DANIEL MCFARLAND ON
Suicide Risk in Patients With Cancer
‘Ambivalence, negotiation, equivocation’

Review Article
Strategies in BRAF-Mutant Metastatic Colorectal Cancer
Hey Min Lee, Van Morris, Stefania Napolitano, Scott Kopetz

Point/Counterpoint
AS in Gleason 3+4 Prostate Cancer
A. Bhat and S. Punnen vs I. Madueke and M.R. Abern

Interview
Gastric Cancer Prevention: Targeting H. pylori
Keith T. Wilson
Meet the New Face of Oncology.

You commit to a calling most never could.

ONCOLOGY has renewed its own commitment by redesigning the delivery and presentation of peer review and perspective.

Across the pages of print issues and online at CancerNetwork, our journal is your journal.

Explore the new ONCOLOGY at cancernetwork.com/oncology-now
Cover | Review

Suicide in Patients With Cancer: Identifying the Risk Factors
Daniel C. McFarland, DO, Leah Walsh, MS, Stephanie Napolitano, MA, Jody Morita, MD, and Reena Jaiswal, MD
PERSPECTIVE: Nora Janjan, MD, MPSA, MBA

Memorial Sloan Kettering Cancer Center researchers review the prevalence of and risk factors for suicide among patients with cancer, as well as how to recognize high-risk patients.

Interview

Subtypes Guide Individualized Soft Tissue Sarcoma Treatment
Margaret von Mehren, MD
PERSPECTIVE: Jill Kestel, PharmD, BCOP

Dr. von Mehren, of Fox Chase Cancer Center, discusses current considerations and challenges in the management of patients with soft tissue sarcoma, as well as recent clinical trial data.

Insights From an Oncology Pharmacist

Considerations When Initiating Neratinib for Breast Cancer
Meagan S. Barbee, PharmD, BCOP

An oncology pharmacist explores the prevention and treatment of diarrhea in patients using neratinib.

Table of Contents continued on page 204
Review Article
206 Evolving Strategies for Managing BRAF-Mutant Metastatic Colorectal Cancer
Hey Min Lee, Van Morris, MD, Stefania Napolitano, MD, and Scott Kopetz, MD, PhD

MD Anderson researchers look at the characteristics of BRAF-mutant colorectal cancer and major advances in targeted therapies.

Clinical Quandaries
217 Red to Violaceous Papules
Mehmet Sitki Copur, MD, FACP, Karine Turcotte, MD, Kai Fu, MD, PhD, and Pornchai Jonglertham, MD

Oncologists review the case of a 70-year-old woman with skin lesions on her neck and abdomen.

Ask the PI
227 Preventing Gastric Cancer by Treating H. pylori Infection
Keith T. Wilson, MD

Perspective: Steven Moss, MD

Point/Counterpoint
235 Active Surveillance for Gleason 3+4 Prostate Cancer?

POINT: Abhishek Bhat, MD, and Sanoj Punnen, MD, MAS
COUNTERPOINT: Ikenna Madueke, MD, PhD, and Michael R. Abern, MD

Interview
239 Novel Therapies for Endometrial Cancer
Vicky Makker, MD

How an Expert Approaches It
243 Extended Adjuvant Endocrine Therapy in Breast Cancer
Shaveta Vinayak, MD, MS, and Nancy E. Davidson, MD

Also in This Issue
215 Latest Acute Myeloid Leukemia Clinical Trials

Published in affiliation with SIO Integrative Oncology

The Editors are pleased to announce the availability of our new parent company’s continuing education activities. We’ve picked this one especially for our ONCOLOGY readers. Go to: https://bit.ly/2IRAknZ

ONCOLOGY (ISSN 0890-9091) is published monthly by Multimedia Healthcare LLC, 325 W 1st St, STE 300, Duluth MN 55802. Annual subscription rates: US, $219 and Canada, $239; students and nurses, $96; international, $249. Single copies: $25 each. Institutional US, $249 Canada, $259 International, $375. Periodicals postage paid at Duluth MN 55806, and at additional mailing offices. POSTMASTER: Please send address changes to Oncology PO Box 6000 Duluth MN 55806-6000, USA. Publications Mail Agreement No 44619088. Return Undeliverable Canadian Addresses to: INFOLINE Global Solutions, PO Box 25042, London ON N6C 6B2, Canadian GST number: R-124213133RT001. Printed in U.S.A.

For address changes, please notify the Circulation Department by visiting www.surveymonkey.com/s/subscriptions, or by mail to ONCOLOGY, Multimedia Healthcare LLC, PO Box 6000, Duluth MN 55806-6000. Send old address, new address and attach a copy of your label, if possible.
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.

EDITORIAL ADVISORY BOARDS

MISSION STATEMENT

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.

EDITORS-IN-CHIEF

Julie M. Vose, MD, MBA
Omaha, NE

Nancy E. Davidson, MD
Seattle, WA

Nora Janjan, MD, MPSA, MBA
Dallas, TX

William C. Wood, MD
Atlanta, GA

EDITORIAL BOARD

BREAST CANCER
William J. Gradishar, MD, FACP
Chicago, IL
I. Craig Henderson, MD
San Francisco, CA
Tari King, MD
Boston, MA
Melanie E. Royce, MD, PhD
Albuquerque, NM
Vered Stearns, MD
Baltimore, MD

CANCER SURVIVORSHIP
Matthew J. Matasar, MD, MS
New York, NY

COLORECTAL/GASTROINTESTINAL CANCER
Edward Chu, MD
Pittsburgh, PA
Daniel Haller, MD
Philadelphia, PA
John L. Marshall, MD
Washington, DC
Matthew B. Yurgelun, MD
Boston, MA

GENITOURINARY CANCER
L. Michael Glodé, MD, FACP
Denver, CO
Paul Mathew, MD
Boston, MA
William U. Shipley, MD
Boston, MA

GYNECOLOGIC ONCOLOGY
Mario M. Leitao, Jr, MD
New York, NY
Franco Muggia, MD
New York, NY

HEAD AND NECK CANCER
Apar K. Ganti, MD, MS, FACP
Omaha, NE

INFECTION DISEASE
Genovefa Papanikolau, MD
New York, NY

INTEGRATIVE ONCOLOGY
Donald L. Abrams, MD
San Francisco, CA
Jun J. Mao, MD, MSCE
New York, NY

LEUKEMIA/LYMPHOMA
Bruce D. Cheson, MD
Washington, DC
Christopher Flowers, MD
Atlanta, GA
Alexandra M. Levine, MD, MACP
Duarte, CA
Steven T. Rosen, MD
Duarte, CA
John W. Sweetenham, MD, FRCP
Salt Lake City, UT

LUNG CANCER
David S. Ettinger, MD
Baltimore, MD
James L. Mulshine, MD
Chicago, IL

MELANOMA
Richard D. Carvajal, MD
New York, NY
Ahmad Tarhini, MD, PhD
Cleveland, OH

NEURO-ONCOLOGY
Stuart A. Grossman, MD
Baltimore, MD
Nicole A. Shonka, MD
Omaha, NE

PEDIATRIC ONCOLOGY
David G. Poplack, MD
Houston, TX

PROSTATE CANCER
Tomasz M. Beer, MD
Portland, OR
E. David Crawford, MD
Denver, CO
Judd W. Moul, MD, FACS
Durham, NC

PSYCHO-ONCOLOGY
Daniel C. McFarland, DO
New York, NY

RADIATION ONCOLOGY
Jay S. Cooper, MD
New York, NY
Louis Potters, MD, FACR
Hempstead, NY
James B. Yu, MD, MHS
New Haven, CT

SARCOMA
Kenneth Cardona, MD, FACS
Atlanta, GA

SUPPORTIVE AND PALLIATIVE CARE
Russell K. Portenoy, MD
New York, NY
Thomas J. Smith, MD, FACP
Baltimore, MD
N. Simon Tchekmedyan, MD
Long Beach, CA

SURGICAL ONCOLOGY
Burton L. Eisenberg, MD
Newport Beach, CA
Armando Giuliano, MD
Los Angeles, CA

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 Jennifer Leavitt at jleavitt@mmhgroup.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. SitkiCopur, 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
Baltimore, NY
Sudhantha 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 Vuky, MD
Portand, OR
Raymond Wadlow, MD
Fairfax, VA
Carolyn Wasserheit-Lieblich, MD
Bronxville, NY
Tracey F. Weisberg, MD
Scarborough, ME
Denise Yardley, MD
Nashville, TN
Amelia Zelnak, MD, MSc
Cumming, GA
Richard Zuniga, MD
Lowell, MA
Introduction: Clinical and Molecular Characteristics of the BRAF Mutation

Colorectal cancer is the second leading cause of cancer-related death in the United States.[1] It initiates from normal colonic epithelia following multiple genetic and epigenetic events.[2] Approximately 5% to 10% of patients with metastatic colorectal cancer (mCRC) have a mutation of the proto-oncogene BRAF.[3,4] Strong associations between BRAF V600E mutations and female gender, elderly age at diagnosis, and a proximal (right-sided) primary colon tumor location have been found.[5-7]

BRAF mutations are detected in many types of cancer, such as melanoma, colorectal cancer, thyroid cancer, non–small-cell lung cancer, and hairy cell leukemia.[7] In all cancer types, they encode a serine/threonine protein kinase that is associated with the RAS/RAF/MEK/ERK pathway.[7] The majority of BRAF mutations result in an amino acid substitution of valine to glutamic acid within codon 600 (V600E).[5] Compared with BRAF wild-type tumors, this missense BRAF V600E mutation results in downstream phosphorylation of MEK and ERK kinase, leading to constitutive activation of the mitogen-activated protein kinase (MAPK) signaling pathway, which drives tumor cell proliferation and metastasis of colorectal cancer.[7] Less commonly, atypical BRAF mutations are present, which can be characterized as either class II or III subtypes. Class II BRAF mutants signal as constitutive dimers and are RAS independent; while they are resistant to vemurafenib, they may be sensitive to novel RAF dimer inhibitors or MEK inhibitors. Class III BRAF mutants, which lack kinase activity, are associated with activation of RAS by receptor tyrosine kinase signaling, and therefore may be sensitive to epidermal growth factor receptor (EGFR) inhibition in some cases.[8,9]

Tumors with BRAF V600E mutations are often associated with a high mutation burden, microsatellite instability (MSI), and a CpG island methylator phenotype (CIMP), with associated high...
levels of epigenetic modulation of gene expression through DNA methylation.\[3,6,10,11\] Furthermore, a recent classification of colorectal cancer, based on intrinsic gene expression profile patterns, described four distinct subgroups called consensus molecular subtypes.\[12\] BRAF V600E–mutated colorectal cancer tumors are highly linked to consensus molecular subtype 1 (CMS1), and the typical features of this subtype overlap with the molecular characteristics associated with BRAF V600E mutations from the aforementioned analysis conducted by The Cancer Genome Atlas project. As in MSI-high tumors, CMS1 colorectal cancer tumors are also associated with significant immune infiltrations and activation of immune response pathways, as seen by higher populations of type 1 T helper cells, cytotoxic T cells, and natural killer cells.\[12,13\] Interestingly, BRAF–mutated mCRC tumors emerge in colorectal cancer pathogenesis as a distinct biological entity, often from the sessile serrated adenomatous pathway.\[14\]

Compared with patients with BRAF wild-type mCRC, patients with BRAF V600E–mutated mCRC have an exceptionally poor prognosis and lower response rates to standard therapy. As shown from one series of patients with mCRC assessed at academic and community centers (Figure 1), the median overall survival for patients with BRAF V600E–mutated mCRC was significantly shorter compared with patients with BRAF wild-type mCRC (11 months vs 35 months, respectively).\[4,6\] Even though BRAF V600E mutations are typically associated with RAS wild-type tumors, several studies have suggested that the BRAF V600E mutation is a predictive marker for limited sensitivity to anti–EGFR monoclonal antibodies (eg, cetuximab, panitumum-

![Figure 1 Kaplan-Meier Survival Curve of BRAF V600E–Mutated mCRC Patients vs BRAF Wild-Type mCRC Patients.](image)

**FIGURE 1** Kaplan-Meier Survival Curve of BRAF V600E–Mutated mCRC Patients vs BRAF Wild-Type mCRC Patients. The Kaplan-Meier survival analysis clearly shows that BRAF V600E–mutated mCRC patients have a worse overall survival outcome compared with BRAF wild-type mCRC patients.

**Advances in Treatment for BRAF-Mutated mCRC Patients**

Standard cytotoxic combinations of folinic acid, fluorouracil, and oxaliplatin (FOLFOX) and folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus bevacizumab. In a subgroup analysis of 28 patients with BRAF V600E–mutated mCRC treated with FOLFOXIRI plus bevacizumab or FOLFIRI plus bevacizumab, a survival trend was noted for patients receiving FOLFOXIRI plus bevacizumab, survival trend was noted for patients receiving FOLFOXIRI plus bevacizumab (hazard ratio [HR], 0.55). However, this finding was not statistically significant, likely due to the small sample size.\[20\] Despite this statistical limitation, FOLFOXIRI plus bevacizumab is currently considered a potential first-line treatment option for BRAF-mutated patients, assuming that they are able to tolerate this combination.\[21\]

BRAF inhibitor monotherapy has been tested in BRAF-mutated colorectal can-
BRAF inhibitors that have been approved by the US Food and Drug Administration (FDA) for BRAF-mutated metastatic melanoma. The median PFS for these agents as monotherapy for metastatic melanoma patients was 5.3 months, 5.1 months, and 9.6 months, respectively. In contrast, response rates to BRAF inhibitors as single agents among patients with BRAF V600E–mutated mCRC have been much lower.

For example, a phase II study of 21 patients treated with vemurafenib reported a 5% response rate. Indeed, suboptimal response to BRAF inhibitor monotherapy is linked to incomplete inhibition of MAPK signaling in colorectal cancer cell lines. Analysis of resistance mechanisms to BRAF-targeted therapies has demonstrated acquired mutations in oncogenes, such as KRAS, NRAS, and MAPK1, as well as copy number amplifications in BRAF, which may be responsible for loss of response. Therefore, it is reasonable that additional targeted agents against effectors in this pathway would result in deeper antitumor responses and provide a rationale for dual inhibition of BRAF and MEK as a means to improve response rates in BRAF V600E–mutated mCRC.

For BRAF V600E–mutated melanoma, one study reported that the addition of a MEK inhibitor to a BRAF inhibitor resulted in improved response rates as high as 76%, compared with 54% with monotherapy. For BRAF V600E–mutated mCRC patients, response rates to dabrafenib plus trametinib (a MEK inhibitor) have been much lower, with 5 of 43 patients (12%) responding to this combination. Together, these data suggest that reductions in tumors harboring BRAF V600E mutations are dependent on the context of the associated primary tumor, with inferior clinical outcomes noted with targeted therapies against BRAF and MEK for colorectal cancer compared with melanoma.

Overcoming Innate Resistance to Targeted Therapies in BRAF V600E–Mutated mCRC

Preclinical studies using in vitro models of BRAF V600E–mutated colorectal cancer have shown that BRAF inhibition induces reflexive feedback activation of EGFR and can propagate constitutive MAPK signaling (Figure 2). Here, EGFR-mediated reactivation of downstream signaling pathways contributes to the innate insensitivity of these tumors to BRAF inhibitor monotherapy. In an early-phase study of patients with BRAF V600E–mutant mCRC testing the combination of vemurafenib together with irinotecan and cetuximab (VIC), 6 of 17 patients (35%) achieved a radiographic response. The median PFS was 7.7 months, longer than the 2 months previously reported in the treatment-refractory population following standard chemotherapy options. A follow-up randomized phase II trial (Southwest Oncology Group 1406) compared irinotecan/cetuximab with or without vemurafenib to test the addition of a BRAF inhibitor to anti-EGFR therapy in BRAF V600E–mutant mCRC patients. The trial demonstrated an improved median PFS of 4.4 months (95% CI, 3.6–5.7 months) compared with 2.0 months (95% CI, 1.8–2.1 months) for patients receiving VIC (HR, 0.42; 95% CI, 0.26–0.66; P < .001), with higher rates of radiographic response and disease control
Based on the results of this prospective study, the VIC regimen has been added to the National Comprehensive Cancer Network (NCCN) guidelines as a recommended therapy for patients with treatment-refractory BRAF V600E–mutated colorectal cancer.[21] Triple-combination therapy with MEK and BRAF inhibition plus EGFR-targeted therapies has been tested; one clinical trial evaluated the combination of dabrafenib, panitumumab, and trametinib in patients with BRAF V600E–mutated mCRC. The response rate reported in the expanded phase II study of the triplet therapy was 21% (95% CI, 12.5%–43.3%) compared with 10% in the dabrafenib plus panitumumab arm (95% CI, 1.2%–31.7%).[32] The response rate reported in the expanded phase II study of the triplet therapy was 21% (95% CI, 12.5%–43.3%) compared with 10% in the dabrafenib plus panitumumab arm (95% CI, 1.2%–31.7%).[32]

A preclinical study suggests that activation of the phosphoinositide 3-kinase (PI3K)/AKT pathway may serve as an additional resistance mechanism to BRAF inhibitors, supported by the anti-tumor activity of dual inhibition of BRAF plus PI3K in BRAF-mutated colorectal cancer.[33] In addition, the ongoing phase III BEACON CRC study is randomizing patients to irinotecan plus cetuximab; encorafenib plus cetuximab; or encorafenib, cetuximab, and binimetinib. Early results from the 29 patients in the safety lead-in portion for encorafenib, cetuximab, and binimetinib showed an impressive overall response rate of 48% (3 complete responses and 11 partial responses), and 15 patients with stable disease, with a PFS of 8 months.[34] Based on the results of this study, the FDA granted a Breakthrough Designation to combination encorafenib, cetuximab, and binimetinib for BRAF V600E–mutated mCRC, as detected by an FDA-approved test, for patients who failed one or two prior lines of therapy for metastatic disease. Finalized mature survival data for this prospective trial are awaited, including the complete results of the phase III trial, but the early signal reported for BRAF plus EGFR plus MEK inhibition in this population appears most promising. An overview of clinical trials of targeted therapies against the MAPK pathway in BRAF V600E–mutated mCRC patients is provided in the Table.

Colon cancer research has finally joined the club of effective targeted therapy. BRAF, once thought only to be a bad prognostic sign, has now become a real target for therapy. The newest data suggest that hitting the pathway in multiple spots further improves outcomes with acceptable toxicity. Enter a world where BRAF testing is a must for all stage IV CRC.

John Marshall, MD, Chief, Hematology/Oncology, Medstar Georgetown University Hospital; Director, Otto J. Ruesch Center for the Cure of Gastrointestinal Cancer

**TABLE** Overview of Clinical Trials Investigating Combination Treatments for BRAF-Mutant mCRC

<table>
<thead>
<tr>
<th>Therapeutic Strategy</th>
<th>Study Drug</th>
<th>Phase</th>
<th>RR</th>
<th>PFS (Months)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Single/Doublet RAF/MEK</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAFi</td>
<td>Vemurafenib</td>
<td>I</td>
<td>5%</td>
<td>2.1</td>
<td>Kopetz et al[4]</td>
</tr>
<tr>
<td>BRAFi</td>
<td>Dabrafenib</td>
<td>I</td>
<td>11%</td>
<td>NR</td>
<td>Falchook et al[42]</td>
</tr>
<tr>
<td>BRAFi + MEKi</td>
<td>Encorafenib</td>
<td>I</td>
<td>16%</td>
<td>NR</td>
<td>Gomez-Roca et al[43]</td>
</tr>
<tr>
<td>BRAFi + MEKi</td>
<td>Dabrafenib + trametinib</td>
<td>II</td>
<td>12%</td>
<td>3.5</td>
<td>Corcoran et al[28]</td>
</tr>
<tr>
<td><strong>Doublet With EGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BRAFi + EGFRi</td>
<td>Vemurafenib + panitumumab</td>
<td>I</td>
<td>13%</td>
<td>3.2</td>
<td>Yeager et al[44]</td>
</tr>
<tr>
<td>BRAFi + EGFRi</td>
<td>Vemurafenib + cetuximab</td>
<td>II</td>
<td>4%</td>
<td>3.7</td>
<td>Hyman et al[45]</td>
</tr>
<tr>
<td>BRAFi + EGFRi</td>
<td>Encorafenib + cetuximab</td>
<td>II/II</td>
<td>19%</td>
<td>3.7</td>
<td>van Geel et al[36]</td>
</tr>
<tr>
<td>BRAFi + EGFRi</td>
<td>Dabrafenib + panitumumab</td>
<td>II</td>
<td>10%</td>
<td>3.4</td>
<td>Atreya et al[46]</td>
</tr>
<tr>
<td><strong>Triplet With EGFR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EGFRi + BRAFi + chemotherapy</td>
<td>Cetuximab + vemurafenib + irinotecan</td>
<td>II</td>
<td>35%</td>
<td>7.7</td>
<td>Hong et al[30]</td>
</tr>
<tr>
<td>EGFRi + BRAFi + chemotherapy</td>
<td>Cetuximab + vemurafenib + irinotecan</td>
<td>II</td>
<td>16%</td>
<td>4.4</td>
<td>Kopetz et al[31]</td>
</tr>
<tr>
<td>EGFRi + BRAFi + PI3Kai</td>
<td>Cetuximab + encorafenib + alpelisib</td>
<td>II/II</td>
<td>18%</td>
<td>4.2</td>
<td>van Geel et al[36]</td>
</tr>
<tr>
<td>EGFRi + BRAFi + MEKi</td>
<td>Panitumumab + dabrafenib + trametinib</td>
<td>II/II</td>
<td>21%</td>
<td>4.2</td>
<td>Corcoran et al[33]</td>
</tr>
<tr>
<td>EGFRi + BRAFi + MEKi</td>
<td>Cetuximab + encorafenib + binimetinib</td>
<td>Ib*</td>
<td>48%</td>
<td>8.0</td>
<td>Van Cutsem et al[34]</td>
</tr>
</tbody>
</table>

BRAFi = BRAF inhibitor; EGFR = epidermal growth factor receptor; MEKi = mitogen-activated protein kinase enzyme inhibitor; NCT = National Clinical Trials; PI3Kai = phosphoinositide 3-kinase a inhibitor; PFS = progression-free survival; RR = response rate.
cancer cell lines.[35] However, the phase Ib study of encorafenib/cetuximab with or without alpelisib (a PI3Kδ inhibitor) in BRAF-mutated mCRC showed no incremental benefit with the addition of alpelisib, with response rates of 19% vs 18% and a median PFS of 3.7 vs 4.2 months for dual- and triple-combination therapies, respectively.[36]

**Recommendations for Patient Management**

Given the aggressive biology seen in this population, including a rapid decline in performance status in the setting of disease progression, additional practical considerations are warranted. Early testing for BRAF mutations is important to identify optimal treatment and appropriately establish expectations. BRAF mutations are highly concordant between primary and metastatic sites and typically have a high rate of detection in circulating tumor DNA (ctDNA) in plasma, which allows for testing with whichever source material is readily available for a given patient.[30] Our practice is to request BRAF testing in conjunction with NRAS and KRAS testing after the diagnosis of mCRC. We will alternatively utilize ctDNA testing if tissue is not readily available at the facility for next-generation sequencing testing to avoid the delay in procuring outside diagnostic material.

Imaging testing is typically limited to CT scans of the chest, abdomen, and pelvis, which is consistent with other mCRC patients. Patterns of metastases are notable for higher rates of peritoneal disease and retroperitoneal lymph nodes. Anecdotally, atypical sites of metastases are also seen with high rates of bone and brain metastases, although these are not sufficiently common to justify routine testing and instead should be triggered by symptoms or lab abnormalities with a high level of suspicion.

Initial chemotherapy in our practice is FOLFOXIRI plus bevacizumab, with approximately 50% of patients being candidates for such an approach. Progression on first-line therapy can occasionally be subtle in patients with peritoneal-predominant disease, and requires close vigilance to avoid missing opportunities for second-line therapy. Based on the limited activity of second-line cytotoxic chemotherapy, we proceed with targeted therapy with the VIC regimen in the second-line setting. Given the encouraging clinical trial data with alternate strategies, enrollment to clinical trials is encouraged in any line. In our experience, trials should be considered early in the disease course, because it is difficult to predict performance status declines, and at least one study suggested improved outcomes of the same regimen in the second-line vs third-line setting.[34]

The VIC regimen is associated with several characteristic symptoms, including arthralgias and secondary cutaneous malignancies.[31] Arthralgias can be dose-limiting in a minority of patients, but can typically be managed with anti-inflammatory agents instead of dose reductions. Secondary cutaneous malignancies, most commonly keratoacanthomas, can been seen and are usually managed via resection by a dermatologist without requiring dose interruption or discontinuation. Nausea, when present, is manageable, although high-dose 5-hydroxytryptamine 3 receptor (5-HT3) antagonists have the potential to induce QTc prolongation in combination with vemurafenib. Attention to electrolyte abnormalities is encouraged to avoid exacerbating QTc concerns. While intermittent use of low- and moderate-dose 5-HT3 antagonists appears safe, patients are cautioned to avoid continuous dosing and instead alternate with other oral antiemetics. Skin toxicity is similar, if not slightly better, than that seen with cetuximab or panitumumab alone, and is managed by counseling on avoiding sun exposure, and prophylactic use of oral antibiotics and topical corticosteroids. Neutropenia and anemia are also seen with the combination, but are at rates consistent with other combination regimens and do not require special management.

There has been some debate about the utility of aggressive strategies to resect liver-limited disease. Surgical series have reported poor outcomes for several patients, although anecdotal cases show-
ing a benefit have been noted.\[37\] Since most patients present with more widely disseminated metastatic disease, only a small number of patients with BRAF V600E–mutant tumors are candidates for such surgical strategies. It is our practice to start with chemotherapy for patients with liver-limited disease, but to still consider resection of liver metastases in carefully selected patients.

Not all patients with BRAF V600E–mutant tumors follow the traditional aggressive path, with a minority manifesting with a more traditional or occasionally indolent behavior. As such, personalized management of these patients is required to manage their presenting biology.

**Future Research Efforts**

Clinical trials on multi-agent combination approaches for the blockade of the MAPK pathway have shown great promise in the treatment of BRAF V600E–mutated mCRC patients. Additional inhibition of ERK, in combination with current targeted therapies, is under investigation. Improvements to targeted therapies could also be useful for treatment of patients with atypical, non–BRAF V600E mutations. However, these mutations are not as common in colorectal cancer, and additional studies are needed to better understand the targetability of them and the associated therapeutic implications.

Another unique molecular characteristics of BRAF–mutated mCRC tumors, such as hypermethylation and immune infiltration, could be potential novel interventions for treatment. For example, epigenetic targeting with DNA methyltransferase (DNMT) inhibitors or histone deacetylase inhibitors in combination with targeted therapy or immunotherapy is under study.\[38,39\] A preclinical experiment has shown a synergistic effect with the combination of a DNMT inhibitor and vemurafenib in cell lines,\[35\] which supports further testing of epigenetic modulators in BRAF V600E–mutated mCRC patients.

Another reasonable treatment for BRAF V600E–mutated mCRC patients with concomitant MSI is immune checkpoint blockade with anti–programmed death 1 agents (eg, nivolumab, pembrolizumab) with or without anti–cytotoxic T-lymphocyte–associated antigen 4 agents (eg, ipilimumab). These patients often have high MSI characteristics, which are considered to be predictive markers for a positive response to immunotherapy.\[12,40\] A phase II study testing nivolumab in patients with MSI-high mCRC found that, among 12 patients with BRAF V600E mutations, an objective response was achieved in 25% (3 patients). The disease control rate (eg, partial response or stable disease lasting at least 12 weeks) was 75% (9 patients).\[41\] Another phase II trial evaluating nivolumab/ipilimumab for MSI-high mCRC found a 55% objective response rate and a 79% disease control rate in the 29 patients with BRAF V600E–mutated mCRC.\[40\] Therefore, it appears that patients with BRAF V600E–mutated, MSI-high mCRC can benefit therapeutically from immune checkpoint blockade agents beyond those that target the MAPK signaling pathway.

While BRAF V600E mutations have historically been associated with poor prognoses for colorectal cancer patients, major advances have significantly extended survival outcomes in recent years, backed by corroborating translational sciences. Further understanding of the interplay between the BRAF V600E mutation and associated tumor biology will lead to further treatment advances in the years to come.

**FINANCIAL DISCLOSURE:** Dr. Morris serves as a consultant to Array Biopharma. Dr. Kopetz receives funding from the National Institutes of Health/National Cancer Institute (grant R01 CA187238); he also serves as a consultant to Amgen, Holy Stone, Merck, and Symphogen. Ms. Lee and Dr. Napolitano 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/BRAF-mutant-mCRC**

---

**Clinical Considerations**

- Detection of the BRAF V600E mutation in metastatic colorectal cancer identifies a subgroup of patients who derive little benefit from standard treatments and have an extremely poor prognosis.
- Response rates in BRAF V600E–mutated colorectal cancer patients with BRAF inhibitor monotherapy are lower compared with other BRAF V600E–mutated advanced cancers.
- The addition of targeted therapies against epidermal growth factor receptor and/or MEK to BRAF inhibitors improves outcomes for patients with BRAF V600E–mutated colorectal cancer.

---

**Ms. Lee** is a Graduate Research Assistant in the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center, Houston, Texas.

**Dr. Morris** is an Assistant Professor in the Department of Medical Oncology at the University of Texas MD Anderson Cancer Center, Houston, Texas.

**Dr. Napolitano** is a Postdoctoral Fellow in the Department of Gastrointestinal Medical Oncology at the University of Texas MD Anderson Cancer Center, Houston, Texas.

**Dr. Kopetz** is an Associate Professor in the Department of Medical Oncology at the University of Texas MD Anderson Cancer Center, Houston, Texas.
Honing in on Subtypes to Guide More Individualized Treatment of Soft Tissue Sarcoma

Dr. von Mehren discusses current considerations and challenges in the management of patients with soft tissue sarcoma, as well as recent clinical trial data.

Soft tissue sarcoma can be challenging to diagnose and treat due to the vast number of different subtypes that comprise the disease. ONCOLOGY recently spoke with Margaret von Mehren, MD, regarding the diagnosis and treatment of soft tissue sarcoma. She reviewed the latest research in this area, including the results of several trials that showed that combining pazopanib with gastric acid-suppressive agents decreased survival in patients—as well as strategies that may aid in alleviating this issue.

Q: First, what is the biology of soft tissue sarcoma, and are there different subtypes of these tumors?

DR. VON MEHREN: The first thing I always like to point out about sarcomas is that we think of them as distinct from carcinomas. They arise from different cell types. While sarcomas come from fat, muscle, bone cartilage, or blood vessels, carcinomas usually come from epithelial structures or the tissue of glands.

Like all malignancies, sarcomas have the ability to grow and metastasize, and truly malignant tumors can be biologically aggressive and fatal.

There are at least 50, if not more, different subtypes of sarcomas. This is one of the elements that makes caring for sarcoma patients so challenging. While some tumors are derived from fat or liposarcoma, others are from smooth muscle from vascular-type structures. Once we classify the sarcoma, we treat patients accordingly in terms of what type of testing we conduct and which specific treatments we select.

Q: Are specific genetic abnormalities associated with any of the various subtypes of soft tissue sarcoma?

Dr. von Mehren is Chief of the Division of Sarcoma Medical Oncology, a Professor in the Department of Hematology/Oncology, and Associate Director of Clinical Research at Fox Chase Cancer Center, Philadelphia, Pennsylvania.
The development of numerous oral chemotherapy agents has led to a new paradigm in cancer treatment. While traditionally most cancer patients have been treated with intravenous cytotoxic drugs, several oral drugs are now being utilized routinely for cancer therapy. Oral cancer therapy makes treatment more convenient for patients by reducing administration time, eliminating infusion center visits, and avoiding complications from having a central line. Moreover, pharmacokinetic considerations may also favor oral delivery of drugs by providing exposure to lower concentrations of cytotoxic drugs and may offer higher antitumor efficacy.

However, a major disadvantage of oral delivery of chemotherapy agents is the risk of subtherapeutic drug concentrations. A number of drugs have reduced or unreliable bioavailability in oral form. Food and concomitant medications can significantly affect the pharmacokinetic profile of orally administered drugs. Food may lead to decreased drug absorption due to drug instability in gastric fluids or binding with food. On the other hand, food may actually increase the absorption of other drugs.

In this interview, Dr. von Mehren provides an articulate summary of soft tissue sarcomas, including the results from a new soft tissue sarcoma trial showing decreased overall and progression-free survival with the concurrent use of pazopanib and gastric acid-suppressive agents. With the increased use of oral administration as the route of various molecularly targeted therapies, drug-drug interactions have become apparent. Many tyrosine kinase inhibitors have shown pH-dependent solubility. This solubility might be decreased by the coadministration of gastric acid-suppressing agents. Pazopanib is most effectively absorbed in an acidic environment, with very little absorption at a pH greater than 4. In patients taking proton pump inhibitors (PPIs), the pH of the stomach readily rises to over 4, leading to limited absorption of this drug.

The sarcoma studies discussed in this interview emphasize the importance of obtaining an accurate and complete medication history, including over-the-counter medications, from every cancer patient. [1,2] Frequently, cancer patients experience gastric upset or acid reflux while undergoing anticancer treatments. Since many PPIs and H2 blockers are available without a prescription, cancer patients may be taking these agents, but may not report them as part of their medication history to their oncologist or healthcare providers. Based on the study findings and the interview with Dr. von Mehren, it is very clear that educating cancer patients as well as cancer care providers about this drug-drug interaction is as important, if not more important, than making treatment decisions and choosing anticancer treatments. In an era of targeted and personalized cancer care with more and more anticancer drugs becoming available in oral formulations, educating cancer patients and caregivers on proper medication administration and adherence to established pharmacologic guidelines, as well as clinically significant drug-drug interactions, is critical to ensure our patients are receiving the best possible cancer care.

**FINANCIAL DISCLOSURE:** Dr. Kestel 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/indv-sarcoma-ther

**Dr. Kestel** is an Oncology Pharmacist and Senior Analyst at Nebraska Medicine, Omaha, Nebraska.

---

**DR. VON MEHREN:** Certainly, classical genetic abnormalities define some tumors. Such abnormalities are much more common in pediatric patients than adult patients, but we do see them in some young adults and older patients as well. Many soft tissue sarcomas, such as synovial sarcoma and myxoid liposarcoma, have very specific chromosomal translocations that can aid in establishing the diagnosis. Other tumors have specific gene mutations that can help in identifying the tumor type, as well as which therapy makes the most sense.

For example, two genes represent about 80% to 85% of gastrointestinal stromal tumors that have mutations. Those genetic abnormalities help to define how to take care of it.

**Q:** What are the main types of therapy for patients diagnosed with soft tissue sarcoma?

**DR. VON MEHREN:** There are three major modalities used to treat soft tissue sarcoma: surgery, radiation, and chemotherapy. A probable fourth modality that remains an active area of...
research is immunotherapy, but we are still in the process of developing immunotherapies for soft tissue sarcoma and understanding which patients will benefit.

Surgery is a mainstay for patients with primary disease that has not spread to other organ sites. However, we also consider adding radiation therapy before or after surgery to help with local control in certain patients, particularly those with tumors that are in the extremity; this approach allows us to avoid amputations. In specific situations, we also discuss the use of chemotherapy to prevent recurrence of the sarcoma. Whether the recurrence is at a local site or elsewhere, we analyze whether the disease can be easily removed surgically or is located in many areas. When the latter situation exists, this usually requires systemic therapy. Essentially, each patient requires highly individualized care.

Of note, we consider surgery to manage metastatic disease more frequently for sarcomas than we do for many other carcinomas. For carcinomas, we often use systemic therapies such as chemotherapy as well as radiation. However, in the treatment of sarcomas, I think we’ve demonstrated a real value in removing tumors by surgery in the appropriate circumstances to help with disease control.

**Q:** The European Organisation for Research and Treatment of Cancer (EORTC) conducted a single-arm phase II trial and a placebo-controlled phase III trial evaluating pazopanib, which is approved for the treatment of advanced soft tissue sarcoma that has been pretreated with doxorubicin-based regimens. Can you discuss the rationale for and findings of these studies?

**DR. VON MEHREN:** The EORTC evaluated single-agent pazopanib for the treatment of soft tissue sarcoma in a nonrandomized phase II trial,[1] as well as a phase III randomized placebo-controlled trial,[2] and then retrospectively studied the effect of gastric acid–suppressing agents on therapy. The authors demonstrated that patients who were taking medications such as ranitidine or omeprazole, particularly those who took them consistently for 80% or more of the time they were on pazopanib therapy, had decreased time to disease progression and survival compared with patients who were not taking these agents. Why would that happen? Pazopanib needs to be in an acidic environment in order for it to be absorbed. Gastric acid–suppressing agents such as ranitidine and omeprazole work to decrease the acidity in the stomach, meaning that pazopanib will not be absorbed as well in patients who are taking these medications.

These data are very important because many patients are on some form of this therapy. We must educate them about this effect, as well as evaluate what we can do if patients require treatment with both pazopanib for sarcoma as well as gastric acid–suppressing agents for reflux disease or other conditions. Some research has focused on this dilemma, in patients taking pazopanib specifically, as well as other drugs that affect the acidity of the stomach. For example, if we test the level of pazopanib in the blood and determine that it is not being absorbed well, we can titrate the dosage. The US Food and Drug Administration–approved dose of pazopanib is 800 mg daily, but we may need to consider increasing the dose in patients taking antacids to reach the level in the blood that will be most effective, much like we do in patients taking digoxin. I would say this method is not likely to become routine, but it may be one way of overcoming this issue.

Another method that has been tested, although not extensively, is spacing out the timing of when the pazopanib and gastric acid–lowering therapy are taken. Spreading them out as much as possible seems to be best, such as taking the pazopanib 10 or more hours after the gastric acid–lowering therapy. Other research has focused on whether the acidity in the stomach can temporarily be increased. One study is evaluating whether taking pazopanib with soda will improve the absorption of pazopanib in patients on acid-lowering agents. I think these studies are all intriguing in terms of what we can do to potentially overcome this issue.

**KEY QUESTION**

Beyond the effect of gastric acid–lowering agents on therapy, are there any other contraindications or considerations for pazopanib that clinicians should consider?

**DR. VON MEHREN:** Patients need to take their medication on an empty stomach, which can be a challenge. There are some medications that need to be avoided since they may change how the drug is metabolized and lead to higher or lower drug levels; higher levels may lead to more side effects, and lower levels to less efficacy. These interactions can occur with some foods as well, such as grapefruit.

**Q:** Lastly, can you talk about some of the broader hurdles that exist in terms of establishing a diagnosis of soft tissue sarcoma, and in selecting the best therapy for patients with these tumors?

**DR. VON MEHREN:** I think the biggest hurdle for soft tissue sarcomas is that they are very biologically diverse, and the large number of subtypes makes the diagnosis challenging. Depending on where...
Current Clinical Trials in Acute Myeloid Leukemia

By ONCOLOGY Editors | Clinically reviewed by Mehmet Sitki Copur, MD

BACKGROUND: Acute myeloid leukemia (AML) is a malignancy of the bone marrow in which development of hematopoietic precursors halts during early stages of marrow formation. Although pre-familial syndromes, existing hematologic disorders, and environmental or drug exposures may be to blame, most patients who present with AML have no identifiable risk factors.[1,2]

Patients with AML experience symptoms stemming from bone marrow failure, infiltration of organs by leukemic cells, or both. Workups to establish diagnosis include blood tests, biopsy and aspiration of bone marrow, and genetic testing.[3-7]

Only a minority of patients with AML respond to chemotherapy, still the leading treatment to date. For this reason, whenever possible, physicians should seek out reputable clinical trials in which to enroll their patients.[8]

Phase III Trials - Recruiting

Daunorubicin and Cytarabine With or Without Uprolesalan in Treating Older Adult Patients with Acute Myeloid Leukemia Receiving Intensive Induction Chemotherapy
ClinicalTrials.gov Identifier: NCT03701308
National Cancer Institute, 121 locations, USA

Response-Based Chemotherapy in Treating Newly Diagnosed Acute Myeloid Leukemia or Myelodysplastic Syndrome in Younger Patients with Down Syndrome
ClinicalTrials.gov Identifier: NCT02521493
Children’s Oncology Group & National Cancer Institute, 173 locations, USA

Venetoclax and Azacitidine for Non-Elderly Adult Patients With Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03579204
University of Colorado Hospital, Aurora, Colorado

Fractionated Gemtuzumab Ozogamycin Followed by Non-engraftment Donor Leukocyte Infusions for Relapsed/Refractory Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03374332
Rhode Island Hospital, Providence, Rhode Island

Phase II Trials - Recruiting

Liposome-encapsulated Daunorubicin-Cytarabine and Venetoclax in Treating Participants With Relapsed, Refractory or Untreated Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03629171
MD Anderson Cancer Center, Houston, Texas

Cytarabine, Idarubicin, Liposom-encapsulated Daunorubicin-Cytarabine or Decitabine in Treating Older Patients With Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03226418
University of Nebraska Medical Center, Omaha, Nebraska

Crenolanib Maintenance Following Allogeneic Stem Cell Transplantation in FLT3-positive Acute Myeloid Leukemia Patients
ClinicalTrials.gov Identifier: NCT02400255
MD Anderson Cancer Center, Houston, Texas

CSF1R Inhibitor JNJ-40346527 in Treating Participants With Relapsed or Refractory Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03557970
OHSU Knight Cancer Institute, Portland, Oregon, UT Southwestern/Simmons Cancer Center-Dallas, Dallas, Texas

For Patients With Acute Myeloid Leukemia at High Risk of Relapse After Donor Stem Cell Transplantation ClinicalTrials.gov Identifier: NCT01841333
University of Colorado Cancer Center, Aurora, Colorado, Ohio State University, Columbus, Ohio

Biomarkers in Predicting Treatment Response to Sirolimus and Chemotherapy in Patients With High-Risk Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT02583893
Thomas Jefferson University, Philadelphia, Pennsylvania
Venetoclax, Cabazitaxel, and Azacytidine in Treating Participants With Previously Untreated Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03586609
MD Anderson Cancer Center, Houston, Texas

Fractionated Gemtuzumab Ozogamicin in Treating Measurable Residual Disease in Participants With Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03737965
Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium, Seattle, Washington

Duratumumab in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome
ClinicalTrials.gov Identifier: NCT03087571
MD Anderson Cancer Center, Houston, Texas

Azacitidine and Venetoclax as Induction Therapy With Venetoclax Maintenance in the Elderly With AML
ClinicalTrials.gov Identifier: NCT03486294
University of Colorado Cancer Center, Aurora, Colorado

Higher or Lower Dose Cladribine, Cytarabine, and Mitoxantrone in Treating Medically Less Fit Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplasia
ClinicalTrials.gov Identifier: NCT03012672
Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium, Seattle, Washington

A Phase II Study of Pembrolizumab as Post-Remission Treatment of Patients ≥ 60 With AML
ClinicalTrials.gov Identifier: NCT02708641
UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania

TET2 Mutations in Myelodysplastic Syndromes and Acute Myeloid Leukemia With Azacitidine + Ascorbic Acid
ClinicalTrials.gov Identifier: NCT0397173
Cleveland Clinic, Taussig Cancer Institute, Case Comprehensive Cancer Center, Cleveland, Ohio

Allogeneic Transplantation Using Timed Sequential Busulfan, Cladribine, and Fludarabine Conditioning in Patients With Acute Myelogenous Leukemia (AML) and Myelodysplastic Syndrome (MDS)
ClinicalTrials.gov Identifier: NCT02250837
MD Anderson Cancer Center, Houston, Texas

Selinexor With Induction, Consolidation, and Maintenance Therapy in Treating Older Patients With Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT02852222
Comprehensive Cancer Center of Wake Forest University, Winston-Salem, North Carolina

Study of Azacitidine in Combination With Pembrolizumab in Relapsed/Refractory Acute Myeloid Leukemia (AML) Patients and in Newly Diagnosed Older (≥65 Years) AML Patients
ClinicalTrials.gov Identifier: NCT02845297
Johns Hopkins Oncology Center, Baltimore, Maryland, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, Medical University of South Carolina Hollings Cancer Center, Charleston, South Carolina

Pevonedistat and Azacitidine as Maintenance Therapy After Allogeneic Stem Cell Transplantation for Non-Remission AML
ClinicalTrials.gov Identifier: NCT03709576
Penn State Hershey Medical Center: Penn State Cancer Institute, Hershey, Pennsylvania

Stem Cell Transplant to Treat Patients With Favorable or Intermediate Risk Minimal Residual Disease Negative Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT03515707
Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium, Seattle, Washington

High Dose Cytarabine Followed by Pembrolizumab in Relapsed/Refractory AML
ClinicalTrials.gov Identifier: NCT02768792
Johns Hopkins School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, Maryland, Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina

Pfizer Immunotherapy Combinations for Acute Myeloid Leukemia (AML) Multi-Arm Study 1
ClinicalTrials.gov Identifier: NCT03392996
MD Anderson Cancer Center, Houston, Texas

A Randomized Trial of a Combination of Nintedanib/Placebo in Combination With Induction Chemotherapy for Patients With Refractory or First Relapse Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT02865143
Yale University, New Haven, Connecticut, Vanderbilt Ingram Cancer Center, Nashville, Tennessee

Donor Natural Killer Cells in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia
ClinicalTrials.gov Identifier: NCT01787474
MD Anderson Cancer Center, Houston, Texas

| Venetoclax, Cladribine, Low Dose Cytarabine, and Azacytidine in Treating Participants With Previously Untreated Acute Myeloid Leukemia |
| ClinicalTrials.gov Identifier: NCT03586609 |
| MD Anderson Cancer Center, Houston, Texas |
| Fractionated Gemtuzumab Ozogamicin in Treating Measurable Residual Disease in Participants With Acute Myeloid Leukemia |
| ClinicalTrials.gov Identifier: NCT03737965 |
| Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium, Seattle, Washington |
| Duratumumab in Treating Patients With Relapsed or Refractory Acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome |
| ClinicalTrials.gov Identifier: NCT03087571 |
| MD Anderson Cancer Center, Houston, Texas |
| Azacitidine and Venetoclax as Induction Therapy With Venetoclax Maintenance in the Elderly With AML |
| ClinicalTrials.gov Identifier: NCT03486294 |
| University of Colorado Cancer Center, Aurora, Colorado |
| Higher or Lower Dose Cladribine, Cytarabine, and Mitoxantrone in Treating Medically Less Fit Patients With Newly Diagnosed Acute Myeloid Leukemia or Myelodysplasia |
| ClinicalTrials.gov Identifier: NCT03012672 |
| Fred Hutchinson Cancer Research Center/University of Washington Cancer Consortium, Seattle, Washington |
| A Phase II Study of Pembrolizumab as Post-Remission Treatment of Patients ≥ 60 With AML |
| ClinicalTrials.gov Identifier: NCT02708641 |
| UPMC Hillman Cancer Center, Pittsburgh, Pennsylvania |
| TET2 Mutations in Myelodysplastic Syndromes and Acute Myeloid Leukemia With Azacitidine + Ascorbic Acid |
| ClinicalTrials.gov Identifier: NCT0397173 |
| Cleveland Clinic, Taussig Cancer Institute, Case Comprehensive Cancer Center, Cleveland, Ohio |
| Allogeneic Transplantation Using Timed Sequential Busulfan, Cladribine, and Fludarabine Conditioning in Patients With Acute Myelogenous Leukemia (AML) and Myelodysplastic Syndrome (MDS) |
| ClinicalTrials.gov Identifier: NCT02250837 |
| MD Anderson Cancer Center, Houston, Texas |
| Selinexor With Induction, Consolidation, and Maintenance Therapy in Treating Older Patients With Acute Myeloid Leukemia |
| ClinicalTrials.gov Identifier: NCT02852222 |
| Comprehensive Cancer Center of Wake Forest University, Winston-Salem, North Carolina |
| Study of Azacitidine in Combination With Pembrolizumab in Relapsed/Refractory Acute Myeloid Leukemia (AML) Patients and in Newly Diagnosed Older (≥65 Years) AML Patients |
| ClinicalTrials.gov Identifier: NCT02845297 |
| Johns Hopkins Oncology Center, Baltimore, Maryland, University of North Carolina Lineberger Comprehensive Cancer Center, Chapel Hill, North Carolina, Medical University of South Carolina Hollings Cancer Center, Charleston, South Carolina |

**Honoring in on Subtypes in Soft Tissue Sarcoma Therapy**

Continued from page 214

A patient is cared for, the pathologist’s familiarity with all of the different subtypes may be limited. Certainly, it can help to obtain a second pathology opinion or to have the patient go to a center that has a dedicated sarcoma team, including a sarcoma pathologist, in place. We are increasingly understanding that these tumors are different, and that certain molecular drivers are responsible for them, so directing and selecting therapy based on the specific subtype is important. Twenty years ago, most of our studies collected or treated all patients with soft tissue sarcoma on one study. Increasingly, however, the studies have become more specific to histology. For example, studies might now focus on just liposarcoma, leiomyosarcoma, or disease sites that are even more rare to evaluate whether very specific molecularly targeted therapies are effective. One current study (ClinicalTrials.gov identifier: NCT03148275) is looking at epithelioid hemangioendothelioma with a very specific drug based on the molecular profile of that tumor. So, I think that familiarity with these different subtypes is paramount in patients getting the best care. We need to ensure that patients are being well served by having a good pathology review, as well as access to physicians who have a good understanding of the subtleties of these unique and often rare subtypes.

**FINANCIAL DISCLOSURE:**
Dr. von Mehren receives research funding from Novartis (previously GlaxoSmithKline) that is provided to her institution for the conduction of a National Comprehensive Cancer Network–funded trial focusing on pazopanib for the treatment of angiosarcoma.

For references visit cancernetwork.com/indv-sarcoma-ther
Progressive Red-to-Violaceous Papules and Plaques on the Neck and Abdominal Skin of a 70-Year-Old Woman

Mehmet Sitki Copur, MD, FACP, Karine Turcotte, MD, Kai Fu, MD, PhD, and Pornchai Jonglertham, MD

A 70-year-old woman developed red-to-violaceous papules, plaques, and nodule-like skin lesions several months prior to her presentation. The skin lesions mostly involved her lower neck and abdominal area (Figure 1). Initial topical and/or systemic treatments with antibiotic, antifungal, and allergy medications failed to provide a definitive clinical improvement, so a skin biopsy was performed. Hematoxylin and eosin staining of the skin biopsy revealed a dense lymphoid infiltrate involving the dermis, with small- to intermediate-sized lymphoid cells (Figure 2). Immunophenotyping confirmed the presence of B cells with positive CD20 and BCL2, as well as partially positive MUM1. Tests for CD3, CD10, BCL6, cyclin D1, CD5, CD23, CD30, terminal deoxy-nucleotidyl transferase, kappa, lamda, and CD34 were negative (Figure 3). The Ki-67 proliferative index was 20%, and the clonality of B lymphocytes was analyzed on paraffin-embedded, unstained slides from the skin biopsy. DNA amplification by polymerase chain reaction using consensus primers to the heavy locus (IGH) gene variable and joining regions was performed. A strong clonal gene rearrangement was detected to the framework II (FR2) region at 282 base pairs, and to the framework III (FR3) region at 142 base pairs (Figure 4).

Based on the clinical presentation and pathology of the skin biopsy, what is the most likely diagnosis?

A. Primary cutaneous follicle center lymphoma
B. Primary cutaneous marginal zone lymphoma
C. Primary cutaneous large B-cell lymphoma
D. Secondary involvement of skin by noncutaneous marginal zone lymphoma
E. Both B and D

The answer and discussion of this case by experts can be found on page 218.
The pathology of the skin biopsy was reported to be extranodal marginal zone lymphoma. The patient denied any palpable lumps, night sweats, fevers, or weight loss. A somewhat limited physical examination due to her overweight condition did not reveal lymphadenopathy or organomegaly. Further workup with CT scans of the chest, abdomen, and pelvis revealed axillary, hilar, and mediastinal lymphadenopathy, as well as splenomegaly (Figure 5). A unilateral bone marrow aspiration and biopsy showed involvement by marginal zone lymphoma. The patient was treated with 6 cycles of combination chemotherapy with rituximab, cyclophosphamide, vincristine sulfate, and prednisone (R-CVP) and achieved a complete response.

**Discussion**

Cutaneous lymphomas are the second most frequent form of extranodal lymphomas and have unique characteristics. They can be defined as lymphoproliferative skin infiltrates of T cell, B cell, or natural killer cell lineage occurring on and remaining confined to the skin in most patients.[2] At the time of diagnosis, cutaneous lymphomas do not cause detectable extracutaneous manifestations. Primary cutaneous B-cell lymphomas represent 20% to 25% of all cutaneous lymphomas and have an overall favorable prognosis.[3,4] Proper recognition is vital in order to select the appropriate therapy and avoid overtreatment. An Italian Study Group reported data for 467 patients with primary cutaneous B-cell lymphoma in order to evaluate prognostic factors. They found that follicle center lymphoma (FCL) accounted for most occurrences (56.7%), followed by marginal zone B-cell lymphoma (31.4%) and diffuse large B-cell lymphoma (DLBCL), leg type (10.9%). The histopathologic tumor type and the extent of cutaneous involvement

---

**FIGURE 2 Skin Biopsy Showing a Dense Lymphoid Infiltrate Involving the Dermis.** The majority of the cells are small to intermediate in size and show slightly irregular nuclei. Plasmacytic differentiation is observed (hematoxylin and eosin stain, original magnification ×40 [top left], ×100 [top right], ×200 [bottom left], and ×400 [bottom right].

**FIGURE 3 Immunophenotyping of the Patient’s Cells.** The immunophenotype is B lymphocytes, which are positive for CD20 and BCL2, and partially positive for MUM1. They are negative for CD3, CD10, BCL6, cyclin D1, CD5, CD23, terminal deoxynucleotidyl transferase, kappa, lambda, and CD43. The proliferative index, evaluated with Ki-67, is 20%. Reactive T lymphocytes, highlighted by T-cell markers CD2, CD3, CD5, CD4, CD8, CD7, and CD43, are associated with the malignant infiltrate.
were the two most relevant prognostic factors.[5,6]

The diagnosis of cutaneous B-cell lymphoma is established via an analysis of the skin biopsy specimen, using histomorphology, cytomorphology, immunohistochemistry, phenotypic features, genotyping, and cytogenetic studies. Marginal zone lymphoma can occur as a primary cutaneous condition or as the result of secondary involvement from noncutaneous marginal zone lymphoma. Distinguishing primary cutaneous marginal zone lymphoma from secondary cutaneous marginal zone lymphoma is of utmost importance to determine the optimal prognostic and therapeutic approach. The histopathological and immunohistochemical features of primary cutaneous marginal zone lymphoma and secondary cutaneous marginal zone lymphoma can be indistinguishable.[7]

Clinical features can be different between the two entities. Primary cutaneous marginal zone lymphoma tends to follow a very indolent course, while nodal marginal zone lymphomas may have a median survival of 5 years.[9] Staging is critical for decision making in the management of patients with lymphoma. In 2007, the International Society for Cutaneous Lymphomas (ISCL) and the Cutaneous Lymphoma Task Force of the European Organisation for Research and Treatment of Cancer (EORTC) proposed a new Tumor, Node, Metastasis (TNM) staging system for primary cutaneous lymphomas other than mycosis fungoides (MF) and Sézary syndrome (SS).[6] Due to the clinical and pathologic heterogeneity of cutaneous lymphomas, this proposed TNM system was intended to be primarily an anatomic documentation of disease extent rather than a prognostic guide.

The ISCL/EORTC recommendation for staging evaluation in cutaneous lymphomas other than MF/SS included proper clinical staging evaluations, beginning with a complete history and review of systems. It also suggested that a thorough physical examination; laboratory studies; appropriate imaging studies assessing at least the chest, abdomen, and pelvis; and a bone marrow biopsy, as indicated by staging assessments, be obtained.[10]

While gastric marginal zone lymphoma is associated with Helicobacter pylori and salivary gland marginal zone lymphoma is associated with hepatitis C infection, primary cutaneous marginal zone lym-
Marginal zone lymphoma has been shown to be associated with *Borrelia burgdorferi* infection in 20% of cases.[11] Due to the different disease associations, treatment options, and prognoses, it is important to distinguish primary cutaneous lymphomas from systemic lymphomas secondarily involving the skin. Considerable overlap in the clinical presentations of patients with primary and secondary cutaneous disease makes it crucial to perform a systemic evaluation for all patients.[7,12]

**Outcomes and Conclusion**

Marginal zone lymphoma can be a primary cutaneous condition or represent a secondary involvement from noncutaneous marginal zone lymphoma. Distinguishing primary cutaneous marginal zone lymphoma from secondary cutaneous marginal zone lymphoma is of utmost importance in determining the proper prognostic and therapeutic approach. However, there are no reliable histopathological and immunohistochemical features to accurately distinguish between the two entities.[4] The case presented here exemplifies this challenge. While the older age of the patient suggested secondary marginal zone lymphoma, distribution of the skin lesions mainly in the trunk indicated primary cutaneous marginal zone lymphoma. Similarly, histopathological and immunohistochemical examination of the skin biopsy specimen was not helpful to differentiate between primary vs secondary marginal zone lymphoma. Only after a complete systemic workup with imaging studies, bone marrow aspiration, and a biopsy, was it possible to establish the diagnosis of secondary cutaneous marginal zone lymphoma of the skin, which then guided the appropriate systemic therapy. The patient achieved a complete response to systemic therapy and remains in complete remission to date.

**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.
Introduction
A diagnosis of cancer invariably brings thoughts of mortality to the forefront of patients’ minds and may be associated with stigma, social isolation, and personal stressors. While there are many risk factors associated with suicide in both cancer and non-cancer settings, the primary issue for patients with cancer is that the disease leads to physical, mental, and spiritual strains on personal resources. These factors overlay predispositional personal characteristics and may lead to depression and suicide. The actual rate of suicide in cancer patient populations is likely underreported due to “accidental” or unintentional deaths resulting from medication mismanagement, for example. Suicidal thinking exists on a spectrum, from transient passive thoughts about suicide, to active thinking, ruminating, planning, enacting (gesturing), and completing suicide. The key to suicide prevention is identification and proactive management of patients in the oncology setting with a team approach. This article will review the prevalence of suicide in patients with cancer, risk factors, related conditions (eg, suicidal ideation, desire for hastened death), and interventions to identify and treat suicidal patients.

Incidence of Suicide in Cancer Patients
Many people who complete suicide have chronic medical conditions. While rates of suicide are higher in patients with cancer compared with the general population, the speculative reasons for an association between cancer and suicide are particularly intriguing. Shneidman conceptualized the core driving characteristic of suicide as psychological pain, which he called “psychache.”[1] In this way, all affective states (rage, hostility, depression, shame, guilt, hopelessness) are relevant to suicide, since they are psychologically painful. Without psychache, there is no suicide. Others have theorized interpersonal loss and the desire to join the lost person as drivers of suicide.[2] Family members and other survivors of a suicide feel confused after the suicide has occurred. It can be extremely difficult to
More Resources Than Ever, but Suicide Risk in Patients and Providers Hasn’t Changed

CONSISTENT WITH THE AMERICAN MEDICAL ASSOCIATION CODE OF MEDICAL ETHICS, THE PREDECATE FOR THIS ARTICLE IS THAT HEALTHCARE PROFESSIONALS SHOULD PREVENT SUICIDE BY ALSO TREATING THE PSYCHOLOGICAL AND PHYSICAL SYMPTOMS THAT CAUSE THE “DESIRE FOR HASTENED DEATH.” ALONG WITH THE FACTORS THAT CONTRIBUTE TO SUICIDAL IDEATION, MCFARLAND AND COLLEAGUES ACKNOWLEDGE LEGAL CONSTRUCTS IN THEIR ARTICLE, SUCH AS PHYSICIAN-ASSISTED SUICIDE AND AID-IN-DYING LAWS THAT NOW EXIST IN THE UNITED STATES. AN ADDED BURDEN IS ON PHYSICIANS, WHO THEMSELVES ARE AT INCREASED RISK FOR SUICIDE. IN FACT, THIS WAS THE TOPIC OF MCFARLAND’S TALK AT THE 2019 AMERICAN SOCIETY OF CLINICAL ONCOLOGY ANNUAL MEETING EARLIER THIS MONTH, “ADDRESSING DEPRESSION, BURNOUT, AND SUICIDE IN ONCOLOGY PHYSICIANS.”

Between 1998 and 2017, more than 4,200 prescriptions were written for physician-assisted suicide drugs, and 63% of these patients chose to end their lives. Of those prescribed these agents, 51% were male, 94% were Caucasian, 48% were college educated, and most were 69 to 89 years old; more than half (63%) had cancer, ranging from 54% in California to 83% in Vermont. [1] Ironically, during the period of time that individual states were passing physician-assisted suicide and aid-in-dying laws, many major shifts in American culture and therapeutic approaches occurred. The populations of the seven states that legalized physician-assisted suicide constitute almost 20% of the total US population.

During this time, marijuana has been legalized in 20 states; while 10 states have fully legalized its use for all purposes, an additional 10 legalized its use for medical reasons. A decade ago, the Affordable Care Act was enacted, which was intended to provide insurance to the uninsured, and to overcome fears of medical bankruptcy through regulatory requirements within insurance plans. Underscoring core principals of medical ethics, pain control and symptom management became important components of healthcare, especially for cancer patients. Social media has also burgeoned, allowing for personal connectivity despite schedules and distance.

Despite all of these changes, the question remains: why do cancer patients still have unmet needs and contemplate or choose suicide? Why do well-paid oncologists need to work an average of 63 hours per week, suffering from burnout at a rate of 25% to 36%, which sometimes also leads to suicide? [2,3] The fact remains that more than 300 physicians die by suicide in the United States each year. Great strides have been made in the culture of cancer care, and yet, suicide persists, among both patients and their providers. Perhaps many of the described symptoms of “psychache,” or suffering, also reflect an existential change in American culture.

FINANCIAL DISCLOSURE: Dr. Janjan 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. Janjan is Senior Fellow at the National Center for Policy Analysis, Dallas, Texas, and an Adjunct Professor in the Department of Environmental and Occupational Health in the School of Public Health at Texas A&M University, College Station, Texas. She is also an Editor-in-Chief of ONCOLOGY.

For references visit cancernetwork.com/suicide-risk-cancer

Risk Factors

Suicide risk factors for patients with cancer include both cancer-related and general suicide risk factors (Table). Risk factors may interact with each other to create a higher...
risk. Cancer as a chronic disease is a risk factor for suicide, as are other comorbid chronic medical conditions. Demographic and disease-related factors are associated with increased risk for suicide among patients with cancer, as well as the general population.[7] Understanding these risk factors can guide medical professionals in discussing a patient’s motivation to commit suicide. Patients with particular demographic characteristics, including gender, age, and marital status, can be at an increased risk for committing suicide. Male patients with cancer generally tend to have higher rates of suicide compared with the general population.[8] When compared across cancer patients, men with cancer are at highest risk for suicide, particularly if they are older, white, and unmarried. [9] Older patients and patients who are not married may be at increased risk for suicide generally, especially older white men; however, other research suggests that at the time of diagnosis, younger patients are at the highest risk for suicide compared with any other age.[8,9]

Specific aspects of patients’ diagnoses can put them at an increased risk for suicide, such as cancer type, stage at diagnosis, length of time since diagnosis, and cancer-related symptoms (eg, pain). Symptoms related to both cancer and its treatment further augment suicide risk. While individual studies have found particular cancer types to be associated with suicide risk, a review of the literature shows a lack of consensus and posits that illness severity and progression are most closely linked to suicide risk compared with disease type.[10] Patients experiencing pain, fatigue, and general physical dysfunction are at a higher risk for suicide.[11] For example, patients with cancers diagnosed at advanced stages or that are unresectable such as lung or pancreatic cancer seem to be at highest risk for committing suicide.[8,9] The cancer types with the highest rates of suicide are lung, head and neck, gastric, and pancreatic cancer.[4,12]

Of particular importance for the clinician assessing suicide risk, patients with cancer are most likely to commit suicide within the first year of diagnosis.[13,14] The relative risk is highest immediately after or during the first week after diagnosis, incurring a relative risk of 12.6 (95% CI, 8.6–17.8), which goes down to a relative risk of 4.8 during the first 3 months after diagnosis. Additionally, the risk is three times more likely during the first year after diagnosis and two times more likely after 1 year.[15] Cancer-related suicide risk generally decreases with time, but remains elevated for the first 5 years after diagnosis.[16,17] On the contrary, patients with certain cancers (eg, bladder and renal cancer) may still have a high risk of suicide over time.[18] In addition to length of time since diagnosis, the stage of disease at diagnosis is related to suicidality, such that patients with more advanced diseases at diagnosis are at higher risk for suicide.[3]

Demographic and clinical risk factors for suicide within specific cancer types have been examined and appear to be cumulative. For example, patients with non–small-cell lung cancer who are male, white, unmarried, and between the ages of 60 to 75 years at diagnosis are at higher risk for suicide than other patients with this specific diagnosis.[19] Interestingly, patients who underwent surgery for their cancer were also at a higher risk for suicide than those who did not undergo surgery.[20] In the context of prostate cancer, even when matched on demographic characteristics, including age and geographic region, elderly men had over a four-fold increase in suicide risk compared with the general population. [21] This may be due to the psycholog-

### TABLE Suicide Risk and Protective Factors in Cancer

<table>
<thead>
<tr>
<th>General Risk Factors</th>
<th>Cancer-Specific Risk Factors</th>
<th>Protective Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Family history of suicide</td>
<td>• Physical debility</td>
<td>• Effective clinical care for mental, physical, and substance abuse disorders</td>
</tr>
<tr>
<td>• Family history of child maltreatment</td>
<td>• Time with cancer (&lt; 1 year)</td>
<td>• Easy access to a variety of clinical interventions and support for help seeking</td>
</tr>
<tr>
<td>• Previous suicide attempt(s)</td>
<td>• Stage of cancer (advanced or unresectable)</td>
<td>• Family and community support (connectedness)</td>
</tr>
<tr>
<td>• Depression or other mental disorder</td>
<td>• Type of cancer (head and neck, gastric, pancreatic, lung)</td>
<td>• Support from ongoing medical and mental healthcare relationships</td>
</tr>
<tr>
<td>• Alcohol and substance abuse</td>
<td>• Treatment type of associated morbidity</td>
<td>• Skills in problem solving, conflict resolution, and nonviolent ways of handling disputes</td>
</tr>
<tr>
<td>• Feelings of hopelessness</td>
<td>• Loss of physical ability</td>
<td>• Cultural and religious beliefs that discourage suicide and support instincts for self-preservation</td>
</tr>
<tr>
<td>• Aggressive tendencies</td>
<td>• Loss of meaning, dignity, or status</td>
<td></td>
</tr>
<tr>
<td>• Cultural and religious beliefs (suicide as noble)</td>
<td>• Symptom burden</td>
<td></td>
</tr>
<tr>
<td>• Local epidemics of suicide</td>
<td>• Survivor of childhood/adolescent cancer</td>
<td></td>
</tr>
<tr>
<td>• Isolation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Barriers to accessing mental health</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss (relational, social, work, or financial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Easy access to lethal methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unwillingness to seek help due to stigma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data from the Centers for Disease Control and Prevention. www.cdc.gov/violenceprevention/suicide/riskprotectivefactors.html

ONCOLOGY CANCERNETWORK.COM 223 REVIEW ARTICLE
ical pain related to impotence or sexual dysfunction.

These augmented risks highlight the cumulative distress and challenges faced by patients with cancer, which may lead to suicide. In contradistinction to decreasing suicide risk over time, patients with bladder and kidney cancer pose the highest risk for committing suicide among the genitourinary cancers, and this risk increases as time since diagnosis increases.[18] Alternatively, in a study by Kam and colleagues using Surveillance, Epidemiology, and End Results (SEER) data, it was noted that thyroid cancer was the only head and neck cancer without an elevated suicide risk, likely due to the high prevalence of localized resectable disease. [17] Head and neck cancer patients who received specific combinations of treatment, specifically those who completed radiation therapy but did not undergo surgery, had the highest rates of suicide. Treatment type and its side effects and sequelae leave a lasting psychological impact that contributes to higher risk of suicide.

Adult survivors of childhood cancers as a group are particularly vulnerable to suicide and should be monitored closely. [22] While epidemiologic risk may identify high-risk patients, any patient may complete suicide; therefore, clinical “red flags” are likely the most worthwhile identification tool that clinicians have to prevent suicide.

**Suicidal Ideation**

Suicidal ideation and thinking about suicide is predictive of suicide.[23] Suicidal ideation and history of suicidal behavior are among the most salient short- and long-term risk factors for suicide.[24,25] While there is usually a prodromal period of suicidal ideation (presuicidal syndrome), which can vary from transient and passive to ruminative and disruptive and lead to suicidal planning or enactment, suicide can occur impulsively without immediate warning. That is to say, suicidal ideation and actual suicide do not always occur together.[26] It is very common for anyone facing mortality via a chronic medical illness, especially those causing significant morbidity (eg, neurologic illness), to contemplate death and even suicide in the form of “maybe X would be better off without me.” These thoughts are related to a life adjustment, and should be transient and not overtly bothersome or persistent. When suicidal ideation becomes persistent or ruminative, patients may begin to feel unsafe. Chochinov et al found that 44.5% of 200 terminally ill patients reported a fleeting desire for death, while 8.5% had a more enduring wish for death.[27] There is always ambivalence, negotiation, and equivocation about suicide and, with this uncertainty, mental health treatment can effectively intervene. Patients may begin having magical thinking or looking for signs to help them decide whether or not to commit suicide. At a further level of suicidality, patients may have formulated a plan that could be enacted either impulsively (eg, due to uncontrolled emotion, lack of ability to regulate emotion, or facing disappointment) or in a deliberately controlled way. Patients often enact a suicidal gesture that is not actually meant to complete suicide but represents internal negation or preparation. Unfortunately, these acts are often unintentionally fatal. Even at this point, few patients are truly sure of their decision and will often reach out through subtle gestures. These patients can be helped greatly by an astute clinician who notices changes in cognition, emotion, and personality.

**Desire for Hastened Death**

Another aspect of suicidal thinking in patients with cancer is the psychological construct known as the desire for hastened death (DHD), or the longing for death to occur more rapidly than it otherwise would.[28] DHD incidence varies but increases while approaching the end of life and is more common in palliative and hospice settings.[29] The most common reasons noted for DHD include depression, hopelessness, perception of being a burden to others, and forfeiture of personal independence.[30] Disease symptoms were also included amongst the most cited factors, along with fear of pain and other anticipatory suffering. Similar to suicidal ideation, depression and hopelessness have been found to be independent factors related to DHD.[28] There are several validated measures for assessing DHD in a clinical setting, including the most commonly used Schedule of Attitudes toward Hastened Death and the Desire for Death Rating Scale.[27,31]

The optimal approach to addressing DHD is unclear. DHD is highly correlated with depression; therefore, addressing underlying depression is an appropriate approach. It has been suggested that DHD responds to psychological support specifically over other forms of comfort care.[32] For instance, pain management does not necessarily correspond to a decrease in DHD.[33] Therefore, it is essential that clinicians provide adequate psychological support.

**Physician-Assisted Suicide (PAS)**

PAS is legal in California, Colorado, Hawaii, Montana, Oregon, Vermont, and Washington, as of January 1, 2019. Death with dignity statues allow adult state residents with a confirmed prognosis of 6 or fewer months to live to hasten their inevitable or imminent death. States vary on procedures to implement PAS, but frequently require more than one physician to agree, as well as mental health evaluations and waiting periods.
While aid-in-dying laws are meant to protect patient autonomy, the act is problematic for physician beneficence or nonmaleficence and remains controversial, with opposition from some medical societies.[35]

**Clinical Factors**

**Depression**
The vast majority of suicides are associated with ongoing depression and underlying psychiatric history. Depression is the most common mental illness associated with suicide, which has been documented in 75% of cancer-related suicides.[36] Depression incurs a 25-fold increased risk of suicide compared with those without depression, irrespective of cancer.[37,38] Depression is most often the strongest predictor of suicide or DHD and is therefore a logical treatment target for preventing suicide. Pathological depression is often difficult to differentiate from appropriate feelings of sadness among patients facing a terminal illness.

**Hopelessness**
Hopelessness is a separate construct from depression and is a unique risk factor for both DHD and suicidal ideation.[39,40] Hopelessness in combination with depression puts patients at particularly high risk for developing suicidal ideation.[41]

**Demoralization**
Demoralization is similar to hopelessness but denotes a perceived inability to cope and is associated with a loss of meaning and a sense of disheartenment. It is quite common in cancer settings and may be a stronger predictor for suicidal ideation than depression.[6] Additionally, it may occur independently of depression.

**Pain**
While pain leads to heightened psychological distress and depression, the relationship with suicide is actually more complex. One study found that pain was not associated with suicide,[42] and other studies have suggested that the physical limitations that pain creates are responsible for suicidal ideation and DHD.[43]

**Social support**
A lack of social support is associated with DHD, suicidality, and requests for euthanasia.[44] Relationships heavily influence suicidal thinking. Restoration of relationships or a corrective interpersonal experience to take the place of actual or perceived interpersonal losses can be healing and protective for many patients.

**Burden to others**
While 19% to 65% of terminally ill patients express feelings of being a burden to others, a retrospective study found that the feeling was universal among those who completed suicide.[45,46]

**Personality traits**
Patients who are accepting and adaptable are less likely to contemplate suicide; however, patients with concerns about loss of autonomy, dependency, and a strong need to control circumstances are more likely to have suicidal ideation.[47]

**Psychiatric history**
Patients with a previous psychiatric disturbance and treatment are more likely to contemplate suicide.[42] In fact, one could argue that it is quite rare for someone without a psychiatric history of some kind to attempt or complete suicide. Many psychiatric conditions are concomitantly associated with depression (eg, bipolar depression, schizoaffective disorder, substance abuse disorders, personality disorders, along with all of the subsyndromal conditions such as adjustment disorders and minor depressive states), which places most patients with psychiatric disorders at higher risk of suicide.

**Existential concerns**
Patients confronted with mortality often struggle with loss of meaning, purpose, and dignity; regret; and an understanding of what happens after death, all of which may lead to suicidal thinking. Reports of low spiritual well-being or loss of dignity are associated with suicidal thinking.[44,48]

**Interventions**
Suicidal thinking is a deliberation between the will to live or die.[49] Intervening to reduce suffering, restore connectedness, and maintain safety defuses suicidal thinking. Oncologists are frequently first responders to cancer patients’ psychological suffering. A strong alliance between patient and oncologist can be protective against suicide.[50] A study of young cancer patients found that therapeutic alliance was associated with less suicidal thinking, even after controlling for well-established predictors of suicidal ideation, social supports, and mental health utilization.[51] This study speaks to the unique relationship between oncologists and their patients and the multidimensional nature of therapeutic alliance. Active listening, concern for patients’ well-being, openness, and providing clear explanations benefit patients beyond providing good oncologic care. Oncologists play a critical role, since many patients refuse to see mental health clinicians. Various studies have shown that communication skills training can improve oncologist–patient communication.[52]

There is a need to normalize conversations about suicide in order to get appropriate resources to the right patients. These conversations can be difficult, but asking and talking about suicide can prevent it even when done by non-professionals.[53] The Columbia-Suicide Severity Rating Scale (C-SSRS) is a suicide screening measure that has been validated in multiple settings and has numerous studies supporting its psychometric validity.[54,55] It can be used by non–mental health clinicians and non-clinicians with reliability.[56] Other suicide assessment tools include the National Institute of Mental Health Ask Suicide-Screening Questions (ASQ) Toolkit and the Distress Assessment and Response Tool (DART), which was developed specifically for cancer patients.[57] Screening instruments should assess...
for any “non-zero” intent to die, since suicidal ideation generally fluctuates and motives may be mixed.[58]

In addition, concomitant mental health services should be made available to patients with cancer who are suffering psychologically. When suicidal thinking is in question, patients should not be started on antidepressant medications without psychological follow-up to assess ongoing cognitions. Distress screening initiatives are designed to triage patients in a step-wise manner to appropriate levels of psychological support.[59] Unfortunately, these services are not always available; efforts to extend psychiatric services through telepsychiatry and collaborative care models are being developed and implemented.[60]

When a Patient Completes Suicide

Almost half of patients who die by suicide are seen by a healthcare provider the month prior to their death.[61] Oncologists may be the last point of contact in the healthcare system for many cancer patients who complete suicide. For the healthcare team, the aftermath of a patient suicide can be a particularly difficult and trying emotional experience that lingers, potentially leading to burnout and compromising the provision of subsequent patient care. “Postvention,” a term coined by the suicidologist Edwin Shneidman, is a series of interventions to support the bereaved after a suicide. The objectives are to provide care to bereaved survivors, caregivers, and healthcare providers; destigmatize the tragedy of suicide; operationalize the confusing aftermath; assist with the recovery process; and act to prevent further suicides by providing support services to survivors.[62] The oncologist may want to assure that mental health care options are offered and provided for staff and for bereaved family members.

Upon initially learning that a patient has completed suicide, oncologists may feel a sense of shock or disbelief. This dissociation from intense feelings—a reaction often reinforced by medical training—can serve a protective function, mitigating the interference caused by grief with a physician’s ability to practice medicine. It is not uncommon to feel a sense of guilt or shame related to the fear that something was missed.[63] These feelings are understandable, but it is important to recognize that the accuracy of suicide prediction models is near zero, even though we can identify patients who may be at an elevated risk for suicide. [64] There is no “one size fits all” model, which is similar to coming to terms with any traumatic event. Many clinicians find it useful to discuss the situation with colleagues and to hear others’ experiences of losing a patient to suicide.[65] This can decrease the sense of isolation that often results from a patient suicide.

Conclusion

Thoughts of suicide in patients with cancer are compounded by chronic disease, advancing age, and multiple losses and reasons for suffering (ie, psychache). Suicide in cancer patients occurs mostly in elderly age groups; older, white, unmarried men are historically most at risk, but patients with head and neck, lung, pancreatic, and stomach cancers are also particularly at risk. Suicidal thinking occurs on a spectrum and presents as suicidal ideation or DHD. In addition, suicide may now be completed legally in certain states with PAS. Depression, hopelessness, demoralization, pain, lack of social support, feeling like a burden to others, a strong need to control circumstances, and existential concerns can all be associated with suicide. Oncologists play an integral role in identifying high-risk patients and providing support. The C-SSRS is a well-accepted and reliable suicide assessment tool; suicide screening should categorize any non-zero intent to die as suicidal ideation. Additionally, it is important to acknowledge the emotional toll that patient suicides have on clinicians and the healthcare team; psychological support should be provided in these situations.

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/suicide-risk-cancer
Preventing Gastric Cancer Development by Inhibiting the Virulence of *H. pylori* Infection

In this interview with *ONCOLOGY*, Keith Wilson, MD, discusses a drug that may help prevent gastric cancer. Dr. Wilson and his colleagues recently published a study showing that a chemopreventive drug can also act directly on *Helicobacter pylori* (*H. pylori*), a bacterium that is the primary cause of gastric cancer.[1]

**Q. First, can you talk about the bacterium *H. pylori* and its role in gastric cancer?**

**DR. WILSON:** A major discovery was published in a landmark paper in the *Lancet* in 1984 written by Australian researchers Barry Marshall and Robin Warren, for which they later were awarded the Nobel Prize in Medicine.[2] This discovery linked infection of the stomach with the bacterium *H. pylori* to inflammation of the stomach and ulcer disease; later, it was recognized that this was linked to gastric cancer.

In terms of the epidemiology, this bacterium infects the stomach in about half of the entire global human population, with especially high prevalence in Latin America, namely Mexico, Central America, and South America, as well as much of Asia. The bacterium is known to have co-evolved with humans for at least 60,000 years and probably longer. Of all those infected, 1% will develop cancer. But if you consider how many people are infected in the world, that’s still a lot—such that there’s close to a million cases a year of gastric cancer worldwide. Gastric cancer is the second leading cause of cancer death in the world. What has been agreed upon, the consensus, is that the process of developing gastric cancer occurs through a histologic cascade from inflammation of the stomach, known as gastritis, which is pretty much universal amongst all those who are infected.

About 40% of people who have this chronic inflammation will progress to the next stage, atrophic gastritis, which consists of loss of acid secreting parietal cells and other specialized epithelial cells, and this is thought to be the big switching point in the lining of the stomach. There has been some thought over the last 10 to 20 years that this atrophy, this loss of acid secretion, may contribute to carcinogenesis by changing the niche and allowing the flourishing of other microbes in the stomach, because we know now that there is a gastric microbiota and that this...
M ost gastric cancers worldwide are attributable to chronic infection with Helicobacter pylori (H. pylori) bacteria. Since H. pylori is usually acquired in infancy, and cancer does not develop until late middle age, there is a wide window of opportunity of several decades in which to intervene and prevent cancer development. Clinical trials indicate that eradication of H. pylori with a short combination antibiotic regimen can reduce the chance of cancer development by about 40%, with most studies suggesting that this effect is greatest in patients who have not yet developed advanced preneoplastic lesions at the time of H. pylori eradication.

There are three major practical challenges when considering instituting programs to prevent H. pylori–associated gastric carcinogenesis: 1) the identification of suitable individuals and populations most at risk; 2) the gradual but steady emergence of multi-antibiotic resistance to H. pylori strains; and 3) the question of whether H. pylori eradication alone is a sufficient cancer prevention strategy in patients with advanced preneoplastic gastric lesions.

In evaluating the possible chemopreventive effects of difluoromethylornithine (DFMO) in patients with H. pylori–associated gastric disease, Dr. Wilson and colleagues discovered in an animal model that DFMO also has anti–H. pylori effects[1]; these effects occur via interference with the bacterial type IV secretion system, which is thought to mediate several of H. pylori’s oncogenic effects. So, might DFMO be clinically useful in inhibiting H. pylori’s function and effects? Hopefully, the important ongoing clinical trials that Dr. Wilson is conducting in Latin America will provide some answers in that regard—though taking a chemopreventive agent over a long duration of time, likely for decades, may prove impractical for many. In the meantime, determining how best to kill H. pylori, whether through anti-cag mechanisms or by addressing and overcoming H. pylori antibiotic resistance, will remain an important priority in gastric cancer prevention.

FINANCIAL DISCLOSURE: Dr. Moss has no significant financial relationship with the manufacturer of any product or provider of any service mentioned in this article.

Dr. Moss is a Professor of Medicine in the Department of Gastroenterology and the Director of the Gastroenterology Fellowship Training Program at Brown University, Providence, Rhode Island.

Dr. Moss

Practical Challenges in Instituting Programs to Prevent H. pylori–Associated Gastric Carcinogenesis

may change when you lose the acid. Then, amongst those who have atrophic gastritis, some will progress to gastric intestinal metaplasia, which is a precancerous lesion that can be quite stable. Some of these patients will progress to dysplasia and then to carcinoma.

Many investigators have studied the cancer development process and one common concept is that the ongoing persistent inflammation of the stomach leads to oxidative stress–induced DNA damage, and if there is survival of cells but DNA damage, this can lead to DNA mutations and cancer risk. The goal is to determine what we can do to prevent this process, because it takes decades.

Q: Are there current ways to detect and treat any primary infection, and is that routinely done anywhere in the world?

DR. WILSON: One of the controversies has been, “when do we really need to test for H. pylori infection?” The only thing that is absolutely firmly agreed upon in the gastroenterology community is that if somebody has peptic ulcer disease of the stomach or intestine, testing for H. pylori should be conducted. This is most commonly done by obtaining a biopsy or a set of biopsies from the stomach. The pathologist will stain with hematoxylin and eosin in the samples from the stomach and will look for the presence of neutrophils, which are the hallmark of H. pylori infection. If they see neutrophils, they will look for H. pylori in the mucous lining and may do a silver stain (also called a Steiner stain) to look for bacteria in the stomach in localization with the epithelial cell. This is not completely specific for H. pylori, but if you see the typical spiral-shaped or helical-shaped bacteria, that’s good evidence of H. pylori infection.

Other histologic techniques that can be used in some hospitals is immunohistochemistry for H. pylori. Other very commonly used strategies to detect H. pylori include a serology test, in which you look for the immunoglobulin G (IgG) antibody signature against H. pylori, indicating that
at some point in the person’s life they had the infection. It does not provide insight into what’s going on in the stomach at that time, and it’s not useful to assess eradication because if the patient is treated with antibiotic regimens, the IgG antibody titer probably won’t change. However, I personally find the serology tests very useful. For example, I order them in patients who have been experiencing GI bleeding, for which you don’t want to take biopsies of the stomach, or for patients who show intestinal metaplasia of the stomach and don’t have active H. pylori seen on the biopsy.

Other tests include a stool antigen that has gained a lot of favor over the serology tests because it’s thought to be equally sensitive and I believe it’s less expensive. This test looks for evidence of H. pylori antigens in the stool. Another test that is sometimes used is the urea breath test, in which the patient takes in a drink that contains radiolabeled urea. Since the bacterium has the enzyme urease that acts upon urea, it produces a reaction that leads to the exhaling of carbon dioxide; so, the patients take in this radiolabeled urea and exhale the carbon dioxide into a bag, which you then put into a machine. That has been used a lot for assessment of eradication, as well as in some countries where they want to do screening instead of having to do biopsies.

In terms of treatment, this is always an ongoing area of investigation, and it’s rather complicated. You need to use a regimen that typically includes two, sometimes three, antibiotics; the original regimen that was popular 20 years ago was metronidazole, tetracycline, and bismuth. Treatment then advanced to a more common regimen of a proton pump inhibitor plus amoxicillin and clarithromycin. The problem with all these regimens is that there can be various antibiotic resistance patterns in the particular location of where the patient lives. This has been very intensively studied.

The latest recommendations are for quadruple therapy, which consists of a proton pump inhibitor, bismuth, and two antibiotics, with the idea being that the antibiotic selection should be based somewhat on the local resistance patterns. More recently, there’s been a lot of concern about clarithromycin resistance, so there are lots of other alternative regimens. The regimens usually consist of at least a proton pump inhibitor plus two antibiotics, but adding bismuth has been shown to be more efficacious. In addition, it has been shown that 14 days is more effective than 10 days, which is more effective than 7 days. We usually use a 14-day regimen. The dosing of the antibiotics is quite high, so, for example, the amoxicillin and clarithromycin doses are much higher than what you might use for something like a respiratory tract infection. It is complicated, and resistance is a concern. The success rate of eradication in the United States is probably suboptimal; with quadruple therapy, it is close to 90%, but with triple therapy it may be less than 80%. Studies out of underdeveloped regions have suggested that eradication is even lower than that.

In an animal model, we showed that DFMO reduced cancer development by about 50%.

Q: Your lab recently identified a compound that can target H. pylori directly. Can you tell us the approach you used to identify this compound and what the compound is?

DR. WILSON: The compound that we studied was difluoromethylornithine, which we call DFMO for short. This is a drug very well known in oncology; it is an inhibitor of the rate-limiting enzyme for the synthesis of polyamines, which is called ornithine decarboxylase, or ODC for short. ODC produces putrescine from ornithine. Putrescine is a polyamine that can be metabolized to spermidine and spermine, which are the two other major mammalian polyamines. The regulation of polyamine homeostasis is quite complex. I mentioned that ODC is the rate-limiting enzyme, but there are other enzymes required for the synthesis, and then there are enzymes involved in the interconversion of the polyamines, both forward and backward conversion. DFMO has been in clinical use since the 1980s because polyamines are important in cell growth. The thinking was that it could be used in oncology to reduce tumor growth, but generally monotherapy with DFMO has not been particularly successful. There is a lot of excitement about its use in neuroblastoma, but in terms of monotherapy for other types of cancer, both solid and hematologic, it wasn’t really that successful.

However, we were interested in it at my lab. We do a lot of work on polyamines in gastrointestinal diseases, in terms of mucosal inflammation and preventing cancer development. DFMO is a drug that’s very tempting to use in animal models because it is approved for clinical use. So, over the years we have done a lot of studies related to ODC and DFMO. We got the idea of looking at whether DFMO could possibly have a direct effect on the bacteria. About 10 years ago, we published a paper in Gastroenterology, showing that when DFMO was put into the drinking water and given to mice, it reduced inflammation and the colonization burden when mice were experimentally infected with H. pylori.[3]

This led to the idea that DFMO could be of benefit to humans, and we...
DR. WILSON: Based on our 2015 data, we wrote a grant proposing to use this drug in patients, which was funded by the National Cancer Institute. We are conducting a clinical trial in patients in Honduras, and we recently added Puerto Rico as another study site. We needed to do this in these locations because that’s where precancerous gastric lesions are very prevalent. This study design involves giving patients with intestinal metaplasia of the stomach DFMO for 18 months; they get a baseline endoscopy to confirm that they still have the metaplasia, and undergo follow-up biopsies at 6 months and 18 months. This study is ongoing, I don’t have any results to report yet. As you can imagine, conducting such studies in places outside of the United States is a bit of a challenge, but that was the plan and we hope that we will have some clinically relevant results.

We also intend to analyze any effects on the H. pylori, from the strains that we would harvest. However, since these patients already have metaplasia, there’s a concept called the point of no return where once patients have metaplasia, it is not thought to be that beneficial to give antibiotics. The data are fairly weak that there’s added benefit of being treated with antibiotics at that point. I think it’s pretty clear from many studies that if patients are treated with antibiotics while they only have gastritis, that does a very nice job of preventing cancer risk, so we’re not certain that we will see a lot of findings related to the bacterium because these patients already have metaplasia. But in the future, we would also really like to do some sort of smaller trial in patients with gastritis and H. pylori that’s readily detectable to show that DFMO for 6 months has some beneficial effect on the microbe, but we haven’t initiated that.

The only other comment I would make is that in the cancer field, there is a lot of interest in combining other drugs with DFMO. We’re still doing mechanistic studies in my lab looking at other components of this polyamine pathway and other potential targets.

wondered whether it could have a direct effect on the bacteria. We published a short paper in 2011,[4] showing that DFMO appeared to, perhaps, have some effects on the growth rate of H. pylori in liquid culture. We next used a gerbil model because gerbils will actually develop adenocarcinoma of the stomach when infected with H. pylori, whereas conventional mice that are genetically manipulated will only develop chronic inflammation. We published a paper in Oncogene in 2015,[5] that showed that when DFMO was given to gerbils, it reduced cancer development by about 50%. This was done in the context of some studies related to clinical strains from patients in Colombia. We were able to get one of the strains that causes dysplasia in a human to cause cancer in gerbils, and we showed that DFMO reduced cancer development.

We had been learning from other articles and the literature that one of the things that could happen spontaneously with H. pylori in animal models is rearrangement of a gene that’s part of a complex that injects the oncoprotein cytotoxin-associated gene A, or CagA, from the bug into the host. Through a type IV secretion system, H. pylori uses a structure that appears like a needle and syringe to inject CagA into host epithelial cells, which causes aberrant signaling that’s been linked to gastric cancer development. It’s been shown that when strains are infecting animals over time, they can develop rearrangements of the cagY gene, which is part of the cag gene apparatus that’s involved in the needle and syringe mechanism, and this rearrangement can lead to dysfunction. Basically, we got the idea that maybe since DFMO was reducing cancer in the gerbils, it could somehow have an effect on this type IV secretion system.

In the paper that we recently published in Proceedings of the National Academy of Sciences of the United States of America,[1] we showed that about one-third of all the output strains from gerbils that were experimentally infected had loss of the type IV secretion function of the bacterium when it was assessed 12 weeks after infection. The experimental design was that animals were infected and then stomachs were harvested 12 weeks later. Half of the animals were on DFMO and half were not, and we found that about one-third of the strains had this loss of the function of the cagY protein encoded by the cagY gene, and none of the control animals that were infected showed any spontaneous loss of this function. So, we took these strains harvested from the tissues and used a reporter system in which we added the bacterium in a co-culture to epithelial cells. Then, we analyze the translocation of the CagA protein into the host epithelial cell by doing an assay for phosphorylation of this protein, because only when it’s translocated into the cell and the host system is hijacked do you get phosphorylation of this protein, which is the hallmark of the translocation. Looking at some other downstream host cell genes that are known to be dependent on this translocation, we saw that they were also altered. We also demonstrated at the protein level that this cagY protein was altered in terms of how it appeared on a gel. We showed the cagY gene rearrangements on DNA gels, and using a polymerase chain reaction–based method, we could show a shift in bands. The ultimate proof was we did specialized sequencing of the

### KEY QUESTION

**What’s next? Are you or others testing or planning to test whether DFMO could prevent gastric cancer in those infected with H. pylori?**

**DR. WILSON:** Based on our 2015 data, we wrote a grant proposing to use this drug in patients, which was funded by the National Cancer Institute. We are conducting a clinical trial in patients in Honduras, and we recently added Puerto Rico as another study site. We needed to do this in these locations because that’s where precancerous gastric lesions are very prevalent. This study design involves giving patients with intestinal metaplasia of the stomach DFMO for 18 months; they get a baseline endoscopy to confirm that they still have the metaplasia, and undergo follow-up biopsies at 6 months and 18 months. This study is ongoing, I don’t have any results to report yet. As you can imagine, conducting such studies in places outside of the United States is a bit of a challenge, but that was the plan and we hope that we will have some clinically relevant results.

We also intend to analyze any effects on the H. pylori, from the strains that we would harvest. However, since these patients already have metaplasia, there’s a concept called the point of no return where once patients have metaplasia, it is not thought to be that beneficial to give antibiotics. The data are fairly weak that there’s added benefit of being treated with antibiotics at that point. I think it’s pretty clear from many studies that if patients are treated with antibiotics while they only have gastritis, that does a very nice job of preventing cancer risk, so we’re not certain that we will see a lot of findings related to the bacterium because these patients already have metaplasia. But in the future, we would also really like to do some sort of smaller trial in patients with gastritis and H. pylori that’s readily detectable to show that DFMO for 6 months has some beneficial effect on the microbe, but we haven’t initiated that.

The only other comment I would make is that in the cancer field, there is a lot of interest in combining other drugs with DFMO. We’re still doing mechanistic studies in my lab looking at other components of this polyamine pathway and other potential targets.
cagY gene and found that it was altered by this exposure to DFMO.

An interesting question is, what is so special about this cagY gene? It is known that it has a middle repeat region that is susceptible to gene rearrangements, meaning insertions or deletions, and that was what we proved with the sequencing. Whereas, when we tested things like the CagA gene, we didn’t see any changes. We also tested some other genes that are known to have middle repeat regions and they were not altered, either. We showed that this was important in this study because when we took an output strain that had this rearrangement and put it back into new gerbils, none of them got cancer. Normally about 50% to 80% of gerbils will get cancer with the infection after 12 weeks. We also transformed the bacteria in that we removed cagY from the parental strain and put in the mutant cagY from the animals that had the rearrangements, in a process called complementation, and we switched them and showed that this switching prevented cancer as well. We were also able to show that we develop gene rearrangements if we simply grow the H. pylori on agar plates with the DFMO.

Finally, in terms of mechanism, we showed in the in vitro experiments that it appeared that oxidative stress on the bacteria was caused by the DFMO and that this led to induction of genes that repair DNA, and then the repair basically fixed the DNA in such a way in which there were actually changes in the DNA. I know this story sounds complicated, but the bottom line is, it is sort of a collateral effect of this drug that it is being used to inhibit polyamine synthesis, but actually, it has a direct effect that was quite specific on this cagY gene.

FINANCIAL DISCLOSURE: Dr. Wilson 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/gastric-ca-prev
Considerations When Initiating Neratinib for Breast Cancer

How to Prevent and Treat Diarrhea

Meagan S. Barbee, PharmD, BCOP

The adjuvant treatment landscape for breast cancer has changed drastically in recent years.[1] For patients with hormone receptor (HR)-positive disease, data suggest that 10 years of hormonal therapy is better than 5 years,[2-4] and that high-risk patients who are premenopausal should receive ovarian suppression and an aromatase inhibitor instead of tamoxifen or tamoxifen with ovarian suppression.[5] Moreover, patients whose Oncotype DX score is less than 26 are unlikely to benefit from chemotherapy based on results from the TAILORx study.[6] In HER2-negative patients who received neoadjuvant therapy but did not achieve a pathologic complete response, adjuvant capcitabine for 6 to 8 cycles (before endocrine therapy in HR-positive patients) should be considered, according to results of the CREATE-X study.[7] Lastly, neratinib was approved by the US Food and Drug Administration (FDA) in 2017 for the extended adjuvant treatment of HER2-positive breast cancer per the results of the ExteNET trial.[8-10]

In the ExteNET trial, patients with early HER2-positive disease who underwent previous chemotherapy received 1 year of extended adjuvant therapy with once-daily oral neratinib 240 mg following a year of standard-of-care adjuvant trastuzumab. The study was eventually amended to include only higher-risk patients (those with node-positive disease, stages II to III) who were no more than 1 year from their last dose of adjuvant trastuzumab and had no evidence of recurrence. In patients who were HR positive (57% of the overall population), neratinib was given concurrently with adjuvant endocrine therapy. Patients with clinically significant cardiac, gastrointestinal, or psychiatric comorbidities and those unable to swallow pills were excluded from the trial. Results showed that 1 year of adjuvant neratinib significantly improved the 2-year invasive disease–free survival rate compared with placebo (93.9% vs 91.3%, respectively; stratified hazard ratio, 0.67; 95% CI, 0.50–0.91; \( P = .0017 \)). However, the clinical benefit was not preserved in the subgroup of patients who were HR negative (hazard ratio, 0.93; 95% CI, 0.60–1.43; \( P = .74 \), \( p_{interaction} = .54 \)).[9] Primary endpoint results were preserved in a 5-year follow-up report.[10]

Neratinib is an irreversible tyrosine kinase inhibitor of HER1 (ErbB1, epidermal growth factor receptor [EGFR]), HER2 (ErbB2), and HER4 (ErbB4).[8] Practical considerations for neratinib use are listed in Table 1. Neratinib is associated with severe skin rash, interstitial
lung disease, hepatotoxicity, and pneumonitis. The most commonly reported adverse event and dose-limiting toxicity of neratinib is diarrhea.[8-10] In the ExteNET trial, 41% of patients experienced a grade 3 or higher diarrhea event, with a median time to onset of 8 days and a median duration of 5 days. Diarrhea of any grade was experienced by 95% of patients in the trial, and led to dose reductions in 26% and study discontinuations in 17% of patients in the neratinib arm, resulting in an overall median relative dose intensity of 82% for neratinib (98% for placebo). Twenty patients (1%) were hospitalized as a result of neratinib-induced diarrhea. Negative changes in quality of life on neratinib were reported at 1 month, though scores recovered to baseline soon after, and the effects of diarrhea on this change were not studied.[9] However, diarrhea can have a notable effect on performance status and the ability to perform activities, resulting in social isolation, time off work, relationship difficulties, and psychological distress.[11]

The mechanism of neratinib-induced diarrhea is likely due to its effect on EGFR, similar to that of erlotinib; EGFR mediates calcium-dependent chloride transport, and blocking EGFR can subsequently induce secretory diarrhea.[11]

Because of the significant incidence of diarrhea with use of neratinib, the original FDA labeling for the approval of neratinib included a recommended prophylaxis of loperamide scheduled for 2 cycles (2 months total), beginning with the first dose, and continuing as needed thereafter.[8] Optimal prevention of neratinib-induced diarrhea is being studied in the phase II CONTROL trial.[12] Early findings (Table 2) suggest that adding colestipol to loperamide beginning with the first dose of neratinib results in the greatest reduction of grade 3 or higher diarrhea incidence (primary endpoint) and severity compared with what was seen in the ExteNET trial.

TABLE 1 Practical Considerations for Neratinib Use[8]

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>240 mg (6 × 40-mg tablets) orally, once daily, with food</td>
</tr>
<tr>
<td>Dose levels</td>
<td>240 mg → 200 mg → 160 mg → 120 mg → discontinue</td>
</tr>
<tr>
<td>Dose adjustments for baseline organ dysfunction</td>
<td>80-mg daily starting dose in severe liver impairment (Child–Pugh score, class C)</td>
</tr>
<tr>
<td>Dose adjustments for toxicities</td>
<td>Hepatotoxicity, diarrhea, or any grade 3 event; permanently discontinue for any grade 4 event</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic via CYP3A4 to active metabolites</td>
</tr>
<tr>
<td>Elimination</td>
<td>Feces (~97%) and urine (~1%)</td>
</tr>
<tr>
<td>Drug interactions and dose adjustments</td>
<td>• Avoid neratinib use with moderate or strong CYP3A4 inhibitors</td>
</tr>
<tr>
<td></td>
<td>• Neratinib inhibits P-glycoprotein</td>
</tr>
<tr>
<td></td>
<td>• Avoid proton pump inhibitors, since neratinib requires acid for absorption</td>
</tr>
<tr>
<td></td>
<td>• Space H2RAs from neratinib by taking neratinib 2 hours before or 10 hours after H2RAs</td>
</tr>
<tr>
<td></td>
<td>• Space neratinib by 3 hours from other antacids</td>
</tr>
<tr>
<td>Monitoring parameters</td>
<td>• Liver function tests: baseline, monthly × 3, then every 3 mos</td>
</tr>
<tr>
<td></td>
<td>• Pregnancy test at baseline in women of child-bearing potential</td>
</tr>
<tr>
<td></td>
<td>• Signs/symptoms of dehydration (from diarrhea)</td>
</tr>
<tr>
<td></td>
<td>• Signs/symptoms of hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>• Adherence</td>
</tr>
<tr>
<td>Grade 3+ adverse events in clinical trials</td>
<td>• Gastrointestinal: diarrhea, nausea, vomiting, abdominal pain, decreased appetite</td>
</tr>
<tr>
<td></td>
<td>• Other: rash, headache, fatigue, dizziness, arthralgia, muscle spasms</td>
</tr>
<tr>
<td>Unique pearls</td>
<td>Crosses the blood-brain barrier</td>
</tr>
<tr>
<td>Access considerations</td>
<td>• Approximately ~ $13,000 for 1 mo of 240-mg neratinib/d</td>
</tr>
<tr>
<td></td>
<td>• Usually requires a prior authorization</td>
</tr>
<tr>
<td></td>
<td>• Must use specialty pharmacy</td>
</tr>
</tbody>
</table>

CYP3A4 = cytochrome P450 3A4; H2RAs = histamine2-receptor antagonists.

TABLE 2 Prevention of Neratinib-Induced Diarrhea[12]

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Incidence of Grade 3+ Diarrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loperamide 4 mg PO TID × 2 wks then 4 mg BID wks 3–8</td>
<td>30.7% (95% CI, 23.1%–39.1%)</td>
</tr>
<tr>
<td>Budesonide ER 9 mg PO daily × 4 wks + loperamide as above</td>
<td>26.6% (95% CI, 16.3%–39.1%)</td>
</tr>
<tr>
<td>Colestipol 1 g PO BID × 4 wks + loperamide as above</td>
<td>10.8% (95% CI, 5.9%–17.8%)</td>
</tr>
<tr>
<td>ExteNET historical cohort (no prophylaxis)</td>
<td>39.9% (95% CI, 37.3%–42.5%)</td>
</tr>
</tbody>
</table>
CTCAE Grade of Diarrhea and Recommended Neratinib Dose Modulation[8,13]

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
<th>Neratinib Modulation</th>
<th>Supportive Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Increase of 1 to 3 stools/d over baseline or mild increase in ostomy output compared with baseline</td>
<td>• Continue at same dose level • Optimize supportive care</td>
<td>• Adjust anti-diarrheal treatment; may need to add agent if already on loperamide or restart loperamide if not already taking</td>
</tr>
<tr>
<td>2</td>
<td>Increase of 4 to 6 stools/d over baseline or moderate increase in ostomy output compared with baseline; limiting instrumental activities of daily living</td>
<td>• Hold if persists for 5 d or longer after optimal supportive care • Resume at same dose if resolves to grade 0 or 1 in ≤ 1 wk • Dose reduce by 1 level if takes &gt; 1 wk to resolve to grade 0 or 1 • Permanently discontinue if recurrence occurs</td>
<td>• Take loperamide with each subsequent dose of neratinib</td>
</tr>
<tr>
<td>3</td>
<td>Increase of ≥ 7 stools/d over baseline; hospitalization indicated; severe increase in ostomy output compared with baseline; limiting self-care activities of daily living</td>
<td>• Hold if persists for 2 d or longer after optimal supportive care • Resume at same dose if resolves to grade 0 or 1 in ≤ 1 wk • Dose reduce by 1 level if takes &gt; 1 wk to resolve to grade 0 or 1 • Permanently discontinue if recurrence occurs</td>
<td>• Diet modifications</td>
</tr>
<tr>
<td>4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
<td>Permanently discontinue neratinib</td>
<td>• Maintain fluid intake of at least 2 L to avoid dehydration</td>
</tr>
<tr>
<td>5</td>
<td>Death</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CTCAE = Common Terminology Criteria for Adverse Events; N/A = not applicable.

proactively prescribe colestipol 1 g PO BID × 4 weeks in conjunction with loperamide 4 mg PO TID × 2 weeks, 4 mg BID for weeks 3 to 8, and then as needed thereafter. If this approach is unsuccessful, dose modulation of neratinib should occur, according to Common Terminology Criteria for Adverse Events (CTCAE) grade (Table 3). Other agents could be employed in the treatment of diarrhea, should it continue, and may include: codeine, octreotide, budesonide, and antibiotics.[11] Supportive care should be maximized at the onset of any grade of diarrhea. Neratinib should be held for complicated diarrhea that includes features of dehydration, fever, hypotension, renal failure, or neutropenia (absolute neutrophil count < 1,000/mm³). If constipation is experienced, the dose of loperamide should first be decreased or the schedule altered to be less frequent, but not initially abandoned. Neratinib should be discontinued if the toxicity does not recover to ≤ grade 1, if the toxicity results in a treatment delay of more than 3 weeks, or in patients unable to tolerate 120 mg in the absence of baseline organ dysfunction.[8]

Patients should be monitored for compliance to neratinib and the prophylactic anti-diarrheal regimen to help preserve adherence and limit unnecessary and preventable dose reductions or neratinib failures. Ongoing drug interaction assessments should be performed at each physician visit to screen for medications that can increase the AUC of neratinib via cytochrome P450 (CYP) inhibition, thus perpetuating diarrhea, as well as for concomitant medications that are independently associated with diarrhea. Patients should be counseled to refrain from over-the-counter stool softeners and laxatives when initiating neratinib therapy.

While patients have received a marginal clinical benefit from extended adjuvant therapy with neratinib in the curative-intent setting, it is likely that utilization of neratinib will expand to the HER2-positive metastatic setting, particularly in patients with brain metastases. In the future, preserving high doses of neratinib to maximize central nervous system concentration in patients with brain metastases who have few alternative options for therapy will rely on adequately preventing and controlling major toxicities, namely diarrhea. While use in the metastatic setting is currently off-label, and it is currently unknown whether adherence or dose preservation affect disease-free survival in the curative-intent setting, providers should still aim to prevent diarrhea in patients receiving neratinib to optimize therapy and maintain a good quality of life.

FINANCIAL DISCLOSURE: Dr. Barbee 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. Barbee is the Clinical Coordinator and an Oncology Clinical Pharmacy Specialist for Breast Cancer at Winship Cancer Institute, Emory University, Atlanta, Georgia.
Should Active Surveillance Be Used for Gleason 3+4 Prostate Cancer?

POINT: Active Surveillance for Intermediate-Risk Prostate Cancer Can Be Beneficial

Abhishek Bhat, MD, and Sanoj Punnen, MD, MAS

While the use of active surveillance among men with low-risk prostate cancer has increased, its role in men with intermediate-risk disease remains debatable. Current American Society of Clinical Oncology (ASCO)/Cancer Care Ontario (CCO) guidelines recommend treatment for most men with intermediate-risk disease, but state that men with low-volume Gleason 3+4 prostate cancer may be considered for active surveillance.[1] The recent National Comprehensive Cancer Network (NCCN) guidelines list active surveillance as an initial therapy option for men with favorable intermediate-risk disease, which they define as clinical stage T2b-T2c, Gleason score 3+4, or prostate-specific antigen (PSA) levels at 10–20 ng/mL, as well as less than 50% of positive biopsy cores.[2] While it remains an option in current guidelines and has been increasing in contemporary clinical practice,[3] there remains significant controversy over the safety of active surveillance in intermediate-risk prostate cancer.

The best evidence supporting active surveillance comes from the Prostate Intervention vs Observation Trial (PIVOT), which random-Continued on page 236

COUNTERPOINT: Active Surveillance Should Not Currently Be Considered for Intermediate-Risk Prostate Cancer

Ikenna Madueke, MD, PhD, and Michael R. Abern, MD

Active surveillance has been proven safe in men with low-risk prostate cancer.[1-3] More recently, it has been suggested that the inclusion criteria for active surveillance should be expanded to include men with Gleason score 3+4 histology. The National Comprehensive Cancer Network (NCCN) guidelines list active surveillance as an option for favorable intermediate-risk prostate cancer, which is defined as confined to the organ, with a clinical stage of T2, Gleason score 3+4, or a prostate-specific antigen (PSA) level of 10–20 ng/mL, as well as less than 50% of positive biopsy cores.[4] Much of the rationale for this guideline is based on the revised International Society of Urological Pathology (ISUP) definition of Gleason pattern 4 disease from 2005, which has resulted in reclassification of cases formerly reported as Gleason score 3+3 to 3+4 and 4+3. [5] However, we propose that active surveillance should not be routinely offered to all men with Gleason score 3+4 prostate cancer, since the drawbacks of active surveillance are potentially magnified in this population.

While Gleason pattern 4 has evolved over time, currently four architectural subtypes

Continued on page 237
ized 731 men with localized prostate cancer to observation vs radical prostatectomy from 1994 to 2002.[4] In a subgroup analysis of 249 men with intermediate-risk prostate cancer, the study found no difference in prostate cancer-specific mortality between the two groups. The authors reported an updated series with a decade more follow-up, again showing no difference in prostate cancer-specific mortality between intermediate-risk patients choosing active surveillance vs radical treatment.[5]

Similarly, the ProteCt trial randomized 1,643 men with localized prostate cancer to undergo treatment with active surveillance, radiotherapy, or surgery from 1999 to 2009.[6] With a median follow-up of 10 years, the study reported a low incidence of prostate cancer mortality, with no difference between the treatment groups. It is worth noting that nearly 80% of the patients on this study were considered low risk, and the follow-up for this endpoint could be considered short. However, both trials provide level 1 evidence in support of active surveillance for localized prostate cancer.

Further evidence supporting active surveillance for intermediate-risk patients comes from various prospective institutional cohorts. In 2011, the University of California, San Francisco, reported their data comparing intermediate- and low-risk patients who underwent active surveillance. Within the first 4 years of follow-up, the study found no difference in the rate of men experiencing progression of cancer or a difference in the proportion of men undergoing treatment between the two groups.[7]

In contrast to this, a previous report from the University of Toronto showed an increased risk of late metastasis in men with intermediate-risk prostate cancer who chose active surveillance.[8] This relationship was primarily driven by men with Gleason 7 prostate cancer. However, these men were selected and monitored by clinical and pathologic criteria only and perhaps underwent serial biopsy too infrequently for their level of risk.

While it remains unclear whether active surveillance in intermediate-risk patients is beneficial, it is likely that some men with intermediate-risk prostate cancer will need treatment, while others may be able to safely avoid it. The evidence suggests that those who are defined as intermediate risk based on their PSA levels, rather than stage or grade, are likely to harbor the same risk as men with low-risk prostate cancer. [9] However, the question of whether active surveillance is beneficial in men with Gleason 7 prostate cancer is more difficult. What is clear is that selection is critical. While some studies based on radical prostatectomy series have suggested that typical clinical and pathologic criteria are incapable of selecting a favorable group of intermediate-risk patients who would not be at risk for an adverse outcome when selecting active surveillance,[10] it is difficult to know whether data based on surgical patients would generalize appropriately to true active surveillance patients who are not choosing immediate radical therapy.

In addition, contemporary methods of risk assessment and novel prognostic markers show much progress for improving risk stratification and decision making regarding treatment vs observation.[11] For instance, the most powerful prognostic tool we have in prostate cancer is the histopathologic Gleason score. However, most prostate cancer reports stratify Gleason 7 into two groups (3+4/4+3), losing valuable information and grossly underestimating the degree of heterogeneity in risk that exists within the Gleason 3+4 group. Recent studies have supported the usage of quantitative Gleason scoring in men with Gleason 3+4 prostate cancer on biopsy to allow better quantification of the pattern 4 cancer that poses the increased risk, thereby facilitating better risk assessment for decision making.[12,13]

Why not take advantage of the most important information we have, especially when we can get it for free? Additionally, there has been a significant emergence of evidence for the role of MRI and tissue genomics in active surveillance.[14,15] Perhaps with these tools we will be able to better discriminate between men with Gleason 7 prostate cancer who can and cannot safely monitor their prostate cancer.

At the University of Miami, we have nearly completed enrollment of 200 men who will monitor their cancer with annual MRI, prostate biopsy, and tissue genomic studies for a funded program by the National Institutes of Health/National Cancer Institute. The study allows men with up to four cores of prostate cancer, of which two can be Gleason 3+4. While most men are still in the follow-up stages of the protocol, we believe this study will provide invaluable information regarding the utility of these novel markers in men with low- and intermediate-risk cancer undergoing active surveillance. Future studies, like this one, incorporating novel risk stratification tools in the selection and monitoring of intermediate-risk patients choosing active surveillance will allow further discovery into the appropriateness of observation in these men, as well as the selection criteria that are unlikely to compromise their outcomes.

**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/active-surv-pro
Counterpoint. **Active Surveillance Should Not Currently Be Considered**
Continued from page 235

exist: ill-formed, fused, glomeruloid, and cribriform.[6] Several groups have shown Gleason score 3+4 prostate cancer with cribriform architecture on biopsy to be associated with distant metastasis and pathologic upstaging on radical prostatectomy (RP).[7,8] While the outcomes of active surveillance for men with cribriform Gleason pattern 4 disease have not been adequately studied, available evidence suggests this to be a relative contraindication.

The percentage of men who will eventually undergo curative treatment after starting active surveillance ranges from 20% to 50%.[9,10] For men with low-risk disease, multiple reports have shown that delayed RP is not associated with adverse pathology on final RP specimen.[11-13] However, we previously retrospectively investigated 1,561 low- and intermediate-risk men from multiple Veterans Affairs centers and showed that a delay >9 months to RP in men with intermediate-risk prostate cancer was associated with biochemical recurrence (BCR) and positive surgical margins (PSMs).[14] The same findings were true in “lower-risk” subgroups of men with intermediate-risk prostate cancer, including those with low-volume Gleason score 3+4 disease. Similarly, Cooperberg et al retrospectively evaluated the CapSURE database for men with intermediate-risk disease as defined by Gleason score 3+4 or a UCSF Cancer of the Prostate Risk Assessment (CAPRA) score of 3–5 managed with active surveillance who ultimately underwent RP.[15] They reported a 50% incidence of pT3 disease in the active surveillance arm compared with 23% in the entire cohort that underwent immediate RP, suggesting that active surveillance may be suboptimal for men with favorable intermediate-risk disease.

Standard-of-care 12-core transrectal ultrasound (TRUS)-guided prostate biopsies are prone to significant sampling error. As a result, about 30% of RP specimens are upgraded and/or upstaged from their biopsy Gleason grade or stage.[9,16,17] A recent retrospective series reported only 57.4% grade concordance on final RP specimen for TRUS-guided biopsy-proven Gleason score 3+4 disease and upgrading of 10.7%, 19.1%, and 6.4% to Gleason score 4+3, 4+4, and 9–10, respectively.[18] Similarly, Epstein et al have previously reported a concordance of 49.7% for 3+4 disease and an upgrade of 25.8%.[9] More recently, Yang et al retrospectively investigated 10,000 patients with Gleason score 3+4 favorable intermediate-risk disease and also found about 30.3% of upgrading and/or upstaging.[19] In this series, 17% of the entire cohort were upstaged to ≥pT3a disease. Risk of more aggressive disease in this cohort was associated with higher PSA levels, older age (>67 years), higher percentage of positive biopsy cores, and cT2a stage. Taken together, these data suggest that as many as one-third of men offered active surveillance for favorable intermediate-risk prostate cancer diagnosed on TRUS-guided biopsy are already harboring higher-risk disease and would not be offered surveillance had the prostate been adequately sampled.

There are also high-risk populations for which the current inclusion of active surveillance must be utilized with caution. For example, African American men on average make up less than 10% of the active surveillance cohorts, but are 2.4 times more likely to die from prostate cancer than their Caucasian counterparts.[20-23] Sundi et al showed that African American men with very-low-risk prostate cancer who met criteria for active surveillance but underwent immediate RP had higher rates of upstaging and PSMs compared with other races.[24] Iremashvili et al included the following in their inclusion criteria for active surveillance: Gleason score <7, two or fewer positive biopsy cores, 20% or less tumor in any core, and clinical stage T1–T2a, with any change from these parameters above these limits considered progression.[21] In their study, they showed that African American men were significantly more likely to have disease progression, with an adjusted hazard ratio of 3.87–4.12. We previously retrospectively analyzed a Duke University active surveillance cohort with inclusion criteria consisting of clinical stage <cT3, PSA level <10 ng/mL, Gleason sum ≤6, and ≤33% positive biopsy cores.[25] On the basis of both objective disease progression and patient-driven decisions, African American men progressed to treatment faster on active surveillance compared with other races. While many unanswered questions remain regarding potential race disparities in prostate cancer, there are insufficient data to support active surveillance for intermediate-risk prostate cancer in high-risk populations such as African American men.

It should be stated that the reported 10-year outcomes from the ProtecT trial did not show an improvement in survival with treatment compared with active monitoring; however, only 21% of the patients on active monitoring had Gleason 7 disease.[26] Despite the
primarily low-risk profile of the ProtecT cohort, there was a statistically significant increase in metastases and clinical progression in the active monitoring arm.[26] In the Prostate Intervention vs Observation Trial (PIVOT), which randomized US veterans to either RP or observation for clinically localized prostate cancer, the overall conclusion was that RP did not improve survival. However, the intermediate-risk subgroup that underwent RP had statistically improved overall survival and prostate cancer–specific survival (hazard ratio, 0.53) that did not reach statistical significance.[27] Taken together, although the active monitoring or observation used in PIVOT and ProtecT were not as intensive as modern active surveillance, and neither trial was powered to detect survival differences for Gleason score 3+4 prostate cancer, these level 1 data do not definitively prove the safety of active surveillance in this population.

We summarize the caveats to offering active surveillance in men with Gleason score 3+4 prostate cancer in the Table. However, how do we move forward? To confidently offer active surveillance in men with Gleason score 3+4 prostate cancer, we feel that confirmatory biomarkers are needed as a safety measure for inclusion. The most data currently exist for multiparametric MRI (mpMRI) and tissue-based genomic panels, which are increasingly utilized clinically for active surveillance. The high negative predictive value of mpMRI for high- and intermediate-risk prostate cancer could

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Type of Study</th>
<th>Participants With Intermediate-Risk Prostate Cancer (low-risk if specified; N)</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keefe et al (2015)[8]</td>
<td>Retrospective</td>
<td>748 (intermediate risk) 813 (low-risk)</td>
<td>Delay of &gt; 9 months to RP is associated with BCR and PSM in intermediate-risk disease</td>
</tr>
<tr>
<td>Cooperberg et al (2011)[15]</td>
<td>Retrospective</td>
<td>16</td>
<td>57.4% grade concordance on final RP specimen for TRUS-guided biopsy-proven GS 3+4 disease and upgrading of 10.7%, 19.1%, and 6.4% to GS 4+3, 4+4, and 9–10, respectively</td>
</tr>
<tr>
<td>D’Elia et al (2014)[18]</td>
<td>Retrospective</td>
<td>1,577</td>
<td>RP concordance of 49.7% for GS 3+4 on PNBx and upgrade of 25.8%</td>
</tr>
<tr>
<td>Epstein et al (2012)[9]</td>
<td>Retrospective</td>
<td>600</td>
<td>53.3% of upgrading and/or upstaging in patients with GS 3+4 disease; 17% of the entire cohort harbored an upgrade to ≤pT3a disease</td>
</tr>
<tr>
<td>Yang et al (2017)[19]</td>
<td>Retrospective</td>
<td>1,801 (AA, 256 Caucasian, 1,473, and other, 72)</td>
<td>AA men with very-low-risk disease who met criteria for AS but underwent AS prior to RP had higher rates of upgrading and PSMs compared with other races</td>
</tr>
<tr>
<td>Sundi et al (2013)[24]</td>
<td>Prospective</td>
<td>249 (AA, 24)</td>
<td>AA men with low-risk disease were significantly more likely to have disease progression, with an adjusted HR of 3.87–4.12</td>
</tr>
<tr>
<td>abern et al (2013)[25]</td>
<td>Retrospective</td>
<td>145 (AA, 32)</td>
<td>On the basis of both objective disease progression and patient-driven decisions, AA men progressed to treatment faster on AS compared with other races</td>
</tr>
<tr>
<td>Hamdy et al (2016)[26]</td>
<td>Prospective randomized</td>
<td>111 (GS, 7) 421 (GS, 6)</td>
<td>10-year outcomes from the ProtecT trial did not show an improvement in survival with treatment compared with AS, and only 21% of the patients on AS had GS 7 disease; despite the low-risk profile of the ProtecT cohort, there was a statistically significant increase in metastases and clinical progression in the active monitoring arm</td>
</tr>
<tr>
<td>Wilt et al (2017)[27]</td>
<td>Prospective randomized</td>
<td>120</td>
<td>The PIVOT trial reported no PCSS benefit of RP in the total cohort; however, there was an improvement in OS in the subgroup of men with intermediate-risk disease who underwent treatment vs AS</td>
</tr>
</tbody>
</table>

AA = African American; AS = active surveillance; BCR = biochemical recurrence; GS = Gleason score; HR = hazard ratio; OS = overall survival; PCSS = prostate cancer–specific survival; PIVOT = Prostate Intervention vs Observation Trial; PNBx = prostate needle biopsy; PSM = positive surgical margins; RP = radical prostatectomy; TRUS = transrectal ultrasound.
For patients with high-risk endometrial cancer, multimodality treatment is typically recommended. Hormone therapy, targeted therapy, and immunotherapy approaches have been utilized in clinical practice. In this interview, ONCOLOGY spoke with Vicky Makker, MD, a medical oncologist who treats patients with gynecologic cancers, including cervical, ovarian, and uterine tumors, about these options, as well as emerging combination therapies that are currently being evaluated in clinical trials.

Q: What is the current standard of care for the treatment of advanced endometrial cancers?

DR. MAKKER: Endometrial cancer is the most common gynecologic cancer in the United States. Alarmingly, the incidence and mortality of this malignancy continue to rise due to several factors. Chief among them is obesity. The National Cancer Institute estimates that more than 63,000 new cases of endometrial cancer and 11,000 related deaths occurred in 2018. Endometrial cancer is usually diagnosed in postmenopausal women. The average age at diagnosis is 62 years, and most women have an early stage of cancer that is confined to the uterus. However, approximately 21% of women have regional spread to pelvic lymph nodes or the surrounding organs, and roughly 9% have distant metastases at the time of diagnosis.[1] The prognosis of endometrial cancer is primarily determined by the stage and histology of the
tumor, as well as the presence of adverse risk factors such as lymphovascular invasion, high-grade histology, advanced patient age, and deep myometrial invasion.

The goal of adjuvant therapy in newly diagnosed endometrial cancer is to reduce the risk of disease recurrence and distant metastases, and treatment is guided by surgical stage, tumor histology, and the number of adverse risk factors. High-risk endometrial cancers include those with type II histologies: serous carcinoma, clear cell carcinoma, and carcinosarcoma, regardless of stage; grade 3 deeply invasive endometrial adenocarcinoma; and pathologic stage III or IV disease, regardless of histology. Due to their aggressive nature and the possibility of early metastases, multimodality treatment is typically recommended for high-risk endometrial cancer, even in the setting of early-stage disease.

For women with stage III or IV endometrial cancer that has been surgically resected, we offer chemotherapy with the addition of radiation therapy in appropriate cases. Women with unresectable stage III or IV cancer are largely treated with chemotherapy, and the role of radiotherapy should be individualized based on tumor burden and location of the tumor. Multiaxial chemotherapy regimens are considered for patients who require chemotherapy, including carboplatin and paclitaxel; cisplatin with doxorubicin; cisplatin with doxorubicin and paclitaxel; carboplatin and docetaxel; carboplatin, paclitaxel, and bevacizumab; or carboplatin, paclitaxel, and trastuzumab. In most cases, the preferred regimen is carboplatin and paclitaxel; this recommendation is based on the results of the phase III Gynecologic Oncology Group (GOG) 209 trial of paclitaxel and carboplatin vs a three-drug regimen of doxorubicin, cisplatin, and paclitaxel, which found that paclitaxel and carboplatin were noninferior to doxorubicin, cisplatin, and paclitaxel with regards to progression-free and overall survival.[2]

According to The Cancer Genome Atlas Project (TCGA), approximately 25% of serous or serous-like endometrial cancers display human epidermal growth factor receptor 2 (HER2) amplification.[3] A phase II trial of paclitaxel and carboplatin vs paclitaxel, carboplatin, and trastuzumab in stage III/IV or advanced HER2-overexpressing uterine cancers found that the triple combination regimen was associated with an improved median progression-free survival compared with carboplatin and paclitaxel (8 vs 12.6 months); therefore, it can be considered for HER2-amplified serous carcinomas or serous-like carcinomas that are advanced or recurrent.[4] Alternatively, combination carboplatin, paclitaxel, and bevacizumab can also be considered in patients with advanced or recurrent disease.[4] In the randomized phase III GOG-86P trial, bevacizumab combined with carboplatin and paclitaxel chemotherapy in advanced chemotherapy-naive patients resulted in an objective response rate of 59.5%, with a significant improvement in overall survival compared with the historic reference of paclitaxel and carboplatin and the other arms in the trial. [5] If patients cannot receive multiagent chemotherapy or have contraindications to it, single therapy options exist, including carboplatin, cisplatin, docetaxel, doxorubicin, paclitaxel, and topotecan. When single agents are utilized in the first-line setting, responses range from 21% to 36%; in the second-line setting, however, responses fall sharply to between 4% and 27%.

That covers chemotherapy, but there are also other options for the treatment of advanced endometrial cancers. Hormone therapy is one such method, and has been mainly studied in the recurrent or metastatic setting. Responses are generally best in low-grade, well-differentiated endometrioid tumors that often overexpress estrogen or progesterone receptors. There are a myriad of hormonal therapy approaches that have been investigated in small phase II trials, with response rates ranging from 10% to 33% and a median progression-free survival ranging from 1 to 10 months.[6-12] The highest responses are seen with tamoxifen alternating with progesterational agents.[10,11] Currently, only megestrol acetate is approved by the US Food and Drug Administration (FDA) for the palliative treatment of advanced endometrial cancers. Other agents that can be utilized include tamoxifen, luteinizing hormone-releasing hormone agonists, and aromatase inhibitors.

Additionally, several classes of targeted therapies have been explored in advanced endometrial cancers. These include agents that target the phosphoinositide 3-kinase (PI3K) and protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathways, as well as angiogenesis inhibitors, epidermal
growth factor receptor inhibitors, mitogen-activated protein kinase inhibitors, and HER2-targeting antibodies. However, only a limited benefit has been seen with these agents thus far. Based on preliminary favorable findings for endometrioid histologies, the combination of letrozole, an aromatase inhibitor, and everolimus, an mTOR inhibitor, can be used in advanced, recurrent endometrioid subtype tumors. Bevacizumab, a vascular endothelial growth factor antibody, was evaluated in a phase II monotherapy trial in advanced endometrial cancer and demonstrated a response rate of 14.3%, with 40% of patients being progression free at 6 months. This agent is often used in patients with advanced endometrial cancers.

Finally, we have pembrolizumab, a humanized monoclonal antibody that targets programmed death 1 (PD-1). In 2017, the FDA granted the first tissue/site-agnostic, accelerated approval for pembrolizumab in adult and pediatric patients with unresectable or metastatic microsatellite instability–high (MSI-H) or mismatch repair–deficient solid tumors that have progressed following prior treatment.

**The results of the GARNET phase I/II trial on dostarlimab (TSR-042) for endometrial cancer** were recently presented at the 2019 Society of Gynecologic Oncology (SGO) Annual Meeting in March. What were the key results, and how do you interpret the findings?

**DR. MAKKER:** Dostarlimab, or TSR-042, is an investigation-al anti–PD-1 monoclonal antibody that blocks the PD-1 receptor, preventing ligand binding. The GARNET study—a phase I, multicenter, first-in-human, dose-escalation study with an expansion cohort—assessed the safety and clinical activity of dostarlimab in patients with solid tumors. Participants received 500 mg every 3 weeks for 4 doses, then were titrated up to 1,000 mg every 6 weeks until disease progression occurred. Results from two expansion cohorts were reported: patients with MSI-H endometrial cancer (n = 65) and patients with microsatellite-stable (MSS) endometrial cancer (n = 125). The primary objectives were overall response rate and duration of response, as well as safety and tolerability. Patients with recurrent or advanced endometrial cancers who had progressed after a platinum-containing regimen and had not received prior anti–PD-1 or anti–programmed death ligand 1 therapy were enrolled. Most patients (56%) had received 1 prior line of therapy, while 29% received 2 prior lines, and approximately 15% received ≥ 3 prior lines of therapy.

 Seventy percent of patients experienced a treatment-emergent adverse event. The most common all-grade treatment-emergent

---

**KEY QUESTION**

**If a patient has an MSI-H tumor, is pembrolizumab the obvious choice for treatment, or are there other considerations? In addition, is there any evidence that pembrolizumab or another immune checkpoint inhibitor could be effective for other subtypes of endometrial cancer?**

**DR. MAKKER:** Pembrolizumab is considered an appropriate second-line therapy for patients with advanced endometrial cancer who have progressed on front-line therapy. Determination of whether a patient should receive pembrolizumab vs another therapy is dependent on the patient’s MSI status, performance status, medical comorbidities, and molecular phenotype. It has become commonplace for patients to have their endometrial cancers sequenced through a number of Clinical Laboratory Improvement Amendments–approved platforms, so these data also factor into the decision-making process. For patients with recurrent endometrial cancer with MSI-H, pembrolizumab is approved and is appropriate for use in the second-line setting.

In terms of whether other subtypes of patients might respond to checkpoint inhibitors, I think there is still much to be learned in this space. Numerous ongoing trials are currently evaluating additional checkpoint inhibitors beyond pembrolizumab, checkpoint inhibitors in combination with other immuno-oncology agents, and other targeted therapy molecules, which I think will help us better understand the role of these agents, especially for subtypes of endometrial cancer that are not MSI-H. Another important consideration regarding these drugs is that not all patients with MSI-H disease respond to checkpoint inhibitors. For example, although the objective response rate for patients with endometrial cancer in the phase II study by Le et al reached an impressive 53%, approximately 20% of the MSI-H patients had progressive disease after treatment with pembrolizumab.

Thus, although these biomarkers are helping us to better isolate the patients who are most likely to respond, biomarker imprecision remains a challenge. To better characterize patients whose tumors may respond to checkpoint inhibition, assessment of additional biomarkers—such as tumor mutational burden and mutation-associated neoantigens—is needed, and this work is ongoing. These efforts will impact our understanding and hopefully better inform us why certain MSI-H patients don’t respond to checkpoint inhibitors, and whether there is a rational path forward to combine checkpoint inhibitors with targeted or immuno-oncology agents to improve treatment efficacy in MSS endometrial cancers.
adverse events that occurred in ≥ 10% of patients included fatigue, diarrhea, and nausea. Only 5.6% of patients had a grade 3 or higher immune-related treatment-emergent adverse event (eg, hyperglycemia, elevated liver function, autoimmune hemolytic anemia, colitis, or an infusion-related reaction). The objective response rate was 49% in the MSI-H patients and 20% in the MSS patients. The responses were durable, and 84% of responders were still on treatment when the results were presented. The median duration of response had not been reached at that time, and the median follow-up was 10 months.\[15\]

These results are encouraging, and we need to follow along as this study matures. Further investigation of dostarlimab in the front-line setting is planned in combination with chemotherapy later in 2019 (ClinicalTrials.gov identifier: NCT02715284).

Q: Are there any other immunotherapy approaches, either as monotherapy or combination therapy, that are currently being tested for endometrial tumors?

DR. MAKKER: There are a number of exciting trials that are recruiting patients in this space. To highlight a few, there are trials of durvalumab vs durvalumab plus tremelimumab (ClinicalTrials.gov identifier: NCT03015129), and of nivolumab vs nivolumab plus cabozantinib in advanced endometrial cancers (ClinicalTrials.gov identifier: NCT03367741). Additionally, there are two phase III trials currently being conducted: one is evaluating pembrolizumab in combination with lenvatinib vs physician’s choice of chemotherapy in the second-line setting (ClinicalTrials.gov identifier: NCT03517449), and the other is evaluating pembrolizumab and lenvatinib vs carboplatin and paclitaxel in the front-line setting (ClinicalTrials.gov identifier: NCT03884101); both are accruing patients. Other combinations that are being evaluated include atezolizumab in combination with chemotherapy (ClinicalTrials.gov identifier: NCT03603184); atezolizumab plus bevacizumab (ClinicalTrials.gov identifier: NCT03526432); and atezolizumab plus bevacizumab and rucaparib (ClinicalTrials.gov identifier: NCT03694262).

It’s encouraging to see various rational combinations being evaluated in patients with both MSI-H and MSS endometrial cancers. There are also trials evaluating immunotherapy in combination with radiation therapy for appropriate patients (ClinicalTrials.gov identifier: NCT03192059), so I anticipate that the treatment landscape of this disease will evolve significantly in the next few years. The number of trials that are ongoing in this space is amazing, and much will be learned over the next number of years.

FINANCIAL DISCLOSURE: Dr. Makker receives personal fees, study fees, and travel expenses from Eisai, IBM, Karyopharm Therapeutics, and Merck. She receives study funding from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, Karyopharm Therapeutics, and Takeda. She also serves on the advisory boards of Eisai, Karyopharm Therapeutics, Merck, and Takeda.

For references visit cancernetwork.com/endo-cancer-updates

Active Surveillance for Gleason 3+4 Prostate Cancer

Continued from page 238

increase confidence in a recommendation for active surveillance, and also provides targets for a re-sampling confirmatory biopsy.\[28\] Other tools that may be alternatives or complementary to mpMRI are the several commercially available tissue-based genomic panels validated to predict adverse RP histology and prostate cancer outcomes, such as metastasis-free survival.\[29\] There are reports of changed and more confident decision making for newly diagnosed prostate cancer with these tests in both physicians and patients compared with groups in which these tests were not utilized.\[30,31\] Our current ongoing study, the ENACT trial, which randomizes men with newly diagnosed very-low-, low-, or favorable intermediate-risk prostate cancer to either standard counseling vs counseling with a tissue genomic panel, should help to determine the clinical utility of a tissue-based biomarker approach to active surveillance selection.

In conclusion, men with Gleason score 3+4=7 prostate cancer represent a heterogeneous group. There are inadequate data regarding the long-term outcomes of active surveillance in these men, especially in high-risk populations such as African American men. The use of imaging and tissue-based biomarkers hold promise in helping us to find the most favorable subset of men with intermediate-risk prostate cancer for which active surveillance may be the favored initial management strategy.

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/active-surv-con
Extending Adjuvant Endocrine Therapy in Breast Cancer: Who, What, and Why?

Shaveta Vinayak, MD, MS, and Nancy E. Davidson, MD

ABSTRACT: Adjuvant endocrine therapy provides substantial benefit by reducing breast cancer recurrences and improving associated mortality in early-stage endocrine-responsive breast cancers (estrogen receptor– and/or progesterone receptor–positive). Residual risk of relapse, even after completion of 5 years of adjuvant endocrine therapy, has fueled development of extended therapy (beyond 5 years) trials. However, several questions remain when recommending extended adjuvant endocrine therapy, such as those concerning patient selection, agent of choice, use of biomarkers or clinical variables to assess residual risk of relapse, and duration of treatment. In this article, we will provide a case-based expert opinion on: 1) the duration of extended adjuvant endocrine therapy in both premenopausal and postmenopausal women; 2) use of biomarkers in guiding this decision; and 3) toxicities to be considered when recommending extended adjuvant endocrine therapy. We also provide key factors to consider, including patient preference, when guiding our patients in this important treatment decision.

Case Scenario
Ms. BC is a 48-year-old woman who was diagnosed with breast cancer in 2012 when she was premenopausal (pT2N1 left breast invasive ductal carcinoma—grade 2, strongly positive estrogen receptor [ER; > 90%], strongly positive progesterone receptor [PR; > 90%], and human epidermal growth factor receptor 2 [HER2]/neu-negative). She underwent left lumpectomy with left sentinel lymph node biopsy, which revealed a 2.5-cm tumor and involvement of 1 of 5 sentinel lymph nodes, with a metastatic focus of 0.5 cm. She received adjuvant anthracycline/taxane-based chemotherapy followed by left breast radiation, and has now completed 5 years of tamoxifen for adjuvant endocrine therapy. She has not had a menstrual period in 3 years.

Several key questions arise in our shared decision-making process on the role of extended adjuvant endocrine therapy with Ms. BC. These include: 1) What is her residual risk of distant breast cancer relapse after 5 years of tamoxifen? 2) Can additional clinicopathologic factors or biomarkers inform this decision? 3) What is the potential additional benefit of extended endocrine therapy? 4) What is the optimal agent—tamoxifen or aromatase inhibitors (AIs)? 5) Does she have any comorbidities that will affect this decision? 6) What side effects are acceptable to Ms. BC? We will provide our expert opinion on Ms. BC’s case throughout this article.
Endocrine-responsive breast cancers (ER- and/or PR-positive) represent the majority of early breast cancers in the United States; therefore, effective treatments for this breast cancer subtype can significantly reduce breast cancer recurrences and improve associated mortality. Indeed, endocrine therapy was the first “precision” cancer therapy for hormone-responsive breast cancers, and it remains the cornerstone. For many years, 5 years of adjuvant endocrine therapy, regardless of the agent, was considered standard of care for early-stage breast cancer. However, the unrelenting risk of relapse for up to 20 years from diagnosis, which is observed despite completing 5 years of endocrine therapy, demands improvement in our standard of care.[1]

Key considerations include residual risk of relapse, expected benefit of extended therapy, menopausal status, medication toxicity, and patient perspective. Independent of menopausal status, two pivotal randomized trials (ATLAS and aTTom) provide high level of evidence supporting the use of tamoxifen for up to 10 years, which shows a large impact on reduction of distant recurrence and overall mortality (seen in the ATLAS trial).[2,3] The largest risk reduction in both recurrence (relative risk [RR], 0.75; \( P = .003 \)) and breast cancer mortality (RR, 0.71; \( P = .002 \)) was seen after year 10, which can be attributed to the carryover benefit of tamoxifen as seen in other studies.[3] Thus, strong evidence supports the use of 10 years of tamoxifen.

Though this patient was diagnosed before the use of ovarian function suppression (OFS) in premenopausal women, the role of OFS as a component of adjuvant endocrine therapy upfront was elucidated in the recent SOFT/TEXT trials, in which premenopausal women received tamoxifen alone or combination therapy with OFS and either tamoxifen or the steroidal AI exemestane for 5 years.[4] Together, these studies showed that OFS plus tamoxifen or OFS plus exemestane improves disease-free survival (DFS) compared with tamoxifen alone; however, overall survival (OS) benefit has not yet been seen. Not surprisingly, the high-risk subgroup with factors such as receipt of adjuvant chemotherapy, lymph node involvement (4 or more positive nodes), and young age (< 35 years) benefitted the most from OFS plus exemestane, with a 10% to 15% improvement in the 5-year breast cancer–free interval.[5] No data exist on the utility of the combined approach beyond 5 years, nor is there information to guide decisions on selection of a strategy of 10 years of tamoxifen vs 5 years of an AI with OFS at the time of diagnosis.

In our practice, a thorough discussion of benefits and toxicities is advised. In general, combination endocrine therapy with OFS is more poorly tolerated than tamoxifen alone. OFS is given as a monthly injection and can lead to abrupt menopause, with symptoms of hot flashes, vaginal atrophy, and sexual dysfunction. AIs may be associated with bothersome symptoms, such as arthralgias and myalgias, which may impact daily activities. Some high-risk women for whom combination endocrine therapy with OFS is recommended may choose not to proceed with this option because of concern about these symptoms. For those who select this option, we typically advise a trial of the OFS-based therapy before proceeding with any permanent procedures, such as bilateral salpingo-oophorectomy, in case they have poor tolerance of either the AI or the OFS injection. We do not generally extend OFS-based therapy beyond 5 years.

For postmenopausal women, several randomized trials, including the National Cancer Institute of Canada Clinical Trials Group MA.17 and MA.17R trials, the Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 6a, and the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 trial,[6-9] have shown that up to 10 years of endocrine therapy (generally involving a switch from tamoxifen to AIs) improves outcomes. In most of these trials, the initial therapy was variable, and a switch to an AI was made later during the treatment. Extended therapy AI trials have predominantly shown a benefit in DFS (eg, MA17.R), but no OS benefit has been shown as of yet. [7] This may reflect the relatively short-term follow-up (median follow-up, 6.3 years), since the hormone-responsive breast cancer subtype tends to have delayed distant recurrences that impact mortality. It is noteworthy that much of the disease-free interval benefit in these trials was related to contralateral breast cancer risk,[7] and we take this into consideration when counseling patients regarding extended use. At present, we
particularly consider extended AI therapy for healthy postmenopausal women with high-risk breast cancer at the time of diagnosis. These recommendations are congruent with the recently updated focused American Society of Clinical Oncology (ASCO) guidelines on adjuvant endocrine therapy in postmenopausal women.[10]

In sum, several questions about treatment selection remain unanswered in clinical practice when recommending adjuvant endocrine therapy. One is the role of subsequent treatment for premenopausal women who have completed 5 years of combination AIs with OFS upfront, based on the SOFT/TEXT trials. For postmenopausal women, we still await evidence of a survival advantage with the use of extended AI treatment, as the data mature. Finally, at this time there are few data on the use of any extended adjuvant endocrine therapy beyond 10 years, though it is possible that there may be a role for this in very high-risk patients.

**Case follow-up**

Given that Ms. BC had premenopausal breast cancer with a tumor size greater than 2 cm and axillary lymph node involvement, and received adjuvant chemotherapy, she fits the high-risk profile. Had she been diagnosed today, use of OFS plus AIs or OFS plus tamoxifen for 5 years might have been recommended, but this was not a standard option when she was diagnosed in 2012. Her last menstrual period was 3 years ago, but it is possible that she is still chemically premenopausal, and evaluation of hormone levels would be important. If she is chemically postmenopausal, her options for extended therapy include AIs or tamoxifen for 5 years. Ms. BC reports a significant history of early-onset osteoporosis in her family and wants to obtain a bone density test before making her decision. Moreover, her friend who is a breast cancer survivor has recommended the Breast Cancer Index test.

### Key Recommendations

1. **Upfront adjuvant endocrine therapy (up to 5 years after diagnosis).** For premenopausal women, options include tamoxifen, an AI with OFS, or tamoxifen with OFS for 5 years; OFS plus an AI or tamoxifen for 5 years is recommended for high-risk women.

2. **Extended adjuvant endocrine therapy (beyond 5 years after diagnosis).** For high-risk women (young age at diagnosis, lymph node positivity) who have become postmenopausal, we recommend extended endocrine therapy (up to 10 years) with an AI or tamoxifen alone, guided by menopausal status and patient preference, after 5 years of initial endocrine therapy. Studies show that both DFS and OS improve with extended tamoxifen use (for up to 10 years), regardless of menopausal status. Extended AI use (for up to 10 years) is associated with DFS, but not OS, in postmenopausal women. No studies support the use of any adjuvant endocrine therapy beyond 10 years.

3. **Use of prognostic factors such as tumor size and nodal status can help predict residual risk of recurrence after 5 years of endocrine therapy.** However, we do not currently recommend use of genomic or circulating assays to inform the decision on the use of extended adjuvant endocrine therapy.

4. **Extended endocrine therapy should only be considered in healthy women without other life-threatening conditions.** If extended AI use is being considered, bone density assessment is recommended. The best choice of endocrine therapy is the one that is well tolerated and acceptable to the patient.

### 2. Can biomarkers help guide us in this decision?

Two important unmet needs in hormone-responsive breast cancer are better identification of patients who are at risk for late recurrences, and demonstration that additional therapy like extended adjuvant endocrine therapy will improve outcomes. There is no consensus on the level of risk that is acceptable for avoiding extended adjuvant endocrine therapy. Several efforts in identifying factors, including tissue-based clinicopathologic features, genomic assays, and circulating markers, that might help predict late relapses are ongoing.

The Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis, which analyzed 62,923 women with hormone-responsive breast cancer, provided significant insight into the risk of late recurrence after 5 years of adjuvant endocrine therapy, based on traditional clinicopathologic features.[1] For example, at 10 years, T1N0 patients had the lowest risk of recurrence at 4%, compared with T1N4–9 patients, who had a recurrence rate of 15%. The risk of recurrence continued to increase, regardless of tumor diameter and nodal status (TN), and reached a 20-year cumulative recurrence risk of 13% for T1N0, 20% for T1N1–3, 34% for T1N4–9, 19% for T2N0, 26% for T2N1–3, and 41% for T2N4–9 patients.[1] Thus, initial tumor size and nodal status—but not PR status, grade, or Ki-67 index—remain critical determinants of recurrence, even decades out from diagnosis.[1] This important meta-analysis provides us with data to inform discussions with our patients who are considering extended endocrine therapy, though some have discounted these studies as an inadequate reflection of the results that we might expect in contemporary practice.

Genomic assays, such as the PAM50 risk of recurrence score, the Breast Cancer Index, Oncotype DX, and EndoPredict, have all shown analytical validity...
and clinical validity by biomarker standards, but their clinical utility in this setting has not been established.[11-15] In the absence of data on clinical utility, we do not recommend use of these assays to make an extended adjuvant endocrine therapy treatment decision. Our practice is congruent with guidelines from national organizations like the ASCO and the National Comprehensive Cancer Network. To our knowledge, there are no planned prospective clinical trials that incorporate these assays to address the issue of clinical utility. Recent interest has turned to studies involving detection of circulating tumor cells or circulating free DNA, which have shown some initial promise in being able to discern late recurrences.[16] Prospective evaluation of these markers in clinical trials will be critical.

Case follow-up

Based on her initial TN status, Ms. BC appears to have a 20-year estimated risk of recurrence of 26%, based on the EBCTCG meta-analysis.[1] We recommended against the use of any additional genomic testing at this juncture. With hormone level testing, she was confirmed to be postmenopausal. She is interested in extended endocrine therapy with continuation of tamoxifen or switching to an AI. The pros and cons of the two approaches were discussed with the patient. Because of a family history of osteoporosis, the patient requested a bone density test to guide her choice.

3. What are the side effects of extended adjuvant endocrine therapy, and how can we help improve our patients’ quality of life while on these agents?

It is estimated that only about half of patients complete their recommended course of adjuvant endocrine therapy, with younger women being at higher risk for treatment interruption and discontinuation.[17,18] Several factors contribute to non-adherence, but, in practice, poor patient tolerance of these agents is the biggest reason for discontinuation. Since non-adherence can alter prognosis significantly, the “optimal” endocrine therapy is the one that the patient takes. This requires constant reassessment and close attention to patient-reported symptoms.

In the studies of extended use of tamoxifen, risks of thromboembolic events (RR for pulmonary embolus, 1.87; \( P = .01 \)) and endometrial cancer (RR, 1.74; \( P = .002 \)) remain of concern.[3] With extended AI use, predominant concerns are related to known toxicities of bone loss, hyperlipidemia, and potential impact on cardiovascular health. Recent studies have shown that nonpharmacologic interventions, such as acupuncture and exercise, may be effective in the management of AI-associated arthralgias,[19,20] a symptom of considerable importance to many patients. Other interventions, such as eliciting patient-reported adverse events between clinic visits and integrating other specialists into our clinics for symptom management, may boost adherence to endocrine therapy. A potential strategy of intermittent vs continuous AI use to reduce time with symptoms can be explored in clinical trials, as long as the effectiveness of therapy is not compromised.

We are also mindful that certain toxicities, such as cognitive dysfunction or sexual symptoms, may be under-reported or poorly captured in clinical trials, and we need to provide an open environment in which patients feel comfortable sharing these concerns. Young women may also struggle with fertility, contraception, and timing of pregnancy during endocrine therapy, and their perspectives must be taken into consideration when making treatment recommendations and designing clinical trials. For example, the POSITIVE clinical trial (International Breast Cancer Study Group 48-14/Breast International Group 8-13; ClinicalTrials.gov identifier: NCT02308085) is currently recruiting premenopausal women who desire pregnancy and have been on endocrine therapy for 18 to 30 months to hold endocrine therapy for pregnancy, and resume after delivery. This is a critical question for many young patients.

Finally, it is important to remember that our imperfect knowledge about optimal endocrine therapy continues to advance. There are exciting novel agents, such as mammalian target of rapamycin (mTOR) inhibitors or cyclin-dependent kinase (CDK) 4/6 inhibitors, being tested in combination with endocrine therapy in the adjuvant setting, which may change the future landscape of how we treat early-stage hormone-responsive breast cancer.

Case follow-up

Ms. BC returns 2 weeks after her last follow-up. Because her bone density test shows significant osteoporosis, she decided to stay on tamoxifen for an additional 5 years, rather than switch to an AI.

FINANCIAL DISCLOSURE: Dr. Vinayak has served on advisory boards for OncoSec and Tesaro. Dr. Davidson has no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.

ACKNOWLEDGMENTS: This article is supported in part by the National Institutes of Health grant P50CA015704 (both authors) and the Breast Cancer Research Foundation (Dr. Davidson).

For references visit cancernetwork.com/adj-endo-therapy
We Are Oncology.

You commit to a calling most never could.

As a vehicle for the best minds in your field, ONCOLOGY has renewed its own commitment by redesigning the delivery and presentation of peer review and perspective. More context—deeper insight.

Across the pages of print issues and online at Cancer Network, our journal is your journal.

Explore the new ONCOLOGY at cancernetwork.com/oncology-now
CDK9 regulation of MCL-1 inhibits apoptosis, enabling AML BLAST SURVIVAL

MCL-1 dependence may drive progression of AML

Disease progression and treatment resistance in a subset of acute myeloid leukemia (AML) have been associated with a key anti-apoptotic protein, myeloid cell leukemia 1 (MCL-1). MCL-1 is a member of the apoptosis-regulating BCL-2 family of proteins.

In MCL-1-dependent AML, the AML blasts depend primarily on the function of MCL-1 for the anti-apoptotic mechanism of survival. MCL-1 inhibits apoptosis and sustains the survival of AML blasts, which may lead to relapse. MCL-1 dependence is also associated with resistance to agents that otherwise have activity against leukemic blasts.

CDK9 is a key regulator of MCL-1

MCL-1 mRNA transcription in AML blasts is regulated by cyclin-dependent kinase 9 (CDK9), a protein that plays a critical role in transcription regulation without directly affecting cell-cycle control.

CDK9-mediated transcriptional regulation of anti-apoptotic genes, including MCL-1, is critical for the survival of MCL-1-dependent AML blasts.

Inhibition of CDK9 as a rational therapeutic strategy in MCL-1-dependent AML

Because MCL-1 has a short half-life of 2-4 hours, the effects of targeting its upstream regulators are expected to reduce MCL-1 levels rapidly. CDK9 inhibition has been shown to block MCL-1 transcription, resulting in rapid depletion of MCL-1 protein, which may restore apoptosis in MCL-1-dependent AML blasts.

Understanding the role of CDK9 in regulating MCL-1 may inform therapeutic targeting strategies in AML.

*The prevalence of MCL-1-dependent AML is under investigation.

References: