NCCN Guidelines® Insights

Featured Updates to the NCCN Guidelines

Richard L. Theriault, DO; Robert W. Carlson, MD; Craig Allred, MD; Benjamin O. Anderson, MD; Harold J. Burstein, MD, PhD; Stephen B. Edge, MD; William B. Farrar, MD; Andres Forero, MD; Sharon Hermes Giordano, MD, MPH; Lori J. Goldstein, MD; William J. Gradishar, MD; Mary Lou Smith, JD, MBA; Brit-Marie E. Ljung, MD; David A. Mankoff, MD, PhD; P. Kelly Marcom, MD; Ingrid A. Mayer, MD; Beryl McCormick, MD; Lori J. Pierce, MD; Elizabeth C. Reed, MD; Lee S. Schwartzberg, MD; Mary Lou Smith, JD, MBA; Hatem Soliman, MD; George Somlo, MD; John H. Ward, MD; Antonio C. Wolff, MD; Richard Zellars, MD; Dorothy A. Shead, MS; and Rashmi Kumar, PhD

Abstract

These NCCN Guidelines Insights highlight the important updates specific to the management of HER2-positive metastatic breast cancer in the 2013 version of the NCCN Clinical Practice Guidelines in Oncology for Breast Cancer. These include new first-line and subsequent therapy options for patients with HER2-positive metastatic breast cancer. (JNCCN 2013;11:753–761)

Disclosures for the NCCN Breast Cancer Panel

Individual disclosures of potential conflicts of interest for the NCCN Breast Cancer Panel members can be found on page 754.

© National Comprehensive Cancer Network, Inc. 2013, All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN.
NCCN: Continuing Education

Accreditation Statement
This activity has been designated to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer. There is no fee for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians. NCCN designates this journal-based CE activity for a maximum of 1.0 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center’s Commission on Accreditation.

This activity is accredited for 1.0 contact hour. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

The National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. NCCN designates this continuing education activity for 1.0 contact hour(s) (0.1 CEUs) of continuing education credit in states that recognize ACPE accredited providers. This is a knowledge-based activity. UAN: 0836-0000-13-009-H01-P

Disclosure of Affiliations and Significant Relationships: NCCN Breast Cancer Panel

The following authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products or devices discussed in this report or their competitors: Dr. Theriault, Dr. Allred, Dr. Burstein, Dr. Edge, Dr. Farrar, Dr. Giordano, Dr. Hudis, Dr. Mayer, Dr. McCormick, Dr. Ward, and Dr. Zellars.

The following authors have disclosed that they have financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products or devices discussed in this report or their competitors: Dr. Carlsson: Investigator for Genentech, Inc., and a PI for sanofi-aventis U.S.

Dr. Anderson: PI for General Electric and sanofi-aventis U.S.

Dr. Forero: Research support from Abbott Laboratories; Biogen Idec; Celgene Corporation; Daiichi-Sankyo Co.; Eisai Inc.; Eli Lilly and Company; Genentech, Inc.; BioCryst Pharmaceuticals, Inc.; Immunomedics, Inc.; and Seattle Genetics, Inc.

Dr. Goldstein: PI for Novartis Pharmaceuticals Corporation and Dompé. Advisory board member for Celgene Corporation; Eisai Inc.; and Genomic Health, Inc. Data monitoring committee for Genentech, Inc. and Novartis Pharmaceuticals Corporation.

Dr. Gradishar: Consultant for Bayer HealthCare. Advisory board member for Eisai Inc.; Genentech, Inc.; Genomic Health, Inc.; Myriad Genetic Laboratories, Inc.; and Onyx Pharmaceuticals, Inc.

Dr. Hayes: PI for Novartis Pharmaceuticals Corporation; Janssen R&D, LLC; Pfizer Inc.; and Veridex, LLC.

Dr. Isakoff: Research funding from Abbott Laboratories. Advisory board member for Myriad Genetic Laboratories, Inc.

Dr. Ljung: PI for National Cancer Institute.

Dr. Mankoff: Research support from Merck & Co., Inc. and Pfizer Inc. Speakers’ bureau member for Genzyme Corporation.

Dr. Marcum: Research support from Genentech, Inc. and Novartis Pharmaceuticals Corporation. PI for DoD/CDMRP. Speakers’ bureau member for Genentech, Inc.

Dr. Pierce: Advisory board member for Genomic Health, Inc.

Dr. Reed: PI for Novartis Pharmaceuticals Corporation. Advisory board member for UnitedHealthcare.

Dr. Schwartzberg: PI for Bristol-Myers Squibb Company. Advisory board member for Amgen Inc. Speakers’ bureau member for Eisai Inc.; Genentech, Inc.; and GlaxoSmithKline.

Ms. Smith: Data safety monitoring board for Genentech, Inc. Advisory board member for AstraZeneca Pharmaceuticals LP. Board member for Gateway for Cancer Research Foundation and National Accreditation Program for Breast Centers.

Dr. Soliman: PI for Agenda BV. Speakers’ bureau member for Agenda BV, Celgene Corporation, and NanoString Technologies, Inc. Advisory board member for Veridex, LLC.

Dr. Somlo: PI for AstraZeneca Pharmaceuticals LP, Celgene Corporation, and National Cancer Institute. Advisor for Veridex, LLC. Advisory board member, consultant, and member of the speakers’ bureau for Genentech, Inc.; Abraxane; and Roche Laboratories, Inc. Advisory board member for Celgene Corporation; Millennium Pharmaceuticals, Inc.; and Novartis Pharmaceuticals Corporation.

Dr. Wolff: PI for Bristol-Myers Squibb Company. The NCCN Guidelines Staff have no conflicts to disclose.

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 70% minimum passing score and complete the evaluation at http://education.nccn.org/node/24674; and 4) viewprint certificate.

Release date: July 12, 2013; Expiration date: July 12, 2014

Learning Objectives:
Upon completion of this activity, participants will be able to:
• Integrate into professional practice the updates to NCCN Guidelines for Breast Cancer
• Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Breast Cancer

EDITOR: Kerrin M. Green, MA, Assistant Managing Editor, JNCCN—Journal of the National Comprehensive Cancer Network, has disclosed that she has no relevant financial relationships.

CE AUTHORS: Deborah J. Moonan, RN, BSN, Manager, CE Supporter Outreach, has disclosed the following relationships with commercial interests: AstraZeneca: Stockholder/Former Employee. Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, has disclosed that she has no relevant financial relationships. James Prazak, RPh, Assistant Director, Continuing Education and Grants, has disclosed the following relationships with commercial interests: Bristol-Myers Squibb Company; Pension; Pfizer, Inc. Stockholder; United Healthcare Group; Stockholder; Johnson & Johnson: Stockholder. Dorothy A. Shead, MS, Director, Patient and Clinical Information Operations, has disclosed no relevant financial relationships. Rashmi Kumar, PhD, Oncology Scientist/Senior Medical Writer, has disclosed no relevant financial relationships.

© JNCCN—Journal of the National Comprehensive Cancer Network | Volume 11 Number 7 | July 2013

PRINCIPLES OF HER2 TESTING

1. Initial testing by IHC:
   - Laboratory meets quality assurance standards for IHC HER2 testing methodology
   - If both IHC and ISH are performed, and one or the other or both are positive, then consider HER2 positive.
   - Borderline IHC samples (e.g., IHC 2+) are subjected to reflex testing by a validated complementary (e.g., in situ hybridization [ISH]) method that has shown at least 95% concordance between complementary testing achieved by the validating laboratory.
   - Borderline ISH samples (e.g., an average HER2 gene/chromosome 17 ratio of 1.8 - <2 or an average HER2 gene copy number of >4 - <6) should be sent to a qualified reference laboratory.

2. Initial testing by ISH:
   - Laboratory meets quality assurance standards for ISH HER2 testing methodology
   - Borderline result transient testing by ISH, or reflex testing by a validated IHC method.
   - Borderline result (See Discussion section)

1 NCCN endorses the ASCO CAP recommendations for quality control performance of HER2 testing and interpretation of IHC and ISH results.
3 HER2 testing should be done only in laboratories accredited to perform such testing. Ongoing proficiency testing and full reporting of HER2 assay methods and results are required. A laboratory may perform only those tests that have been demonstrated to conform to these quality assurance standards. All other HER2 testing should be sent to a qualified reference laboratory.
4 Either an immunohistochemistry (IHC) assay or an in situ hybridization (ISH) assay can be used to make an initial assessment of HER2 tumor status. All HER2 assays, whether FDA-approved or not, must be validated. Validation of a HER2 test is defined as at least 95% concordance when the testing method performed in a laboratory is compared with one of the following: a validated HER2 testing method performed in the same laboratory; a validated HER2 testing method performed in another laboratory; or validated reference lab results. Borderline samples should not be included in the validation study. These algorithms are based on the assumption that all validated HER2 tests have been shown to be at least 95% concordant with the complementary form of the HER2 test, either by direct testing or association with the levels of concordance between complementary testing achieved by the validating laboratory.
5 If both IHC and ISH are performed, and one or the other or both are positive, then consider HER2 positive.
6 Borderline IHC samples (e.g., IHC 2+) are subjected to reflex testing by a validated complementary (e.g., in situ hybridization [ISH]) method that has shown at least 95% concordance between IHC 0, 1+ results and ISH non-amplified results, and IHC 3+ results and ISH amplified results.
7 Borderline ISH samples (e.g., an average HER2 gene/chromosome 17 ratio of 1.8 - <2 or an average HER2 gene copy number of >4 - <6) should undergo: counting of additional cells, retesting by ISH, or reflex testing by a validated IHC method.

Version 2.2013 © National Comprehensive Cancer Network, Inc. 2013. All rights reserved. The NCCN Guidelines® and this illustration may not be reproduced in any form without the express written permission of NCCN®.

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Breast cancer is the most common malignancy in women in the United States and is second only to lung cancer as a cause of cancer death. The American Cancer Society estimates that 234,580 Americans will be diagnosed with breast cancer and 40,030 will die of the disease in the United States in 2013.¹ The therapeutic options for patients with noninvasive or invasive breast cancer are complex and varied. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer include up-to-date guidelines for the clinical management of patients with carcinoma in situ, invasive breast cancer, Paget disease, phyllodes tumor, inflammatory breast cancer, and breast cancer during in pregnancy (to view the complete and most recent version of these guidelines, visit NCCN.org). These NCCN Guidelines Insights highlight the important updates/changes specific to the management of HER2-positive metastatic breast cancer in the 2013 version of...
the NCCN Guidelines. These include clinical data and NCCN recommendations regarding the new therapeutic options, pertuzumab and ado-trastuzumab emtansine (T-DM1), available for patients with HER2-positive metastatic breast cancer.

**HER2-Targeted Therapy for Stage IV or Recurrent Metastatic Disease**

HER2 is a proto-oncogene located on chromosome 17 and is amplified in 15% to 20% of breast carcinomas. Before the approval of trastuzumab, amplification of HER2 was considered a poor prognostic factor in patients with metastatic breast cancer. With the introduction of trastuzumab, the outcomes of patients with HER2-positive metastatic breast cancer dramatically improved. However, in most of these patients, the disease ultimately develops resistance to trastuzumab; therefore, effective targeted therapies are needed. In an attempt to further improve the outcomes of these patients, newer drugs targeting the HER2 pathway, including lapatinib, pertuzumab, and ado-trastuzumab (T-DM1), have been developed and added to the current standard of care.

**HER2 Testing**

Adequate standardization and validation of HER2 assays used in clinical practice is a concern, and data suggest that false-positive determinations are common. The NCCN Breast Cancer Panel endorses the ASCO/College of American Pathologists recommendations for quality control performance of HER2 testing and interpretation of results. The panel recommends that HER2 testing be performed only in laboratories accredited to perform such testing.

Either the immunohistochemistry (IHC) with the anti-HER2 antibodies or in situ hybridization (ISH) assay can be used to make an initial assessment of HER2 status. The NCCN Breast Cancer
Panel recommends selecting patients for HER2-targeted therapy if their tumors are positive for HER2 by either ISH or IHC. The NCCN Guidelines consider IHC 3+ and HER2 gene/chromosome 17 ratio of 2 or greater as HER2-positive. According to the guidelines, borderline IHC samples (eg, IHC 2+) should be subjected to reflex testing by a validated complementary method, such as ISH, that has shown at least 95% concordance between IHC 0, 1+, results and ISH nonamplified results, and immunohistochemistry 3+ results and ISH amplified results. Also, it is recommended that borderline ISH results (average HER2/chromosome 17 ratio of 1.8 to <2 or average HER2 gene copy number >4 to <6) should undergo counting of additional cells, retesting by ISH, or reflex testing by a validated immunohistochemistry method (see BINV-A, page 755).

**Pertuzumab**

Pertuzumab is a recombinant humanized monoclonal antibody that inhibits the ligand-dependent dimerization of HER2 and its downstream signaling. Pertuzumab and trastuzumab bind to different epitopes of the HER2 receptor and have complementary mechanisms of action. Therefore, the rationale for administering the drugs together is to achieve a more powerful blockade of the HER2 pathway. This was demonstrated to be true in tumor models and in humans, wherein combining pertuzumab with trastuzumab provided a greater overall antitumor effect than either alone.8,9

In a randomized, double-blind, phase III study (CLEOPATRA), 808 women with HER2-positive metastatic breast cancer were randomized to receive trastuzumab and docetaxel with or without pertuzumab as their first-line treatment.10 The results demonstrated a 6.1-month improvement in median progression-free survival with the addition of pertuzumab (12.4 vs 18.5 months; hazard ratio [HR] for progression or death, 0.62; 95% CI, 0.51–0.75; P<.001). In addition, a strong trend was seen toward...
an overall survival benefit with pertuzumab, with a 34% reduction in the risk of death (HR, 0.66; 95% CI, 0.52–0.84; P = .0008). The median overall survival was 37.6 months in the nonpertuzumab group and had not yet been reached at the time of analysis in the group treated with pertuzumab. Notably, no significant difference was seen in health-related quality of life or toxicities between the treatment arms, including no increase in either symptomatic or asymptomatic cardiac dysfunction.

Phase II trials have also assessed the activity and tolerability for pertuzumab, pertuzumab with trastuzumab, and other regimens combining pertuzumab and trastuzumab together with other active cytotoxics, such as paclitaxel and vinorelbine (ClinicalTrials.gov identifier: NCT01276041). Phase III trials of pertuzumab plus chemotherapy without trastuzumab have not been reported.

Pertuzumab has antitumor activity in patients beyond the first-line setting. The results of a multicenter, open-label, single-arm, phase II study show that the combination of pertuzumab and trastuzumab is active and well tolerated in patients with HER2-positive metastatic breast cancer that has progressed on prior trastuzumab therapy. The trial reported an objective response rate of 24.2% and a clinical benefit rate of 50%. To determine whether the clinical benefit seen in the study was from pertuzumab alone or was a result of the combined effect of pertuzumab and trastuzumab, a cohort of 29 patients whose disease progressed during prior trastuzumab-based therapy received pertuzumab monotherapy until progressive disease or unacceptable toxicity. Of these, 17 patients with disease progression continued to receive pertuzumab with the addition of trastuzumab. In the 29 patients who received pertuzumab monotherapy, the objective response and clinical benefit rates reported were 3.4% and 10.3%, respectively, whereas in the 17 patients who received dual blockade after progression on pertuzumab, the objective response rate and clinical benefit rate were 17.6% and 41.2%, respectively.

**DOsing schedules for chemotherapy regimens for HER-2 positive recurrent or metastatic breast cancer**

**Preferred first-line agents for HER2-positive disease:**
- Pertuzumab + trastuzumab + docetaxel
- 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/m² IV day 1
  - Cycled every 21 days.
- Pertuzumab + trastuzumab + weekly paclitaxel
- Pertuzumab 840 mg IV day 1 followed by 420 mg IV every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - 6 mg/kg IV day 1 followed by 3 mg/kg IV every 21 days
- Paclitaxel 80 mg/m² IV day 1 weekly.

**Other first-line agents for HER2-positive disease:**
- TCH chemotherapy
  - Carboplatin AUC 6 IV day 1
  - Paclitaxel 175 mg/m² IV day 1
  - Cycled every 21 days.
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    - 6 mg/kg IV day 1 followed by 6 mg/kg IV every 21 days
- Weekly TCH chemotherapy
  - Paclitaxel 80 mg/m² IV days 1, 8, & 15
  - Carboplatin AUC 2 IV days 1, 8, & 15
  - Cycled every 28 days.
  - Trastuzumab
    - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
    - 8 kg/m² IV day 1 followed by 6 kg/m² IV every 21 days

**Trastuzumab + paclitaxel**
- Paclitaxel
  - 175 mg/m² IV day 1 cycled every 21 days
  - or
  - 80-100 mg/m² IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - or
  - 8 kg/kg IV day 1 followed by 6 kg/kg IV every 21 days

**Trastuzumab + docetaxel**
- Docetaxel
  - 80-100 mg/m² IV day 1 cycled every 21 days
  - or
  - 35 mg/m² IV days 1, 8, and 15 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - or
  - 8 kg/kg IV day 1 followed by 6 kg/kg IV every 21 days

**Trastuzumab + vinorelbine**
- Vinorelbine 25 mg/m² IV day 1 weekly
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - or
  - 8 kg/kg IV day 1 followed by 6 kg/kg IV every 21 days

**Trastuzumab + capecitabine**
- Capecitabine 1000-1250 mg/m² PO twice daily days 1-14
- Cycled every 21 days
- Trastuzumab
  - 4 mg/kg IV day 1 followed by 2 mg/kg IV weekly
  - or
  - 8 kg/kg IV day 1 followed by 6 kg/kg IV every 21 days
Further research is expected to determine the ideal sequencing strategy for anti-HER2 therapy. **NCCN Recommendations:** Based on the available data, the NCCN Breast Cancer Panel recommends pertuzumab plus trastuzumab in combination with a taxane as a preferred option for first-line treatment of patients with HER2-positive metastatic breast cancer (see BINV-21, page 756). Pertuzumab plus trastuzumab in combination with docetaxel is a category 1 recommendation, and in combination with paclitaxel is a category 2A recommendation (see BINV-O 1 of 7, page 757, and BINV-O 4 of 7, page 758, for dosing schedule).

For patients with disease progression after treatment with trastuzumab-based therapy without pertuzumab, the NCCN Breast Cancer Panel recommends considering a line of therapy containing both trastuzumab plus pertuzumab with or without a cytotoxic agent (eg, vinorelbine or taxane; see BINV-21, page 756).

**T-DM1**
T-DM1 is a first-in-class antibody–drug conjugate. Through a stable linker, the HER-2 targeting antitumor portion of trastuzumab is conjugated with the microtubule-inhibitory agent DM1 (derivative of maytansine). Therefore, T-DM1 delivers its antitumor activity to HER2-overexpressing cells through combining the specificity of trastuzumab with cytotoxicity of maytansine, thus increasing the therapeutic index.\(^1\)

A recent randomized, multicenter, open-label, phase III study (EMILIA) showed overall and progression-free survival benefits for T-DM1 compared with the combination of lapatinib and capecitabine in patients with HER2-positive or metastatic breast cancer previously treated with a taxane-trastuzumab regimen.\(^2\) The median progression-free survival (assessed by independent review) with T-DM1 was 9.6 months versus 6.4 months with lapatinib plus capecitabine; the HR for progression or death from any cause was 0.65 (95% CI, 0.55–0.77; \(P < .001\)).
stratified HR for death from any cause with T-DM1 versus lapatinib plus capecitabine was 0.62 (95% CI, 0.48–0.81; \( P=.0005 \)). Rates of grade 3 or 4 adverse events were higher with lapatinib plus capecitabine than with T-DM1 (57% vs 41%). The incidences of thrombocytopenia and increased serum aminotransferase levels were higher with T-DM1 (frequency >25%), whereas the incidences of diarrhea, nausea, vomiting, and palmar-plantar erythrodysesthesia were higher with lapatinib plus capecitabine.\(^{19}\)

**NCCN Recommendations:** Based on the available data, the NCCN Breast Cancer Panel recommends T-DM1 as a preferred option for treatment of patients with HER2-positive metastatic breast cancer who were previously treated with a trastuzumab-based regimen (see BINV-21, page 756, and BINV-O5 of 7, page 759, for dosing schedule).

**Conclusions**

The NCCN Guidelines for Breast Cancer are in continuous evolution. They are updated annually or sometimes more often, if new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines, with few exceptions, are based on the evidence from clinical trials. Expert medical clinical judgment is required to apply these guidelines in the context of an individual patient to provide optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the NCCN Breast Cancer Panel strongly encourages patient/physician participation in prospective clinical trials. The full version of the 2013 NCCN Guidelines for Breast Cancer is available online (NCCN.org).

**References**


Posttest Questions

1. True or False: The NCCN Guidelines consider IHC score of 3+ and HER2 gene/chromosome 17 ratio ≥2 as HER2-positive.

2. For a woman who has been newly diagnosed with HER2-positive, ER/PR-negative metastatic breast cancer, which of the following treatment options is listed as category 1 in the current NCCN Guidelines?
   a. Pertuzumab plus trastuzumab in combination with paclitaxel
   b. Pertuzumab plus trastuzumab in combination with docetaxel
   c. Trastuzumab with or without chemotherapy
   d. a and b
   e. All of the above

3. A 55-year-old woman with HER2-positive breast cancer treated with trastuzumab and paclitaxel has clear progression of the disease with documented metastases to the lungs, liver, and bones. According to the NCCN Guidelines, which of the following is a preferred treatment option for this individual?
   a. Ado-trastuzumab emtansine (T-DM1)
   b. Trastuzumab + laptinib
   c. Trastuzumab + pertuzumab
   d. a and b
   e. All of the above

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 70% minimum passing score and complete the evaluation at http://education.nccn.org/node/24674; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on “New Member? Sign up here” link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.