, venous thromboembolic events and hot flashes. On the other hand, when compared to tamoxifen, anastrozole resulted in significantly more myoskeletal disorders and fractures, which may have significant implications for the long-term use of this drug in patients with DCIS and in the chemoprevention setting.

Based upon the above results, the NSABP recently initiated a new clinical trial in patients with DCIS (NSABP B-35). In this trial, patients with localized ER- or progesterone-receptor (PR)-positive DCIS, after undergoing a lumpectomy with negative margins, are randomized to radiotherapy and tamoxifen for five years or to radiotherapy and anastrozole for five years (figure 5). The primary aim of the study is to evaluate the effectiveness of anastrozole compared to tamoxifen in preventing the subsequent occurrence of breast cancer (local, regional, and distant recurrences, and contralateral breast cancer). In addition, the trial will ascertain the effects of anastrozole on patient symptoms and quality of life as compared to tamoxifen.

ADJUVANT THERAPY TRIALS IN PATIENTS WITH NEGATIVE NODES

During the last 20 years the NSABP has also played a significant role in the acceptance of adjuvant chemotherapy and adjuvant hormonal therapy for the treatment of breast cancer patients with negative nodes. Beginning in the early 1980s several important trials were conducted evaluating the worth of combination chemotherapy and the worth of tamoxifen in such patients.

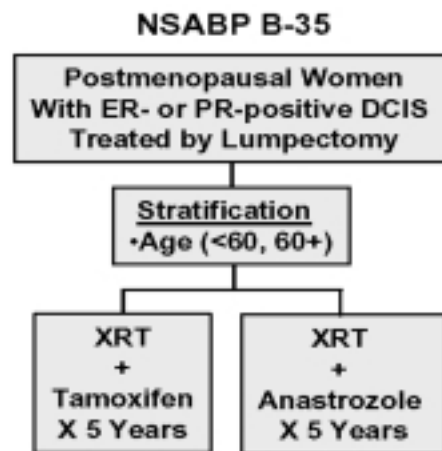


Figure 5. Schema of NSABP B-35 trial comparing tamoxifen with anastrozole in postmenopausal patients with localized DCIS treated with lumpectomy and breast radiotherapy (XRT).

Studies in patients with ER-negative tumors

The first trial (NSABP B-13) randomized patients with negative nodes and negative estrogen receptors to surgery alone, or surgery followed by 12 months of adjuvant chemotherapy with methotrexate and sequentially administered 5-FU [methotrexate and fluorouracil (MF)] followed by leucovorin (figure 6). Findings over the course of 14 years of follow-up⁴² demonstrate that the improvements from MF in DFS and OS, previously reported after five⁴³ and eight⁴⁴ years, have persisted ($P<0.0001$ in the former and $P=0.02$ in the latter, figure 6). A statistically significant benefit in DFS was evident both for women <50 years of age ($P=0.005$) as well as those ≥ 50 years ($P=0.001$). A statistically significant benefit in terms of survival was evident only in women ≥ 50 years of age ($P=0.02$). For women <50 years of age, there was a non-significant trend towards improvement in OS with MF ($P=0.3$). However, there was no statistically significant evidence of an interaction between treatment group and age relative to OS ($P=0.34$).

A subsequent trial in the same patient population (NSABP B-19) attempted to determine whether the alkylating agent cyclophosphamide contributed additional benefit when administered with methotrexate and 5-FU [cyclophosphamide, methotrexate, fluorouracil regimen (CMF)] as developed by the Milan Group (figure 7). Over a 6-month period, patients received either 6 courses of MF or six courses of CMF. A total of 1095 patients were randomized. Over 8 years of follow-up,⁴² Just as first reported after 5 years,⁴⁴ the results continue to demonstrate a statistically significant DFS and OS advantage with CMF over MF ($P=0.003$ and $P=0.03$ respectively, figure 7). Those advantages were most evident in women aged <50 years ($P=0.0004$ and $P=0.007$ respectively). In women aged ≥ 50 years, there was a small but non-significant advantage in both DFS ($P=0.2$) and OS ($P=0.8$). As was also observed in the B-13 trial, there was no evidence of a statistically significant interaction between treatment and age group relative to DFS ($P=0.22$) and OS ($P=0.08$).

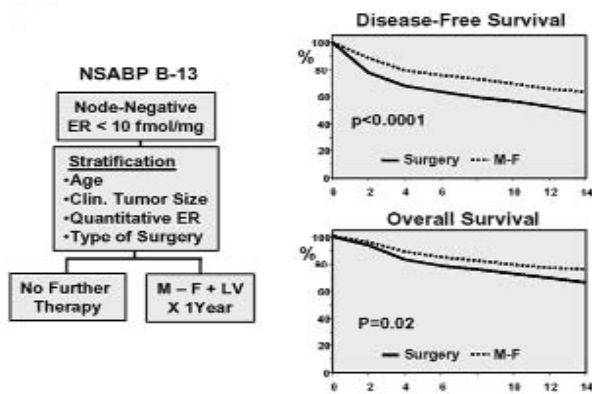


Figure 6. Schema of the NSABP B-13 trial comparing surgery alone with surgery followed by adjuvant methotrexate and 5-fluorouracil with leucovorin (M – F + LV) in node-negative patients with estrogen receptor (ER)-negative tumors and comparison of the 14-year disease-free and OS rates between the two groups.

(Adapted with permission from Fisher B, Jeong J-H, Dignam J, et al. Findings from Recent National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies in Stage I Breast Cancer. *J Natl Cancer Inst Monogr* 2001; 30:62-6.)

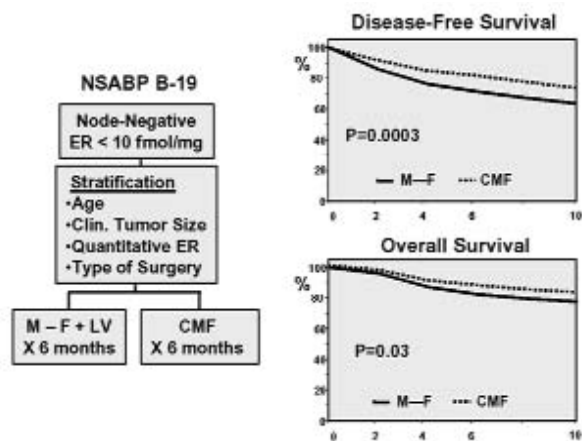


Figure 7. Schema of the NSABP B-19 trial comparing adjuvant methotrexate/5-fluorouracil/leucovorin (MF+LV) with adjuvant cyclophosphamide/ methotrexate/5-fluorouracil (CMF) in node-negative patients with estrogen receptor (ER)-negative tumors and comparison of the 8-year DFS and OS rates between the two groups.

(Adapted with permission from Fisher B, Jeong J-H, Dignam J, et al. Findings from Recent National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies in Stage I Breast Cancer. *J Natl Cancer Inst Monogr* 2001; 30:62-6.)

Following completion of the B-19 trial the NSABP initiated protocol B-23, which attempted to address whether tamoxifen has a role in patients with ER-negative tumors. In this study, patients with negative nodes and ER-negative tumors were randomized to 4 cycles of adjuvant doxorubicin/cyclophosphamide (AC) or six cycles of adjuvant CMF with or without tamoxifen. The rationale for evaluating tamoxifen in patients with ER-negative tumors came both from preclinical and clinical observations.

Results from several preclinical studies demonstrated that tamoxifen acts not only through a blockade of the estrogen receptor pathway but also by modulating production of growth factors such as TGF- α and TGF- β , by increasing the levels of sex hormone binding globulin in the serum, by

increasing natural killer cell counts and by decreasing insulin-like growth factor. In addition, at the time of initiation of this study there was considerable clinical information suggesting that tamoxifen prolongs DFS and OS irrespective of receptor status although the benefit in ER-negative tumors was of less magnitude.⁴⁵⁻⁴⁸ Since that time, an increasing body of evidence has demonstrated that tamoxifen confers no significant advantage in patients with ER-negative tumors. The results of the B-23 trial confirmed these observations and demonstrated no significant prolongation in DFS or OS with the addition of tamoxifen to chemotherapy (DFS: CMF: 83%, CMF + tamoxifen: 83%, AC: 83%, AC + tamoxifen: 82%; OS CMF: 89%, CMF + tamoxifen: 89%, AC: 90%, AC + tamoxifen: 91%).⁴⁹ The results of the B-23 trial also confirmed (in the node-negative setting) the previous observation from the NSABP B-15 trial (in node-positive patients) that 4 cycles of AC were equivalent to six cycles of CMF in terms of DFS and OS prolongation.

One interesting observation in this trial was that tamoxifen did not confer a significant reduction in the incidence of contralateral breast cancer as it has been shown in patients with ER-positive tumors and negative nodes.^{23,42} Explanation for this discrepancy was recently provided by a retrospective review of several NSABP trials, which found that there was significant concordance between the ER-status of the primary breast cancer and that of contralateral breast cancer.⁵⁰ Thus, in about 80% of patients who initially present with an ER-negative primary and who develop contralateral breast cancer, the contralateral breast tumor is also ER-negative making the potential chemopreventive effect of tamoxifen negligible.

Studies in patients with ER-positive tumors

In parallel to the studies evaluating chemotherapy and tamoxifen in patients with node-negative, ER-negative breast cancer, the NSABP launched a series of trials evaluating tamoxifen and the combination of tamoxifen plus chemotherapy in patients with node-negative, ER-positive disease.

The NSABP B-14 trial randomized patients after surgery to 5 years of tamoxifen or 5 years of placebo (figure 8). Published results from this trial over 10 years of follow-up²⁴ continue to demonstrate a statistically significant DFS benefit from tamoxifen (69% vs. 57%, $P < 0.0001$). In addition, a significant survival advantage was demonstrated in this update (80% vs. 76%; $P = 0.02$). The DFS and OS advantage with tamoxifen was evident both in women < 50 years of age as well as in those ≥ 50 years of age. Tamoxifen therapy continued to demonstrate a significant reduction in the rate of contralateral breast cancer (4.0% vs. 5.8%, $P = 0.007$). The significant DFS and OS advantage with tamoxifen has now persisted through 14 years of follow-up (figure 8).⁴²

One of the most common questions asked while the NSABP B-14 trial was being conducted related to the optimal duration of tamoxifen administration. By design, patients were to receive 5 years of tamoxifen or 5 years of placebo. To answer the question of optimal tamoxifen duration beyond

5 years, patients randomized to tamoxifen who were alive and recurrence-free following 5 years of treatment, were asked to be re-randomized to 5 additional years of tamoxifen or 5 years of placebo.²⁴

Results reported through 4 years from re-randomization, demonstrated a significant disadvantage in DFS (86% vs. 92%, $P=0.003$) and distant DFS (90% vs. 96%, $P=0.01$) for patients who continued tamoxifen for more than 5 years versus those who discontinued the drug at 5 years. OS was 96% for those who discontinued tamoxifen compared with 94% for those who continued ($P=0.08$). Results, through 7 years from the time of re-randomization, continue to demonstrate no additional benefit from the prolonged tamoxifen administration.⁵¹ In fact, a slight advantage continues to exist for patients who discontinued tamoxifen after 5 years relative to those who continued to receive it (DFS:82% vs. 78%, $P=0.03$; relapse-free survival: 94% vs. 92%, $P=0.13$; OS: 94% vs. 91%, $P=0.07$, respectively). The lack of benefit from additional tamoxifen therapy was independent of age or other characteristics.

Since, based on the above information, adjuvant tamoxifen is optimally given for a period of about 5 years, the majority of patients are disease-free at the time they discontinue tamoxifen. Some of these seemingly disease-free patients, however, harbor residual or micrometastatic tumor cells even after several years of tamoxifen therapy. In a proportion of these patients, the residual or micrometastatic tumor cells may still be responsive to tamoxifen. The clinical data, however, support the notion that in a greater proportion of patients these tumor cells would potentially be stimulated by tamoxifen if the drug was continued for a longer period of time. Thus, although discontinuing tamoxifen may benefit the latter group, it would be detrimental to the former group of patients.

In both groups the tumor cells are hormonally sensitive. Therefore, reducing the level of estrogenic stimulation at the time of tamoxifen discontinuation appears to be a reasonable

strategy to further reduce the probability of recurrence. No information exists on whether additional hormonal interventions after discontinuation of tamoxifen therapy would prove of benefit in breast cancer patients who are recurrence-free at the time. However, abundant information is available, demonstrating that substantial antitumor responses in a proportion of recurring patients during or after tamoxifen therapy with sequential administration of aromatase inhibitors.³⁴⁻³⁸ The downside of the “wait and treat upon recurrence” approach is that at the time of recurrence an additional proportion of tumors may already have become hormone resistant and another proportion would remain hormone sensitive only for a short time.

Thus, attempting to further reduce the risk of subsequent recurrence in patients who remain disease-free after completion of adjuvant tamoxifen therapy has theoretical advantages. Moreover, studies have shown that 10% to 20% of patients who are recurrence-free at 5 years (usual time of tamoxifen discontinuation), would suffer an event during the following 5 years if left untreated.

Based on the above rationale, the NSABP developed protocol B-33, a randomized trial comparing exemestane with placebo in postmenopausal patients who complete 5 years of tamoxifen and are recurrence-free (figure 9). Exemestane is a potent, orally active, selective, long-lasting irreversible steroidal inhibitor of aromatase. Phase I/II studies in patients with advanced breast cancer, it has demonstrated significant antitumor activity and favorable toxicity profile.⁵²⁻⁵⁵ More importantly, in a phase III study, as second line treatment in patients with advanced breast cancer, exemestane was equivalent to Megace in objective response, but was significantly superior to Megace in duration of overall success, time to progression, time to treatment failure and OS.³⁸

Eligible patients for the B-33 trial must have completed approximately 5 years of adjuvant tamoxifen therapy, must be postmenopausal, and disease free at the time of randomization. The original tumor must be ER and/or PR-receptor positive. The primary aim of the trial is to determine whether exemestane will prolong DFS compared with placebo. Secondary aims are to determine whether exemestane will prolong OS, and to evaluate the effect of exemestane and that of tamoxifen withdrawal on fracture rate, bone mineral density, markers of bone turnover, levels of lipids and lipoproteins, and quality of life. Since May 2001, over 1,400 patients have been randomized into this trial.

An important observation from the B-14 trial was that through 10 years of follow-up of tamoxifen-treated patients with ER positive, node-negative breast cancer, the DFS (69%) and OS (80%) were not as good as originally thought for this group of patients generally considered to have favorable prognosis.²⁴ These numbers further decreased after 14 years of follow-up,⁴² with DFS being around 60% and OS around 75%. Although a small proportion of events

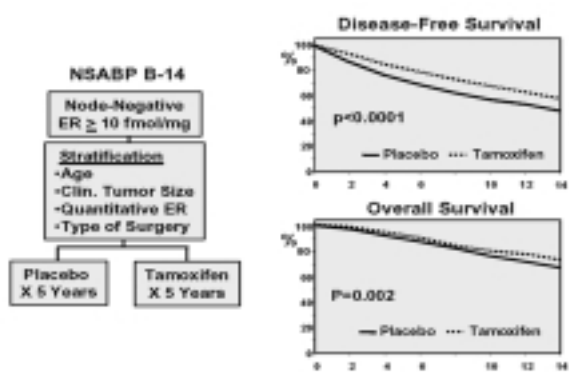


Figure 8. Schema of the NSABP B-14 trial comparing 5 years of placebo with 5 years of tamoxifen in node-negative, estrogen receptor (ER)-positive patients and comparison of 14-year disease-free and OS rates between the two groups. (Adapted with permission from Fisher B, Jeong J-H, Dignam J, et al. Findings from Recent National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies in Stage I Breast Cancer. *J Natl Cancer Inst Monogr* 2001; 30:62-6.)

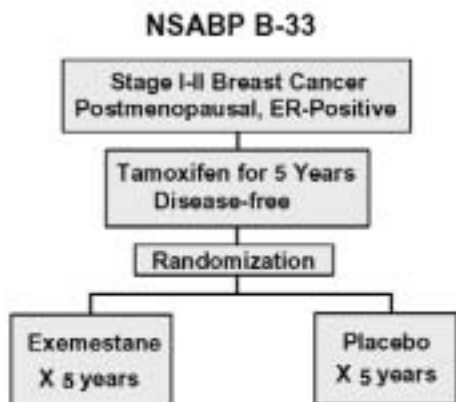


Figure 9. Schema of the NSABP B-33 trial evaluating adjuvant exemestane in postmenopausal patients who complete five years of tamoxifen and are recurrence-free.

included in the DFS and OS analyses are non-breast cancer related, these results under-score the need for further improvement in this group of patients.

Subsequent to the B-14 trial, the NSABP conducted protocol B-20 that evaluated the worth of adding chemotherapy to tamoxifen in patients with negative nodes and positive estrogen receptors (figure 10). Between 1988 and 1993, 2,363 patients were randomized to receive either tamoxifen for 5 years, tamoxifen plus six cycles of sequential methotrexate and 5-fluorouracil followed by leucovorin (MFT) or tamoxifen plus 6 cycles of cyclophosphamide, methotrexate and 5-fluorouracil (CMFT). Through 5 years of follow-up, the combination of chemotherapy plus tamoxifen resulted in significantly better DFS survival than tamoxifen alone (90% for MFT versus 85% for tamoxifen, $P=0.01$; 89% for CMFT versus 85% for tamoxifen, $P=0.001$). A similar benefit was observed in both distant DFS (92% for MFT vs. 87% for tamoxifen, $P=0.008$; 91% for CMFT vs. 87% for tamoxifen, $P=0.006$) and OS (97% for MFT vs. 94% for tamoxifen, $P=0.05$; 96% for CMFT vs. 94% for tamoxifen, $P=0.03$).⁵⁶

Compared with tamoxifen alone, MFT and CMFT reduced the risk of IBTR after lumpectomy and the risk of recurrence at other local, regional and distant sites. Risk of treatment failure was reduced after both types of chemotherapy, regardless of tumor size, tumor estrogen or progesterone receptor level, or patient age. However, the reduction was greatest in patients aged 49 years or less. No subgroup of patients evaluated in this study failed to benefit from chemotherapy.

Results from the B-20 study were recently updated with 8 years of follow-up data and continue to demonstrate a significant improvement in DFS and OS with the addition of chemotherapy to tamoxifen when compared to tamoxifen alone (84% vs. 77%, $P=0.001$, for DFS; 92% vs. 88% for OS, $P=0.018$) (figure 10).⁴²

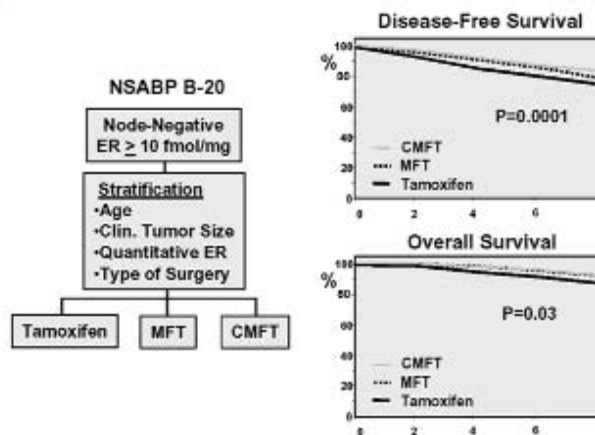


Figure 10. Schema of the NSABP B-20 trial comparing adjuvant tamoxifen alone with adjuvant tamoxifen plus methotrexate/5-fluorouracil plus leucovorin (MFT) and with tamoxifen plus cyclophosphamide/methotrexate/5-fluorouracil (CMFT) in node-negative patients with estrogen receptor (ER)-positive tumors and comparison of the 8-year DFS and OS rates between the three groups of patients.

(Adapted with permission from Fisher B, Jeong J-H, Dignam J, et al. Findings from Recent National Surgical Adjuvant Breast and Bowel Project Adjuvant Studies in Stage I Breast Cancer. *J Natl Cancer Inst Monogr* 2001; 30:62-6.)

An additional update of the NSABP B-20 data was recently presented at the 2002 San Antonio Breast Cancer Symposium.⁵⁷ In that analysis, the effect of chemotherapy when added to tamoxifen was examined according to age among the groups of <50, 50 to 59, and 60 years or older. It was evident from that analysis that the effect of chemotherapy when added to tamoxifen was limited to patients <60 years of age and it was not seen in patients 60 years or older.

The results of the above trials in patients with node-negative, ER-positive breast cancer clearly demonstrate that significant progress has been made in this group of patients with the combination of tamoxifen and adjuvant chemotherapy. As a result, the majority of patients are not in need of any further treatment.

One approach in order to reduce the over-treatment of node-negative patients in future research protocols is to attempt to identify clinical, patient and tumor characteristics that correlate with risk for recurrence (prognostic factors) or with the probability of response to a certain adjuvant treatment regimen (predictive factors). Analyses from the NSABP B-14 trial have shown that several independent prognostic factors exist that can be used in categorizing patients to high- and low-risk groups, thus aiding in the selection of appropriate adjuvant therapy regimens (i.e., age, tumor size, progesterone receptor status and S-phase).⁵⁸ In the future, these factors will be valuable when attempting to select appropriate patient populations for addressing new research questions.

For example, one approach for the low-risk group of patients might be the evaluation of low-toxicity therapies such as drugs with hormonal, biologic or immunologic mechanisms of action (i.e., Cox-2 inhibitors). Drugs with

little or no toxicity become prime candidates for evaluation in groups of patients where the absolute benefit in terms of reduction in recurrence and death is expected to be only few percentage points. On the other hand, for high-risk patients, additional chemotherapy-related questions can be explored either alone or in conjunction with biological questions. This approach was taken in a new NSABP clinical trial comparing 4 cycles of AC to 6 cycles of FEC (fluorouracil, epirubicin, cyclophosphamide) with or without celecoxib.

PREOPERATIVE CHEMOTHERAPY TRIALS

The establishment of lumpectomy as the surgical treatment of choice for the majority of patients with operable breast cancer and the demonstration of a significant improvement in DFS and OS with adjuvant systemic chemotherapy in patients with positive, as well as those with negative axillary nodes have offered clinical justification for consideration of the use of systemic chemotherapy prior to surgical resection (preoperative or neoadjuvant chemotherapy).

In addition, several preclinical and clinical observations have provided biological rationale as to why such an intervention may have an advantage over the administration of chemotherapy in the conventional postoperative fashion.⁵⁹⁻⁶² Several single-institution, non-randomized clinical series did evaluate preoperative chemotherapy in patients with operable breast cancer, but before such treatment could become standard clinical practice it had to be evaluated in prospective randomized clinical trials.

In 1988, the NSABP initiated protocol B-18, a randomized trial in patients with operable breast cancer to compare preoperative versus postoperative administration of adjuvant chemotherapy (figure 11). Following diagnosis of breast cancer by fine needle aspiration or core needle biopsy, patients were randomized to receive either surgery (lumpectomy and axillary node dissection or modified radical mastectomy) followed by 4 cycles of AC chemotherapy every 21 days, or the same chemotherapy followed by surgery. Patients 50 years of age or older were also given 10 mg tamoxifen twice daily for 5 years starting after completion of adjuvant chemotherapy.

The primary objective of the study was to determine whether preoperative chemotherapy would more effectively prolong DFS and OS than the same chemotherapy given postoperatively. Secondary objectives of the study included the evaluation of clinical and pathologic response of primary breast cancer to preoperative chemotherapy, the determination of the downstaging effect of preoperative chemotherapy in the axillary nodes, and the determination of whether preoperative chemotherapy increases the rate of breast-conserving surgery. In addition, the study attempted to determine whether primary breast cancer response to preoperative chemotherapy correlates with DFS and OS.

Between October 1988 and April 1993, 1,523 patients were accrued into the trial. Results pertaining to the effect of preoperative chemotherapy on tumor response^{63,64} indicated

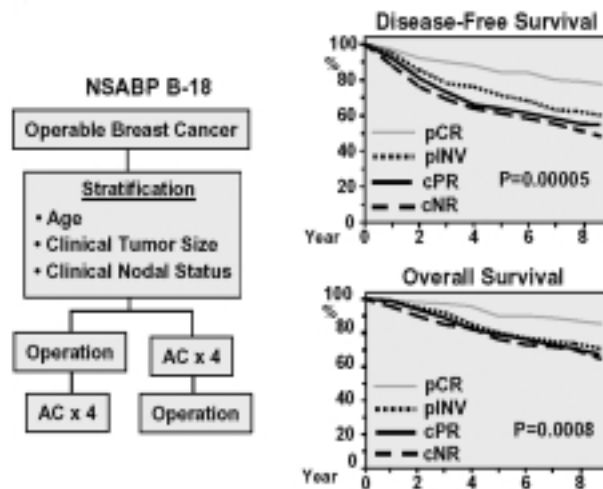


Figure 11. Schema of the NSABP B-18 trial comparing preoperative (neoadjuvant) doxorubicin/cyclophosphamide (AC) to postoperative (adjuvant) AC in patients with operable breast cancer and comparison of the DFS and OS according to clinical and pathologic breast tumor response.

(Adapted with permission from Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer. Nine-year results from NSABP B-18. *J Natl Cancer Inst Monogr* 2001; 30:96-102.)

that, following administration of preoperative chemotherapy, 36% of patients obtained a clinical complete response (cCR) and 43% of patients obtained a clinical partial response (cPR) for an overall response rate of 79%. Seventeen percent of patients were classified as having stable disease and 3% as having progressive disease. More importantly, 9% of the patients were found to have no tumor present on pathologic examination of the lumpectomy or mastectomy specimen, while another 4% were found to have only non-invasive tumor present in the surgical specimen, for an overall pathologic complete response rate (pCR) of 13%.

Administration of preoperative chemotherapy resulted in pathologic axillary lymph node downstaging. Whereas 59% of the patients receiving postoperative chemotherapy were found at surgery to have pathologically positive axillary nodes, only 43% of patients receiving preoperative chemotherapy were found to have nodal involvement. This difference was statistically significant ($P < 0.001$) and amounted to axillary nodal downstaging in 16% of all patients receiving preoperative chemotherapy or in 37% of the patients presumed to be node-positive at the time of administration of preoperative chemotherapy.

Patients receiving preoperative chemotherapy were significantly more likely to receive a lumpectomy than were patients receiving postoperative chemotherapy (67% vs. 60%, $P = 0.002$). When the two treatment groups were compared in terms of outcome,⁶⁵ there was no difference in the DFS, distant DFS or OS between the two groups. There was evidence of significant correlation between pathologic response of primary breast tumors to preoperative chemotherapy and DFS and OS. Patients achieving a pCR had a statistically significant improvement in DFS and OS compared to those who had a cCR but residual invasive

carcinoma in the breast specimen (pINV) or those who had a cPR or those who had a clinical non-response (cNR). When the prognostic effect of pCR was examined after adjusting for other known clinical prognostic factors such as clinical nodal status, clinical tumor size and age, pCR remained a significant independent predictor for DFS and a borderline significant predictor for OS.

Recently updated outcome results from the B-18 study continue to demonstrate that the equivalence between preoperative and postoperative chemotherapy, and the significant correlation between pCR and outcome has persisted through 9 years of follow-up (figure 11).⁶⁶ At 9 years, the DFS rate for patients achieving a pCR was 75% as compared with 58% for patients with pINV. For OS, the respective rate was 85% for patients achieving a pCR and 73% for patients with pINV. Overall, primary tumor response graded as pCR, pINV, cPR and cNR was strongly associated with all outcome measures (OS: $P=0.0008$; DFS: $P=0.00005$; relapse-free survival: $P=0.0002$). Similar to the previous results, these significant associations persisted after adjustment for clinical tumor size, clinical nodal status and age at randomization (OS: $P=0.006$; DFS: $P=0.004$; relapse-free survival: $P=0.00006$). The results further demonstrated that primary tumor response in the breast contributed additional prognostic information over and above pathologic nodal status (OS: $P=0.06$; DFS: $P=0.006$; relapse-free survival: $P=0.004$).

The results from the B-18 trial strengthened the biologic and clinical rationale for continuing to evaluate the role of preoperative chemotherapy in patients with operable breast cancer.⁶⁷ If response to preoperative chemotherapy continues to correlate with patient outcome when newer preoperative chemotherapy regimens are used, then response to chemotherapy can be used as an intermediate endpoint in testing new chemotherapy regimens or new drugs administered after standard regimens. This approach may also facilitate the evaluation of many of the proven and putative prognostic tumor markers (e.g., estrogen-receptors, progesterone-receptors, ploidy and S-phase, erb-B2 and p53 oncogene) in material obtained by FNA or core needle biopsies and the potential correlation of these markers, individually or in combination, with tumor response to preoperative chemotherapy and eventually with outcome.

As a result, subgroups of patients with a high likelihood of pCR may be identified that could be spared from additional local or systemic therapy interventions. Furthermore, serially monitoring tumor marker changes while a tumor is undergoing preoperative chemotherapy may provide biological insight into the nature and function of these markers. Knowledge may also be obtained regarding the mechanisms of action of new chemotherapeutic agents or new treatment modalities.

The demonstration of significant antitumor activity with taxanes in patients with advanced breast cancer provided the opportunity to take results from the NSABP B-18 trial a step further and also address some of the above questions. In

1995 the NSABP implemented protocol B-27. This was a randomized trial that evaluated the worth of docetaxel when administered in the preoperative or the postoperative setting following 4 cycles of preoperative AC chemotherapy⁶⁸ (figure 12). The main objective of the study was to determine whether the addition of 4 cycles of preoperative or postoperative docetaxel, following 4 cycles of preoperative AC, could more effectively prolong DFS and OS in patients with operable breast cancer than 4 cycles of preoperative AC alone. Secondary objectives of the B-27 protocol were to determine whether the addition of preoperative docetaxel following preoperative AC could increase the rate of loco-regional response, pCR, pathologic axillary nodal downstaging and breast conserving surgery. Additional secondary objectives were to determine whether any benefit from the addition of postoperative docetaxel after preoperative AC, might be limited to specific subgroups of patients, (i.e., those with residual positive nodes after preoperative AC).

Patients were randomized to receive one of three regimens:

- Four cycles of preoperative AC chemotherapy followed by surgery (group 1),
- Four cycles of preoperative AC followed by four cycles of preoperative docetaxel, followed by surgery (group 2),
- Four cycles of preoperative AC followed by surgery, followed by four cycles of postoperative docetaxel (group 3).

All patients received 20 mg tamoxifen PO daily beginning on day one of the first AC course and continuing for 5 years. The eligibility criteria included localized, operable carcinoma of the breast diagnosed by FNA or core biopsy and palpable on physical examination. Palpable axillary nodes of any size were allowed but they had to be movable in relation to the chest wall and surrounding structures.

The trial opened in December 1995 and closed in December 2000 after accruing 2,411 patients. The preliminary results from this trial relative to the comparison of response rates between patients treated with preoperative AC and those treated with preoperative AC followed by preoperative

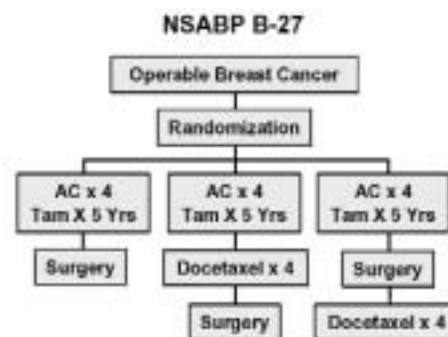


Figure 12. Schema of NSABP B-27 trial comparing neoadjuvant AC to neoadjuvant AC followed by neoadjuvant docetaxel and to neoadjuvant AC followed by adjuvant docetaxel in patients with operable breast cancer (Tam: tamoxifen).

docetaxel were presented at the 2001 San Antonio Breast Cancer Symposium.⁶⁹ The results demonstrated that, compared to the group that received preoperative AC alone, the group that received preoperative AC followed by preoperative docetaxel achieved significantly higher rates of cCR (cCR: 40.4 vs. 65.4%; $P < 0.001$), overall clinical response (cCR + cPR: 85.7% vs. 91.1%; $P < 0.001$) and pCR (pCR: 25.6% vs. 13.7%; $P < 0.001$). The addition of pre-operative docetaxel to preoperative AC also resulted in significant downstaging of axillary lymph nodes. Whereas 50.7% of the patients were node-negative after preoperative AC alone, 58.1% did so after preoperative AC and preoperative docetaxel ($P < 0.01$).

In contrast the observations from the B-18 trial, the increase in clinical and pathologic response rates with preoperative docetaxel did not translate to a significant increase in the rate of breast conservation. Breast-conserving surgery was performed in 61.4% of AC treated patients and in 63.1% of patients treated with AC followed by docetaxel ($P = 0.70$). As was also previously shown in the B-18 trial, clinical and pathologic primary breast tumor response was a significant predictor of pathologic nodal status. DFS and OS data are not yet available.

Two ancillary studies were conducted along with the main B-27 trial. These evaluated serum and tumor biomarkers as they relate to outcome and response to preoperative AC or docetaxel chemotherapy. The first (NSABP B-27.1) evaluated the worth of serum Erb-B2 extra-cellular domain (ECD) and serum Erb-B2 antibodies in predicting response to preoperative chemotherapy and long-term outcome. In addition, by obtaining serum at specified times (i.e., before administration and after completion of preoperative chemotherapy, after surgery, 1 year after randomization, and at the time of recurrence), this study is able to evaluate whether potential changes in the levels of erb-B2 ECD and erb-B2 antibodies are induced by chemotherapy or are associated with breast cancer recurrence.

The second ancillary trial (NSABP B-27.2) evaluated the worth of tumor biomarkers obtained by FNA or core biopsy in predicting response to preoperative chemotherapy and long-term outcome in B-27 patients. The study also evaluated whether preoperative chemotherapy results in changes in tumor biomarker expression, and whether these changes can be correlated with tumor response and long-term outcome. The following biomarkers were evaluated: nuclear grade, estrogen and progesterone receptors, proliferation markers, p53 oncogene mutations, erb-B2 over-expression, P-glycoprotein, and apoptosis markers (bcl-2). Results from these two ancillary trials are not yet available.

The NSABP is currently developing new neoadjuvant trial concepts that seeks to incorporate high throughput technology to identify patients with tumors at high likelihood of achieving a pCR when treated with a certain neoadjuvant chemotherapy regimen. The plan is to compare the activity (in terms of inducing pCR) of various sequential anthracycline/taxane regimens that incorporate new agents

such as capecitabine, vinorelbine and carboplatin in combination with taxane. By using high throughput technology, genomic signatures could be identified that are associated with tumors with high likelihood of pCR when exposed to a certain neoadjuvant regimen. If the same regimen is then found to induce high rates of pCR in patients from another cohort whose tumors express that particular genomic signature, the potential of tailoring neoadjuvant chemotherapy according to differences in tumor gene expression profiles might become a reality.

TRIALS IN PATIENTS WITH POSITIVE NODES

Studies evaluating dose-intensification

The question of whether dose intensity and increase in total chemotherapy dose are important in improving patient outcome became important during the previous decade. The NSABP conducted two randomized trials of dose intensification in patients with histologically positive nodes. These studies attempted to intensify and increase the total dose of cyclophosphamide in the AC combination. In the first study (NSABP B-22), patients with histologically positive axillary lymph nodes were randomized to receive either:

- (1) Standard dose AC for 4 cycles (A: 60 mg/m² and C: 600 mg/m²),
- (2) AC where the cyclophosphamide was administered only for the first two cycles at double the dose (1200 mg/m² X 2),
- (3) AC where the cyclophosphamide was given for all 4 cycles at double the dose (1200 mg/m² X 4).

In all three groups, patients 50 years of age or older also received 10 mg tamoxifen PO twice a day for 5 years. Patients receiving lumpectomy also received radiation after the completion of their assigned chemotherapy. Results from this study, after four years of follow-up, did not demonstrate a benefit from dose-intensification.⁷⁰ There were no significant differences between the three different treatment groups in terms of DFS, distant DFS and OS. Overall toxicity was more pronounced in the groups receiving the intensified dose and increased total dose of cyclophosphamide.

Around the time of completion of the NSABP B-22 study, colony stimulating factors became available in the clinic and made it feasible to administer even higher cyclophosphamide doses in the outpatient setting.⁷¹ As a result, the NSABP conducted a second study of dose intensification (NSABP B-25). In this study, patients with histologically positive axillary lymph nodes were randomized to receive either:

- (1) AC for 4 cycles as used in the third arm of NSABP B-22 (A: 60 mg/m² and C: 1200 mg/m²),
- (2) AC where the cyclophosphamide was administered only for the first two cycles at double the dose (2400 mg/m² X 2),
- (3) AC where the cyclophosphamide was given for all 4 cycles at double the dose (2400 mg/m² X 4).

In all three groups, all patients received prophylactic G-CSF. In all three groups, patients 50 years of age or over also received tamoxifen 10 mg PO twice a day for 5 years. Patients receiving lumpectomy also received radiation after the completion of their assigned chemotherapy.

Results from this second study were also recently published and are similar to those from the B-22 study in that they did not demonstrate an added benefit from dose intensification or from increasing the total dose of cyclophosphamide in the AC combination.⁷²

Studies evaluating taxanes as adjuvant therapy

Given the disappointing results from the studies of dose intensification in patients with node-positive breast cancer, the introduction of new agents with novel mechanisms of action became an important alternative approach to increase treatment effectiveness. Among the agents that have become available for clinical testing in the past several years, taxanes seem to possess the most favorable antitumor properties. Preclinical data and clinical studies in advanced breast cancer indicate that these agents have significant antitumor activity and are worth evaluating in the adjuvant setting. Furthermore, some have argued that the sequential administration of chemotherapeutic agents may be more beneficial than the administration of these agents in combination.

Thus, in 1995 the NSABP initiated a randomized trial (NSABP B-28) to evaluate the worth of paclitaxel following standard dose AC chemotherapy in breast cancer patients with positive axillary nodes. Eligible patients were randomly assigned to receive 4 cycles of AC chemotherapy or 4 cycles of AC followed by 4 cycles of paclitaxel at 225 mg/m² given as a 3-hour infusion.

Beginning on the first day of administration of their assigned chemotherapy, all patients ≥50 years of age and those <50 years of age with tumors that are ER-positive or progesterone receptor (PgR)-positive also received tamoxifen at 20 mg PO daily for 5 years. All patients in both groups who underwent lumpectomy also received radiation after completion of their assigned chemotherapy.

This study completed accrual in 1998. Preliminary results from an interim analysis were presented at the NIH Consensus Development Conference in November of 2000 and, at that time with 34 months of median follow-up they did not demonstrate a statistically significant advantage for the group of patients receiving paclitaxel.⁷³ Definitive DFS and OS analyses were recently presented at the 2003 American Society of Clinical Oncology (ASCO) meeting. With 64 months of median follow-up, there is now a significant improvement in DFS in favor of the group randomized to AC followed by paclitaxel, but no significant difference in survival at this point.⁷⁴

The next logical step in the clinical development of taxanes as adjuvant treatment for breast cancer was to compare the sequential AC-taxane regimens (as administered in the first

generation adjuvant studies with taxanes) with combination regimens of taxanes with other active existing agents. Thus far, doxorubicin and docetaxel are among the most active agents against breast cancer. Combinations of doxorubicin with paclitaxel have demonstrated excellent response rates in phase II studies of patients with advanced breast cancer but have also been associated with a significant increase in cardiotoxicity.^{75,76} Similar cardiotoxicity was not seen in phase I-II studies when docetaxel was used in combination with doxorubicin, although the increased efficacy was maintained.⁷⁷⁻⁸⁰

Based on the above studies, as well as phase III trials,⁸² the NSABP B-30 study was designed to directly compare the sequential regimen of AC followed by docetaxel to the combination of doxorubicin plus docetaxel and to the triple combination of doxorubicin plus docetaxel plus cyclophosphamide. (figure 13) This trial was initiated in 1999 and has accrued more than 4,500 of the 5,300 patients needed.

Studies evaluating biologically targeted therapies in the adjuvant setting

Despite considerable progress with adjuvant chemotherapy, there are still significant limitations with this approach both in terms of efficacy and, more importantly, in terms of toxicity. Thus, alternative adjuvant treatments that will increase the efficacy of therapy without significantly increasing side effects are highly desirable.

During the past decade there has been an explosion in development of biologically-targeted therapies that have the promise of improving adjuvant therapy efficacy without significant increase in toxicity. Several approaches have been validated in the advanced disease setting and are currently being evaluated in adjuvant trials. The evaluation of trastuzumab and bisphosphonates in NSABP adjuvant trials represent examples of how new molecular targeted therapies are being evaluated in the adjuvant setting.

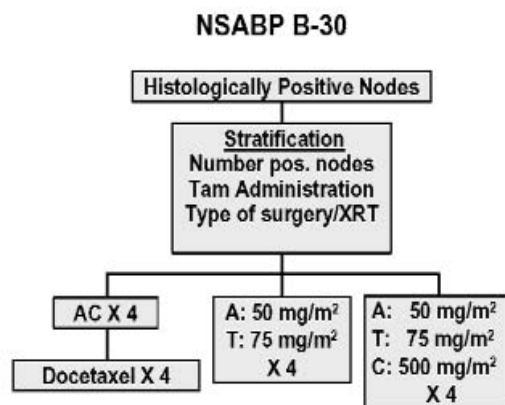


Figure 13. Schema of the NSABP B-30 trial comparing the sequential administration of AC followed by docetaxel with the combination of doxorubicin(A)-docetaxel(T) and with the triple combination of doxorubicin(A)-docetaxel(T)-cyclophosphamide(C) in patients with node-positive breast cancer.

NSABP study evaluating adjuvant trastuzumab

During the 1990s, a substantial amount of information accumulated in support of a significant role for the HER-2/neu oncogene in breast cancer, both as a predictor of benefit from anthracycline-containing chemotherapy⁸³⁻⁸⁶ as well as a therapeutic target for antibody development.^{87,88} As results from dose intensification studies strongly suggested the existence of a “limit of cytoreduction” and as the over-expression of the HER-2/neu oncogene indicated chemo resistance, it was hypothesized that targeting HER-2 with an inhibitory antibody such as trastuzumab (humanized monoclonal antibody against the extracellular domain of HER-2/neu) might overcome resistance and augment the chemotherapy effect. In the advanced-disease setting, trastuzumab has activity as a single agent⁸⁷ and significantly increases the efficacy of chemotherapy in terms of response rates, time to progression and OS.⁸⁸ However, these improvements were associated with a substantial increase in cardiotoxicity, particularly when an anthracycline-containing regimen was combined with trastuzumab.

The NSABP B-31 trial is a randomized trial designed to evaluate the role of trastuzumab in the adjuvant setting. This trial tests the worth of trastuzumab when added to the AC followed by paclitaxel regimen but trastuzumab administration begins with the first cycle of paclitaxel (figure 14).

The study is being conducted in two parts. The primary objective of the first part is to evaluate the cardiac safety of the AC followed by paclitaxel plus trastuzumab regimen compared to the AC followed by paclitaxel regimen. The primary objective of the second part is to compare these two regimens in terms of efficacy.

This is a unique trial in that it attempts to promptly incorporate a new, exciting agent into the adjuvant setting and at the same time pays particular attention to the toxicity concerns raised from studies in the advanced disease setting. Furthermore, important, built-in biological correlative studies

aim to discover markers that predict benefit from the addition of Herceptin to chemotherapy such as phosphorylation status of HER-2, extracellular domain levels, auto-antibodies and array-based comparative genomic hybridization (CGH).

Studies evaluating bisphosphonates as adjuvant therapy

Bisphosphonates are emerging as a class of drugs with great potential for improving the outcome of breast cancer without adversely affecting patients’ quality of life and without causing significant toxicity. Bisphosphonates act by inhibiting osteoclast function with subsequent reduction in bone loss. They have been found effective in patients with Paget’s disease, osteoporosis and malignant bone disease. Other mechanisms of action of bisphosphonates include a reduction in malignant cell adhesion to bone as well as decreased osteoblast-mediated-osteoclast stimulation and adsorption to bone resorption surfaces leading to protection against osteoclast action.

Bisphosphonates have been shown to reduce skeletal complications in patients with various malignancies. Phase III trials in patients with metastatic breast carcinoma involving bone have shown a reduction in skeletal complications in patients treated with either chemotherapy or hormonal therapy.⁸⁹ Patients with carcinoma of the breast who receive adjuvant chemotherapy have a higher rate of vertebral fracture than an age-matched population of patients who do not receive chemotherapy.⁹⁰ It is hypothesized that the increased bone loss, particularly in premenopausal and perimenopausal women, is one of the causes of the propensity of breast cancer to metastasize to bone.

One of the bisphosphonates—oral clodronate—has been shown to reduce the incidence of new bone metastases in patients with recurrent breast cancer and has been shown to reduce the incidence of bone relapse in patients with operable breast cancer who had cancer cells present in the bone marrow by an immunohistochemical assay.⁹¹ This latter trial was randomized but used an open-label design. The trial also showed a reduction in the incidence of recurrence at sites other than bone. At the 7-year follow-up, there was a significant survival benefit for patients receiving clodronate.

A mature analysis of a larger, placebo-controlled, randomized trial from the United Kingdom and Canada showed a significant reduction in the incidence of new bone metastases during the two-year period in which clodronate was administered. The difference lost its statistical significance with further follow-up when placebo/clodronate was stopped. This study further showed a non-significant reduction in the rate of non-skeletal metastases and a significant improvement in OS.⁹²

On the other hand, a recently reported small, randomized Scandinavian study in 299 node-positive breast cancer patients showed that the addition of oral clodronate to adjuvant therapy did not reduce the rate of bone metastases.

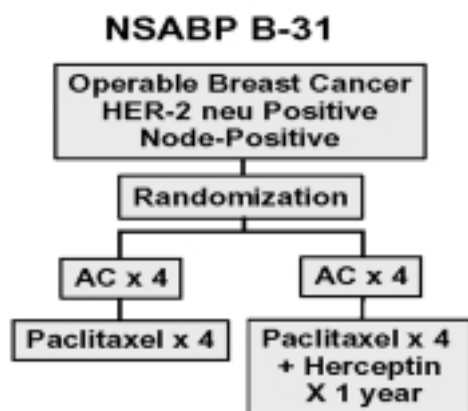


Figure 14. Schema of the NSABP B-31 study evaluating the effect of adjuvant Herceptin in patients with node-positive, resected operable breast cancer, over-expressing the HER-2/neu oncogene.

In addition, clodronate seemed to have a negative effect on DFS by increasing the development of non-skeletal metastases.⁹³

Based on the above, although the results of some of the early trials are encouraging, sufficient controversy remains relative to the value of bisphosphonates as adjuvant therapy justifying the conduct of a large confirmatory trial to test this important hypothesis. The NSABP is currently accruing patients into protocol B-34, a double-blinded, placebo-controlled, randomized clinical trial evaluating oral clodronate as adjuvant therapy (figure 15). The primary aim of the study is to determine whether oral clodronate administered for 3 years either alone or in addition to adjuvant chemotherapy and/or hormonal therapy will reduce the incidence of skeletal metastases and improve DFS. Secondary aims are to determine whether the addition of adjuvant clodronate will improve OS, reduce the incidence of non-skeletal metastases, prevent skeletal events, improve patient quality of life, and reduce the rate of bone loss in a subgroup of patients. Provided the results from the B-34 study are encouraging, additional trials may be needed in order to evaluate more potent oral and parenteral bisphosphonates (i.e., risedronate or zoledronate).

SUMMARY

This review summarizes the results from several pivotal NSABP breast cancer clinical trials that in a step-wise fashion, evaluated various loco-regional and systemic therapy approaches in the management of patients with operable breast cancer. Results from these trials have contributed to the reduction in the extent of surgery for invasive and non-invasive breast cancer, to the establishment of radiation as an effective method of controlling in-breast recurrence following lumpectomy, and more importantly, to significant improvements in overall survival with the use of adjuvant systemic therapy in patients with positive, as well as for those with negative nodes.

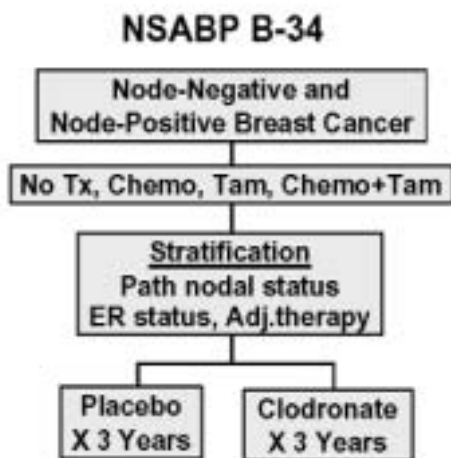


Figure 15. Schema of the NSABP B-34 trial evaluating adjuvant oral clodronate in patients with resected stage I and II operable breast cancer (No Tx: no adjuvant therapy, Chemo: adjuvant chemotherapy, Tam: adjuvant tamoxifen).

Ongoing trials, as well as those in development, aim to further reduce the extent of surgical resection in the breast and axilla by evaluating neoadjuvant chemotherapy and sentinel node biopsy, to optimize adjuvant chemotherapy and adjuvant hormonal therapy by evaluating taxanes, epirubicin, and aromatase inhibitors, and to introduce novel molecular targeted approaches to the adjuvant setting such as Cox-2 inhibitors (celecoxib), HER-2/neu antibodies (trastuzumab) and bisphosphonates (clodronate), it is hoped that these strategies will yield results that will further reduce morbidity from surgical and adjuvant therapy while maximizing their efficacy.

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