How an Expert Approaches it

Prostate Cancer: When to Order an MRI
Annerleim Walton-Diaz, MD, Soroush Rais-Bahrami, MD

Genomics in Practice

EGFR-Mutated Lung Cancer
Emily Wynja, MSIV, Jenna Hove, BSN, Steven F. Powell, MD

Review Article

Immunotherapy in Colorectal Cancer
Cara Wilt, CRNP, Dung T. Le, MD

CAREY ANDERS ON

Dual HER2 Targeting in the Adjuvant Setting

‘We must consider the financial toxicities’
Contemporary OB/GYN
Timely, authoritative, expert advice.

www.ContemporaryOBGYN.net

From the publishers of ONCOLOGY
Dual HER2-Targeting in the Adjuvant Setting
Anureet C. Copeland, MD, and Carey K. Anders, MD
PERSPECTIVE: Nancy E. Mills, MD, FACP
Oncologists from the University of North Carolina Chapel Hill review clinical relevance and potential toxicities related to the latest developments in dual HER2-targeted therapy.

Managing Psychosocial Distress
Elizabeth Ercolano, DNSc, RN, Emma Hoffman, BS, MSN, Hui Tan, MSN, Nicholas Pasacreta, BA, Mark Lazenby, PhD, APRN, and Ruth McCorkle, PhD, RN
PERSPECTIVE: Daniel McFarland, DO
Yale researchers and faculty discuss psychosocial distress and identify optimal strategies for the oncology setting.

Incorporating Immunotherapy Into the Management of Colorectal Cancer
Cara Wilt, CRNP, and Dung T. Le, MD
PERSPECTIVE: Leonard B. Saltz, MD
Amidst new FDA approvals, Johns Hopkins authors review how to incorporate immunotherapy into colorectal cancer care.
Genomics in Practice
499 EGFR-Mutated Lung Cancer Progressing on Erlotinib: Evaluating for T790M Mutation With Limited Tissue
Emily Wynja, MSIV, Jenna Hove, BSN, and Steven F. Powell, MD
Mutation may play an important role in treatment.

How an Expert Approaches It
501 When to Order an MRI in the Initial Evaluation and Management of Prostate Cancer
Annerleim Walton-Diaz, MD, and Soroush Rais-Bahrami, MD
PERSPECTIVE: L. Michael Glodé, MD, FACP
Clinical tools expanding for detection, risk stratification.

Ask the PI
510 Gene Expression Assays in Early-Stage Breast Cancer
INTERVIEW WITH: Joseph Sparano, MD

Clinical Quandaries
513 Approaching Use of CDK4/6 Inhibitors in Metastatic HR+, HER2-Breast Cancer
Jennifer Weiss, MD, Anosheh Afghahi, MD, Elena Shagisultanova, MD, PhD, and Jennifer R. Diamond, MD
SERIES EDITOR: E. David Crawford, MD
A 58-year-old woman presents with newly diagnosed metastesas.

Integrative Oncology
516 Herbs and Drugs
K. Simon Yeung, PharmD, LAc, Jyothirmai Gubili, MS, and Jun J. Mao, MD, MSCE
PERSPECTIVE: Donald I. Abrams, MD
Memorial Sloan Kettering oncologists discuss interactions.
ONCOLOGY and its website, CancerNetwork.com, provide oncologists with the practical, timely, clinical information they need to deliver the highest level of care to their patients. Expert authors and peer review ensure the quality of ONCOLOGY and CancerNetwork.com’s articles and features. Focused discussions capture key clinical take-aways for application in today’s time-constrained practice environment.

COMMUNITY ONCOLOGIST ADVISORY BOARD The Community Oncologist Advisory Board plays a vital role in helping ONCOLOGY fulfill its mission. They peer-review articles to ensure that they are clinically relevant and applicable to the realities of day-to-day oncology practice. Community oncologists who are interested in joining the Advisory Board are welcome to contact Teresa McNulty at teresa.mcnulty@ubm.com.

Caroline Behler, MD San Francisco, CA
Ralph V. Boccia, MD Bethesda, MD
Adam M. Boruchov, MD Hartford, CT
Michelle S. Boyar, MD Bronxville, NY
Nitin Chandramouli, MD Salt Lake City, UT
M. Sitkí Copur, MD, FACP Grand Island, NE
William Donnellan, MD Nashville, TN
David Eagle, MD Mooresville/Huntersville, NC
Erika P. Hamilton, MD Nashville, TN
Ted Huang, MD Portland, OR
Barbara L. McAneny, MD Albuquerque, NM
Nancy Mills, MD Bronxville, NY
Sudhanshu B. Mulay, MD Hartford, CT
W. Charles Penley, MD Nashville, TN
Jondavid Pollock, MD Wheeling, WV
Steven Powell, MD Sioux Falls, SD
Ryan Ramaekers, MD Grand Island, NE
Sonia Seng, MD Fairhaven, MA
Stephanie Smith-Marrone, MD Bronxville, NY
Christian Thomas, MD Colchester, VT
Jacqueline Visky, MD Portland, OR
Raymond Wadlow, MD Fairfax, VA
Carolyn Wasserheit-Liebling, MD Bronxville, NY
Tracey F. Weisberg, MD Scarborough, ME
Denise Yardley, MD Nashville, TN
Amelia Zelnak, MD, MS Cummimg, GA
Richard Zuniga, MD Lowell, MA
Welcome to the New Face of Oncology

Dear Reader,

I am so honored to be taking the helm as Executive Editor following the retirement of Sue Beck, who served readers with such integrity from 2010 until August of this year. Also delighted to be joining ONCOLOGY and CancerNetwork.com is Traci DeVito, our new Managing Editor.

It takes great intellect, empathy, and grit to succeed in Oncology. Traci and I have such reverence for oncologists, who commit to a calling that most people never could. We know that you share that same esteem for your peers, whose research, experiences, and perspectives are profoundly relevant to your own work.

In the 1987 inaugural issue of ONCOLOGY, our first Editor, Robert E. Wittes, described a world full of medical journals, and yet one with a distinct gap when it came to professional insight that can be applied here and now. Although medical journals are even more prolific today, we know that our mission is also more important than ever.

We have renewed our commitment to bringing you the perspectives of key opinion leaders, augmenting our delivery and presentation in the process. Instrumental to our success are Editor Melissa Owen, Associate Editor Dylan Fisher, and Art Director Kristen Morabito. We also owe special thanks to Nicole Slocum, who stepped in to beautifully redesign the journal.

It is a privilege to serve you, and to facilitate intellectual connections between you and your peers across the United States and around the world. Our journal is your journal. By oncologists, for oncologists. Please let us hear from you, as an author or a reader.

And welcome to the new ONCOLOGY.

Jennifer Leavitt
Executive Editor
Dual HER2 Targeting in the Adjuvant Setting

Where We Have Been and Where We Are Going
Anureet C. Copeland, MD, and Carey K. Anders, MD

ABSTRACT: Adjuvant human epidermal growth factor receptor 2 (HER2)-directed treatment has changed dramatically over the past decade. Historically, the addition of 1 year of trastuzumab to adjuvant chemotherapy has significantly improved both disease-free survival and overall survival across several studies. More recently, and in the metastatic setting, dual HER2-targeted therapy—beyond that of trastuzumab alone, and in combination with monoclonal antibodies such as pertuzumab and tyrosine kinase inhibitors such as lapatinib—has shown a survival benefit. As is common in drug development, promising agents in the metastatic setting are then examined in the curative setting. This article will provide an overview of the efficacy of dual HER2-targeted therapy in the adjuvant setting as reported in the APHINITY, ExteNET, and ALTTO trials. Potential toxicities with dual HER2-targeted therapy and the financial consequences of adding additional HER2-targeted therapy, beyond trastuzumab, in the adjuvant setting will also be discussed.

Nancy E. Mills, MD, FACP, discusses key clinical points on page 484.

Introduction
Over the past decade, adjuvant human epidermal growth factor receptor 2 (HER2)-targeted therapy has transformed considerably. HER2-directed systemic therapy has dramatically altered the prognosis of patients with HER2-positive breast cancer. The development of HER2-directed monoclonal antibodies and tyrosine kinase inhibitors (TKIs) has improved the natural history of HER2-positive disease. This article discusses the advances in HER2-targeted therapy, in both the metastatic and adjuvant settings, with a focus on those with early-stage breast cancer.

HER2-Targeted Therapy in the Adjuvant Setting
Adjuvant HER2-targeted therapy was initially examined in the North Central Cancer Treatment Group N9831 and the National Surgical Adjuvant Breast and Bowel Project B-31 trials.[1,2] N9831 was a phase III trial that enrolled patients with HER2-positive, node-positive, or high-risk node-negative disease. Patients received 4 cycles of adjuvant doxorubicin/cyclophosphamide (AC) followed by treatment in one of the three arms: weekly paclitaxel for 12 weeks (control arm), paclitaxel followed by trastuzumab for 52 weeks, or weekly paclitaxel given with trastuzumab for 12 weeks followed by trastuzumab alone to complete a total of 52 weeks. B-31 was a two-arm phase III trial in which patients received AC followed by 4 cycles of paclitaxel alone or 4 cycles of paclitaxel plus weekly trastuzumab to complete a total of 52 weeks.

Combined analysis of N9831 and B-31 demonstrated that adding 1 year of trastuzumab to standard anthracycline plus taxane–based adjuvant chemotherapy improved disease-free survival (DFS; hazard ratio [HR], 0.60; 95% CI, 0.53–0.68; \( P < .001 \)) and overall survival (OS; HR, 0.63; 95% CI, 0.54–0.73; \( P < .001 \)) at 10 years.[3] The HERceptin Adjuvant (HERA) trial, which assigned women to 1 year of trastuzumab vs observation after completion of adjuvant therapy, also showed improved DFS (HR, 0.76; 95% CI, 0.68–0.86) and OS (HR, 0.74; 95% CI, 0.64–0.86) at 11 years.[4]

The optimal duration of trastuzumab has been studied in the HERA and PHARE (Protocol for Herceptin as Adjuvant Therapy with Reduced Exposure) trials. HERA, an international random-
Dr. Copeland and Anders’ main point is that there is no “one size fits all” for breast cancer patients who require adjuvant therapy, and that individualized decisions must be made, weighing risks and benefits for each patient.

Even in the highest-risk patients, for whom the evidence does show benefit from the dual-antibody approach, the APHINITY trial showed those benefits to be somewhat modest. Therefore, issues regarding toxicity must be taken into account. The main toxicities to keep in mind are cardiac and gastrointestinal, most notably diarrhea. Oncologists are obligated to discuss these issues with patients before embarking on dual-antibody therapies.

The addition of 1 year of neratinib, as per the ExteNET trial, is also a decision that needs to be individualized. Data suggest a potential benefit in high-risk patients, but there is a significant probability that marked diarrhea will occur. Moreover, the patients in ExteNET did not receive adjuvant pertuzumab, making it difficult to know whether there is any benefit to neratinib for those who did receive pertuzumab. These patients also tend to be the highest-risk patients.

Thus, given the potential for toxicity and the somewhat modest benefits, the use of dual HER2 targeting in the adjuvant setting remains somewhat controversial. The best approach to ensure appropriate use of dual HER2 targeting as adjuvant therapy in breast cancer is one in which the clinician and patient discuss all options in terms of risks, benefits, and quality of life.

Dr. Mills is a Medical Oncologist and Director of Cancer Survivorship at New York Presbyterian Lawrence Hospital Cancer Center in Bronxville, New York and Assistant Professor of Medicine at Columbia University Medical Center, New York, New York.

FIGURE 1 HER2 activates several signaling pathways in the ErbB family of receptors
OS rate at 5 years (95.1% vs 95% in the longer and shorter groups, respectively). In subset analysis, patients with stage III disease or those with multiple positive lymph nodes benefited from the longer duration of treatment.[7]

**Dual HER2-Targeted Approaches in Metastatic Breast Cancer**

As is common in drug development, novel strategies like dual HER2-targeted approaches were first explored in the metastatic patient population and demonstrated notable efficacy. Pertuzumab is a humanized monoclonal antibody that targets the extracellular domain II of HER2, blocking heterodimerization of HER2 with other HER receptors, namely HER3, leading to inhibition of downstream signaling pathways.[8]

The phase III CLEOPATRA trial looked at the efficacy of dual HER2 inhibition with the addition of pertuzumab to trastuzumab with docetaxel in the first-line treatment of metastatic HER2-positive breast cancer. Patients were randomized to docetaxel and trastuzumab plus placebo or docetaxel and trastuzumab plus pertuzumab. CLEOPATRA showed a significant improvement in median progression-free survival (PFS) of 18.5 months in the pertuzumab group vs 12.4 months in the control group (HR, 0.62; 95% CI, 0.51–0.75; P < .001).[9] Median OS was 56.5 months in the pertuzumab group (95% CI, 49.3 months–not reached) compared with 40.8 months in the control group (95% CI, 35.8–48.3 months).[10]

In addition to monoclonal antibodies, HER2-directed TKIs have also changed the landscape of HER2-positive breast cancer. Lapatinib is a reversible small-molecule inhibitor that binds to the intracellular tyrosine kinase domain of HER1 and HER2.[11] EGFR104900, a multicenter, phase III, open-label trial, showed that the combination of lapatinib plus trastuzumab vs lapatinib alone improved PFS (HR, 0.74; 95% CI, 0.58–0.94; P = .011) and OS (benefit of 4.5 months; HR, 0.74; 95% CI, 0.57–0.97; P = .026) in patients with metastatic disease.[12,13] Neratinib, an irreversible small-molecule TKI of the HER1 and HER2 receptors, has also been studied in the HER2-positive setting. Burstein et al showed that neratinib demonstrated a durable clinical benefit in patients with metastatic breast cancer, who were both trastuzumab-pretreated and trastuzumab-naive.[14] Median PFS for the groups was 22.3 and 39.6 weeks, respectively.[14]

**Dual HER2-Targeted Therapy in the Adjuvant Setting**

Given the success of dual HER2-targeted therapy in the metastatic setting, the efficacy of this approach has more recently been reported in the adjuvant setting. Historically, the addition of trastuzumab to adjuvant chemotherapy in HER2-positive breast cancer has significantly improved DFS.[15] The APHINITY trial looked at adding a second HER2-directed agent, pertuzumab, to trastuzumab postoperatively in women with HER2-positive disease. More than 4,800 women were randomized to receive 18 weeks of standard-of-care chemotherapy with trastuzumab plus placebo or trastuzumab plus pertuzumab for 1 year. At 3 years, 94.1% of patients in the trastuzumab plus pertuzumab arm were disease-free compared with 93.2% in the trastuzumab plus placebo arm (HR for an invasive event, 0.81; 95% CI, 0.66–1.00; P = .045).

In a subset analysis of patients with node-positive disease, the 3-year DFS rate was 92% in the pertuzumab arm compared with 90.2% in the placebo arm (HR for invasive event, 0.77; 95% CI, 0.62–0.96; P = .02). Additionally, in the cohort with hormone receptor (HR)-negative disease, the 3-year DFS rate was 94% in the pertuzumab arm compared with 91.3% in the placebo arm (HR for invasive event, 0.80; 95% CI, 0.65–0.99; P = .04).

**Trastuzumab and pertuzumab work in synergy, binding to different regions on HER2.**
Trastuzumab was approved by the FDA in 1998 and is on the World Health Organization’s List of Essential Medicines. Pertuzumab gained FDA approval in 2012.

rate was 92.8% in the pertuzumab arm and 91.2% in the placebo arm (HR, 0.76; 95% CI, 0.56–1.04; \( P = .101 \)). These results indicate a modest benefit for a dual HER2-targeted approach in the adjuvant setting, particularly in patients with higher-risk disease (eg, node-positive or HR-negative disease).[16]

Dual Monoclonal Antibody HER2-Directed Therapy vs HER2-Directed TKIs Plus Trastuzumab

How does dual monoclonal antibody HER2-directed therapy compare with the addition of HER2-directed TKIs to trastuzumab? The ExteNET study evaluated the addition of neratinib for 1 year vs placebo in patients with stage I–IIIc HER2-positive breast cancer who were previously treated with 1 year of trastuzumab in the neoadjuvant or adjuvant setting. Patients had no evidence of recurrent or metastatic disease at enrollment. At 5 years, the DFS rate was 90.2% in the neratinib group and 87.7% in the placebo group (HR, 0.73; 95% CI, 0.57–0.92; \( P = .0083 \)). Interestingly, in subset analysis, the HR-positive cohort derived greater DFS benefit (HR, 0.60; 95% CI, 0.43–0.83) from the addition of neratinib as compared with the HR-negative cohort (HR, 0.95; 95% CI, 0.66–1.35).[17]

Lapatinib Plus Trastuzumab vs Trastuzumab Alone

The phase III ALTTO trial compared the efficacy of the addition of lapatinib to trastuzumab (sequentially after completion of 12 weeks of trastuzumab or concurrently with 52 weeks of trastuzumab) vs trastuzumab alone for 1 year in 8,000 patients. A fourth arm of lapatinib alone was closed early due to futility. Comparing 6-year DFS between treatment groups, the HR was 0.86 (95% CI, 0.74–1.00) for lapatinib plus trastuzumab vs trastuzumab alone; the HR was 0.93 (95% CI, 0.81–1.08) for trastuzumab followed by lapatinib sequentially vs trastuzumab alone. No difference was seen for OS between groups. In subgroup analysis, those with HR-negative disease derived the greatest DFS benefit from dual therapy (a 4% absolute benefit).[18,19]

Toxicity Considerations

With the addition of HER2-directed agents in the adjuvant setting, clinicians must consider potential toxicities, with gastrointestinal and cardiac adverse effects emerging as the most significant sequela. In APHINITY, the addition of pertuzumab to trastuzumab led to primary cardiac events in 9 additional patients compared with trastuzumab alone, but occurrences were still low (0.7% in the pertuzumab arm and 0.3% in the placebo arm).[16] Grade 3 diarrhea was more commonly seen with pertuzumab.

In the ALTTO trial, more cardiac events occurred in the trastuzumab-alone arm compared with the lapatinib-containing arms (11% (T) vs 9% (L+T) and 7% (T–L), respectively); however, fewer events in the trastuzumab-only arm were deemed to be serious cardiac events.[18] In the ExteNET trial, diarrhea was the most common adverse effect from neratinib, with 40% of patients reporting grade 3 diarrhea at the 2-year follow-up.[17] Finally, in the Short-HER study, there were fewer cardiac events in the shorter arm (9 weeks) vs the longer arm (12 months) of trastuzumab (5.1% vs 14.4%, respectively); however, the majority of these events were grade 2 in nature.[7]

Financial Implications

When considering all aspects of dual HER2-targeted therapy in the adjuvant setting, providers must also consider the financial implications. Standard adjuvant trastuzumab averages $55,000 USD per patient annually, based on US Medicare data.[20,21] As expected, the addition of dual HER2-targeted therapies results in increased cost compared with trastuzumab alone. The addition of 1 year of pertuzumab to trastuzumab results in an additional $95,000 USD per patient, while 1 year of lapatinib increases the cost by $42,000 USD.[20] Decreasing the duration of trastuzumab to 9 weeks, per Short-HER data, would reduce costs by nearly $45,000 USD per patient annually.[20]

To place these costs into the larger context of historical modifications to standard-of-care adjuvant treatment, 4 cycles of adjuvant paclitaxel added to AC increases costs by $12,500 USD per patient, while extension of aromatase inhibitor treatment from 5 years to 10 years adds approximately $15,000 USD per patient.[20] Today, we are faced with the challenge of providing exceptional individualized care utilizing newer HER2-directed therapies in an era in which healthcare costs continue to rise.
substantially increase. Careful balance between risk, benefit, and financial toxicity must be considered when making decisions about adjuvant HER2-directed therapy.

Summary, Recommendations, and Future Directions
In summary, systemic therapy for HER2-positive breast cancer patients has changed remarkably over the last several years. As clinicians consider the use of HER2-targeted agents in the adjuvant setting for early-stage disease, an approach tailored to individual risks and benefits must be taken into consideration. We are no longer in a “one size fits all” scenario. In lower-risk patients with node-negative, HR-positive disease, treatment with chemotherapy plus 1 year of adjuvant trastuzumab is appropriate. For higher-risk patients with node-positive or HR-negative disease, 1 year of dual HER2-targeted therapy (trastuzumab with pertuzumab) in combination with chemotherapy in the adjuvant setting can be considered. In the adjuvant setting for higher-risk, node-positive, HR-positive disease, it may be reasonable to consider adding 1 year of neratinib after 1 year of trastuzumab based on ExteNET data. Finally, with regards to the duration of HER2-directed therapy, we still recommend 1 year of adjuvant therapy; however, in those with high-risk cardiac disease who experience a reduction in ejection fraction while on therapy, the Short-HER data do give us some reassurance that there is benefit from a shorter duration of HER2-directed therapy. Finally, when making all of the above decisions, we as a medical community must consider the financial toxicities as they relate to our global health economy, as well as the sustainability of such approaches.

FINANCIAL DISCLOSURE: Dr. Anders receives research funding from Cascadian, Genentech, GI-Therapeutics, Lilly, Merck, Merrimack, Nektar, Novartis, Puma, Seattle Genetics, and Tesaro. Dr. Copeland has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

Dr. Copeland is a Clinical Hematologist and Oncologist, University of North Carolina REX Hematology/Oncology, Raleigh, North Carolina

Dr. Anders is Associate Professor, University of North Carolina at Chapel Hill, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina

For references visit cancernetwork.com/dual-HER2-targeting
Managing Psychosocial Distress: Lessons Learned in Optimizing Screening Program Implementation

Elizabeth Ercolano, DNSc, RN, Emma Hoffman, BS, MSN, Hui Tan, MSN, Nicholas Pasacreta, BA, Mark Lazenby, PhD, APRN, and Ruth McCorkle, PhD, RN

ABSTRACT: The estimated prevalence of psychosocial distress in cancer patients is 29.6% to 43.4%. Psychosocial distress is associated with depression, a common comorbidity in cancer patients. Untreated distress can contribute to early morbidity and mortality and can worsen other comorbidities. In 2012, the American College of Surgeons (ACoS) Commission on Cancer (CoC) required accredited cancer centers to integrate psychosocial distress screening into cancer care by the end of 2015. Uptake of screening has been minimal, with only 47% to 73% of eligible patients being screened. The Screening for Psychosocial Distress Program (SPDP) is a 2-year educational and implementation-support program designed to help cancer care clinicians meet the ACoS CoC mandate. Through the SPDP, we have trained cancer care clinicians on how to optimize the distress screening process to increase the likelihood that patients’ distress will be detected, evaluated, and triaged. We report here on our “lessons learned” and the optimal strategies to promote institutions’ adoption of distress screening.

Introduction
As cancer treatment evolves and survival rates improve, more attention needs to be paid to other medical diagnoses beyond cancer. Cancer patients’ morbidity and mortality may be hastened by the presence of other medical conditions. Diabetes, chronic pulmonary disease, congestive heart failure, and cerebrovascular disease are the most common comorbid conditions in all cancer types.[1] Patients with lung cancer have the highest prevalence of comorbid conditions; those with colorectal cancer have the second highest.[1] Clinicians need to consider the number and severity of patients’ other medical conditions, as well as their age and cancer stage, since they have the potential to influence morbidity and mortality.[1] Radiation therapy, chemotherapy, hormonal therapy, and surgery for the treatment of cancer can also have late effects on patients’ physical health.[2] With chemotherapy and radiation therapy, treatment-related conditions include secondary cancers, congestive heart failure, diabetes, sterility, impaired immune function, lymphedema, cognitive impairment, neuropathies, and impaired kidney function.[2] Late effects from surgical management include pain, cosmetic effects, lymphedema, sexual dysfunction, infertility, neurologic impairments, gastrointestinal upset, and bowel obstruction.[2]

Psychosocial distress is associated with depression in cancer patients, which is considered a comorbid condition.[3,4] Depression is one symptom of psychosocial distress that has been linked specifically to increased mortality in cancer patients.[5] Of note, cancer patients with preexisting emotional problems or physical limitations have increased mortality compared with patients who develop these problems after diagnosis. [6] The data are still inconclusive as to whether untreated clinical depression increases the risk of cancer progression. [5,7] Cancer progression, however, raises the risk of clinical depression, with a prevalence greater than the general population. [8] Cancer patients with psychosocial distress may experience mental, emotional, social, physical, and/or spiritual problems.[9] Research has found that if distress is not detected and is left
unmanaged, unintended consequences to quality and quantity of life may occur.[3] These consequences include increased mortality rates, delayed time to treatment, poor adherence to treatment, and dysregulation of the immune system (see Figure).[2,10-14]

While all cancer patients must be considered at risk for developing psychosocial distress, patients with a history of depression, psychiatric disorders, substance abuse disorders, cognitive impairments, severe comorbid illnesses, social issues, spiritual concerns, and uncontrolled symptoms are at increased risk.[9] Cancer patients may also experience increased vulnerability to psychosocial distress during major events through the course of their disease. Finding suspicious symptoms, the cancer diagnosis workup, learning one’s diagnosis, and genetic predisposition contribute to heightened psychosocial distress. After the diagnosis is learned and the treatment plan is established, other pivotal events linked to psychosocial distress symptoms and addressing cancer patients’ concerns have helped extend their lives; however, additional work is still needed in this area.[6,7,8,15]

The Screening for Psychosocial Distress Program (SPDP)

In 2012, the American College of Surgeons (ACoS) Commission on Cancer (CoC) required accredited cancer centers to integrate psychosocial distress screening into cancer care by the end of 2015 to improve quality of life and prevent morbidity. However, uptake of screening has been minimal, with only 47% to 73% of eligible patients being screened.[16] The slow rate of compliance to the CoC mandate may be due to institutional barriers, including inadequate administrative support; lack of an interdisciplinary oncology team; no established distress screening protocols; undereducated staff; confusion about which screening tool to use; immature electronic medical systems to aid in integrating the steps of comprehensive distress screening; and inadequate internal or external psychosocial resources to assist in managing distress.[17-19]

Cancer care clinicians, therefore, require training and support to develop and implement psychosocial distress screening programs in order to be successful in meeting the mandate and overcoming institutional barriers. There have been few formalized educational and implementation-support programs to train cancer care clinicians on distress screening, despite the ACoS CoC mandate and other recommendations.[20] Funding, therefore, was obtained through the National Cancer Institute R25 Cancer Education Research Grant # R25CA177553 (R. McCorkle, primary investigator; 2013–2019) to develop and implement the SPDP, a national 2-year training and implementation-sup-
Continued on page 492

Awareness Alone Isn’t Enough

Unlike the symptomatic relief and overall survival benefit seen with reporting physical symptoms, there is something inherently different and more complicated about addressing psychological symptoms. We know that awareness of distress or other psychological symptoms by itself doesn’t ameliorate symptoms. [1] This may be due to the limited number of patients who actually accept distress screening recommendations (only about 1 in 5 patients follow through with at least one follow-up appointment), the challenges of providing mental healthcare in a medical setting, and other systemic issues inherent in delivering broad psychosocial care. [2] Therefore, the crucial second step in distress screening is what happens after distress screening? How do we bring limited psychosocial resources to those patients who need them the most in order to provide the most help to those with the most need?

The identification of psychologically high-risk individuals is only half the battle. The second half is to provide the most effective strategies for treating psychological symptoms in the context of cancer care. That will be borne out of well-integrated distress screening programs. [3]

This serves to underscore the importance of the first step in this process—that of increasing distress screening at cancer centers. Although guidelines have been in place since 1997, cancer centers tend to overestimate how much distress screening is actually performed, and many have yet to accept distress screening into their practices. [4] This remains a systemic problem. The lessons learned from the Screening for Psychosocial Distress Program are invaluable for psychosocial oncology practitioners looking to forge the way at their respective oncology centers.

Daniel McFarland, DO is Fellow of the Department of Psychiatry and Behavioral Sciences, Memorial Sloan Kettering Cancer Center, New York, New York

For references visit cancernetwork.com/psychosocial-distress

port program. The SPDP was advertised to institutions nationally. Two cancer care clinicians (dyads) representing 18 institutions were selected for each training cohort (cohorts 1–5; 180 participants and 90 institutions). The training consisted of in-person workshops and conference calls; the content was developed and delivered by psychosocial oncology leaders. [21] An expert panel in psychosocial oncology reviewed participants’ applications, and then chose applicants based on the strength of their administrators’ commitment to and goals of implementing a distress screening program, as well as professional qualifications. [22] We report here on “lessons learned” from training and guiding cancer clinicians in their development and implementation of psychosocial distress screening programs. These lessons represent optimal strategies to help cancer care clinicians achieve successful psychosocial distress screening programs, so that timely detection and management occurs. [22] The Table summarizes our lessons learned and the optimal strategies to promote institutions’ adoption of distress screening programs.

Lessons Learned: Optimal Implementation Strategies for Distress Screening Programs Getting buy-in at all levels: administration, clinical staff, information technology Support of an institution’s distress screening program requires backing from key stakeholders, including administration, clinical staff, a continuous quality improvement team, the information technology department, and others. Our experience has demonstrated that buy-in of key stakeholders may happen at the level of the oncology interdisciplinary team and/or at the clinic level. Having buy-in allows departments to leverage their support when institutional barriers are encountered. [20] Administrators represent a key stakeholder group that should be engaged early in the development of distress screening programs, since they have control over resources and finances, and oversee/enforce policy compliance.

Building supportive clinician relationships (formation of a dyad)

Establishing a supportive relationship between two or more clinicians experienced with distress screening ensures a more enduring and successful distress screening program. Supportive dyadic relationships enable clinicians to distribute equitably relevant organizational tasks; share one or more common goals; and influence institutional communication and work. [23] We have learned that committed dyads become recognized as legitimate and powerful distress screening program leaders who are better prepared to focus and sustain programs during challenges. Having a consistent set of clinicians who have the expertise and dedication to an institution’s distress screening program supports the program.
Contemporary PEDIATRICS.

Peer-reviewed articles, case studies and more.

www.ContemporaryPediatrics.com
Psychosocial Distress.
Continued from page 490

during times of upheaval, including administrative reorganization, turnover of distress screening staff, and updates in evidence-based practice guidelines requiring dissemination.

Formation of an oncology interdisciplinary psychosocial committee
The formation of an oncology interdisciplinary group (social work, nursing, psychology, psychiatry, oncology, chaplaincy, administration, and others) to set, direct, and evaluate distress screening policy and program objectives is invaluable. The CoC standard identifies the oncology interdisciplinary team as the group responsible for the screening, evaluation, treatment, referral, and follow-up of moderate or severe distress.[21] An interdisciplinary psychosocial committee, therefore, has the knowledge, experience, and authority to establish distress screening policy that is in alignment with other institutional policies, external regulations, and practice guidelines. This committee is best suited to enforce compliance with the institution’s distress screening policy and procedures and recommend corrective strategies if noncompliance is found.[8]

Developing a distress screening policy
A distress screening program policy documents the overall purpose and scope, rationale, procedures, and evaluation criteria for auditing and monitoring compliance of distress screening activities. This policy results in a uniform set of processes and procedures across all cancer types and settings, and allows for a consistent institutional response to the problem of distress. Each discipline’s accountability to screen for, assess, manage, and follow up on a significant distress score is clearly spelled out, thereby minimizing confusion and fragmentation.[21] Through our training program, we have found that many institutions lacked distress screening policies, resulting in inconsistent practices, duplication of efforts, and lack of accountability.

Staff training
The successful implementation of distress screening programs depends on trained staff who possess both knowledge about psychosocial distress and skills on distress screening.[24] Required training for clinical staff should include sessions on introducing screening to patients and families, learning the scoring procedures for distress screening tools, notifying other clinicians due to a clinically significant distress score at the proper time, and monitoring follow-up of distress screening referrals. To maintain a standardized, comprehensive approach to psychosocial distress screening, it is advocated that clinical staff undergo initial and ongoing training.[25] Our experience with the SPDP has shown that institutions recognize the importance of training staff who will be involved in distress screening, but often lack the administrative support or tools to conduct the training. Ideally, staff would be introduced to training early to support a smooth and effective distress screening process and a consistent/structured training program would be in place for newly hired staff and current employees.[26]

Selection of a distress screening tool
Optimal distress screening procedures need to be based on patients’ and families’ self-report of their rating of psychosocial distress and the problems contributing to the distress.[26] Screening tools for psychosocial distress should yield reliable and valid results. The major goal of a screening tool is to detect clinically significant distress to prompt further evaluation. Screening results should be documented in the medical record, and should show direct and straightforward administration of screening, scoring, referral, outcomes, and monitoring over a period of time. Currently, various screening tools are in use; the predominant tool is the National Comprehensive Cancer Network (NCCN)

### TABLE Optimal Implementation Strategies of Distress Screening Programs

<table>
<thead>
<tr>
<th>Lessons Learned</th>
<th>Optimal Implementation Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Getting buy-in</td>
<td>Institutional support at all levels to help clinicians overcome barriers to distress screening</td>
</tr>
<tr>
<td>Building supportive clinician relationships</td>
<td>Identified and legitimized program leaders to sustain program through successes and failures</td>
</tr>
<tr>
<td>Creation of an oncology interdisciplinary psychosocial committee</td>
<td>Interdisciplinary working group that establishes distress screening policy and monitors compliance</td>
</tr>
<tr>
<td>Developing a distress screening policy</td>
<td>Formalized and uniform institutional distress screening processes</td>
</tr>
<tr>
<td>Staff training</td>
<td>Educated staff resulting in the necessary knowledge and skills to identify, assess, and manage distress</td>
</tr>
<tr>
<td>Selection of a distress screening tool</td>
<td>Use of a valid and reliable self-report measure of distress that can yield clinically useful information</td>
</tr>
<tr>
<td>Establishing a referral network</td>
<td>Established and coordinated internal and external resources to manage distress-related concerns</td>
</tr>
<tr>
<td>Follow-up and documentation</td>
<td>Follow-up information provided (and documented) to the oncology team and patients represents integrated, high-quality care</td>
</tr>
</tbody>
</table>

Currently, various screening tools are in use; the predominant tool is the National Comprehensive Cancer Network (NCCN)
Distress Thermometer (NCCN-DT). The NCCN-DT is a single-item visual analog scale and is administered with a problem list describing sources of the distress.[9] Many institutions use multiple tools to aid in their efforts to understand the specific attributes of distress and to rule out or rule in psychopathology, such as clinical depression, anxiety disorders, or other psychiatric disorders. It is recommended that institutions adopt screening tools that align with the needs of their patient population.[8]

Establishing a referral network

Once moderate or severe levels of psychosocial distress are detected, additional services are required to evaluate and treat the causes underlying the distress. Therefore, a process needs to be established and coordinated with distress screening detection procedures.[8] Cancer care clinicians, including oncologists, social workers, and nurses, are encouraged to have a resource list containing names of psychiatrists, psychologists, pastoral care providers, palliative care providers, and others who have the clinical expertise to manage distress-related concerns. Institutions are also encouraged to seek resources beyond those offered onsite.[8] Having an ample supply of cancer care clinicians who can treat distress-related concerns ensures that all patient needs will be met. We have found through the SPDP that it takes time and ongoing work to establish a well-coordinated referral network with the appropriate type and amount of cancer care clinicians to serve an institution’s specific patient population. Importantly, if the patient has seen a therapist before, he or she is encouraged to reestablish that relationship.

Follow-up and documentation

Following up on a clinically significant distress screening score ensures that distress-related problems have been further triaged, evaluated, and managed. It is encouraged that all steps of the distress screening process be documented in the medical record,[22] including detection (screening), assessment and evaluation, management (including referral), and follow-up. Documentation of the distress screening process lends itself to determining whether the care follows the institutions’ policies and guidelines.[9] Although the CoC mandate strongly recommends that the electronic record be used to document the seamless and coordinated steps of psychosocial distress screening, many of our participating institutions are still using paper and pencil, which presents challenges in accomplishing audits. A strength of our program has been to help institutions reach and communicate with information technology departments to begin the process of designing platforms to build electronic documentation into their distress screening programs.[27]

Conclusion

Psychosocial distress associated with depression is considered a major comorbid condition of cancer. It is estimated at any given time that 29.6% to 43.4% of cancer patients experience psychosocial distress, depending on cancer type.[4] Unmanaged psychosocial distress has strong potential to negatively impact both morbidity and mortality and to exacerbate other comorbid conditions associated with cancer.[3,4] Comprehensive distress screening allows for the timely identification, evaluation, and management of psychosocial distress over the cancer experience. Distress screening tools and procedures may also result in the discovery of other medical or psychiatric comorbid conditions. This comprehensive support allows for the care of the “whole patient.” Although cancer care providers are well-intentioned in treating psychosocial distress, they report obstacles to accomplishing and sustaining comprehensive distress screening.[18,19] Through the SPDP, we have trained cancer care clinicians on how to optimize the distress screening process to increase the likelihood that patients’ distress will be detected, evaluated, and triaged.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/psychosocial-distress
Introduction
Colorectal cancer is the third leading cause of cancer-related deaths in the United States and is expected to cause approximately 50,630 deaths during 2018.[1] Chemotherapy with fluorouracil (5-FU)-based regimens has been the gold standard for treatment, but with the 5-year survival rate for metastatic disease at only 12%, additional treatment options are highly needed.[1] Recent groundbreaking cancer research utilizes immunotherapy, which is now considered a key treatment for many other tumor types, such as melanoma and non–small-cell lung cancer. As a result, oncology care providers are now being tasked with integrating immunotherapy into their daily practice for patients, including those with colorectal cancer.

In general, colorectal cancer has been impervious to immunotherapy, except for a small subset of patients with hypermutated tumors due to a deficient DNA mismatch repair protein. These cancers are referred to as microsatellite instability high (MSI-H). They tend to have high mutational burden and increased tumor neoantigen load, which is coupled with a dense immune cell infiltration.[2] About 15% of all colorectal cancers harbor this now targetable molecular underpinning.[3] Approximately 2.5% of MSI-H colorectal cancers arise from a genetic inheritance associated with Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), and 12.5% are sporadic.[4] The majority of colorectal cancers (85%) have no microsatellite instability and are referred to as microsatellite stable (MSS). Dudley et al evaluated responses to programmed death 1 (PD-1) therapy with pembrolizumab and reported a 0% response rate for patients with mismatch repair–proficient colorectal cancers.[4] In contrast, the objective response rate was 52% in patients with mismatch repair–deficient colorectal cancers.[5] Until these recent studies were reported, immunotherapy was thought to be ineffective for colorectal cancer. Now, intensive research is ongoing to improve outcomes for both MSI-H and MSS disease unresponsive to immunotherapy. In particular, various clinical trials are exploring strategies to alter the immune inhibitory tumor microenvironment.

Pathogenesis of MSI-H in Colorectal Cancer
In normal tissue, mismatch repair proteins correct errors in DNA during replication. Tumors with mismatch repair deficiency are missing one or more of these mismatch repair proteins, which is now considered a key treatment for many other tumor types, such as melanoma and non–small-cell lung cancer. In general, colorectal cancer has been impervious to immunotherapy, except for a small subset of patients with hypermutated tumors due to a deficient DNA mismatch repair protein. These cancers are referred to as microsatellite instability high (MSI-H). They tend to have high mutational burden and increased tumor neoantigen load, which is coupled with a dense immune cell infiltration.[2] About 15% of all colorectal cancers harbor this now targetable molecular underpinning.[3] Approximately 2.5% of MSI-H colorectal cancers arise from a genetic inheritance associated with Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), and 12.5% are sporadic.[4] The majority of colorectal cancers (85%) have no microsatellite instability and are referred to as microsatellite stable (MSS). Dudley et al evaluated responses to programmed death 1 (PD-1) therapy with pembrolizumab and reported a 0% response rate for patients with mismatch repair–proficient colorectal cancers.[4] In contrast, the objective response rate was 52% in patients with mismatch repair–deficient colorectal cancers.[5] Until these recent studies were reported, immunotherapy was thought to be ineffective for colorectal cancer. Now, intensive research is ongoing to improve outcomes for both MSI-H and MSS disease unresponsive to immunotherapy. In particular, various clinical trials are exploring strategies to alter the immune inhibitory tumor microenvironment.

Identifying Patients
The National Comprehensive Cancer Network (NCCN) guidelines recommend MSI testing for all patients with metastatic colorectal cancer.[3] Several
testing methods are available, including immunohistochemistry, polymerase chain reaction, and next-generation sequencing. Deciding which test to order often depends on cost to the patient and institutional availability.

Immunohistochemistry is commonly used and can detect the majority of mismatch repair–deficient tumors. It evaluates four different markers (MLH1, MSH2, PMS2, and MSH6) to predict mismatch repair status. If all four proteins are intact, then the tumor is considered mismatch repair-proficient, or MSS. Loss of one or more of these markers signals that the patient has a mismatch repair–deficient or an MSI-H tumor. From 5% to 11% of MSI-H tumors will not show protein loss but will show a retained antigen of a nonfunctional protein.[4] Immunohistochemistry is widely considered the most cost-effective method.

Polymerase chain reaction analysis looks at five different microsatellites. It involves amplification of the microsatellites in tumor and normal tissues and comparison of the shifts between them. New shifts in the tumor sample not found in the corresponding normal sample indicate the presence of MSI. A shift in the size of at least 2 of the 5 regions is needed to be considered MSI-H.[3,4] Normal tissue is not always available, which can make this test problematic.

Next-generation sequencing is now available to most patients via commercial or academic entities. Its broad genomic sequencing looks for the MSI and also for hundreds of other mutations, which may open future doors for treatment. Unfortunately, it is expensive, and not all insurance companies cover it, which is a deterrent for many. When a company is chosen to perform the testing, we encourage patients to review its financial assistance programs. The amount of assistance provided is often based on household income and actual insurance coverage.

As testing becomes more prevalent, which MSI-H patients with colorectal cancer should be referred for genetic counseling needs to be considered. At the very least, young patients or patients with a strong family history of cancer and an MSI-H cancer may need genetic testing, as these are concerning for a primary germline mutation and Lynch syndrome. This is especially true of tumors not associated with BRAF mutations, since BRAF mutations are more commonly seen in sporadic cancers. Lynch syndrome is an autosomal dominant genetic disorder that carries a significant risk of colon cancer, as well as endometrial, ovarian, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin cancers. Carrying this genetic mutation has a significant impact not only on the patient's treatment and prognosis but also on family members and cancer screening recommendations.

Reasons for Excluding Patients
Because immunotherapy unbridles the body's immune response, this can lead to dangerous adverse effects (AEs) with the potential for life-threatening toxicity. Patients with a prior history of autoimmune disorders have been excluded from immunotherapy trials due to the risk of “ramping up” the immune response in patients who already have an overactive immune system. Immunotherapy often exacerbates autoimmune conditions.[6] In a cohort of 30 patients with prior autoimmune disease treated with ipilimumab, 27% experienced exacerbation of their condition, 33% had high-grade adverse reactions, and 1 death was reported related to colitis. [7] Patients who have had transplants are also excluded for fear of transplant rejection with an immune system now on high alert for foreign tissues. Lipson et al reported a renal transplant rejection during pembrolizumab treatment.[8] On the other hand, Hertz et al reported ipilimumab tolerability in three renal transplant patients.[7,9] Chronic steroid users also are excluded from immunotherapy trials because steroids are thought to dampen the treatment effect. Again, actual data on treating patients who have autoimmune disorders with immunotherapy are lacking, and caution should be used in this patient population. The choice is very personal and requires an in-depth conversation about the potential risks vs benefits with the patient. For example, a flare in an autoimmune condition such as psoriasis is typically manageable, but a multiple sclerosis flare could be life-threatening if exacerbated by immunotherapy.

Incorporating Immunotherapy in Colorectal Cancer
Immunotherapy is generally well-tolerated and lacks the typical chemotherapy AEs such as nausea, vomiting, neuropathy, taste bud changes, and severe fatigue. However, at this time, no immunotherapy agents given alone or in combination are recommended by the NCCN guidelines for the majority of patients with colorectal cancer. For patients with MSS tumor types, no immunotherapy agent is currently approved by the US Food and Drug Administration (FDA). For these patients, access to new immunotherapy agents requires enrollment in a clinical trial. Only colorectal cancer patients with metastatic MSI-H tumors meet current treatment guidelines for immunotherapy.

Popat et al systematically reviewed previously collected data on systemic therapy for patients with stage II and III MSI-H colorectal cancer. They noted two prior studies that looked directly at the potential benefit of adjuvant 5-FU for these patients. MSS
Assessing Eligibility in a Small Patient Subset

Immunotherapy has revolutionized the care of a number of malignancies, including melanoma, renal cell carcinoma, and non–small-cell lung cancer, to name a few. For most patients with colorectal cancer, however, effective immunotherapy remains unavailable. In this article, Wilt and Le review the data supporting the use of programmed death 1 (PD-1) inhibitors—both alone and in combination with a low-dose cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) inhibitor—in patients with metastatic microsatellite instability–high (MSI-H) colorectal cancer.

It is important that clinicians note the small percentage of the colorectal cancer population that actually has MSI-H disease. As noted by Wilt and Le, approximately 15% of new colorectal cancer cases are MSI-H. However, MSI-H is a favorable prognostic indicator in early-stage disease, and this means that a substantial proportion of individuals with stage I, II, or III MSI tumors will never develop metastatic cancer. As a result, only 3% to 4% of metastatic colorectal cancer patients have MSI tumors. For the other 96% of patients with metastatic disease, currently available immunotherapies are ineffective and should not be used. Numerous clinical trials of novel immunotherapeutic agents and strategies are currently in progress, and providers should strongly encourage patients with metastatic microsatellite-stable colorectal cancer to consider enrolling.

Eligibility for immunotherapy can be assessed using immunohistochemistry (IHC) for mismatch repair status, polymerase chain reaction (PCR) for MSI status, or a multigene next-generation sequencing (NGS) assay. While IHC has the shortest turnaround time and is currently the most widely used approach, the ability of NGS assays to combine MSI data with mutational information, such as KRAS, NRAS, and BRAF status, will likely render this approach the preferred technique going forward.

Dr. Saltz is a Medical Oncologist; Executive Director for Clinical Value & Sustainability; Head, Colorectal Oncology Section, Gastrointestinal Oncology Service at Memorial Sloan Kettering Cancer Center, New York, New York.
immunotherapies? Overman et al evaluated the benefit of dual therapy with combined nivolumab (a PD-1–blocking antibody) and ipilimumab (a CTLA-4–blocking antibody) in 119 patients with MSI-H colorectal cancer. The progression-free survival rate was 76% at 9 months and 71% at 12 months.[14] The overall survival rate was 87% at 9 months and 85% at 12 months. The combination showed a response rate of 55% and a disease control rate for 12 weeks or more of 80%.[14] However, there were higher rates of grade 3 and 4 toxicities.[14] While promising, these data are not from a randomized study and therefore may not support the routine use of a more toxic, more expensive regimen when a good alternative exists. The FDA recently approved an indication of nivolumab/ipilimumab combination for patients with MSI-H metastatic colorectal cancer, and this regimen can now be considered for select patients.

As the appeal of immunotherapy grows among patients, many desire to utilize it as a first-line treatment. The results of KEYNOTE-177, a phase III randomized study comparing first-line use of pembrolizumab with investigator-choice chemotherapy for mismatch repair–deficient or MSI-H metastatic colorectal cancer, will help providers evaluate if immunotherapy is an option for the first-line treatment of MSI-H metastatic colorectal cancer.[15]

Potential AEs
Immunotherapy can result in a wide range of toxicities and AEs that can occur at any point in therapy. Most are noted within weeks to the first 3 months of treatment; however, first onset of an AE has been documented as late as a year after discontinuing treatment.[6] Providers must have a clear understanding of potential toxicity and a firm grasp on management. Immunotherapy can cause organ inflammation anywhere in the body. Life-threatening side effects, while rare, can occur and require rapid identification and management (Table 1).[7] Given the wide range of AEs and toxicities, providers should familiarize themselves with the National Cancer Institute’s Common Terminology Criteria for Adverse Events and its descriptive terminology, which can be utilized for grading AEs.[16] The grading scale ranges from 1 (minimal) to 5 (death). Once an AE is graded, the NCCN recommendations for treatment of toxicity can be implemented.[17] Broad guidelines for grading and treatment are noted in Table 2.

Treating Toxicity
Follow-up and laboratory monitoring are key to identifying potential toxicities early. The majority of toxicities are low grade and respond well to symptom management. For example, low-grade pruritus can respond to antihistamines, rash to topical steroids, and arthralgias to nonsteroidal anti-inflammatory drugs. Thyroid dysfunction, which is often identified by laboratory results before the patient reports symptoms, is easily treated.
Infliximab has been with specialist consultation.

Duration of Treatment
Duration of treatment is largely influenced by treatment response and tolerability. In the phase II study with pembrolizumab, patients were treated for a maximum of 2 years. The average time to response was 21 weeks and to complete response was 42 weeks.[5] Eleven patients with complete responses were taken off therapy after 2 years and followed by surveillance. At last report, no evidence of cancer recurrence was observed, and their average time off therapy was 8.3 months. An additional 7 patients with residual disease on scans also discontinued therapy at 2 years or earlier because of toxicity. The average time off therapy at publication was 7.6 months, with no evidence of progression at the data cutoff.[5] In the nivolumab phase II study, patients were treated indefinitely, and average time to response was 2.8 months. At publication, the median response duration had not yet been reached, all responders were alive, and 8 patients had responses lasting longer than 12 months.[2] Similarly, the combination therapy of nivolumab and ipilimumab did not reach the median duration of response at the time of data collection cutoff.[14] The durable responses seen during these studies are very encouraging, but the actual length of treatment needed to achieve them remains to be clarified.

Overcoming Barriers to Access
With recent FDA approvals and the addition of these immunotherapies to the NCCN drug compendium, insurance approval should be less of an issue if MSI status has been documented. Both PD-1 manufacturers, Merck and Bristol-Myers Squibb, offer assistance programs; exact coverage depends on income. Since the online application takes 7 to 10 days to process, interested patients should apply as soon as they are being considered for therapy.

Conclusions
Immunotherapy offers exciting new treatment options with lasting results. It is vital that providers test patients for molecular alterations, such as MSI status. MSI testing should be routine for all patients with colorectal cancer and can be performed with immunohistochemistry, polymerase chain reaction, or next-generation sequencing. Two PD-1–blocking antibodies, nivolumab and pembrolizumab, are available for clinical use. The first combination immunotherapy treatment with nivolumab and ipilimumab was also recently approved for use in MSI-H colorectal cancer. For patients with MSI-H colorectal cancer, durable responses can be achieved with immunotherapy agents. While high-grade toxicity is a risk, it is usually manageable with steroids if diagnosed and treated early. As extensive research continues, providers are encouraged to stay up-to-date on treatment guidelines and recommendations in the ever-changing world of colorectal cancer treatment.

FINANCIAL DISCLOSURE: Dr. Le serves on the advisory board and receives research funds from Bristol-Myers Squibb and Merck; she also receives speaker’s honoraria from Merck. Ms. Wilt has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/colorectal-integrating-immunotherapy

Ms. Wilt is a Certified Registered Nurse Practitioner, Medical Oncology, GI Malignancies at the Skip Viragh Cancer Building at Johns Hopkins University, Baltimore, Maryland

Dr. Le is Associate Professor, GI Medical Oncology, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, Maryland
A Patient With *EGFR*-Mutated Lung Cancer Progressing on Erlotinib

Evaluating for a T790M Mutation With Limited Tissue

Emily Wynja, MSIV, Jenna Hove, BSN, and Steven F. Powell, MD

**THE CASE**

The patient is a 69-year-old woman with metastatic lung adenocarcinoma who is progressing despite treatment with erlotinib. She was diagnosed in September 2016 with widespread bilateral pulmonary nodules, sclerotic bony lesions, and brain metastases. An initial CT-guided biopsy of the left upper lobe mass showed primary lung adenocarcinoma, which was confirmed through standard polymerase chain reaction testing to have an *EGFR* exon 19 deletion mutation.

The patient was treated with palliative whole-brain radiation therapy and then started on first-line therapy with erlotinib on 11/16/16 as part of the control arm of the BMS-370 study (NCT02574078). Her disease remained stable for 14 months, with mild side effects, including nausea, vomiting, diarrhea, weight loss, and lower extremity edema. She eventually developed slow progression of several pulmonary lesions and had recurrence of symptomatic pleuritic chest pain, concerning for disease progression. Due to the high rate of *EGFR* T790M mutations seen in this population, the thoracic tumor board recommended genomic testing for this alteration. Tissue biopsy was deemed challenging due to the small size of the diffuse pulmonary nodules and the high risk for pneumothorax, so circulating cell-free DNA (cfDNA) testing was recommended.

**Determining the Presence of a T790M Mutation**

A T790M mutation was suspected, as these occur in approximately 60% of patients treated with first-generation EGFR tyrosine kinase inhibitors (TKIs).[1] While TKI resistance can develop through a number of different mechanisms—including transformation to small-cell lung cancer, *MET* amplification, and downstream *PIK3CA* mutations—T790M mutations are the most common mechanism of resistance.[2] Patients with non–small-cell lung cancer (NSCLC) with activating *EGFR* mutations typically respond well to initial TKI therapy for the first 1 to 2 years of therapy.[3]

After this period, resistance frequently develops, with identifiable disease progression. Patients may re-respond to TKI therapy after a hiatus from targeted therapy; however, most will eventually need to change to other systemic therapies.[2] Repeat biopsy at the time of progression detects acquired T790M resistance mutations in exon 20 in approximately half of all cases.[3] However, tissue biopsies at the time of progression are often difficult to obtain in patients with advanced disease. This was the case with this patient: tissue biopsy was considered challenging due to poor lung function and technical difficulties with getting adequate tissue. This restricted our ability to identify the presence of the T790M mutation via tissue biopsy and direct DNA sequencing.[4] Howev-
er, recent studies show that T790M may be identifiable by cfDNA. In cases where an initial activating EGFR mutation was present, T790M mutations were identified by cfDNA in approximately 30% to 40% of cases.[2,5] Still, discordance rates of 20% to 30% when comparing cfDNA testing with tissue-based testing have been reported.[6] The most recent American Society of Clinical Oncology guidelines for molecular testing concerning cfDNA testing state that cfDNA may be used to identify EGFR mutations in lung carcinoma cases with progression on TKIs; however, if plasma results are negative, then tissue sample testing should be pursued.[7]

After reviewing the case at thoracic tumor board, the recommendation was to obtain cfDNA testing for T790M mutation analysis. This was performed and did not reveal the presence of an EGFR T790M mutation. Due to high suspicion for the presence of this mutation, the molecular tumor board also reviewed the case and strongly recommended tissue biopsy. Repeat biopsy was challenging due to progressive disease and the military pattern of the diffuse pulmonary nodules. However, successful CT-guided biopsy obtained a small tissue sample. Due to the limited tumor specimen available, restriction fragment length polymorphism (RFLP) testing was recommended over other assays to test for T790M.

**What the Test Showed**

RFLPs are molecular marker DNA sequences specific for certain restriction endonucleases. Differences in homologous DNA samples can be identified by the presence of DNA fragments of differing lengths following digestion.[8] In the case of the T790M mutation in EGFR exon 20, restriction endonucleases are specific for the CATG sequence of the mutant T790M allele with a C to T base substitution at the third position, which is not present in the wild-type allele.[4] These fragment products are then assessed via RFLP probes that are labeled DNA sequences that hybridize with the DNA fragments following separation via gel electrophoresis, which then correlates with identification of the mutant sequence.[8] RFLP is beneficial in that it can generally be performed reliably in situations where direct DNA sequencing may have a low detection rate, as in when the tumor sample may be small and contaminated with normal tissue or fibrosis, or when < 30% of DNA in the sample is mutated.[4]

**What You Need to Know About Using cfDNA vs RFLP Testing for T790M Mutation**

**ASCO Guidelines:** cfDNA testing for EGFR T790M mutations may be used in patients with lung adenocarcinoma who have progression or secondary resistance to initial TKI therapy

**Case Example:** Patient had EGFR-positive NSCLC previously treated with erlotinib and was symptomatically progressing

**ASCO Guidelines:** cfDNA testing is recommended in situations where obtaining sufficient tumor tissue for molecular testing may prohibit identification of the mutation

**Case Example:** Obtaining lung tissue biopsy was difficult due to poor lung function and location of lung mass; therefore, cfDNA testing was obtained

**ASCO Guidelines:** Tumor tissue testing is recommended if plasma results are negative

**Case Example:** cfDNA results were negative. CT-guided tissue biopsy was obtained, and RFLP testing for EGFR T790M was positive

**KEY SUMMARY**

While recent evidence for cfDNA shows high concordance rates with various other forms of testing, discordance is still reported in 20% to 30% of cases. Therefore, although cfDNA methods are a valuable diagnostic tool, tumor biopsy remains the gold standard.

**How RFLP Testing Informed Management in This Patient**

Osimertinib is a third-generation TKI that is highly selective for EGFR T790M mutations vs wild-type EGFR. It binds covalently to the cysteine-797 residue of the EGFR binding site[9] and has demonstrated clinical activity in EGFR T790M–mutated NSCLC. The drug received US Food and Drug Administration approval in November 2015 for patients with T790M-positive NSCLC who had progressed on other EGFR TKI therapy.[10] National Comprehensive Cancer Network (NCCN) guidelines give a category 1 recommendation to osimertinib for patients with prior EGFR TKI therapy and

Continued on page 504

**T790**

is a gatekeeper mutation of the epidermal growth factor receptor (EGFR). It affects the ATP binding socket of the EGFR kinase domain by substituting a threonine (T) with a methionine (M) at position 790 of exon 20. T790M is also known as Thr790Met.
When to Order an MRI in the Initial Evaluation and Management of Prostate Cancer

Annerleim Walton-Diaz, MD, and Soroush Rais-Bahrami, MD

ABSTRACT: Prostate cancer remains the only solid tumor diagnosed using transrectal ultrasound–guided sampling of the gland, and not an image-based, lesion-directed approach. This technique has limitations in that it underdiagnoses clinically significant disease and overdiagnoses indolent tumors resulting in overtreatment of patients. Technical advances in MRI in the last decade have made this method the preferred imaging modality for prostate anatomy and for risk assessment of prostate cancer. As of 2018, the indications for MRI in the diagnosis and risk assessment of prostate cancer have expanded from preoperative evaluation to the pre-biopsy setting, as well as for surveillance protocols. This article summarizes the current role of multiparametric MRI in the diagnosis, risk assessment, and treatment of prostate cancer.

Transrectal ultrasound–guided (TRUS) biopsy is considered the standard of care for the diagnosis of prostate cancer in men presenting with elevated prostate-specific antigen (PSA) levels or abnormal digital rectal examination. This systematic sextant extended biopsy approach samples approximately 0.04% of the prostate volume and yields cancer detection rates of only up to 40%. [1] Since TRUS biopsies are not targeted, they can lead to overdiagnosis of clinically indolent tumors, while missing clinically significant prostate cancer foci. Recently, several advances in prostate imaging have led multiparametric MRI (MP-MRI) to be the preferred imaging modality for detecting areas suspicious for prostate cancer and allowing for targeted biopsy sampling. Once these areas have been identified, targeted biopsies can be performed using three methods: in-bore MR-guided biopsy, cognitive fusion biopsy, and software-based fusion biopsy. In-bore biopsy involves performing the biopsy with the patient in the MR gantry; cognitive fusion involves using the MRI to estimate the location of the lesion during the ultrasound procedure; and software-based fusion platforms (UroNav, Artemis, Koels, etc) use complex algorithms to register and simultaneously display MR and TRUS images to guide targeted biopsies. [2, 3] Research on MP-MRI and targeted biopsies is ongoing, providing radiologists and urologists with more evidence on their use in the detection and risk stratification of prostate cancer. Herein, we present a summary and our perspective on how to apply this literature to clinical practice.

Biopsy-Naive Setting
Overdiagnosis and overtreatment of indolent prostate cancer is a major concern. As a result, the focus has shifted from merely detecting prostate cancer to identifying clinically significant disease. MRI can identify suspicious areas for cancer and allows for targeted biopsies of these regions.
In a study by Siddiqui et al, 1,003 patients underwent MRI plus concurrent targeted and systematic biopsy sampling. Targeted biopsy detected 30% more high-risk cancers and 17% fewer low-risk cancers compared with the systematic approach.[4] A limitation of this study was its retrospective nature and heterogeneous population. In an attempt to answer this question in prospective randomized trials including only biopsy-naive patients, recent data from the PROMIS study showed that in patients with elevated PSA levels and no prior biopsy, MRI could help safely avoid 25% of unnecessary biopsies. In this study, all patients with elevated PSA levels underwent a 1.5 Tesla MRI. If they had a suspicious lesion on imaging, they underwent transperineal mapping biopsy (as control) plus standard systematic 12-core biopsy. The primary definition used for clinically significant cancer was a Gleason score ≥ 4+3 or median core length (MCL) ≥ 6 mm for which MRI demonstrated a negative predictive value of 89% and a sensitivity of 93%, which is concordant with other previous results published in the literature.[5]

Recently, data from the PRECISION study was published to answer the question of whether MRI plus targeted biopsy vs standard biopsy. If the MRI showed a lesion with a Prostate Imaging Reporting and Data System (PI-RADS) score ≥ 3, the patient underwent targeted biopsy only. The primary outcome was detection of clinically significant prostate cancer defined as Gleason score ≥ 3+4. Clinically significant cancer was detected in 38% of men in the MRI/targeted biopsy group vs 26% in the standard biopsy group (P = .005). Furthermore, the MRI/targeted biopsy group detected fewer clinically insignificant cancers compared with standard biopsy (9% vs 22%; P = .05). The authors stated that MRI with or without targeted biopsy was noninferior to the standard approach.[6] Considering the newest data, increasing evidence supports a possible role of upfront MRI in the biopsy-naive setting. However, since most urologic guidelines do not recommend this approach, it is still not widely adopted as the standard of care.

**Biopsy-Negative Setting**

A particular challenge exists when a patient presents with a persistently elevated PSA level and a negative systematic biopsy. Several approaches, including repeat sextant extended biopsies, anteriorly directed core biopsies, and saturation and transperineal template biopsies, have been attempted to rule out prostate cancer. [7,8] However, since none is targeted to any area of known suspicion, they have yielded inconsistent results. Vourganti et al reported that for 195 men with elevated PSA levels and prior negative biopsies, MRI/ultrasound fusion biopsy plus 12-core TRUS biopsy detected prostate cancer in 37% of patients, 11% of whom had a Gleason score ≥ 8. Standard TRUS biopsy missed 55% of high-grade tumors.[9] Similarly, in a series of 105 patients, Sonn et al reported that targeted biopsy detected more clinically significant prostate cancers and less clinically insignificant cancers compared with TRUS biopsy alone.[10]

Detection of clinically significant cancer in a re-biopsy setting is up to 54%. [11] Sufficient evidence supports a targeted approach in the setting of elevated PSA levels following a negative TRUS biopsy. However, little evidence compares targeted approaches. The National Comprehensive Cancer Network and the American Urological Association recommend MRI and targeted biopsy after one prior negative biopsy.[11-13] The Figure shows a proposed flow diagram for the use of MP-MRI.

**Biopsy-Positive, Low-Risk Patients**

Various management options are available for low-risk prostate cancer, from active...
surveillance to radical treatments, including radical prostatectomy and radiation therapy. Low-risk prostate cancer can harbor either indolent disease or slowly progressive cancer, so safe monitoring for a period of time is possible without losing the window of opportunity to treat the cancer with curative intent when it progresses to higher-risk disease. However, for active surveillance protocols to be effective, they require accurate risk assessment, which means adequate characterization of tumor grade and volume at diagnosis, as well as assertive evaluation of disease progression.

The problem with current active surveillance protocols is that adequate characterization of tumor grade/volume at diagnosis and evaluation of disease progression cannot be reliably assessed with direct comparison to prior sampling using a systematic biopsy approach. Studies have shown that up to 30% of active surveillance candidates are upstaged to higher-risk disease on confi rmatory biopsy. This could be partly explained by the random nature of standard prostate biopsies, which tend to underestimate the burden of disease. Consequently, active surveillance candidates may harbor occult high-risk prostate cancer in lesions missed by a standard biopsy approach. MRI offers the advantage of high image quality for clinical use in this population, providing a high negative predictive value.

Several studies have found MRI can rule out clinically significant cancer, with negative predictive values ranging from 67% to 100%.[14–16] This allows us to counsel patients diagnosed with low-grade and low-volume disease and no visible lesions on MRI who are seeking active surveillance on the low likelihood of presenting with clinically significant prostate cancer. MRI is also useful in risk stratification and diagnosing clinically significant cancer, determined primarily by International Society for Urological Pathology grade on biopsy specimen, which is crucial in counseling patients on best treatment options.

In a study by Stamatakis et al, 85 patients who were active surveillance candidates according to Epstein criteria underwent confi rmatory MRI/ultrasound fusion targeted biopsy and systematic biopsy, after which 29% (25 patients) no longer met the active surveillance protocol criteria.[17] Similarly, in a study by Hu et al, confi rmatory fusion biopsy for men on active surveillance resulted in reclassification of 36% of patients. Men presenting with higher-grade lesions on MRI (grades 4 and 5) were 3 times more likely to be reclassified (odds ratio, 3.2; 95% CI, 1.4–7.1; P = .006).[18]

In a recent study published by Recabal et al, 206 patients with Gleason 3+3=6 disease who were active surveillance candidates underwent MP-MRI and targeted biopsy. The researchers reported that 66% of patients presented with regions of interest on their MRI, and 37% were subsequently reclassified upon biopsy.[19] The efficacy of MP-MRI with targeted biopsy has been confi rmed by other studies that have shown that two-thirds of patients on active surveillance harbor suspicious lesions on MRI, and this increases their likelihood of presenting with clinically significant prostate cancer on repeat biopsy.[20,21] It has been established that MRI improves the diagnostic yield of intermediate- and high-risk prostate cancer by using a targeted approach. This has been of use in identifying safe candidates for active surveillance protocols, and the use of MRI has been shown to increase the confidence and use of active surveillance.[22] However, it must be noted that current data support its use as an adjunct to a standard diagnostic approach.
Expert Approaches Prostate Cancer

Prostate MRI Interpretation Learning Curve

Despite prostate MRI being used worldwide, achieving accurate, consistent interpretations continues to be a challenge. PI-RADS has been of great value in unifying criteria and standardizing terminology.[1] However, it is still a work in progress. There is limited literature evaluating the learning curve of radiologists and how to best implement this technology in the clinic. Despite this, there is consensus that there should be a multidisciplinary effort between urologists, radiologists, and pathologists to enhance image interpretation and utilization in order to achieve the most accurate biopsy results. It appears that the best outcomes are achieved when the radiologist is exposed to a high volume of cases, but also has access to both direct feedback from more experienced colleagues and the patient’s pathology results, as well as through direct participation in focused educational initiatives, such as multidisciplinary tumor boards to enhance the interpretation of prostate MRI images.

Summary

MP-MRI is the preferred imaging modality for prostate anatomy and for risk assessment of prostate cancer. It has proven to be useful in the setting of prior negative biopsies, diagnosis of clinically significant disease, and risk characterization of possible active surveillance candidates. Growing evidence supports its superior detection of clinically significant disease in biopsy-naive patients with elevated PSA levels. However, care must be taken since the implementation of the MRI/targeted biopsy approach requires a multidisciplinary effort, in order to provide appropriate quality and interpretation of images, as well as an effective biopsy to ensure optimal results. One major issue that remains is its high cost, which may improve once the technology becomes more available and more physicians become proficient in the associated biopsy techniques.

Financial Disclosure: Dr. Rais-Bahrami is a consultant for Philips/Invivo Corporation. Dr. Walton-Diaz has no significant financial interest in or other relationship with the manufacturers or providers mentioned in this article.

FINANCIAL DISCLOSURE:

Ms. Wynja, Ms. Hove, and Dr. Powell have no significant financial interest in or other relationship with the manufacturers or providers mentioned in this article.

For references visit cancernetwork.com/lung-EGFR-T790M

Lung Cancer Genomics: EGFR T790M Mutation

Continued from page 500

a known T790M mutation with brain or other symptomatic disease progression. This was largely based on the results of the phase II AURA2 trial, which demonstrated a disease control rate of 92%, with median progression-free survival of 8.6 months, in patients who progressed on previous EGFR TKI therapy.[9] The NCCN guidelines were recently updated to include osimertinib (category 1 recommendation) in previously untreated patients with metastatic NSCLC harboring any sensitizing EGFR mutation based on the FLAURA trial results.[11] Despite activity in T790M–mutated disease, recent evidence suggests resistance to third-generation TKIs can develop after 6 to 17 months via C797S mutation, causing loss of TKI covalent binding site.[9] Still, osimertinib remains the standard of care for NSCLC harboring a T790M mutation.

Outcome of This Case

Once a T790M mutation was confirmed via RFLP testing, osimertinib was started on 05/13/18. Since that time, the patient is doing well and tolerating therapy, without any significant adverse effects. Repeat CT scans following completion of 4 months of therapy show that she is currently responding to therapy, with an overall reduction in tumor burden, consistent with stable disease.

Financial Disclosure: Ms. Wynja, Ms. Hove, and Dr. Powell have no significant financial interest in or other relationship with the manufacturers or providers mentioned in this article.

For references visit cancernetwork.com/when-MRI-prostate

Medical Student Profile

Ms. Wynja is a fourth year medical student at University of South Dakota Sanford School of Medicine, Sioux Falls, South Dakota

Ms. Hove is an Oncology Project Manager, Clinical Researcher, and Registered Nurse with Sanford Health, Sioux Falls, South Dakota

Dr. Powell is an Associate Scientist with the Cancer Biology & Immunotherapies Group at Sanford Research; a Medical Oncologist at Sanford Cancer Center; and Associate Professor with the Department of Internal Medicine at University of South Dakota Sanford School of Medicine, Sioux Falls, South Dakota

cancernetwork.com Visit our coverage of the IASLC 19th World Conference on Lung Cancer at cancernetwork.com/WCLC
All new expanded coverage of hematologic malignancies is available now for the hematology and oncology professional.

- Expanded conference coverage
- Deeper coverage of key topics
- More up to date news

Available at your fingertips!

WWW.CANCERNETWORK.COM/CN/HEMONC
Gene Expression Assays in Early-Stage Breast Cancer

Dr. Sparano discusses the implications of TAILORx, the first trial to use Oncotype DX in clinical decision making.

Results from the first clinical trial to incorporate a gene expression assay—which may potentially facilitate clinical decisions in women with early-stage breast cancer—were recently published in the New England Journal of Medicine in July.[1] The trial, known as the Trial Assigning Individualized Options for Treatment, or TAILORx, examined adjuvant therapy for early-stage, estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

Q: First, can you describe the design of the study, the treatment arms, and how this 21-gene expression assay was incorporated into the trial?

DR. SPARANO: TAILORx is the largest cancer treatment trial ever conducted. It was sponsored by the National Cancer Institute, and the primary purpose of the trial was to integrate the 21-gene assay called Oncotype DX into the clinical decision-making process or paradigm for patients with early-stage breast cancer, based on what we knew at the time about the prognostic and predictive information that the assay told us. We designed the trial to address the questions that remained unanswered at that time, including the potential benefit of adjuvant chemotherapy and how to manage patients with a midrange recurrence score on the 21-gene panel assay.

The target population included patients with ER-positive, HER2-negative, axillary node-negative breast cancer. Together, this represents about 50% of all breast cancers and 8% of all cancers in the United States. Adjuvant chemotherapy is typically recommended for women who have ER-positive breast cancer with a tumor of at least 1 mm, according to a prior position statement issued by the National Institutes of Health in 2000. This was based on prior evidence indicating that even patients who had a relatively low risk of recurrence could potentially benefit from adjuvant chemotherapy. What we embarked upon in the trial was to take patients who met established clinical criteria for a recommendation, or who at least should be considered for adjuvant chemotherapy in accordance with National Comprehensive Cancer Network guidelines, and to either assign or randomize their treatment based on their Oncotype DX recurrence score. Patients who had a recurrence score of 10 or less (17%), which is considered low or very low, were assigned to endocrine therapy alone and followed. Those with a recurrence score of 26 or higher (15% to 20%), which is considered high, were assigned to chemotherapy plus adjuvant therapy. The remaining two-thirds of patients who had a recurrence score between 11 and 25 were assigned to either chemotherapy plus endocrine therapy (standard arm) or endocrine therapy alone (experimental arm). The trial was designed to determine whether endocrine therapy alone was inferior or noninferior to chemotherapy plus endocrine therapy.
Q: What are the key results of this trial, and was anything particularly surprising?

DR. SPARANO: The key results were as follows: in 2015, we reported in the New England Journal of Medicine that patients with a low recurrence score (defined in the study as between 0 and 10) had a 1% risk of recurrence at 5 years with endocrine therapy alone. Obviously, this indicates that these patients would be unlikely to benefit from chemotherapy, and this information was integrated into the 8th edition of the American Joint Committee on Cancer staging and prognostic staging beginning in January of this year. Updated results from this most recent analysis indicated that at 9 years, there was about a 3% distant recurrence rate. Again, this confirms that chemotherapy is unlikely to benefit this population.

The second major finding, which involved the primary endpoint of invasive disease–free survival, was that endocrine therapy was not inferior to chemotherapy in patients who had an Oncotype DX recurrent score of 11 to 25, with very similar clinical outcomes at 5 years and 9 years. At 9 years, the rate of invasive disease–free survival was 83.3% in the endocrine therapy arm and 84.3% in the chemotherapy/endocrine therapy arm, which was not significantly different. There were also similar rates of local, regional, and distant recurrence at 9 years, so the study did meet its primary endpoint.

One of the findings that was of some surprise was that there was an interaction between age and potential chemotherapy benefit. For example, a woman age 50 or younger who had a recurrence score between 21 and 25 did derive some benefit from chemotherapy. Specifically, there was about a 7% difference in distant recurrence rates at 9 years for patients who received chemotherapy, so some benefit was seen in this age group in the 21-to-25 score group. In the overall group, however, there was no benefit, and, certainly, there was no benefit in women over the age of 50 who had a recurrence score of between 11 and 25.

Q: Will the results alter the way clinicians and their patients make decisions about which adjuvant therapy to use?

DR. SPARANO: I think at this point, clinicians can make decisions and treatment recommendations with a much higher level of evidence—really, an unprecedented amount of evidence—and we have a greater degree of precision than we’ve ever had.

One of the key differences in TAILORx vs previous trials was how recurrent score ranges were defined. For example, in the TAILORx study, we defined low as a score of 0 to 10 rather than 0 to 17; this is the group of patients who were assigned to endocrine therapy alone, and we did that because we wanted to be absolutely sure that we were not undertreating these patients. Patients who had a recurrence score of between 11 and 25 were defined as midrange, while the intermediate recurrence score range was originally defined as between 18 and 30. The reason we made this change was also to make sure that we were not undertreating patients who would or would not be randomized to chemotherapy/endocrine therapy.

The 10-year distant recurrence rate of about 5% observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial—the original trial in which patients were randomized to chemotherapy/endocrine therapy or endocrine therapy alone—was irrespective of chemotherapy use for patients with a recurrence score between 11 and 25 and turned out to be almost identical to what we observed in TAILORx. This supported our decisions regarding changing the recurrence score ranges that we used in TAILORx compared with the ranges that were initially defined as low, intermediate, or high.

Q: Are these trial results particularly practice-changing?

DR. SPARANO: I think practice has already changed since the introduction of this assay to clinical practice in 2004. There has definitely been a decline in the use of chemotherapy, largely in patients who had a recurrence score in the lower range of this study. For those who had a recurrence score in the middle range, which was the group that was randomized in this study, there was still some variability in chemotherapy use, but chemotherapy use had declined. What this study did, however, was provide much more definitive information about potential benefit or lack of benefit in patients who had a midrange recurrence score.

Q: Are there any other details from the trial that you think are particularly important that may be overlooked from just reading the trial result publication? Can any results be interpreted in different ways by different clinicians?

DR. SPARANO: I think one of the most important and misunderstood aspects of the trial relates to what I described earlier. By this, I mean the recurrence score ranges we used in the TAILORx trial compared with the ranges that were initially reported in the NSABP B-14 validation study conducted in patients with ER-positive,
node-negative disease treated with 5 years of tamoxifen, and in the NSABP B-20 trial, in which patients with ER-positive, node-negative disease were randomized to receive chemotherapy plus tamoxifen or tamoxifen alone. When we designed the trial back in 2004 and 2005, we actually re-analyzed the B-20 data using these different recurrence score cutoffs, defining a score of 11 to 25 as midrange, and we did that for several reasons. First, the original B-20 cohort included patients who had HER2-positive disease, about 12% of the population. Almost all of these patients have a high recurrence score. Since we were designing this trial exclusively for a HER2-negative population, we needed to adjust the recurrence score ranges to actually reflect the population to whom we were offering the trial. This was one of the reasons that we dialed down the recurrence score at the upper range of a high score from 31 or higher to 26 or higher. That was a key point. Plus, when we analyzed the B-20 data, we found a similar chemotherapy benefit for both of these ranges. A similar benefit from chemotherapy was also seen after excluding HER2-positive patients, regardless of whether the high score cutoff was 26 or higher or 31 or higher. And, finally, if a score of 26 or higher was used as the high score cutoff point rather than 31 or higher, more patients who could potentially benefit from chemotherapy will be captured, therefore minimizing the potential for chemotherapy undertreatment. I think that this is one of the most critical and misunderstood issues about the trial. In addition, I think the results of the trial will change the definitions of low-, intermediate-, and high-risk scores. Eventually, I think the recurrence score will become more or less a binary test used to identify a group of patients who have a high recurrence and will benefit from chemotherapy, as well as those with a low or intermediate score who won’t benefit from chemotherapy.

Q: Lastly, in the context of this trial, do you think the way the 21-gene expression assay is utilized in the clinic has evolved?

DR. SPARANO: Yes, absolutely. I think the next potential application is expanding the use of this assay to patients who have node-positive disease. This has already been tested in the RxPONDER trial, which enrolled patients with 1 to 3 positive axillary nodes and ER-positive, HER2-negative disease. Individuals with a recurrence score of 25 or lower were randomized to chemotherapy plus endocrine therapy, the standard arm, or endocrine therapy alone, the experimental arm. The trial has been completed and we are awaiting the results. However, some early evidence from the prospective Plan B trial is that women with a recurrence score of 11 or less with up to 3 involved axillary lymph nodes do well with endocrine therapy alone, suggesting that some women with small-volume disease involving one axillary node may be spared chemotherapy.

Other ongoing trials are integrating other gene expression assays into clinical decision making, and their results will also be important. Lastly, ongoing efforts to develop tools that integrate information from both the recurrence score—which captures both prognostic and predictive information—and clinical and pathologic features such as age, tumor size, and grade, may be able to provide more accurate and refined estimates for prognosis (risk of recurrence with endocrine therapy alone) and prediction (chemotherapy benefit when chemotherapy is added to endocrine therapy). I think that we will see these tools becoming available in the near future. One such tool, called the RSPC (Recurrence Score-Pathology-Clinical), is available right now. This is an online tool for providers available on the Genomic Health website, and it allows clinicians to plug in the recurrence score, as well as age, tumor size, and tumor grade, to help provide patients with more accurate estimates about their individual risk of recurrence. A revision of this tool is being developed now, and it may be able to provide predictive information regarding chemotherapy benefit.

FINANCIAL DISCLOSURE: The author has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/breast-gene-expression-assays
Approaching Use of CDK4/6 Inhibitors in Metastatic HR+, HER2- Breast Cancer

This case reviews the proper use of initial systemic therapy with the three FDA-approved CDK4/6 inhibitors: palbociclib, ribociclib, and abemaciclib.

An otherwise healthy 58-year-old woman with a history of breast cancer presents to the clinic with newly diagnosed metastatic disease. Nine years prior, she received a diagnosis of left-sided, stage IIIA (T2N2M0), grade 1 infiltrating lobular carcinoma (ILC). She was premenopausal at the time. Her original breast biopsy revealed ILC, with estrogen receptor (ER) positivity (44%), progesterone receptor (PR) negativity, and human epidermal growth factor receptor 2 (HER2) negativity by fluorescence in situ hybridization (FISH). Left mastectomy was completed, and an axillary lymph node dissection showed a 4.0-cm tumor and 6/12 positive axillary nodes. Postoperative staging with PET/CT showed no evidence of distant metastatic disease. She completed 6 cycles of adjuvant docetaxel, doxorubicin, and cyclophosphamide chemotherapy followed by postmastectomy chest wall and regional nodal radiation, and was started on tamoxifen. A contralateral risk-reducing mastectomy and bilateral salpingo-oophorectomy were completed about 1 year after diagnosis. The patient stopped her adjuvant tamoxifen after approximately 1 year due to side effects and loss of health insurance. Recently, the patient developed increasing abdominal pain, bloating, and constipation with smaller-caliber stools. Abdominal CT showed a mass in the transverse colon with ascites and peritoneal nodularity (Figure). No obvious liver metastasis or cirrhosis were present. Colonoscopy was attempted, but the stricture resulting from the colon mass was unable to be traversed. A palliative exploratory laparotomy with...
CORRECT ANSWER: A. Letrozole + palbociclib
Continued from page 513

subtotal colectomy was performed due to impending complete obstruction. The pathology report revealed infiltration of poorly differentiated carcinoma—most consistent with breast primary—in the sampled small intestine, large intestine, appendix, and mesentery. Margins were positive. Immunologic stains were positive for mammaglobin, GATA binding protein 3 (GATA-3), and cytokeratin 7 (CK7). The sample was positive for ER (3+, 90%) and PR (3+, 5%) but negative for HER2. Following surgery, the patient’s normal bowel function returned, and she was referred to oncology for treatment of her newly diagnosed metastatic breast cancer.

Discussion
This case involves a postmenopausal woman with a history of ILC who has newly diagnosed ER/PR-positive, HER2-negative metastatic breast cancer, with disease that has spread to the gastrointestinal tract. She is presenting for initial systemic therapy.

Breast cancer is the most common cancer diagnosed in women in the United States; about 60% to 70% of cases are hormone receptor (HR) positive.[1] While infiltrating ductal carcinoma (IDC) is the dominant histologic breast cancer subtype, ILC represents about 10% to 15% of cases.[2] As illustrated in this case, ILC has unique patterns of potential metastatic recurrence with more frequent involvement of the gastrointestinal tract, gynecologic organs, and peritoneum compared to IDC.[3] Systemic treatment of ILC does not differ from that of IDC at present, and therapy in the metastatic setting should be based on the patient’s HR and HER2 status.

The preferred first-line treatment of metastatic HR-positive, HER2-negative breast cancer is endocrine therapy, unless the patient has impending visceral crisis.[4,5] For postmenopausal women with no prior endocrine therapy and metastatic disease, the current National Comprehensive Cancer Network (NCCN) guidelines recommend either an aromatase inhibitor (AI) such as anastrozole; tamoxifen, a selective ER modulator; fulvestrant, a selective ER downregulator; or a combination of a cyclin-dependent kinase (CDK) 4/6 inhibitor with an aromatase inhibitor.

If single-agent endocrine therapy is desired, an AI or fulvestrant is preferred over tamoxifen based on reduced time to progression.[6,7] The FALCON trial compared fulvestrant vs the nonsteroidal AI (NSAI) anastrozole in patients with HR-positive, HER2-negative advanced breast cancer in the first-line setting. Progression-free survival (PFS) was significantly improved in the fulvestrant arm compared with the anastrozole arm, further supporting the use of fulvestrant (16.6 months vs 13.8 months; hazard ratio [HR], 0.797; 95% CI, 0.637–0.999; P = .0486).[8]

While single-agent endocrine therapy remains an option for some patients, adding CDK4/6 inhibitors to NSAIIs markedly increases the PFS in patients with metastatic HR-positive, HER2-negative breast cancer in the first-line setting.[9] The CDK4/6-cyclin D-retinoblastoma (RB) pathway functions as a critical checkpoint for cell cycle progression and is particularly active in HR-positive breast cancer.[10] CDK 4 and 6 bind to D-type cyclins to form an active complex, which phosphorylates the RB protein, resulting in the release of the E2F transcription factor. This leads to cellular transition from G1 (pre-DNA synthesis) to the S (DNA synthesis) phase of the cell cycle, allowing cell cycle progression.[11] Cyclin D is a transcriptional target of the ER and can be upregulated by ER signaling and the MAPK-ERK and PI3K-AKT signaling pathways.[12] In HR-positive breast cancer, RB function is generally retained, making CDK4/6 inhibition effective at stopping cell cycle progression.[13]

In the first-line setting, three CDK4/6 inhibitors—palbociclib, ribociclib, and abemaciclib—are all approved by the US Food and Drug Administration (FDA) in combination with NSAIIs based on the results of the phase III PALOMA-2, MONALEESA-2, and MONARCH-3 trials, respectively. PALOMA-2 was a double-blind randomized clinical trial that enrolled 666 postmenopausal patients with HR-positive, HER2-negative advanced breast cancer. Patients were randomized to letrozole plus palbociclib or letrozole plus placebo; the primary endpoint was PFS. Significant improvement in median PFS was seen at 14.4 months with letrozole-placebo and at 24.8 months with letrozole-palbociclib (HR, 0.58; 95% CI, 0.46–0.72; P < .001).[14] Improved PFS was seen in all subgroups, including those with visceral metastasis (HR, 0.63; 95% CI) and lobular carcinoma (HR, 0.46; 95% CI), which is relevant to this case. Overall survival data are not yet available for PALOMA-2, MONALEESA-2, or MONARCH-3.

The MONALEESA-2 trial also enrolled patients with HR-positive, HER2-negative advanced breast cancer without prior systemic treatment for metastatic disease. Participants were randomized to letrozole plus ribociclib or letrozole plus placebo.[15] As with the PALOMA-2 trial, this study also found an increase in the primary endpoint of PFS in the letrozole plus ribo-
significant improvements in PFS seen with fulvestrant as second-line therapy based on FDA-approved combination with anastrozole or letrozole.[18] Bo-NSAI arm and the abemaciclib-NSAI arm, respectively. Follow-up analysis found median PFS to be 14.8 months and 28.2 months for the placebo-NSAI arm and the abemaciclib-NSAI arm, respectively.[18] Beyond their first-line indications, palbociclib, ribociclib, and abemaciclib are all FDA-approved in combination with fulvestrant as second-line therapy based on significant improvements in PFS seen in the PALOMA-3, MONALEESA-3, and MONARCH-2 trials.[19-21] Additionally, the MONALEESA-3 trial included patients with up to one prior line of endocrine therapy in the advanced setting and led to the recent approval of ribociclib and fulvestrant in the first-line setting. Data also support the use of CDK4/6 inhibitors in premenopausal women. Namely, the MONALEESA-7 trial showed an increased PFS in premenopausal women with advanced HR-positive breast cancer with ribociclib plus goserelin and either tamoxifen or a NSAI.[22] Finally, abemaciclib is unique in its single-agent activity in heavily pretreated patients and in those with brain metastasis.[23,24] In summary, palbociclib, ribociclib, and abemaciclib all significantly prolong PFS when added to an NSAI in the first-line setting. Overall survival data are not yet available, and extensive subset analysis has not revealed a predictor of response beyond HR positivity.[25] Response rates are high for combination therapy with a CDK4/6 inhibitor, and this treatment may be considered in patients with symptomatic visceral disease.

The decision on which CDK4/6 inhibitor to use for an individual patient should be based on the unique features of these agents, including their side effect profiles. The most common dose-limiting toxicity seen with palbociclib and ribociclib is neutropenia. In the PALOMA-2 trial, 66.4% of patients on palbociclib developed grade 3 or 4 neutropenia compared with 1.4% of patients in the placebo group.[14] Febrile neutropenia was uncommon. Administration of palbociclib or ribociclib requires complete blood count monitoring, and dose modifications may be necessary. QT interval prolongation has been reported with ribociclib (3.3% of patients in MONALEESA-2), and electrocardiography monitoring is recommended. Abemaciclib results in less neutropenia, with only 21.1% of patients having grade 3 or 4 neutropenia compared with 1.2% of patients taking placebo in the MONARCH-3 trial.[17] Diarrhea is the most common dose-limiting toxicity of abemaciclib: 81.3% of patients developed diarrhea compared with 29.8% of those taking placebo. However, most experienced grade 1 (44.6%) or grade 2 diarrhea (27.2%), while only 9.5% experienced grade 3 and no patients experienced grade 4. Increased thrombembolic events have also been observed with abemaciclib (4.9% vs 0.6% with placebo).

Based on these new trials, letrozole and palbociclib (Answer A) is the recommended first-line treatment for this patient with postmenopausal, HR-positive, HER2-negative metastatic breast cancer rather than endocrine therapy alone (Answer B). Specifically, the PALOMA-2 trial, including the lobular carcinoma and visceral metastasis subgroup analysis, demonstrated increased PFS with letrozole and palbociclib. Given the patient’s recent colectomy, the side effect profile of palbociclib is more desirable than that of abemaciclib, which includes increased risk of severe diarrhea. Combination therapy with ribociclib and letrozole is another reasonable option for our patient. Currently, fulvestrant and abemaciclib (Answer C) is approved only as second- or third-line therapy based on the results of the PALOMA-3 trial discussed previously, making this answer choice incorrect. Chemotherapy, such as capecitabine (Answer D), is not recommended for first-line treatment of metastatic HR-positive breast cancer, since the patient is not in visceral crisis.

Outcome of This Case

The patient was started on letrozole and palbociclib for initial treatment of her HR-positive, HER2-negative metastatic breast cancer. She is still receiving treatment and is being monitored for disease progression.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/CDK4-CDK6-inhibitors

---

Dr. Weiss
is Resident Physician, Department of Internal Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Dr. Afghahi
is Assistant Professor of Medicine, Department of Oncology, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Dr. Shagisultanova
is Assistant Professor of Medicine, Department of Oncology, University of Colorado Anschutz Medical Campus, Aurora, Colorado

Dr. Diamond
is Associate Professor of Medicine, Department of Oncology and Program Chair, Department of Medicine, University of Colorado Anschutz Medical Campus, Aurora, Colorado

---

CANCERNETWORK.COM    ONCOLOGY | 515
Herb-Drug Interactions in Cancer Care

K. Simon Yeung, PharmD, LAc, Jyothirmai Gubili, MS, and Jun J. Mao, MD, MSCE

ABSTRACT: Herbs have served as medicine throughout human history. Since the passage of the Dietary Supplement Health and Education Act (DSHEA), inconsistent regulatory practices have resulted in widespread, indiscriminate use of herbal supplements. Available data indicate that cancer patients use these products (along with standard treatments) more often than the general population. The reasons cited for such use include improving health, reducing the risk of recurrence, and reducing the side effects of cancer treatments. Herbs, however, contain biologically active compounds and can potentially interact with prescription medications, including chemotherapy drugs. We describe the mechanisms via which these interactions may occur, as divided into pharmacokinetics and pharmacodynamics. We highlight four popular herbs and a medicinal mushroom commonly used by cancer patients—turmeric, green tea, ginger, ashwagandha, and reishi mushroom—along with reports of their interactions with standard drugs. We conclude by emphasizing the need to inform patients and physicians about herb-drug interactions and how to advise patients on appropriate use of herbal supplements to minimize the risk for interactions.

Introduction
Before the era of modern pharmaceuticals, plants were the major source of medicine. Today, herbal products are classified as “dietary supplements” under the Dietary Supplement Health and Education Act (DSHEA), and are used as part of a complementary health approach by many in the United States.[1] Compared with healthy populations, cancer patients appear to be more frequent users of these supplements.[2,3] The majority employ them as adjuncts to chemotherapy or other cancer treatments to alleviate symptoms and to prevent recurrence. In addition, cancer survivors have reported greater use, with one-third having taken herbs.[4] This use is driven by specific health beliefs and as recommended by families and healthcare providers.[3,6] Herbal products typically are considered “natural” and “safe” compared with invasive treatments.

These products, however, are not regulated as drugs by the US Food and Drug Administration (FDA).[7] Poor manufacturing practices, lack of standardization, varied amounts of active ingredients, product contamination, and serious herb-drug interactions have been reported.[8] In this article, we focus on “herbs” used by cancer patients and survivors. These products are derived from botanical sources used as traditional medicine, dietary supplements, food, or spices.

Herb-Drug Interactions
Herb-drug interactions started appearing in the literature in the 1980s, when reports described the interactions of St. John’s wort and grapefruit juice with several prescription drugs. Despite increasing concerns, the term “herb-drug interactions” was only introduced as a Medical Subject Headings (MeSH) term in 2004. It was defined as “the effect of herbs, other plants, or plant extracts on the activity, metabolism, or toxicity of drugs.”

To fully appreciate the clinical impact, both the drug and the herb must be studied together in humans. Very few herbs and drugs have been studied in this way,
however, and much of the current knowledge rests on data from in vitro, animal, and in silico models. Therefore, understanding the mechanisms of interaction is crucial in predicting the clinical effects.

The basic mechanisms of herb-drug interactions are similar to other drug interactions. They can be divided into pharmacokinetics, which describe how herbs can influence the absorption, distribution, metabolism, and excretion of other drugs; and pharmacodynamics, which define how herbs can alter the actions of other drugs when used concurrently.

**Pharmacokinetic Studies**

Studies of pharmacokinetics focus on the actions of microsomal enzymes of the cytochrome P450 (CYP) family and membrane transporters such as P-glycoprotein (P-gp), which play important roles in the absorption and metabolism of many prescription drugs. Compounds derived from botanicals are known to interfere with CYP enzymes and transporters, thereby affecting the way substrate drugs are metabolized. Early studies found that furanocoumarins from the rind of grapefruit irreversibly bind with CYP3A4, resulting in a sevenfold increase in the intestinal absorption of simvastatin.\[^9\] Among the drugs used in cancer care, grapefruit juice can increase the blood levels of cyclosporine by 38%, tacrolimus by 110%, and oxycodone by 67%.\[^10\]

Another compound, hyperforin, is a major constituent of St. John’s wort, an herb commonly used to treat depression. It induces both CYP and P-gp by activating the pregnane X receptor.\[^11\] Studies in humans show that it can reduce the blood levels of irinotecan, a major CYP3A4 and P-gp substrate, by 40% when used concomitantly.\[^12\] Tyrosine kinase inhibitors such as imatinib, osimertinib, and lapatinib, as a group, are also major CYP3A4 substrates.\[^13\] Dose adjustments may be required when they are used concomitantly with another drug or herb that is a strong inducer or inhibitor of the CYP3A4 enzyme. Tamoxifen is another widely used medication that relies on CYP2D6 and CYP3A4 to be metabolized to its active form. Herbs that inhibit these enzymes can lower the drug’s efficacy. Genetic polymorphisms may also play a role in drug metabolism.

**Pharmacodynamic Interactions**

These comprise the interactions between drugs and herbs resulting in changes in their physiologic effects. In cancer care, medications that are prone to pharmacodynamic interactions include chemotherapeutic agents, anticoagulants, hormones, and immunosuppressive agents.

**Chemotherapeutic agents vs herbs with antioxidant properties**

As a class, chemotherapeutic agents have the potential to interact with herbs that possess antioxidant properties. For example, vitamin C, vitamin E, and coenzyme Q10—often used as supplements during cancer treatment—may interfere with the absorption or metabolism of chemotherapeutic agents. It is important for cancer patients to discuss their use of herbs and supplements with their healthcare providers to ensure that the treatment plan is optimized for maximum benefit and minimal risk.

---

**Perspective by Donald I. Abrams, MD**

Botanicals: Weighing Patients’ Individualized Needs is Best

The use of complementary therapies is one way that cancer patients can empower themselves during their course of treatment. Rather than a blanket proscription against use of all supplements during treatment, it is best to keep each patient’s goals of care in mind when discussing the use of botanicals. If the goal is to cure the patient’s cancer or treatment is being given adjunctively to decrease the risk of recurrence, delaying most botanicals until after active treatment seems prudent. That said, while Yeung and colleagues caution against use of the reishi mushroom, a large body of literature, mostly from Asia, suggests that mushrooms are safe and effective to combine with both radiation and chemotherapy during active cancer therapy (See NCI’s PDQ Cancer Information Summaries: Integrative, Alternative and Complementary Therapies). However, because of their immune-enhancing potential, I recommend against their consumption by patients with lymphoproliferative malignancies or those on immunotherapies. This caution is based totally on theoretical concerns, without supporting evidence from the literature to date.

If treatment is palliative and cure is not likely, allowing the patient to experience some sense of control through judicious use of supplements during treatment seems acceptable. I am often faced with patients bringing in a shopping bag full of supplements that have been recommended to them. If they seem wedded to a regimen they are currently taking, trying to dissuade them seems inappropriate. If some of their botanicals seem unsafe or excessively expensive, I will advise them to consider discontinuing those. Patients are frequently advised, most often by radiation oncologists, to eat only white foods. Although it is wise to avoid potent antioxidant supplements—vitamin C, vitamin E, and coenzyme Q10—during radiation and chemotherapy, eating antioxidant-rich foods is generally regarded as safe.

---

Dr. Abrams is an Oncologist at Zuckerberg San Francisco General Hospital; Integrative Oncologist, UCSF Osher Center for Integrative Medicine; and Professor of Clinical Medicine, University of California, San Francisco
with many herbs, but their interactions with herbs that possess antioxidant activity have drawn much attention. Drugs such as anthracyclines, platinum compounds, and alkylating agents generate free radicals for their cytotoxic effects. Theoretically, antioxidants may render these drugs less effective. Reviews of studies, however, showed mixed results that suggest a potential for reducing toxicities but no impact on survival times.[14,15] The variation in forms and dosages of antioxidants and chemotherapy drugs used may contribute to the differences in these findings.

Some also argue that antioxidants can help minimize chemotherapy-induced adverse effects. Studies in which low-dose antioxidants were used following chemotherapy suggest that they may reduce toxicity and prolong survival. [16] Unlike prescription drugs such as amifostine and mesna, however, which can protect organs by neutralizing free radicals, no definitive data exist to show that antioxidant supplements can selectively protect the healthy tissues without reducing the cytotoxic effects of chemotherapy drugs. Until conclusive evidence becomes available, oncologists should advise patients to avoid supplements, including herbs, with antioxidant effects during cancer treatment.[17]

**Anticoagulants vs herbs that have anticoagulant effects**

Anticoagulants are commonly used to prevent deep vein thrombosis and pulmonary embolism in bedridden cancer patients. Warfarin is from an older generation of anticoagulants that has a narrow margin of safety and requires careful monitoring. Earlier studies showed that botanicals such as dang gui may have additive effects, thereby elevating the risk of bleeding and hemorrhage.[18] Patients who are thrombocytopenic secondary to cancer, or due to chemotherapy, should avoid herbs that have anticoagulant effects to decrease the risk of major bleeding. Those undergoing surgery should not use these herbs at least 2 weeks prior to avoid prolonged bleeding time or excessive blood loss during surgery.[19,20]  

**Hormonal therapies vs phytoestrogenic herbs**

Hormonal therapies are often used as adjuvants for treating hormone-sensitive cancers. Tamoxifen, a drug that is widely used for treating estrogen receptor–positive breast cancer, acts by blocking the estrogen receptor, resulting in disease remission and prolonged survival. Botanicals such as red clover and soy products are known to have mild estrogenic effects and may stimulate the growth of hormone-sensitive cancers.[21,22] Furthermore, genistein, an isoflavone found in soy, has been shown to interfere with tamoxifen.[23,24] Data from clinical studies, however, have shown positive associations between soy food consumption postdiagnosis and a nonsignificant reduced risk of breast cancer–specific mortality, as well as a statistically significant reduced risk of recurrence.[25] Consumption of soy foods also reduced mortality and recurrence, regardless of tamoxifen use, in breast cancer patients.[26] For patients who wish to incorporate soy for cancer prevention, oncologists should recommend soy foods but not dietary supplements.

**Immunosuppressive agents vs immunostimulant herbs**

Transplantation patients often rely on immunosuppressive agents to minimize rejection of the transplanted organ. These drugs, however, are prone to interact with herbs. For instance, the commonly used herb St. John’s wort reduces the plasma level of cyclosporin and tacrolimus by more than 50%.[27] Astragalus, a well-known herb used for its tonic property in traditional Chinese medicine, can also potentially negate immunosuppressive drugs due to its immune-stimulatory effects.[28]

**Common Herbs and Their Potential Interactions**

**Turmeric**

Native to South Asia, turmeric (Curcuma longa, Curcuma domestica) has a long history of use. The “ginger-like” yellow-orange–colored rhizome is used as a spice. In traditional medicine, it is often used to improve circulation and digestion. Turmeric extracts are marketed as dietary supplements for arthritis and for cancer prevention. The active constituent is curcumin, which has been researched extensively. Preliminary data indicate that curcumin helps relieve adverse effects due to cancer treatments. A topical turmeric-based cream was reported to reduce radiotherapy-induced dermatitis.[29] Oral curcumin also improved cachexia and general health in colorectal cancer patients.[30] In a phase II trial involving 21 patients with advanced pancreatic cancer, curcumin demonstrated bioactivity by downregulating nuclear factor-κB and cyclooxygenase-2. Despite limited absorption, antitumor response was seen in two patients.[31] Curcumin has been reported to be safe, but due to its antioxidant properties, it can interact with chemotherapy drugs such as cyclophosphamide and doxorubicin.[32] It is also known to interfere with CYP450 enzymes and may interact with substrate drugs.[33] In addition, because of its antiplatelet property, curcumin can increase the risk of bleeding when used with anticoagulants.[34]

**Green tea**

The leaves of green tea (Camellia sinensis) are used to prepare tea. With origins in Asia and now consumed worldwide, green tea...
and its extracts have been used to prevent and treat hyperlipidemia, hypertension, atherosclerosis, and cancer. The active constituent of green tea extract is epigallocatechin-3-gallate (EGCG).

Green tea extract has demonstrated chemopreventive activity by preventing formation of precancerous polyps, inhibiting proliferation of breast cancer cells, and by inducing apoptosis in bladder cancer cells.[35-37] A large case-control study reported a reduction in the risk of breast cancer following intake of mushrooms (both fresh and dried forms) and green tea in premenopausal and postmenopausal women.[38] It may also reduce the risk of myelodysplastic syndromes.[39] A meta-analysis, however, failed to find any benefits for prevention of gastric cancer.[40]

Topical application of green tea extract has been shown to be effective against external genital and perianal warts.[41] One such extract, seneocatechins, is approved by the FDA. Preclinical studies, however, have shown that the polyphenolic constituents in green tea can negate the therapeutic effect of bortezomib, an anticancer drug, while increasing the risk of toxicity when used with tamoxifen and irinotecan.[42-44] Elevated risk of hepatotoxicity has also been reported when used with acetaminophen and when consumed on an empty stomach.[45,46]

A clinical study showed that taking 800-mg EGCG is associated with elevated liver enzymes, which was reversible following cessation of consumption.[47] According to an observational study, intake may enhance the risk of breast cancer in postmenopausal women. Daily consumption of green tea varied between 1 and 3 cups. The risk appears to be modified by the age at onset of tea drinking, with a protective effect for women who started before age 20 years and an increased risk for those who started after age 50 years.[48] Green tea extract is also known to interfere with the CYP450 3A4 enzyme and may affect the intracellular concentration of drugs metabolized by this enzyme.[49]

**Ginger**

Ginger, the rhizome of the plant *Zingiber officinale*, has long been used as a culinary spice and medicine in Asian and Arabic traditions to treat the common cold, headache, and fevers, as well as gastrointestinal and inflammatory disorders. Clinical trials indicate that ginger can effectively reduce nausea and vomiting due to pregnancy, motion sickness, and following surgery.[50-53] Findings of its efficacy in preventing chemotherapy-induced nausea are also promising.[54,55] A systematic review of randomized, controlled, and crossover trials, however, found that data are inconclusive to recommend clinical use.[56]

A longitudinal study reported that in patients receiving warfarin, concomitant use of ginger elevated the risk of bleeding (odds ratio, 3.20; 95% CI, 2.42–4.24).[57] A common warning is to discontinue use of ginger supplements in the perioperative setting due to the potential risk for increased bleeding.[58] According to a recent systematic review, findings of platelet aggregation and coagulation properties of ginger are equivocal.[59] Future studies are needed for definitive data.

### TIPS How to discuss herb-drug interactions with patients

**ASK ABOUT HERBAL USE.** Be aware that some patients may consider these products as food or spices. Many also use multiple products that have similar ingredients, making the cumulative effect more potent.

**KEEP AN OPEN MIND.** Even though very few herbs have been proven useful in treating cancers, some can help relieve symptoms.

**EXPLAIN THE REASONS.** If you think a product is not the right choice, tell patients why. For example, the herb may increase the risk of toxicity or it may reduce the effectiveness of chemotherapy drugs. If this is not discussed, the patient may continue to use these products, but refrain from divulging that information.

**EDUCATE.** Inform patients about the potential interactions with other drugs or lab tests.

**MONITOR FOR ADVERSE EFFECTS.** When you determine that an herbal product is suitable, encourage the patient to report any signs and symptoms following use.

**CONSIDER RECOMMENDING NONPHARMACOLOGIC INTERVENTIONS.** When herbal supplements are not appropriate, you can recommend therapies such as acupuncture, yoga, and meditation. These have been proven effective in mitigating symptoms and improving quality of life. More patients are beginning to be receptive to such suggestions.

**REFER TO AN INTEGRATIVE MEDICINE SPECIALIST** who has training in balancing the benefits and risks of herbal therapy and other integrative approaches to cancer treatment and survivorship.
Ashwagandha
A shrub valued in Ayurveda for its medicinal effects, ashwagandha (*Withania somnifera*) is used to relieve stress, anxiety, and fatigue; to treat osteoarthritis and skin diseases; to rejuvenate; and to improve endurance. It is being widely promoted as an anxiolytic.

The active constituents include alkaloids, saponins, and steroidal lactones known as withanolides. Clinical studies show its utility in relieving anxiety; in producing analgesic, anti-inflammatory, and chondroprotective effects in patients with knee joint pain; and in mitigating chemotherapy-induced fatigue, along with improving quality of life, in a small study of breast cancer patients.[60-62]

Although it is generally considered safe, ashwagandha has been reported to potentiate the sedative effects of triazolam.[63] Future studies to evaluate safety are warranted because of the recent rise in the popularity of this herb.

Reishi mushroom
Although not a botanical, reishi (*Ganoderma lucidum*) is a medicinal mushroom that is commonly used by cancer patients. It is an important component of traditional medical systems in Asia and is used to strengthen the body, increase vitality, and to treat insomnia.

Preliminary data show that reishi is effective in enhancing immune responses in advanced-stage cancer patients.[64] Remission of hepatocellular carcinoma has also been reported in a few cases.[65] Extracts from the fruiting body as well as spores have been employed in clinical trials for cancer. Nevertheless, preclinical studies have led to concerns about its use. Because of its antiplatelet effects, reishi can increase the risk of bleeding when used with anticoagulant/antiplatelet medications.[66] Additionally, due to its antioxidant property, it may potentially reduce the effectiveness of some chemotherapeutic agents.[67] It can also alter immune responses.[64] Additionally, reishi has been reported to inhibit CYP450 enzymes and may increase the toxicity of substrate drugs.[68]

Advising Patients
Research suggests that patient–provider communication about herbal use is very rare in the oncology setting.[69] Although many oncologists are not trained in the use of herbs, they have an important role in advising and guiding patients as part of the overall treatment plan. Where scientific evidence is lacking, physicians often advise against supplementation by erring on the safe side. But such a conservative approach can also discourage communication about dietary supplement use.

For many oncologists, finding credible information about dietary supplements, especially herbs, can also be tricky. Standard drug databases (eg, Lexicomp) have comprehensive information on prescription drugs, but the entries on herbal supplements are often limited. On commercial websites that promote herbal products, information about potential adverse effects or interactions is often minimized or ignored. To address this issue, the Integrative Medicine Service at Memorial Sloan Kettering Cancer Center has developed the “About Herbs” website: www.mskcc.org/aboutherbs. It contains objective information on more than 280 dietary supplements and bogus treatments used by cancer patients. Mechanisms of action underlying the effects of these products and the drugs with which they can potentially interact are listed. This award-winning site, which has both healthcare professional and consumer versions, is available free of charge to clinicians and patients. Other databases that provide reliable information include the National Institutes of Health’s Office of Dietary Supplements (https://ods.od.nih.gov), which is free to access, and ConsumerLab.com and the Natural Medicines Comprehensive Database (www.naturaldatabase.com), both of which charge for their services.

Herbal product use by cancer patients has significantly risen in the last few decades. However, these agents lack governmental oversight and are biologically active, with a potential for interactions with chemotherapy and other cancer drugs. Fostering open communication on herbal product use between patients and physicians is therefore important. Physicians should discuss expectations with their patients, clearly communicating the potential benefits and risks involved.

**FINANCIAL DISCLOSURE:** The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

For references visit cancernetwork.com/herb-interactions