Recommendations for research priorities in breast cancer by the Coalition of Cancer Cooperative Groups Scientific Leadership Council: systemic therapy and therapeutic individualization

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Abstract Over 9,000 women with breast cancer are enrolled annually on clinical trials sponsored by the National Cancer Institute (NCI), accounting for about one-third of all patients enrolled on NCI-sponsored trials. Thousands are also enrolled on pharmaceutical-sponsored studies. Although breast cancer mortality rates have recently declined for the first time in part due to systemic therapeutic advances, coordinated efforts will be necessary to maintain this trend. The Coalition of Cancer Cooperative Groups convened the Scientific Leadership Council in breast cancer (BC), an expert panel, to identify priorities for future research and current trials with

greatest practice-changing potential. Panelists formed a consensus on research priorities for chemoprevention, development and application of molecular markers for predicting therapeutic benefit and toxicity, intermediate markers predictive of therapeutic effect, pathogenesis-based therapeutic approaches, utilization of adaptive designs requiring fewer patients to achieve objectives, special and minority populations, and effects of BC and treatment on patients and families. Panelists identified 13 ongoing studies as High Priority and identified gaps in the current trial portfolio. We propose priorities for current and future clinical breast cancer research evaluating systemic therapies that may serve to improve the efficiency of clinical trials, identify individuals most likely to derive therapeutic benefit, and prioritize therapeutic strategies.

This analysis was conducted by the Scientific Leadership Council in Breast Cancer of the Coalition of Cancer Cooperative Groups.

Scientific Leadership Council in breast cancer writing group is given in [Appendix](#).

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Introduction

The probability of an American woman developing breast cancer (BC) at some point in her life is 1 in 8 [1]. In 2008, it was estimated that 182,460 new cases of invasive and 67,770 cases of in situ BC were diagnosed in women, and 40,480 women died from the disease in the US [1]. Worldwide, it is the second most common type of cancer (1.15 million new cases), and the fifth most common cause of cancer death (502,000 deaths), accounting for about 7% of cancer deaths and 1% of all deaths in 2002 [2]. It is estimated that there are about 4.4 million breast cancer survivors worldwide [2].

Clinical trials have radically altered how localized BC is managed now compared with 30 years ago, at which time

the standard was radical mastectomy alone or followed by regional irradiation without systemic therapy [3]. Randomized clinical trials have demonstrated that local excision resulted in comparable cure rates as mastectomy [4], and that adjuvant chemotherapy, endocrine therapy, and trastuzumab reduced local and systemic recurrence [5, 6]. In order to bring about additional therapeutic advances, large, randomized clinical trials (CTs) remain critical. Approximately 25,000 patients are enrolled on trials sponsored by the National Cancer Institute each year, of whom ~9,000 have breast cancer; thousands more are enrolled on pharmaceutical-sponsored trials [7]. A search for publicly available clinical trials databases reveals that there are 1,190 BC trials open to accrual [8], of which 202 are Phase III trials, with many of these competing for the same pool of patients with BC. To compound the problem, only a small fraction of potentially eligible patients participate in CTs. Focused, consensus-based recommendations or research priorities are needed to illustrate which CTs most urgently need the limited pools of patients to answer the most pressing questions. Coordinated efforts and prioritization of the research may present the most effective and efficient way to confirm advances and integrate this knowledge quickly into clinical practice.

To provide this leadership, the Coalition of Cancer Cooperative Groups (CCCCG), a nonprofit service organization working to improve physician and patient access to cancer clinical trials through education, outreach, advocacy, and research, created the Scientific Leadership Council (SLC) program. Disease-specific SLCs are convened by the CCCC to identify research priorities for evaluation in future research and current clinical trials that should be considered of the highest priority for their practice-changing potential. CCCC charges its SLCs to communicate these recommendations to the cancer community-at-large. Council members are among the nation's leading cancer researchers, representing the full spectrum of clinical research. We herein provide a report of the SLCs analysis and recommendations for research prioritization.

Methods

The SLC in breast cancer is the third disease-specific forum of the CCCC; previous SLCs established research priorities for colorectal cancer [9] and non-small-cell lung cancer (www.CancerTrialsHelp.org) [10]. The SLC in BC held a series of meetings to review, debate, and discuss the state of BC clinical research and to formulate a consensus in areas of importance, including screening, chemoprevention, surgery/neoadjuvant therapy, radiation therapy, adjuvant systemic therapy, advanced disease, the application of genomics and personalization of treatment, special

population patients, and quality of life. In each area, the SLC discussed the greatest unanswered questions and established a baseline of research gaps, reviewed a large portfolio of existing or planned trials and identified those which are addressing some of the priority issues, and then finalized a list of trials it judged to be of the highest priority for having the greatest potential to change clinical practice. This manuscript summarizes the consensus of the SLC in BC on systemic therapy and treatment individualization. A planned second manuscript will summarize the consensus reached in screening and localized therapy.

Results

Prevention

Options for preventing BC include removal of the target organ (i.e., prophylactic mastectomy) in very high-risk individuals (e.g., germ line BRCA1 or 2 mutations, lobular carcinoma in situ plus a strong family history) [11], chemoprevention (i.e., tamoxifen, raloxifene) for those at elevated risk (i.e., family history), and lifestyle modification (e.g., reducing weight [12] and/or alcohol consumption [13, 14]) for those with an average or elevated risk, which may also have secondary health benefits.

Chemoprevention

Most prevention efforts to date have focused on selective estrogen receptor modulators (SERMs) such as tamoxifen or raloxifene; “risk reduction” may be a more accurate term than “chemoprevention”, because these agents may be delaying the clinical appearance of disease rather than preventing it. The risk of contralateral BC is known to be reduced by about 50% in women with prior BC treated with adjuvant tamoxifen [6, 15]. This observation generated interest in evaluating tamoxifen in healthy women at increased risk because of family history or other factors, and several studies confirmed that a 5-years course of tamoxifen reduces BC risk by 50% in both pre- and postmenopausal women; it appears to only reduce the risk of developing hormone-receptor (HR)-positive disease and does not reduce BC mortality [16–22]. Adverse effects include hot flashes and gynecological effects that contribute to nonadherence in up to 25% [23, 24] and more serious problems such as thromboembolic effects and uterine carcinoma in postmenopausal women that alter the benefit–risk ratio [25]. More recently, raloxifene was shown to be comparable to tamoxifen in reducing invasive BC risk in postmenopausal women but was slightly less effective for preventing in situ disease; it was also associated with a lower risk of thromboembolic disease, uterine cancer, cataracts, and need for

cataract surgery [22]. There is limited information regarding the effectiveness of SERMs in BRCA1 or 2 mutation carriers [26, 27].

Identifying high-risk individuals

Although tamoxifen has been available as a chemopreventive option since 1998, the proportion of potentially eligible women who receive it is low due to low rates of physician recommendation and patient acceptance [15, 28]. Contributing factors include the potential adverse effects of therapy, but also the imprecise nature of defining risk in individuals not known to be BRCA mutation carriers. Although the Gail model is accurate in estimating 5-years and lifetime risk in Americans [29, 30] and Europeans [31] who undergo annual mammography, and the CARE model provides greater accuracy for African-American women [32], individuals predicted to be at increased risk typically have a 5-years risk of 2–4%, which is often judged not to be sufficiently high to warrant intervention [15]. Recent efforts to identify single-nucleotide polymorphisms (SNPs) associated with BC risk may lead to improved ability to identify truly high-risk individuals likely to benefit from chemoprevention [33, 34].

Council recommendations

Based on the currently available clinical trial data and information, the following research priorities were identified:

- *Determine the best measure of efficacy outcome in chemoprevention trials.* Should we look at only validated intermediate markers, BC incidence, or mortality?
- *Development and validation of biomarkers.* The major priority in chemoprevention is the development and validation of reliable, reproducible, and easy-to-implement biomarkers that can also be used to monitor the biologic effects of chemopreventive agents.
- *Evaluation of tamoxifen and raloxifene as chemoprevention agents.* What is the role of these agents in women with BRCA mutations? When should they be started, and what is the optimal duration of treatment? Will reduction in BC risk persist after discontinuation of treatment? What is the best way to identify optimal candidates for chemoprevention?
- *Optimal agent selection for chemoprevention studies.* Several agents are under investigation as potential chemoprevention strategies, including selective third-generation aromatase inhibitors.

Adjuvant systemic therapy for operable breast cancer

Systemic therapy given after surgical resection with cytotoxic chemotherapy regimens, endocrine therapies, or

targeted biologic therapies constitutes the standard of care and has been referred to as “adjuvant” therapy. The results of pivotal CTs evaluating the role of adjuvant chemotherapy, endocrine therapy, and biologic therapy, and which have altered the standard of care, are shown in Table 1.

Adjuvant chemotherapy

Anthracyclines and taxanes are commonly used as components of adjuvant cytotoxic therapy and are recommended in current practice guidelines [35]. The Early Breast Cancer Trialists’ Collaborative Group reported that adjuvant anthracycline-containing polychemotherapy substantially reduces the risk of recurrence and death compared with no chemotherapy after 15 years of follow-up, with comparable benefit observed in patients with HR-positive and HR-negative disease [6], although other studies with shorter follow-up suggest less benefit for HR-positive disease [36]. When compared with non-anthracycline-containing cytotoxic regimens, anthracycline-containing regimens reduced the risk of recurrence and death by an additional 10% [6]. Moreover, subsequent studies demonstrated that the administration of taxanes given every 3 weeks either concurrently (with docetaxel) [37] or sequentially (with paclitaxel) [38, 39] after anthracycline-containing therapy further reduced the risk of recurrence and death. Although interpretation of initial studies was confounded by a longer duration of therapy for the taxane arms (8 treatment cycles over 24 weeks) compared with the nontaxane arms (4 cycles over 12 weeks) [38, 39], subsequent studies confirmed a benefit for the sequential anthracycline–taxane strategy when the comparator arm included anthracycline-containing therapy given alone for a comparable duration [40, 41]. A meta-analysis of phase III randomized trials including over 15,500 patients confirmed that taxane-based adjuvant chemotherapy significantly improves disease-free and overall survival [42]. In addition, paclitaxel is more effective when given weekly for 8–12 cycles [41, 43] or biweekly for 4 cycles [44] compared with an every 3-weeks schedule for 4 cycles. A single study involving 1,016 patients with 0–3 positive axillary nodes demonstrated that when compared with 4 cycles of standard doxorubicin (60 mg m^{-2}) and cyclophosphamide (600 mg m^{-2} every 3 weeks) (AC), 4 cycles of docetaxel (75 mg m^{-2}) plus the same cyclophosphamide dose (TC) was associated with a significantly improved disease-free and overall survival and an acceptable toxicity profile, including patients 65 years or older [45, 46]. Therefore, patients with operable BC have a variety of therapeutic options, ranging from 12 (TC or AC) to 24 weeks (AC for 12 weeks followed by weekly paclitaxel for 12 weeks). The choice of adjuvant cytotoxic regimen is individualized

Table 1 Treatment effect of adjuvant systemic therapies

Intervention	Comparison	Patient selection	Median follow-up (years)	Hazard rate for disease-free survival	Hazard rate for overall survival	References
Chemotherapy	Anthracycline-containing chemotherapy + tamoxifen vs. tamoxifen alone	ER-positive	15	0.85 (SE $\pm$ 0.04)	0.89 (SE $\pm$ 0.04)	Breast Cancer Trialists' Overview [5, 6]
	Anthracycline-containing chemotherapy vs. no chemotherapy	ER-negative	15	0.67 (SE $\pm$ 0.07)	0.74 (SE $\pm$ 0.08)	Breast Cancer Trialists' Overview [5, 6]
	Taxane vs. nontaxane-containing chemotherapy	None	~5	0.86 (95% CI 0.81, 0.91)	0.87 (95% CI 0.81, 0.93)	Bria et al. [42]
Endocrine therapy	Tamoxifen vs. none	ER-positive	15	0.61 (SE $\pm$ 0.04)	0.69 (SE $\pm$ 0.05)	Breast Cancer Trialists' Overview [5, 6]
	Anastrozole vs. tamoxifen	ER-positive	8.3	0.85 (95% CI 0.76–0.94)	0.97 (95% CI 0.86–1.11)	ATAC Trialists' Group [53, 54]
Trastuzumab	Letrozole vs. tamoxifen	ER-positive	4.3	0.82 (95% CI 0.71–0.95)	0.91 (95% CI 0.75, 1.11)	Coates et al. [53, 54]
	Chemotherapy plus trastuzumab vs. no trastuzumab	HER2/neu positive	~2	0.53 (95% CI 0.46, 0.60)	0.52 (95% CI 0.44, 0.60)	Viani et al. [5, 6]

SE standard error, CI confidence intervals

based upon the patient's underlying risk of recurrence, comorbidities, and risk of toxicity, and to some extent physician experience and bias.

Adjuvant endocrine therapy

Tamoxifen Tamoxifen was the first widely studied and approved endocrine therapy for HR-positive BC that is effective for the treatment of metastatic disease [47], reduces the risk of recurrence by about 50% when used as adjuvant therapy [5, 6] and reduces the risk of BC by about 50% when used as preventive therapy in healthy women at high risk [16–21]. When used as adjuvant therapy, a 5-years course was considered the standard, as several trials failed to demonstrate greater benefit from a 10-years course [48, 49], including two trials that collectively included over 9,200 patients [50, 51]. A 5-years course of tamoxifen was also considered the standard for prevention [16–21]. Tamoxifen is effective in pre-, peri-, and postmenopausal women.

Aromatase inhibitors Aromatase inhibitors (AIs) inhibit the aromatase enzyme in tumor and peripheral tissues (e.g., liver, adipose tissue, adrenal glands) and reduce plasma and intratumoral estrogen concentrations by greater than 95% [52]. Several large randomized phase 3 trials have evaluated adjuvant AIs either as initial adjuvant endocrine therapy compared with tamoxifen [53, 54], as sequential therapy after 2–3 years of tamoxifen (compared with continued tamoxifen) [55–57], and as extended adjuvant therapy after 5 years of tamoxifen (Table 1) [58–60]. These trials have consistently shown improved disease-free survival (but not overall survival) when the AI is used as initial therapy and improved overall survival when used as extended adjuvant therapy after tamoxifen for node-positive disease [57, 61]. Tamoxifen is associated with more thromboembolic events, endometrial pathology, hot flashes, night sweats, and vaginal bleeding, whereas AIs are associated with more arthralgias and bone fractures. There is also evidence that AIs may reduce recurrence when initiated well after completion of a 5-years course of adjuvant tamoxifen [60]. AIs have replaced tamoxifen as the preferred adjuvant endocrine therapy for postmenopausal women [35, 62].

Ovarian suppression Chemotherapy-induced amenorrhea is a common complication of adjuvant chemotherapy, which is usually but not always indicative of menopause [63]. AIs should be used only in postmenopausal women (defined as absence of menses for at least 1 year), and tamoxifen should be used in pre- or perimenopausal women. For those with chemotherapy-induced amenorrhea lasting <1 year, estradiol and follicle-stimulating hormone

(FSH) levels should be obtained in order to confirm menopause prior to initiating an AI, and tamoxifen may be preferred endocrine therapy in this setting [64]. There is evidence that when added to tamoxifen, chemotherapy, or chemotherapy plus tamoxifen [65], ovarian suppression may further reduce the risk of recurrence in HR-positive operable BC occurring in premenopausal women, although there is currently insufficient evidence to routinely recommend ovarian suppression in this setting [66].

Adjuvant biological therapy

Anti-Her2 therapy Trastuzumab is a humanized monoclonal antibody directed against the HER2/*neu* protein and was approved for the treatment of HER2-positive metastatic disease, when it was shown to prolong survival and improve response and time to disease progression [67, 68]. Five randomized trials that included 9,117 patients with HER2-positive disease compared chemotherapy alone or in combination with trastuzumab for up to 1 year or longer as adjuvant therapy for early stage disease [5, 69–71]. Pooled results from these trials demonstrated significant reductions in recurrence (HR 0.53, $P < 0.00001$) and death (HR 0.052, $P < 0.00001$) for trastuzumab, but more grade 3–4 cardiac toxicity (4.5 vs. 1.8%) [5, 6]. One trial in 528 patients that was reported after this pooled analysis found no benefit for adjuvant trastuzumab (reviewed in [72]). This has generated considerable enthusiasm for evaluating biologically targeted agents, including other agents targeting HER2 (e.g., lapatinib, a small molecule tyrosine kinase inhibitor [73]) and other agents targeting other pathways that are up-regulated in HER2-positive disease (e.g., angiogenesis [74]).

Antiangiogenic therapy Considerable preclinical and clinical evidence supports the role of angiogenesis as a potential therapeutic target [75]. A phase III trial comparing weekly paclitaxel (90 mg m⁻² on days 1, 8, and 15 every 28 days) alone or in combination with bevacizumab (10 mg kg⁻¹ every 2 weeks) found that the addition of bevacizumab significantly improved median progression-free survival (PFS; 11.8 vs. 5.9 months, HR 0.60, $P < 0.001$) and objective response rate (37 vs. 21%, $P < 0.001$), although there was no difference in overall survival [76]. Similar findings were observed when bevacizumab (7.5 or 15 mg kg⁻¹ every 3 weeks) was combined with docetaxel (100 mg m⁻² every 3 weeks), although the treatment effect for bevacizumab was not as pronounced [77]. Bevacizumab did not prolong PFS when used as the second or greater-line therapy in combination with capecitabine, although it did significantly improve the response rate (20 vs. 9%, $P = 0.01$) [78]. Adjuvant trials are now in progress to evaluate the role of bevacizumab in combination with chemotherapy.

Organ-specific therapies In up to 75% of patients with metastatic BC, cancer recurs in the bones, and may be the only site of metastases in up to 25% [79]. Bisphosphonates reduce skeletal complications in patients with bone metastases [80, 81], and four adjuvant bisphosphonate trials have shown mixed results [82]. In two trials, the oral bisphosphonate clodronate (1,600 mg PO daily for 3 years) was associated with significantly reduced bone metastases and improved survival [83, 84], whereas in the third, clodronate was associated with a higher risk of recurrence [85]. Gnant reported that intravenous zoledronic acid (4 mg every 6 months for 5 years) significantly reduced recurrence in premenopausal women with HR-positive disease who received adjuvant endocrine therapy without chemotherapy and also significantly reduced bone loss [86]. Currently, there is an insufficient amount of evidence to recommend adjuvant bisphosphonate therapy to reduce BC recurrence, although several trials that have been completed or are accruing patients may serve to clarify their role in the near future.

Council recommendations

Based on the currently available clinical trial data and information, four major research priorities were identified, and five ongoing clinical trials were designated as high priority (Table 2).

Preoperative neoadjuvant systemic therapy

Preoperative administration of chemotherapy is a standard of care for inoperable locally advanced disease (e.g., inflammatory disease, fixed axillary nodes) or operable disease that may benefit from tumor cytoreduction to facilitate breast conservation surgery; this is often referred to as “neoadjuvant” therapy or “primary systemic therapy” (PST) [87]. Inflammatory carcinoma is a distinct clinicopathologic entity that has been associated with a higher risk of local and systemic recurrence than noninflammatory disease [88, 89]. For individuals who are suitable operative candidates, a meta-analysis of nine randomized studies which included 3,946 patients comparing PST with adjuvant chemotherapy showed no difference in recurrence or survival, although PST was associated with an increased risk of loco-regional recurrence [90]. Radio opaque clip placement prior to PST is associated with a lower local recurrence rate in patients who are candidates for breast conservation [91]. Disease is less likely to recur in individuals who exhibit a pathologic complete response (pCR) in the breast [92] or breast and lymph nodes [93, 94], making this a short-term surrogate that is potentially useful for predicting long-term outcomes. Several methods have been proposed for estimating recurrence in those with less

Table 2 Research recommendations and high priority studies in adjuvant systemic therapy

- *Integration of biologic agents with existing chemotherapy or hormonal therapy regimens.* Biologic agents, such as bevacizumab, trastuzumab, and the dual tyrosine kinase inhibitor, lapatinib, are under investigation to determine the optimal ways to integrate these therapies into standard adjuvant therapy. Further research is needed on several issues surrounding biologic and targeted therapies: optimal duration of administration, understanding why and how intrinsic and acquired resistance to these agents develops, how to predict and minimize treatment-related toxicities; and how to design trials to assess their efficacy
- *Optimizing chemotherapy.* Further research is needed on new chemotherapy drug classes and formulations and on current therapies to optimize drug scheduling, sequencing, and combinations
- *Identification and integration of genetic or molecular biomarkers into treatment selection.* Genetic and molecular biomarkers will identify patients who may benefit from therapy versus those who will not, determine patients who are more likely to experience toxicity and assist in risk stratification for disease recurrence over time. We need prospective data to confirm the prognostic or predictive value of these markers. Multigene assays have been developed to predict outcome and benefit from adjuvant therapy, but to date, the optimal set of genes is unknown
- *Evaluation of new hormonal therapies.* Several questions remain to be answered, including competing endocrine effects of chemotherapy and ovarian suppression, optimal duration of interventions, long-term effects, and role in perimenopausal women

Study	Target accrual	Study population	Research questions
ALTTO (NCT00490139)	8000	HER2-positive	Adjuvant lapatinib and/or trastuzumab: sequential versus in combination
SWOG S0307 (NCT00127205)	4500	Stage I–III with no evidence of metastatic disease	Bisphosphonates on bone metastases prevention
SOFT (NCT00066690)	3000	ER-positive, premenopausal	Ovarian suppression + tamoxifen or exemestane versus tamoxifen alone
ECOG E5103 (NCT00433511)	4950	Lymph node-positive and high-risk lymph node-negative	Chemotherapy ± bevacizumab
NSABP B-42 (NCT00382070)	3840	ER-positive/node-positive or node-negative	Letrozole versus placebo following AI therapy or tamoxifen followed by an AI
MA.17-R (NCT00754845)	1800	ER-positive/node-positive or node-negative	Optimal duration of letrozole: additional 5 years of letrozole therapy after 5 years of tamoxifen therapy

than a pCR based upon the posttreatment stage [95] or an algorithm based upon posttreatment pathologic features [96, 97]. For patients who have clinically negative nodes after PST, sentinel lymph node biopsy appears to have similar accuracy as when done preoperatively [98]. Preliminary experience with preoperative endocrine therapy in older individuals with HR-positive disease has also been advocated by some experts, because changes in proliferation index after a short course of therapy correlate with recurrence [99], although this approach has generally been restricted to patients enrolled on CTs [100]. Primary endocrine therapy without surgery may also be an acceptable approach in elderly patients who may not be suitable candidates for surgery [101].

Council recommendations

The council identified several research priorities related to optimizing the role of surgery in the neoadjuvant setting (discussed in a subsequent review) and designated three ongoing clinical trials as high priority:

- NSABP B-41 (NCT00486668) evaluating preoperative combination of CT regimens with trastuzumab and/or lapatinib in patients with HER2-positive disease (target accrual 522);

- ACOSOG-Z1031 (NCT00265759) evaluating preoperative efficacy of exemestane versus letrozole versus anastrozole in patients with ER-positive/node-positive or node-negative disease (target accrual 375); and
- ACOSOG-Z1041 (NCT00513292) evaluating preoperative CT ± trastuzumab in patients with HER2-positive disease (target accrual 391).

Metastatic breast cancer

Metastatic BC remains an incurable disease, but systemic therapy palliates symptoms [102], delays disease progression and prolongs survival [103]. Current options for systemic therapy include endocrine therapy for ~70% of patients with HR-positive disease, anti-Her2/neu-directed therapies (i.e., trastuzumab, lapatinib) for 15–20% of patients with Her2/neu overexpressing disease [67, 104], bisphosphonate therapy for 30–50% of patients who develop bone metastases [81], and cytotoxic chemotherapy [104]. Chemotherapy is generally reserved for patients with HR-positive disease who have disease progression after one or more endocrine therapies, or HR-negative disease. The sequential use of single cytotoxic agents at their optimal dose/schedule is recommended, since numerous studies have shown that combination cytotoxic therapy is

associated with more toxicity but does not improve survival [105, 106]. Likewise, the combination of endocrine therapy plus chemotherapy does not appear to be more effective than either modality used alone [107, 108]. However, for patients with HER2-positive disease who require chemotherapy, the combination of chemotherapy with trastuzumab is associated with survival benefit compared with trastuzumab alone [67].

Regulatory approval of new agents

The United States Food and Drug Administration (FDA) uses clinical benefit as its criterion for approving new agents [109]. Regular approval is granted based on the end points demonstrating that the drug provides a longer life, a better life, or a favorable effect on an established surrogate for a longer or better life. Accelerated approval is granted based on the surrogate end points that are less well established but reasonably likely to predict a longer or a better life. During the past decade, new agents that have been approved include the selective estrogen receptor down-regulator fulvestrant for HR-positive disease [110, 111] and cytotoxic agents such as nab-paclitaxel [112], gemcitabine combined with paclitaxel for the first-line therapy [113], capecitabine for anthracycline and taxane-resistant disease [114, 115], and ixabepilone alone [116] or plus capecitabine for anthracycline and taxane-resistant disease (Table 3) [117]. Biologic agents that have been approved include trastuzumab combined with paclitaxel or used alone for HER2-positive disease [67, 118], lapatinib, a tyrosine kinase inhibitor, combined with capecitabine for trastuzumab-refractory HER2-positive disease [73], and bevacizumab plus paclitaxel for the first-line therapy of Her2/neu negative disease [76]. For the first-line therapy, improved overall survival was used as the endpoint supporting regular approval for both trastuzumab and gemcitabine but improved PFS was recently used as the basis for accelerated approval of bevacizumab for the first-line therapy [76], and for ixabepilone for the second or greater-line therapy [117]. PFS has been recognized as a potentially useful endpoint that is predictive of clinical benefit and has been recognized by the FDA if of “sufficient magnitude”, evaluated in a properly conducted trial and evaluated in the context of measuring survival.

Council recommendations

Based on the currently available clinical trial data and information, five major research priorities were identified, one ongoing clinical trial was designated as high priority, and one concept was deemed as a high priority need (Table 4).

Application of genomics to therapeutic individualization

The application of knowledge about the human genome into clinical practice has been referred to “genomic medicine”, which may include evaluation of somatic or germ line genome.

Somatic single gene and multigene markers

Classical clinicopathologic features that are associated with clinical endpoints such as recurrence in operable disease (or progression in metastatic disease) have been called “prognostic” factors (e.g., tumor grade, tumor size, positive axillary nodes for operable disease), whereas those associated with response to specific therapeutic interventions have been referred to as “predictive” factors (e.g., ER status in response to endocrine therapy HER2 expression in response to anti-HER2-directed therapy) [119, 120]. There has also been considerable interest in topoisomerase 2A (*TOP2A*) as a predictive factor for anthracycline therapy [121]. Numerous somatic “multigene markers” have been developed which provide prognostic information independent of classical clinicopathologic features, several of which are commercially available, including a 21-gene assay (Oncotype DXTM, Genomic Health, Inc. Redwood City, CA) [122–124], a 70-gene assay (Mammaprint[®], Molecular Profiling Institute, Inc., Phoenix, AZ) [125, 126], and a 7 gene assay [127, 128] (Avaria Breast Cancer IndexTM, BioTheragnostics, Inc., San Diego, CA). Several other multigene prognostic markers have also been identified and validated [127, 129–154]. The potential utility and pitfalls of marker development have been reviewed elsewhere [131, 132], and there are established criteria for the level of evidence required to define and support their clinical utility [120]. Although these markers vary considerably in the clinical contexts in which they were developed and validated, and the genes comprising the signature, their prognostic utility is generally driven by proliferation genes [133]. Although most of these markers appear to provide prognostic information in both treated and untreated populations, few have been shown to predict response to specific therapies or to impact clinical decision-making [134]. Research is ongoing regarding therapeutic individualization using epigenomic, proteomic, and metabolomic technology [135–138].

Germ line markers

Genetic profiling of germ line DNA for SNPs has identified several common genetic variants that are associated with altered drug metabolism. For example, polymorphisms of *CYP2D6* that result in diminished enzyme activity and

Table 3 Selected pivotal trials resulting in FDA approval of new agents for metastatic breast cancer

Drug approved	Setting	Comparison	Response rate	Median TTP (months)	Median survival (months)	References
Trastuzumab	HER2-positive, first line chemotherapy	Chemotherapy alone ($N = 234$) Chemotherapy plus trastuzumab ($N = 235$)	32% 50% ($P < 0.001$)	4.6 mo. 7.6 mo. (HR 0.51, $P < 0.001$)	20.3 mo. 25.1 mo. (HR 0.80, $P = 0.046$)	Slamon et al. [6]
Fulvestrant	HR-positive, postmenopausal, relapse or progression after prior antiestrogen therapy	Anastrozole 1 mg PO daily ($N = 194$) Fulvestrant 250 mg IM monthly ($N = 206$)	17.5% 17.5%	3.4 mo. 5.4 mo. (HR 0.92, $P = 0.43$)	NR	Osborne et al. [110]
Gemcitabine	First-line chemotherapy	Paclitaxel 175 mg m^{-2} every 3 weeks ($N = 262$)	22%	2.9 mo.	15.8 mo.	Albain et al. [113]
Nab-Paclitaxel	First or second-line chemotherapy	Paclitaxel plus gemcitabine 1,250 mg m^{-2} days 1, 8 ($N = 267$)	41% ($P < 0.0001$)	5.2 mo. (HR 0.65, $P < 0.0001$)	18.5 mo. (HR 0.78, $P = 0.018$)	Gradishar et al. [112]
		Paclitaxel 175 mg m^{-2} every 3 weeks ($N = 225$)	19%	3.9 mo.	13.0 mo.	
		Nab-paclitaxel 260 mg m^{-2} every 3 weeks ($N = 229$)	22% ($P = 0.001$)	5.4 mo. (HR 0.75, $P = 0.006$)		
Ixabepilone	15.2 mo. ($P = 0.374$) Anthracycline and taxane-resistant	Capecitabine 2,500 mg m^{-2} days 1–14 every 3 weeks ($N = 377$)	14%	4.2 mo.	NR	Thomas et al. [117]
		Capecitabine 2,000 mg m^{-2} days 1–14 plus ixabepilone 40 mg m^{-2} IV every 21 days ($N = 355$)	35% ($P < 0.0001$)	5.8 mo. (HR 0.75, $P < 0.0003$)	NR	
Lapatinib	HER2-positive, trastuzumab resistant	Capecitabine 2,500 mg m^{-2} day $^{-1}$ days 1–14 every 21 days ($N = 161$)	14%	4.4 mo.	NR	Geyer et al. [73]
		Capecitabine 2,000 mg m^{-2} day $^{-1}$ days 1–14 every 21 days plus lapatinib 1,250 mg daily ($N = 161$)	22% ($P = 0.09$)	8.4 mo. (HR 0.49, $P < 0.001$)	NR	
Bevacizumab	HER2-negative, first-line chemotherapy	Paclitaxel 90 mg m^{-2} day 1, 8, 15 every 28 days ($N = 326$)	21%	5.9 mo.	25.2 mo.	Miller et al. [76]
		Paclitaxel plus bevacizumab 10 mg kg^{-1} IV every 2 weeks ($N = 347$)2	37% ($P < 0.001$)	11.8 mo. (HR 0.60; $P < 0.001$)	26.7 mo. (HR 0.88, $P = 0.16$)	

TE too early, HR hazard ratio, NR not reported

Table 4 Research recommendations and high priority studies in advanced disease

- *Implementation of novel trial testing new agents.* Trial designs that allow for fewer patients, data analysis at interim basis, and modifications to the trial design may be more appropriate in this setting. Correlative trials are also needed to address basic research questions, such as mechanism of action, and clinical questions, such as identification of molecular predictive and prognostic factors
- *Understand the mechanism of resistance to HER2- and endocrine-targeted therapies.* How do we predict the patients who will develop resistance to anti-Her2 therapy prior to initiation of therapy? How do we treat patients who develop resistance during anti-Her2 therapy? How do we define HER2-positive?
- *Combinations of targeted therapies.* The redundancy of cellular pathways and multiple concurrent aberrations in cancer cells needs to be addressed to maximize clinical effect. How many and what effect does inhibition of multiple pathways have on patients?
- *Obtain research biopsies to gain an understanding of metastatic disease biology.* However, obtaining tumor biopsies for research may discourage patient accrual
- *Optimal duration of bisphosphonate therapy.* Is there continued efficacy of bisphosphonate therapy for treatment of advanced BC with bone metastases beyond 1 year?

Study	Target accrual	Study population	Research questions
OPTIMIZE-2 (NCT00320710, CZOL446E2352)	705	Stage IV	What is the optimal dosing schedule during the second year or later years of bisphosphonate therapy?
New study concept (to be approved)			CT ± bevacizumab after progression on a bevacizumab-containing regimen

Table 5 Research recommendations and high priority studies in pharmacogenomics

- *Prospective trials using Oncotype Dx.* The SLC recommends prospective trials to determine the additional benefit of chemotherapy for patients with ER-positive, node-positive BC treated with optimal endocrine therapy using Oncotype Dx to determine recurrence score
- *Validation of biomarkers.* Substantial data are available on genes and gene expression profiles that are associated with the different behaviors of tumors and with prognosis prediction. However, the clinical value of these signatures cannot be made without prospective clinical trials to validate their benefit over standard clinico-pathologic prognostic variables
- *Tissue banks.* Although genomic assays may provide additional opportunities to study tissue, few patients consent to a second biopsy. The SLC recommends proactive tissue collection for correlative studies when designing clinical trials. Moreover, guidelines regarding handling of tissues and specimens need to be developed

Study	Target accrual	Study population	Research questions
TAILORx (PACCT-1) (NCT00310180)	10406	ER-positive, node-negative	Best therapy using Oncotype DX: hormonal therapy alone versus hormonal therapy plus chemotherapy in patients with RS 11–25

biotransformation of tamoxifen to its active metabolite, endoxifen, have been associated with a higher risk of recurrence in patients with operable BC treated with adjuvant tamoxifen [139, 140]. In addition, agents used to manage hot flashes such as fluoxetine are known to be potent inhibitors of *CYP2D6*, producing reduced endoxifen levels comparable to poor metabolizers, thus raising concern that these agents may abrogate the effects of tamoxifen [141–143]. Evaluation of other SNPs associated with benefit and toxicity associated with tamoxifen and aromatase inhibitors is an area of active investigation.

Council recommendations

Based on the currently available clinical trial data and information, three major research priorities were identified, and one ongoing clinical trial was designated as high priority (Table 5).

Effects of cancer and cancer therapy on overall health

It is standard practice to evaluate the acute adverse effects of cancer treatment in CTs, but more recent measures have been developed to assess the effects of the disease and its treatments on overall health. Such measures are referred to as “health related quality of life” (HRQOL) [144].

HRQOL and the short-term effects of therapy

Factors that must be weighed when considering inclusion of a HRQOL measure in CTs include increased trial complexity, respondent burden, and cost versus the expected gain in knowledge. A systematic analysis of BC CTs concluded that the utility of HRQOL analyses depended on the setting, but in some scenarios provided added information for clinical decision-making beyond that of traditional medical outcomes [145]. For example,

HRQOL measurement did not influence clinical decision-making in adjuvant therapy and provided little information beyond that obtained from traditional medical outcomes such as toxicity in metastatic trials. However, results of HRQOL questionnaires targeting specific symptoms (e.g., emesis) guided treatment decisions when evaluating symptom control and was the only measure in psychosocial intervention trials [145]. In order to address some of the challenges of measuring the outcomes and provide guidance regarding the settings in which they should be measured, efforts are underway to standardize effective patient-reported outcomes (PRO). These are measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) Network, part of the National Institutes of Health Roadmap Initiative [146]. PROMIS is establishing a publicly available resource of standardized, accurate, and efficient PRO measures of major self-reported health domains (e.g., pain, fatigue, emotional distress, physical function, social function) that are relevant across chronic illnesses including cancer.

HRQOL and the long-term effects of therapy in cancer survivors

Health related quality of life measurements may be particularly important for individuals receiving adjuvant or preventive endocrine therapy who are treated chronically for 5–10 years with endocrine therapies [24, 144, 147, 148]. In addition, there is concern about the long-term adverse effects of chemotherapy, including preservation of fertility in young women [149], acute leukemia [150–153], cardiac dysfunction after anthracyclines and/or irradiation [154, 155], peripheral neuropathy after taxanes [156], and cognitive dysfunction [157]. Limitations of research into

cognitive dysfunction have included a lack of consistency in defining cognitive impairment, the neuropsychiatric batteries used, the sensitivity of the measures to mild impairment, and the preponderance of cross-sectional and dearth of more informative longitudinal studies [157].

Council recommendations

Based on the currently available clinical trial data and information, four major research priorities were identified, and one ongoing clinical trial was designated as high priority (Table 6).

Special populations

Breast cancer in the elderly

Breast cancer is a disease of aging, with the incidence of the disease increasing with each decade of life, and the median age at diagnosis is currently 61 years. As the life expectancy of the US population increases, it is anticipated that there will be a substantial increase in the incidence of BC, and that there will be more elderly women with BC than ever before. Elderly women lacking significant comorbidities can expect to live an average of 20 years if they are 65 years of age and 12.8 years if they are 75-years-old [158]. Evidence-based expert recommendations for screening and management of BC in the elderly have been proposed [159]. Older women have been generally underrepresented in CTs [160–162]. Older individuals who participated in trials tended to have higher risk disease and fewer comorbidities, had more adverse effects from adjuvant chemotherapy than younger women, but experienced comparable benefits [151].

Table 6 Research recommendations and high priority studies in quality of life

<ul style="list-style-type: none"> • <i>Acceptability of chemotherapy toxicity, particularly late effects, including fatigue and related function.</i> Patients with early disease often consider the balance between possible treatment benefit and treatment burden (including work and work performance) in treatment decision or adherence. We need to include validated measures of QOL in clinical trials of treatment of early disease. In patients with advanced disease, we need to consider the value of life extension versus QOL and cost • <i>Impact of cognitive function.</i> Research to date has been cross-sectional in nature but has yielded evidence to support a possible association between chemotherapy and cognitive impairment. Additional prospective studies are needed to make definitive conclusions regarding this association • <i>Impact of neuropathy.</i> Incidence of neurotoxicity is increasing because of higher doses and longer duration of treatment regimens. Further research is needed to prevent or minimize these neurotoxic effects • <i>Effects of long-term use of hormonal therapy.</i> We need to reconcile increased efficacy with the increased toxicities that affect QOL 			
Study	Target accrual	Study population	Research question
E2Z04 (NCT00309933)	1707	Breast cancer survivors treated on studies C9741, E1199, E2197, E2198, and N9831 (or treated off protocol with similar regimens) and their spouses, partners, or acquaintances	Survivorship trial; results of this trial will help develop interventions for breast cancer survivors

Breast cancer in minority populations

Variations in BC incidence, stage at presentation, and mortality among women of differing race and ethnicity have been attributed to environmental, genetic, dietary, socioeconomic, cultural, and reproductive endocrinologic factors [163–168]. BC is less common in African-Americans and Hispanics than non-Hispanic Caucasians, but African-Americans present at a younger age and with more advanced stage disease have a poorer prognosis than Hispanic or non-Hispanic Caucasian women [169] and are also less likely to participate in CTs [162]. African-Americans and Hispanics are more likely to present with triple-negative BC [170, 171], a BC subtype characterized by absent expression of ER, PR, and HER2.

Breast cancer in males

Male BC accounts for about 1% of all BCs in the US, with 2,000 new cases and 450 deaths estimated in 2008 [1]. Men are more likely to present with advanced stage disease, are more likely and to have HR-positive disease [172]. Men appear to derive similar benefit from adjuvant endocrine therapy and chemotherapy as women and should be managed in a similar manner [173].

Council recommendations

Based on the currently available clinical trial data and information, the following research priorities were identified:

- *Underrepresentation of elderly and minority women in clinical trials.* Clinical trial participation of these patient populations is low because of multiple factors, including toxicity issues, existing comorbidities, socioeconomic status, and cultural issues. An important clinical question is whether enrollment of elderly women should be integrated into all clinical trials. Efforts should be made to improve accrual of these minority patients.
- *Identification of targets in triple-negative disease.* Further research is needed to understand the pathways that drive proliferation of these tumors and to assess whether subclassification of triple-negative tumors will have value in identifying patient subsets who may respond uniquely to different treatment strategies.

Conclusions

Breast cancer mortality decreased in the US in 2000 for the first time [174], which is partly attributable to improvements in systemic therapy [175]. The progress has been

incremental, with each new therapeutic intervention applied to the entire population, including individuals who may have been adequately treated with minimal or no systemic adjuvant therapy. Our current challenges include continuing to find novel ways to further reduce the risk of recurrence and to also more selectively recommend systemic therapies for those most likely to benefit. Improved understanding of the molecular pathogenesis of BC will serve to identify new therapeutic targets and to improve therapeutic individualization. The current challenge in BC therapy is to individualize treatment to each patient, uniquely taking into account patient-specific factors (i.e., performance status, age, drug metabolism) and tumor-specific factors (i.e., tumor size, nodal status, phenotype, and molecular profile). Considerable therapeutic advances have been made in the past 30 years, many important questions remain, and further improvement in outcomes will require coordinated efforts.

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Appendix: Scientific Leadership Council in Breast Cancer Writing Group

Information included in this manuscript was taken from the consensus-based document finalized September, 2008—“Research Priorities in Breast Cancer: Recommendations of the Scientific Leadership Council in Breast Cancer of the Coalition of Cancer Cooperative Groups”. The Writing Group for these documents include:

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