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The *Hospital Physician Oncology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in oncology. Each manual reviews a topic essential to the current practice of oncology.

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Adjuvant Systemic Therapy for Early-Stage Breast Cancer

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INTRODUCTION

Over the past 20 years, substantial progress has been achieved in our understanding of breast cancer and in breast cancer treatment, with mortality from breast cancer declining by more than 25% over this time.[1–3] This progress has been characterized by a greater understanding of the molecular biology of breast cancer, rational drug design, development of agents with specific cellular targets and pathways, development of better prognostic and predictive multigene assays, and marked improvements in supportive care. Specifically, 4 main factors have brought us closer to using the term "cure" for early breast cancer and led to a significant improvement in the quality of life of patients: (1) early detection through mammography;[4] (2) a better understanding of breast cancer as both a local and a systemic disease leading to the demonstration that breast-conserving surgery (lumpectomy) followed by radiation therapy is unequivocally comparable to mastectomy;[5,6] (3) the implementation of early systemic therapy;[7–9] and (4) the understanding that breast cancer is a heterogeneous disease.[10] These advances have led to the development of newer systemic chemotherapies, hormonal therapies, and targeted (biologic) therapies. One of the great advances made during this time, and in the history of breast cancer, was the recognition of the crucial role played by amplification of the *human epidermal growth factor receptor 2* (*HER2*) gene for a subset of breast cancer patients and the implementation of anti-HER2 therapies in early breast cancer.[11–14] However, important questions remain regarding how to further tailor therapy based on better predictive and prognostic markers. In this manual, we review the current approach to systemic therapy for early-stage disease (stages 0, I, II, III) in the adjuvant setting.

PRINCIPLES OF SYSTEMIC THERAPY

The improvement in breast cancer mortality over the past 2 decades has been a direct result of both advances in early detection through screening and advances in adjuvant treatment.[9] Depending on the model of risk reduction, adjuvant therapy has been estimated to be responsible for 35%

to 75% of that reduction.[15] *Adjuvant treatment* of breast cancer is the term given to systemic therapies (chemotherapy, endocrine/hormonal therapy, or targeted biologic therapy) designed to treat micrometastatic disease, or breast cancer cells that have escaped the breast and regional lymph nodes but have not yet established an identifiable metastasis. Treatment is aimed at reducing the risk for future recurrence, thereby reducing breast cancer–related morbidity and mortality.[16]

In recent years, there has been an explosion of endocrine therapy and chemotherapeutic advances against breast cancer. Drugs were developed based on fundamental investigations of normal and cancer cells and the pathophysiological peculiarities and intracellular pathway signals of cancer cells.[17] Combination chemotherapy regimens became a standard recommendation in the adjuvant setting.[18] The decision to give chemotherapy is typically based on several factors including the cancer's stage and grade; lymph nodes status; hormone receptor (HR) assay results (ie, estrogen receptor [ER] and progesterone receptor [PR] status); HER2 status; and more recently multigene assays.[19,20]

Advances in genomic profiling, mostly based upon gene expression microarrays, have permitted simultaneous examinations of thousands of genes and pathways in a specific tumor and the description of comprehensive portraits of malignant cells.[10] The Oncotype DX breast cancer assay (Genomic Health, Redwood City, CA)[20] is a 21-gene reverse transcription polymerase chain reaction (RT-PCR) assay that generates a recurrence score (RS) reflecting the relative expression levels of 16 cancer-related genes and 5 reference genes. The RS quantifies the risk of recurrence so that the benefit of chemotherapy in patients with early-stage node-negative, ER-positive breast cancers can be assessed. Cases are grouped into 3 categories of risk of recurrence—low, intermediate, and high—based on the expression levels of the cancer-related genes (low <18, intermediate 18 to 30, and high >30). The American Society of Clinical Oncology (ASCO)[19] and National Comprehensive Care Network (NCCN)[21] guidelines recommend the use of the Oncotype DX assay in clinical practice to identify patients who may not require adjuvant chemotherapy.

The Oncotype DX is used when evaluating patients with primary tumors characterized as >0.5 cm in size, node-negative, HR-positive, and HER2-negative.[21] Patients with tumors classified as low risk by RS are not likely to benefit from chemotherapy and should receive endocrine therapy alone. Patients in the high-risk RS category would need to receive chemotherapy in addition to endocrine therapy. For patients in the intermediate-risk category, the benefit of chemotherapy is unclear and randomized controlled trials are ongoing to help address this question. Other prognostic criteria and clinical judgment should be exercised when deciding on the treatment plan in the intermediate-risk group. The Oncotype DX can be used in selected patients with 1 to 3 involved ipsilateral axillary lymph nodes to guide the addition of combination chemotherapy to standard hormone therapy.[21]

In view of the refined classification of breast cancer, we need to address the following questions when deciding on the optimal adjuvant systemic therapy in a patient with early breast cancer:

- What patient subsets need chemotherapy?
- What are the available chemotherapy options and is there an optimal chemotherapy for any particular patient subset?
- What patient subsets need endocrine (hormonal) therapy and for how long?

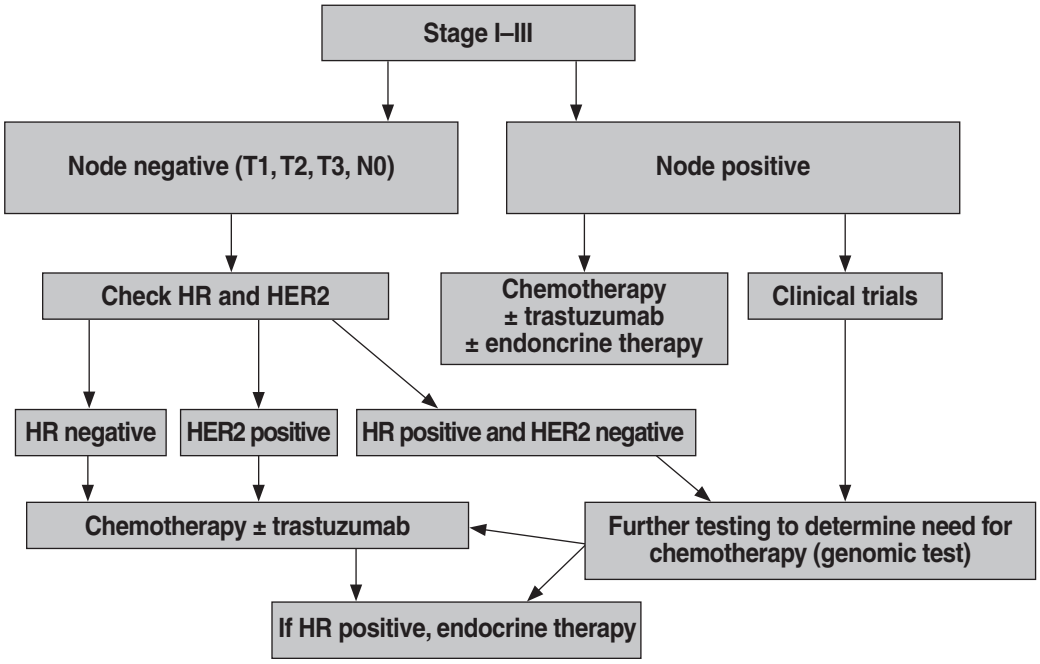

Figure. Algorithm to guide the initial treatment approach for early-stage breast cancer with tumor size >0.5 cm. HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

DETERMINING WHICH PATIENTS NEED CHEMOTHERAPY

In general, the majority of patients with early-stage breast cancer with a tumor size larger than 0.5 cm need systemic therapy following local treatment of breast cancer. The **Figure** illustrates the general approach in the decision-making process on which patients need chemotherapy and other systemic therapies. This algorithm applies to primary tumor (T) larger than 0.5 cm. For tumors that are 0.5 cm or smaller, the benefit of chemotherapy may be too small to warrant the potential toxicity and is generally not offered. The recommendation for chemotherapy assumes the patient is fit and able to tolerate chemotherapy. For patients with exclusively micrometastasis (<2 mm axillary node metastasis) in lymph nodes (N1mi), the treatment is based on tumor size.[21] T0 and T1 tumors with nodal micrometastasis only are excluded from stage IIA and are classified as Stage IB.

The following general principles apply when deciding which patients need chemotherapy:

- Chemotherapy should be considered when there is lymph node involvement regardless of tumor size. However, ongoing trials (Southwest Oncology Group [SWOG] RxPONDER/S1007 in the United States and MINDACT in Europe) will help determine whether a subgroup of women with ER-positive, node-positive disease might not benefit from chemotherapy and can safely be treated with endocrine (hormonal) therapy without chemotherapy.
- For node-negative (N0) disease, the specific

choice of treatment is based mainly on HR status (ie, the ER and/or PR) and HER2 status.

- In ER/PR-negative disease, chemotherapy is the mainstay of adjuvant chemotherapy, regardless of nodal status.
- In HER2-positive disease, chemotherapy and the anti-HER2 trastuzumab should be offered, regardless of the nodal or HR status. HER2-positive disease is defined as a finding of HER2 protein 3+ by immunohistochemistry (circumferential membrane staining that is complete, intense, and in >10% of tumor cells) or as the presence of *HER2* gene amplification by FISH defined as either (1) dual probe *HER2*/CEP17 ratio ≥2.0 with an average *HER2* copy number ≥4.0 signals per cell; (2) dual probe *HER2*/CEP17 ratio of ≥2.0 with an average *HER2* copy number <4.0 signals/cell; (3) dual probe *HER2*/CEP17 ratio <2.0 with an average *HER2* copy number >6.0 signals/cell; or (4) single-probe average *HER2* copy number ≥6 signals/cell.[22] In ER-positive and/or PR-positive breast cancer, endocrine (hormonal) therapy should be used as adjuvant therapy for almost all women, regardless of nodal or HER2 status. Hormonal therapy is generally given after completion of chemotherapy, if chemotherapy is indicated.
- In ER-positive and/or PR-positive and HER2-negative breast cancer that is node negative (N0), additional tests are recommended to determine the benefit of chemotherapy. The most widely used genomic test in the United States is the 21-gene RS assay, the Oncotype DX,[20] as noted above. Use of the Oncotype DX assay is limited to ER-positive tumors. This assay helps predict the benefit from adding chemotherapy to hormonal therapy compared with hormonal therapy alone. The subset of patients with a high RS (defined as ≥31) benefit from chemotherapy.
- In ER-positive and/or PR-positive and HER2-negative breast cancer that is node-negative, clinical judgment should always be exercised in assessing the benefit from adding chemotherapy to endocrine therapy, and additional factors should be considered in the decision making regarding chemotherapy, such as high histologic grade and young age (younger than 50 years).
- The role of the RS assay (Oncotype DX) in ER-positive and/or PR-positive, HER2-negative, and node-positive disease is less certain and is being tested in a large randomized trial (SWOG S1007). S1007 randomizes patients with node-positive disease who have an RS of 25 or lower to chemotherapy plus endocrine therapy or endocrine therapy alone.

CURRENT CHEMOTHERAPY OPTIONS

EVOLUTION OF ADJUVANT CHEMOTHERAPY

The first chemotherapy combination regimen used on a large scale for breast cancer was the CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) regimen.[23] Six cycles of CMF was the gold standard of adjuvant chemotherapy in breast cancer for decades, and it significantly improved early and long-term results and conferred better rates of relapse-free survival and overall survival (OS) compared with no chemotherapy.[24] Multiple subsequent regimens were developed and contributed to improved outcome in breast cancer.

Anthracycline-Based Chemotherapy

Anthracycline-containing adjuvant chemotherapy regimens were introduced for the treatment of early-stage breast cancer in the early 1980s. Compared with standard CMF, anthracycline-containing regimens reduced both the annual risk of recurrence and the annual risk of death by more than 10%, equating to about a 5% absolute reduction in recurrence and 3% and 6% absolute reduction in mortality at 5 and 10 years follow up, respectively.[7,8,24–27] This small but real difference established anthracyclines (epirubicin, doxorubicin) as one of the most active drugs for breast cancer. Multiple schedules, dose densities, and intensities have been tested; common regimens in use contain 3 or more agents including cyclophosphamide (C), fluorouracil (F), epirubicin (E), or doxorubicin (A) (eg, CEF and CAF, FAC, FEC). Two-drug regimens (eg, AC or EC) appear to be equivalent to 6 cycles of CMF. Anthracyclines remain the most commonly used drugs for breast cancer, but not without concerns regarding anthracycline-associated cardiotoxicity or leukemogenic potential.

In the 2000 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis,[7] anthracycline-based regimens were associated with an annual risk for cardiac mortality of 0.08% per year as compared with 0.06% per year in patients treated with nonanthracycline-based regimens. This is the largest meta-analysis of individual patients in cancer care, with data from 145,000 women with breast cancer at an early stage who participated in 194 randomized trials of adjuvant systemic therapy (chemotherapy and/or hormonal therapy). However, the question of long-term cardiac safety remains, particularly for older women with early-stage breast cancer.

Multiple subsequent trials conducted by the Cancer and Leukemia Group B (CALGB) over the past several decades using anthracycline regimens confirmed the advantages of this chemotherapy in terms of improving disease-free survival (DSF) and OS, particularly in patients with ER-negative disease, without significant nonhematologic toxicity.[28–31] Additionally, a meta-analysis of 8 trials involving 6564 women with early-stage breast cancer that compared anthracycline- to nonanthracycline-based regimens suggested a benefit with anthracycline administration only in patients with HER2-positive disease.[32] The role of ER, HER2, as well as other biomarkers as predictive markers of response to anthracyclines needs further validation. Until then, many experts believe that patients should not be deprived of anthracycline-based adjuvant chemotherapy if their risk assessment so determines it.[33]

Taxane-Based Chemotherapy

During the 1990s, the taxanes emerged among the most active and commonly used chemotherapeutic agents for the treatment of early-stage breast cancer. The CALGB 9344 was one of the largest trials evaluating taxanes in the adjuvant setting for early-stage breast cancer and included more than 3000 women with node-positive breast cancer.[34] This study demonstrated a 5-year survival benefit of 80% versus 77% for the sequential use of paclitaxel following AC (doxorubicin, cyclophosphamide) chemotherapy, compared to AC alone. This important trial led to the incorporation of paclitaxel following AC administration for adjuvant polychemotherapy in women with lymph node-positive disease.

Some questions that were raised remain, specifically whether any patient subset will benefit most from taxane chemotherapy and what taxane and schedule are optimal. In a retrospective analysis of CALGB 9344 testing for HER2 status using 1322 original participant tumor blocks,[35] HER2 positivity, irrespective of ER status, predicted a significant

benefit from paclitaxel in terms of reduced disease recurrence (HR 0.59, $P = 0.01$). Patients with ER-positive, HER2-negative, node-positive breast cancer did not seem to benefit from the addition of a taxane.[36] However, the Breast Cancer International Research Group (BCIRG) 001 docetaxel trial, in which significant improvement was documented in DFS with 6 cycles of TAC (docetaxel, doxorubicin, cyclophosphamide) compared with 6 cycles of FAC (82% vs 74%), showed significant benefit of the taxane-anthracycline regimen over the anthracycline-nontaxane regimen in both ER-positive and ER-negative tumors.[36] A subsequent Cochrane meta-analysis including 12 studies and more than 21,000 patients evaluated the role of taxanes in the adjuvant treatment of operable breast cancer (stage I–III).[37] This review did not identify a subgroup of patients where taxane-containing treatment may have been more or less effective.[37] The totality of evidence, therefore, supports the use of taxane-containing adjuvant chemotherapy regimens, with improvement of OS and DFS for women with operable early breast cancer. To date, there is not enough evidence to support withdrawing taxane therapy in any subgroup of breast cancer patients.

Although the precise role of adjuvant taxane therapy remains controversial, the optimal scheduling of taxane administration has been well studied. The Eastern Cooperative Oncology Group (ECOG) 1199 trial randomly assigned 4950 women with lymph node-positive or high-risk lymph node-negative early-stage breast cancer to 4 cycles of AC followed by 4 different taxane regimens: (1) paclitaxel 175 mg/m^2 every 3 weeks, (2) paclitaxel 80 mg/m^2 weekly, (3) docetaxel 100 mg/m^2 every 3 weeks, and (4) docetaxel 35 mg/m^2 weekly. After a 64-month median follow-up, paclitaxel weekly and docetaxel every 3 weeks were superior to the other 2 regimens in terms of DFS.[38] A 10-year update of the ECOG 1199 was presented at the 2014 San Antonio Breast Cancer Symposium (Abstract S3-03). In the entire population, adjuvant weekly paclitaxel and docetaxel every 3 weeks were associated with significantly improved DFS and marginally improved OS compared with paclitaxel every 3 weeks, when given sequentially after adjuvant AC. There was no difference between the combined paclitaxel arms and the combined docetaxel arms in terms of DSF or OS. There was also no difference in the combined weekly versus combined every-3-weeks arms. However, for the 1025 patients with triple-negative disease, the most effective taxane regimen was weekly paclitaxel.

A phase 3 trial (S0221) conducted by the SWOG compared AC plus filgrastim with paclitaxel in different combinations and sought to test 2 hypotheses: that a novel continuous schedule of AC was superior to 6 cycles of AC once every 2 weeks and that paclitaxel once per week was superior to 6 cycles of paclitaxel once every 2 weeks in patients with node-positive or high-risk node-negative early-stage breast cancer. Interim analyses crossed the futility boundaries for demonstrating superiority of both once-per-week regimens and once-every-2-weeks regimens.[39] After a median follow-up of 6 years, patients achieved a similar DFS with weekly paclitaxel or the dose-dense once-every-2-weeks paclitaxel regimens. Subset analysis suggests that once-every-2-weeks dosing may be best for patients with HR-negative/HER2-negative tumors.

BCIRG 005 compared TAC (docetaxel, doxorubicin, cyclophosphamide) for 6 cycles versus AC for 4 cycles followed by 4 cycles of docetaxel. It did not demonstrate a difference between the 2 strategies in terms of efficacy, but TAC was associated with more febrile neutropenia and thrombocytopenia, and

AC followed by docetaxel was associated with more sensory neuropathy, nail changes, and myalgia. The incidence of neutropenic infection was similar in both groups.[40]

NSABP-B38 compared 6 cycles of TAC with 2 regimens: either 4 cycles of AC followed by 4 cycles of paclitaxel given every 2 weeks, or this regimen with gemcitabine added to the paclitaxel arm.[41] The addition of gemcitabine did not add benefit; however, 6 cycles of TAC was comparable to AC followed by docetaxel in DFS and OS, but TAC caused more neutropenic fever and diarrhea.

In an effort to identify nonanthracyclines, and therefore potentially less cardiotoxic regimens for the treatment of early-stage breast cancer, the US Oncology 9735 trial randomized 1016 women with operable breast cancer (stages I–III) to 4 cycles of TC (docetaxel plus cyclophosphamide) versus 4 cycles of standard-dose AC.[42] After a median 7-year follow-up, both DFS and OS were superior in the TC arm with less cardiotoxicity. This trial introduced TC as a viable option for treating women with early-stage breast cancer, especially those at high risk for cardiotoxicity.

In summary, it appears that an anthracycline plus cyclophosphamide followed by a taxane is the most optimal adjuvant therapy for HER2-negative breast cancer patients, especially those with ER-negative tumors with no medical contraindications, using either weekly paclitaxel or every-2-weeks paclitaxel or every-3-weeks docetaxel-dosing schedules. However, it remains unclear what the optimal combination chemotherapy regimen is for each subset of breast cancer. Currently, CMF and TC remain additional reasonable nonanthracycline-based options. **Table 1**[21,30,38,42,44–51] and **Table 2**[13,21,52–55] summarize the commonly used and accepted chemotherapy regimens in clinical practice based on the NCCN recommendations.[21]

ADJUVANT THERAPY FOR TRIPLE-NEGATIVE BREAST CANCER

Standard regimens in both HR-positive and HR-negative breast cancer are the same. Triple-negative breast cancer (TNBC) is chemosensitive, and the benefit of chemotherapy among TNBC is well documented in the adjuvant setting.[56] The role of incorporating platinum compounds in adjuvant chemotherapy in ER-negative/TNBC has not been well defined in the adjuvant setting and platinum is not currently standard of care for adjuvant chemotherapy for TNBC. A meta-analysis of platinum-based neoadjuvant chemotherapy in TNBC showed higher pathological complete response (pCR) and clinical complete response in the TNBC group compared to the nonTNBC group.[57]

Recently, the results of the CALGB 40603 (Alliance) trial were reported.[58] The study was a 2 × 2 factorial, open-label, randomized phase 2 trial that evaluated the impact of adding carboplatin and/or bevacizumab for the neoadjuvant (preoperative) treatment of TNBC. The study enrolled 443 patients with stage II to III disease who received paclitaxel 80 mg/m^2 once per week for 12 weeks, followed by AC (doxorubicin plus cyclophosphamide) once every 2 weeks for 4 cycles, and were randomly assigned to concurrent carboplatin (area under curve [AUC] 6) once every 3 weeks for 4 cycles and/or bevacizumab 10 mg/kg once every 2 weeks for 9 cycles. The effects of adding these agents on pCR and toxicities were analyzed. The study showed that patients assigned to either carboplatin or bevacizumab were less likely to complete weekly paclitaxel and AC without skipped doses, dose modification, or early discontinuation resulting from toxicity. Neutropenia grade 3 or higher, thrombocytopenia, hypertension, infection, thromboembolic events, and bleeding were more common with carboplatin, and post-

Table 1. Common Chemotherapy Regimens for Early-Stage Breast Cancer: HER2-Negative Disease

*TC chemotherapy:[42] docetaxel 75 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 with myeloid growth factor support for all cycles cycled every 21 days for 4 cycles
*Dose-dense AC followed by paclitaxel chemotherapy:[30] doxorubicin 60 mg/m^2 IV on day 1 + cyclophosphamide 600 mg/m^2 IV day 1 with myeloid growth factor support for all cycles, cycled every 14 days for 4 cycles, followed by paclitaxel 175 mg/m^2 by 3-hour IV infusion day 1, cycled every 14 days for 4 cycles
*Dose-dense AC followed by weekly paclitaxel chemotherapy:[30] doxorubicin 60 mg/m^2 IV on day 1 + cyclophosphamide 600 mg/m^2 IV day 1 with myeloid growth factor support for all cycles, cycled every 14 days for 4 cycles, followed by paclitaxel 80 mg/m^2 by 1-hour IV infusion weekly for 12 weeks
Dose-dense AC chemotherapy:[30] doxorubicin 60 mg/m^2 IV on day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 14 days for 4 cycles
AC chemotherapy:[43] doxorubicin 60 mg/m^2 IV on day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles
AC followed by docetaxel chemotherapy:[44] doxorubicin 60 mg/m^2 IV on day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles, followed by docetaxel 100 mg/m^2 IV on day 1 cycled every 21 days for 4 cycles
AC followed by weekly paclitaxel chemotherapy:[38] doxorubicin 60 mg/m^2 IV on day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles, followed by paclitaxel 80 mg/m^2 by 1-hour IV infusion weekly for 12 weeks
CAF chemotherapy:[45] cyclophosphamide 100 mg/m^2 orally days 1–14 + doxorubicin 30 mg/m^2 IV days 1 and 8 + 5-fluourouracil 500 mg/m^2 IV days 1 and 8 cycled every 28 days for 6 cycles
CEF chemotherapy:[46] cyclophosphamide 75 mg/m^2 orally days 1–14 + epirubicin 60 mg/m^2 IV days 1 and 8 + 5-fluourouracil 500 mg/m^2 IV days 1 and 8 with cotrimoxazole support cycled every 28 days for 6 cycles
CMF chemotherapy:[47] cyclophosphamide 100 mg/m^2 orally days 1–14 + methotrexate 40 mg/m^2 IV days 1 and 8 + 5-fluourouracil 600 mg/m^2 IV days 1 and 8 cycled every 28 days for 6 cycles
EC chemotherapy:[48] epirubicin 100 mg/m^2 IV day 1 + cyclophosphamide 830 mg/m^2 IV day 1 every 21 days for 8 cycles
FAC chemotherapy:[49] 5-fluourouracil 500 mg/m^2 IV days 1 and 8 or days 1 and 4 + doxorubicin 50 mg/m^2 IV day 1 (or by 72-hour continuous infusion) + cyclophosphamide 500 mg/m^2 IV day 1 cycled every 21 days for 6 cycles
FAC followed by weekly paclitaxel chemotherapy:[21] 5-fluourouracil 500 mg/m^2 IV days 1 and 8 or days 1 and 4 + doxorubicin 50 mg/m^2 IV day 1 (or by 72-hour continuous infusion) + cyclophosphamide 500 mg/m^2 IV day 1 cycled every 21 days for 6 cycles followed by paclitaxel 80 mg/m^2 by 1-hour IV infusion weekly for 12 weeks
FEC followed by weekly paclitaxel chemotherapy:[50] 5-fluourouracil 600 mg/m^2 IV day 1 + epirubicin 90 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1, cycled every 21 days for 4 cycles, followed by paclitaxel 100 mg/m^2 IV infusion weekly for 8 weeks
FEC followed by docetaxel chemotherapy:[51] 5-fluourouracil 500 mg/m^2 IV day 1 + epirubicin 100 mg/m^2 IV day 1 + cyclophosphamide 500 mg/m^2 IV day 1 cycled every 21 days for 3 cycles, followed by docetaxel 100 mg/m^2 IV day 1 cycled every 21 days for 3 cycles
TAC chemotherapy:[40] docetaxel 75 mg/m^2 IV day 1 + doxorubicin 50 mg/m^2 IV day 1 + cyclophosphamide 500 mg/m^2 IV day 1 with myeloid growth factor support for all cycles cycled every 21 days for 6 cycles

*Preferred regimens per National Comprehensive Cancer Network guidelines.[21]

operative complications were more common with bevacizumab. Addition of either carboplatin (60% vs 44%; $P = 0.0018$) or bevacizumab (59% vs 48%; $P = 0.0089$) significantly increased the pCR in breast, whereas only carboplatin (54% vs 41%; $P = 0.0029$) significantly raised the pCR in breast and axilla. The study concluded that the addition of either carboplatin or bevacizumab to neoadjuvant AC/paclitaxel increased pCR rates, but whether this will improve relapse-free survival or OS is unknown.[58]

The addition of the antiangiogenic agent bevacizumab to adjuvant chemotherapy has also been investigated. However, the results of the randomized phase 3 BEATRICE trial were disappointing, showing no benefit of adding beva-

Table 2. Common Chemotherapy Regimens for Early-Stage Breast Cancer: HER2-Positive Disease

*AC followed by T chemotherapy with trastuzumab:[13] doxorubicin 60 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles followed by paclitaxel 80 mg/m^2 by 1-hour IV weekly for 12 weeks with trastuzumab 4 mg/kg with first dose of paclitaxel followed by trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment (alternative: trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 year of trastuzumab treatment)
*Dose-dense AC followed by paclitaxel chemotherapy with trastuzumab:[52] doxorubicin 60 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 14 days for 4 cycles followed by paclitaxel 175 mg/m^2 by 3-hour IV infusion day 1 cycled every 14 days for 4 cycles with trastuzumab 4 mg/kg with first dose of paclitaxel followed by trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment (alternative: trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 year of trastuzumab treatment)
*TCH chemotherapy:[53] docetaxel 75 mg/m^2 IV day 1 + carboplatin AUC 6 IV day 1 cycled every 21 days for 6 cycles with trastuzumab 4 mg/kg IV week 1 followed by trastuzumab 2 mg/kg IV for 17 weeks followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy
AC followed by docetaxel chemotherapy with trastuzumab:[53] doxorubicin 60 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles followed by docetaxel 100 mg/m^2 IV day 1 cycled every 21 days for 4 cycles with trastuzumab 4 mg/kg IV week 1 followed by trastuzumab 2 mg/kg IV weekly for 11 weeks followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy
Paclitaxel + trastuzumab:[54] paclitaxel 80 mg/m^2 IV weekly for 12 weeks with trastuzumab 4 mg/kg IV with first dose of paclitaxel followed by trastuzumab 2 mg/kg IV weekly to complete 1 year of treatment (alternative: trastuzumab 6 mg/kg IV every 21 days may be used following the completion of paclitaxel, and given to complete 1 year of trastuzumab treatment)
*TCH chemotherapy (docetaxel, carboplatin, trastuzumab) + pertuzumab:[55] pertuzumab 840 mg IV day 1 followed by 420 mg IV + trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV + docetaxel 75 mg/m^2 IV day 1 plus carboplatin AUC 6 IV day 1 cycled every 21 days for 6 cycles followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy
*AC followed by T chemotherapy with trastuzumab + pertuzumab:[21] doxorubicin 60 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles followed by pertuzumab 840 mg IV day 1 followed by 420 mg IV + trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV + paclitaxel 80 mg/m^2 IV days 1, 8, and 15 cycled every 21 days for 4 cycles followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy
AC chemotherapy followed by docetaxel chemotherapy with trastuzumab and pertuzumab: 60 mg/m^2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 4 cycles followed by pertuzumab 840 mg IV day 1 followed by 420 mg IV + trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV + docetaxel 75–100 mg/m^2 IV day 1 cycled every 21 days for 4 cycles followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy
FEC chemotherapy followed by pertuzumab + trastuzumab + docetaxel: 500 mg/m^2 IV day 1 + epirubicin 100 mg/m2 IV day 1 + cyclophosphamide 600 mg/m^2 IV day 1 cycled every 21 days for 3 cycles followed by pertuzumab 840 mg IV day 1 followed by 420 mg IV + trastuzumab 8 mg/kg IV day 1 followed by 6 mg/kg IV + docetaxel 75–100 mg/m^2 IV day 1 cycled every 21 days for 3 cycles followed by trastuzumab 6 mg/kg IV every 21 days to complete 1 year of trastuzumab therapy

AUC = area under the curve; IV = intravenously.

*Preferred regimens per National Comprehensive Cancer Network guidelines.[21]

cizumab to adjuvant chemotherapy in TNBC.[59] The study randomized 1290 patients to receive a minimum of 4 cycles of chemotherapy either alone or with bevacizumab (equivalent of 5 mg/kg every week for 1 year). No difference in OS was noted between the groups, but the bevacizumab group had more hypertension and cardiac toxicities.[59]

ADJUVANT THERAPY FOR HER2-POSITIVE BREAST CANCER

Breast cancer has long been recognized as a heterogeneous disease. One of the most important success stories in breast cancer over the past 2 decades was the identification of HER2 as a driver of prognosis.[11] Overexpression of HER2 occurs in approximately 20% of breast cancers

and correlates with a more aggressive phenotype and worse prognosis overall. However, the development of HER2-targeted therapies with the advent of trastuzumab, a monoclonal antibody targeting the extracellular domain of the receptor, has changed the treatment paradigm and history for HER2-positive breast cancer. Trastuzumab was approved by the US Food and Drug Administration (FDA) in combination with chemotherapy for the treatment of HER2-positive disease in the adjuvant setting in 2005. To date, results are available from larger randomized trials (NSABP B31,[13] HERA,[14] N9831,[40] FinHer,[60] and BCIRG006[53]) that randomly assigned around 11,650 women with early-stage HER2-positive breast cancer to trastuzumab versus adjuvant chemotherapy without trastuzumab. All 5 trials have demonstrated that the inclusion of trastuzumab produces roughly a 50% improvement in DFS and 35% improvement in OS regardless of the chemotherapy regimen.

Doxorubicin/cyclophosphamide (AC) followed by concurrent paclitaxel/trastuzumab (TH) is recommended for a patient at substantial risk for disease recurrence and who is not at high risk for cardiac toxicities (Table 2). For patients at lower risk of recurrence who carry risk factors for cardiac toxicities, docetaxel, carboplatin, and trastuzumab (TCH) is a reasonable alternative, as assessed in BCIRG 006 (Table 2). When trastuzumab is continued as a single agent following chemotherapy, it is given every 3 weeks.

To answer the important question regarding the optimal durations of treatment with trastuzumab, the HERA trial compared 1 year versus 2 years using adjuvant trastuzumab in patients with HER2-neu positive breast cancer and showed no differences in terms of PFS.[61] Another phase 3 randomized trial (PHARE trial) compared 6 months versus 12 months of adjuvant trastuzumab for patients with HER2-positive early breast cancer.[62] After 3.5 years follow-up, 6 months of treatment with trastuzumab was noninferior to 12 months of trastuzumab; the authors concluded that despite the higher rates of cardiac events, 12 months of adjuvant trastuzumab should remain the standard of care. Therefore, the standard of care for patients with HER2-positive early breast cancer is established as 1 year of adjuvant trastuzumab after surgery.

More recently, a phase 2 trial of adjuvant paclitaxel and trastuzumab was conducted to assess the benefit of 12 weeks of standard paclitaxel and trastuzumab followed by 9 months of trastuzumab for patients with node-negative, HER2-positive breast cancer measuring 3 cm or less. The 3-year DFS was 98.7% at a median follow up of 3.6 years.[63] These results are being explored in the ATEMPT trial, a large randomized phase 2 study of trastuzumab (T-DM1) versus paclitaxel plus trastuzumab for patients with stage 1 HER2-positive breast cancer (T-DM1 vs Paclitaxel/Trastuzumab for Breast [ATEMPT Trial]; available at: https://clinicaltrials.gov/ct2/show/NCT01853748).

Ongoing trials are currently testing whether the combination of 2 anti-HER2 targeted therapies with chemotherapy will prove beneficial in early-stage disease. The early results from the phase 3 ALTTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization) trial[64] showed a nonsignificant reduction in DFS hazard rate for adding lapatinib, a HER-family tyrosine kinase inhibitor, to trastuzumab and chemotherapy; this finding was inconsistent with the results of the neoadjuvant (preoperative) NeoALTTO trial reported in 2012 in which a statistically significant improvement in the rate of pCR (ie, absence of residual disease) was noted with this combination.[65] The benefit seen with combined anti-HER2 targeted therapy in the neoadjuvant setting prompted the evaluation of

additional novel agents in this setting. The NeoSphere trial, a multicenter phase 2 trial, randomly assigned 417 patients to 4 cycles of docetaxel combined with either trastuzumab alone, pertuzumab alone, or both agents versus a nonchemotherapy arm (pertuzumab and trastuzumab). The combination of pertuzumab plus trastuzumab and docetaxel showed an increased rate of pCR from 29% to 45.8%.[66] All patients in the NeoSphere trial also received adjuvant treatment with 3 cycles of FEC chemotherapy concomitant with trastuzumab, which was then continued to complete 1 year of trastuzumab therapy. Based on these results, pertuzumab was approved by the FDA in the neoadjuvant setting for HER2-positive stages II-III (T2 or greater, or N1 or greater) breast cancers.[67] Based on the encouraging results from neoadjuvant trials, the use of pertuzumab in the adjuvant setting has also been considered an accepted option by the NCCN,[67] but is not considered a required standard of care.

ENDOCRINE (HORMONAL) THERAPY

By the first half of the twentieth century, endocrine (also known as hormonal) therapy, which involves reducing the amount of estrogen in the body or blocking the effect of estrogen, became recognized as a viable treatment for breast cancer. This was based on strong evidence that estrogen plays a role in the development and progression of breast cancer.[68,69] This process depends on the presence of the hormone receptors ER and/or PR.[69,70] Approximately 70% to 80% of breast cancers are ER-positive, and nearly 65% of ER-positive breast cancers are also PR-positive. Nearly 10% of cases are ER-positive and PR-negative. From this point, all breast tumors generally can be divided into HR-positive and HR-negative cases and HR, specifically ER, can be considered the first target of biologic therapy in breast cancer. Hormonal therapy is now considered the main systemic treatment for HR-positive breast cancers; it is not effective against HR-negative breast cancer.[71]

There are currently 4 main modalities of hormonal therapies:[16] (1) ovarian suppression or ablation using irreversible oophorectomy, irradiation, or more commonly luteinizing hormone-releasing hormone (LHRH) analogs, which effects a temporary loss of ovarian function; (2) selective estrogen receptor modulators (SERM) (eg, tamoxifen, toremifene); (3) aromatase inhibitors (anastrozole, examestane, letrozole); and (4) estrogen receptor downregulators (fulvestrant). The first 3 modalities are used for the treatment of early stages of breast cancer, while all 4 modalities can be used for the treatment of advanced metastatic breast cancer.

TAMOXIFEN

Tamoxifen is the oldest and most-prescribed SERM; it binds to and inhibits ER signaling in the breast.[72] As a receptor antagonist, it is effective in both premenopausal and postmenopausal women. It has ER-stimulating effects in other tissues, including bone (resulting in preservation of bone density) and endometrium (leading to a two- to fourfold increased risk of endometrial cancer).[7,8] Tamoxifen has been approved for breast cancer treatment since the early 1980s. It has been shown in multiple studies to decrease breast cancer–associated mortality and recurrence in the adjuvant treatment of breast cancer. Five years of tamoxifen therapy has been the standard, resulting in an approximately 50% reduction in recurrence and 25% reduction in mortality.[7,8] Common side effects associated with tamoxifen use include hot flashes (up to 80%), vaginal bleeding (2%–25%) or discharge (10%–55%),

urinary frequency or urgency (10%), mood changes (15%–20%) or depression (2%–12%), and venous thromboembolism (1%–2%).

For premenopausal women diagnosed with HR-positive breast cancer, tamoxifen remains the hormonal therapy treatment standard.[18] To determine the optimal duration of tamoxifen, the ATLAS (Adjuvant Tamoxifen: Longer vs. Shorter) trial enrolled 12,894 women (90% postmenopausal) and compared tamoxifen therapy durations of 5 versus 10 years.[73] Continued tamoxifen use reduced the rate of recurrence and improved OS (the absolute mortality reduction was 2.8% at 15 years following diagnosis). Prolonged tamoxifen use is recommended based on this and other studies. However, for patients with early-stage disease who are at low risk of disease recurrence, the potential toxicities (eg, increased risks of venous thromboembolism and endometrial cancer) should be weighed against the small benefit.

Studies have tested whether ovarian suppression, achieved using LHRH analogs such as goserelin and leuprolide (temporary) or by surgically removing the ovaries (permanent suppression), is also necessary in premenopausal women diagnosed with HR-positive breast cancer, where estrogens are mostly produced in the ovaries. Most recently the outcomes from the Suppression of Ovarian Function study randomizing 3066 premenopausal women with breast cancer to receive 5 years of tamoxifen, tamoxifen plus ovarian suppression, or exemestane plus ovarian suppression showed that adding ovarian suppression to tamoxifen did not provide a significant benefit in the overall study population, after a median follow up of 67 months.[74] Despite the lack of benefit in the overall population, exploratory analyses suggested that patients at higher risk for relapse might derive benefit from the addition of ovarian suppression to tamoxifen, including those treated with chemotherapy and very young women (under the age of 35 years at the time of diagnosis of breast cancer). In those who were considered to have sufficient risk for recurrence to warrant chemotherapy and who remained premenopausal, the breast cancer–free interval (BCFI; freedom from invasive recurrence or contralateral breast cancer) at 5 years was 82.5% in the tamoxifen–ovarian suppression group and 78% in the tamoxifen-alone group (hazard ration [HR] 0.78, 95% confidence interval [CI] 0.6 to 1.02). In the secondary analysis comparing exemestane plus ovarian suppression to tamoxifen alone in patients who had received chemotherapy, the 5-year BCFI was further improved to 85.7% (HR 0.65, 95% CI 0.49 to 0.87). Similarly, most recurrences of breast cancer at distant sites occurred in patients who had received chemotherapy previously. In the chemotherapy cohort, the 5-year OS was significantly better in patients assigned to tamoxifen plus ovarian suppression than in those assigned to tamoxifen alone (95.5% versus 90.9%; HR 0.64, 95% CI 0.42 to 0.96), although these survival data are premature. The most striking differences in outcomes were seen in the 350 women younger than 35 years of age. Of the women in this subgroup who were included in the primary analysis (n = 223), the 5-year BCFI was 67.7% for women assigned to tamoxifen, 78.9% for those assigned to tamoxifen plus ovarian suppression, and 83.4% for those assigned to exemestane plus ovarian suppression. Notably, 94% of this subgroup had received prior chemotherapy. In conclusion, this study demonstrated that adding ovarian suppression to tamoxifen did not improve DSF in the overall population, but that in certain high-risk cohorts of women, the addition of ovarian suppression might be associated with decreased risk of recurrence.

Because of the variability in the study designs addressing the issue of ovarian suppression, results are inconclusive and tamoxifen alone continues to be the standard endocrine therapy for premenopausal women.

Controversy exists regarding how to determine who benefits the most from tamoxifen. Tamoxifen is a prodrug that is metabolized primarily by the cytochrome P450 (CYP2D6) system to its active metabolite, endoxifen.[75] More than 80 different alleles of the *CYP2D6* gene have been identified with varying activity levels. Consequently, patients can be categorized by their level of CYP2D6 activity into high/extensive or low/poor metabolizers. Around 10% of the population are poor metabolizers of tamoxifen. It is not known whether variations in CYP2D6 genotype account for differences in outcomes among patients treated with tamoxifen.[71] Several laboratories now offer CYP2D6 testing for patients treated with tamoxifen, but recommending this testing is still controversial, especially in women who have no alternative treatment options. However, considerable attention has been paid to the use of concomitant medications, especially potent inhibitors of CYP2D6 activity such as the selective serotonin-reuptake inhibitors fluoxetine and paroxetine. These drugs can decrease conversion of tamoxifen to endoxifen, but their association with increased cancer recurrence has been controversial.[76,77] The concomitant use of potent CYP2D6 inhibitors like bupropion, fluoxetine, paroxetine and quinidine should be avoided, if possible, in patients taking tamoxifen.

AROMATASE INHIBITORS

Although tamoxifen is efficacious in postmenopausal women, the use of aromatase inhibitors (AIs) should be considered for the optimal treatment of HR-positive breast cancer in these women, either as initial therapy for 5 years or following 2 to 5 years of tamoxifen.[71] A number of studies have compared AIs with tamoxifen.[71,78] Aromatase is the enzyme (found in body fat, adrenal glands, and breast tissue as well as tumor cells) responsible for converting other steroid hormones into estrogen.[79] Aromatase is the sole source of estrogen in postmenopausal women. Having no effect on ovarian estrogen production, AIs are therefore only effective in postmenopausal women.

Based on the overall evidence, it appears that AIs are slightly superior in decreasing breast cancer recurrence (by around 4%) in postmenopausal women with early-stage HR-positive breast cancer and may have fewer serious side effects but show no improvement in OS compared to tamoxifen.[78] Common side effects of AIs include hot flashes (10%–35%), arthralgia/arthritis (20%), headache (10%–15%), vaginal dryness (2%), and mood changes (20%).[80,81]

AIs are approved for the adjuvant treatment of postmenopausal women with HR-positive breast cancer.[71] With maturation of clinical data and accumulating clinical experience, it is clear that AIs cause untoward effects that might lead to a high rate of treatment discontinuation. These effects include vaginal dryness, dyspareunia and musculoskeletal/arthralgia syndrome, characterized by pain, stiffness, or achiness that is symmetric.[71] The prevalence of these symptoms is unclear, although it seems to be widespread and should be addressed. There are no known interventions of proven value for AI-associated musculoskeletal symptoms. Supportive measures are recommended (eg, nonhormonal vaginal lubricants for vaginal dryness; nonsteroidal anti-inflammatory agents and exercise for arthralgias). Most patients have mild to moderate musculoskeletal symptoms that

are usually relieved within 8 to 10 weeks by discontinuation of AI therapy. Other acceptable options include switching to an AI after taking tamoxifen for 2 or 3 years (for a total of 5 years of hormonal therapy) as this approach has been shown to offer more benefits than 5 years of tamoxifen.[81–83]

To date, the optimal duration and sequence for the use of AIs have not been clearly defined, but their benefits in terms of breast cancer recurrence and survival clearly support their use in all postmenopausal women. The Canadian MA17 trial randomly assigned patients to an additional 5 years of AI therapy with letrozole after completion of 5 years of tamoxifen therapy.[84] The additional 3 to 5 years of AI therapy resulted in improved DSF in all patients randomized and improved OS in the higher-risk lymph node-positive subset of patients. This study was the first to suggest that prolonged hormonal therapy may be more effective than 5 years of therapy. There are currently no data supporting an extended duration of AI treatment beyond 5 years, but ongoing trials are expected to provide insights on that question (NSABP B42 and IBCSG 35-07).

In summary, in HR-positive early-stage breast cancer, hormonal therapy plays a major role in adjuvant treatment, either alone or in combination with chemotherapy. Hormonal treatments function to decrease estrogen's ability to stimulate existing micrometastases or dormant cancer cells. Adjuvant hormonal therapy can reduce the relative risk of distant ipsilateral and contralateral breast cancer recurrence by up to 50% in tumors with high ER expression. Hormonal therapy is used typically after other local and systemic breast cancer treatments are completed. FDA-approved endocrine therapies for adjuvant treatment of breast cancer include tamoxifen for 5 to 10 years in premenopausal women and the AIs (only in postmenopausal women; anastrozole, letrozole, exemestane) given upfront for 5 years or sequentially for an additional 3 years after 2 to 3 years of tamoxifen.[71]

SUMMARY

The improved understanding that breast cancer is a systemic heterogeneous disease with identifiable subsets has led to significant improvement in scientific research and its clinical application. The ability to selectively target a driving molecule of importance is best illustrated by the isolated inhibition of ER and HER2, which led to improving the cure rate in the adjuvant setting and providing long-term disease control in the metastatic setting. Today, we are working to further refine treatment recommendations and tailor therapy.

Identifying women who benefit most from hormonal and chemotherapy through evaluation of molecular and genomic features of the tumor is now becoming possible. A practical example is the 21-gene recurrence assay (Oncotype DX) currently available in clinical practice, which classifies patients with node-negative, HR-positive tumors into low-, intermediate-, and high-risk categories for the future development of distant metastatic disease.[20] The Oncotype DX allows for the prediction of benefit from the addition of chemotherapy to hormonal therapy compared with hormonal therapy alone for patients with ER-positive node-negative tumors. The routine clinical use of Oncotype DX has led to a reduction in the use of chemotherapy, without apparent worsening of clinical outcomes. However, prediction of tumor sensitivity to the different types of systemic therapies has not reached a high level of confidence, and further efforts are urgently needed. Currently, high-throughput genomic techniques are promising but not widely available, so clinical decisions continue to be based on immu-

nohistochemistry, fluorescence in situ hybridization (FISH), and other broadly available assays. Progress in molecular diagnostics and therapeutics is evolving quickly and is likely to result in additional improvements in targeted therapies and outcome.

The theme of the past 2 decades will continue to dominate: we will continue to move away from maximal tolerated treatment and a one-size-fits-all approach to minimum effective treatment, less invasive procedures, and more tailored therapy. A refined classification of breast cancer based on molecular features may allow a better prediction of prognosis and response to several types of treatment and would allow a more optimal design of future clinical trials.

BOARD REVIEW QUESTIONS

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