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‘We could actually have response rates of 50 to 60%’

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A Notable Year

When considering the key advances in oncology this past year, the candidates are numerous. Oncology, by necessity, evolves at an ever more rapid pace. In 2018, the US Food and Drug Administration (FDA) approved a record 59 new drugs across all medical specialties; of these, 17 (29%) approvals were relevant to oncology/hematology specifically.[1] This represents an increase from 2017, in which the FDA approved 12 new oncology/hematology agents.[2] Of note, 8 of the 17 oncology/hematology approvals in 2018 are indicated for the treatment of various blood cancers, illustrating that particularly significant progress was made in this cancer subtype.[1]

In addition to noting newly approved oncology/hematology agents, it is important that oncology clinicians also familiarize themselves with the most impactful research in order to continue to improve safety, survival, and quality of life in cancer patients. Here, members of ONCOLOGY’s Editorial Board, as well as the wider oncology community, provide feedback on the most significant advances of 2018.

Breast Cancer

When it comes to breast cancer, one study in 2018 stands out, according to I. Craig Henderson, MD, an adjunct professor in the Department of Medicine (Hematology/Oncology) at the University of California San Francisco’s Helen Diller Family Comprehensive Cancer Center and a member of ONCOLOGY’s Editorial Board. Chemotherapy and trastuzumab, he explained, reduced the risk of invasive recurrence of human epidermal growth factor receptor 2–positive, early-stage breast cancer by 50%, backing the agent as a new standard of care in these patients.[3]

“I believe these results will be practice-changing,” wrote study author Charles E. Geyer, Jr, MD, a professor of medicine at Virginia Commonwealth University School of Medicine and the associate director for clinical research at Massey Cancer Center in Richmond, Virginia, in a statement. “The results should form the foundation of a new standard of care in patients with residual invasive breast cancer following neoadjuvant therapy.”

For more top breast cancer news from SABCS 2018, see our Oncology Conference Highlights, Q4 on pages 8–10 of this issue.

Hematologic Cancer

“Probably the most significant [studies of 2018] were the two CLL [chronic lymphocytic leukemia] studies that establish ibrutinib as the standard of care for front-line treatment of CLL in the younger and older populations, respectively,” according to John Sweetenham, MD, executive medical director and senior director of clinical affairs at Huntsman Cancer Institute in Salt Lake City, Utah, and a member of the ONCOLOGY Editorial Board. The results of both studies were presented at the 2018 ASH Annual Meeting and Exposition, held in December in San Diego.

One of these studies—a phase III trial conducted by Shanafelt et al (LBA-4)—found that a combination of ibrutinib and rituximab enhanced pro-
gession-free survival (PFS) and overall survival (OS) compared with fludarabine, cyclophosphamide, and rituximab (FCR) in patients aged 70 years or younger with treatment-naïve CLL. According to the researchers, these findings establish ibrutinib-based therapy as the most effective first-line therapy for patients with CLL.[4]

The other study—a phase III trial conducted by Woyach et al—concluded that ibrutinib produces superior PFS compared with standard chemoimmunotherapy in patients aged 65 years or older with treatment-naïve CLL. However, the addition of rituximab to ibrutinib failed to lengthen PFS. These results support ibrutinib as a standard-of-care treatment in elderly patients.[5] Looking forward, the researchers hope to reduce continuous therapy of ibrutinib in light of its high cost and associated toxicities.

**Immunotherapy**

One particularly noteworthy highlight in the field of immunotherapy occurred in October of this year, when the Nobel Prize in Physiology or Medicine was awarded to James P. Allison of the United States and Tasuku Honjo of Japan for their work on cancer immunotherapy. Their findings on checkpoint inhibitors “brought immunotherapy out from decades of skepticism,” Dr. Jedd Wolchok, a cancer specialist at Memorial Sloan Kettering Cancer Center in New York, wrote in a *New York Times* article announcing the award.[6]

Mario M. Leitao, Jr, MD, a gynecologic-oncologist and director of the Minimal Access and Robotic Surgery Program at Memorial Sloan Kettering Cancer Center, pointed to the clinical impact of several Poly(ADP-ribose) polymerase (PARP) inhibitors: niraparib, olaparib, and rucaparib. These agents, which received FDA approval in short order starting in 2014, fundamentally change the management of *BRCA*-associated ovarian cancer.[7-9] Of interest, niraparib is also effective at treating ovarian tumors without alterations in *BRCA* 1/2. Nevertheless, it remains to be elucidated how to best integrate PARP inhibitors into combination treatment strategies.

**Integrative Oncology**

Santosh Rao, MD, the medical director of integrative medicine at Banner MD Anderson Cancer Center in Gilbert, Arizona, told *ONCOLOGY* he is excited about the advances made in integrative oncology. He and his colleagues foresee the inclusion of integrative medicine approaches in cancer management guidelines in the near future.

“Every year, there’s an increase in interest in integrative medicine. In 1996, integrative medicine was not well accepted,” he said. “We have come a long way in the last 20 years. More and more, positions are looking [to be filled by] clinicians and researchers who practice integrative oncology, and there will be more and more need as evidence grows. It’s definitely becoming more popular.”

Among many notable integrative oncology studies in 2018, Rao noted one that evaluated the effects of yoga on cognitive function in breast and ovarian cancer survivors as a standout. Lapen et al found that restorative yoga was better at enhancing functions with regard to past memories.[10]

Rao also highlighted a study by Chen et al that examined the effects of Quxie capsules, a type of traditional Chinese medicine used in antiquity to treat various tumor types, on colorectal cancer. The researchers found that, in mouse models, Quxie capsules suppressed the growth of colorectal cancer, in part mediated by alterations in the gut microbiome. Moreover, possibly secondary to changes in the gut microbiome, Quxie capsules also upregulated the expression of myosin 11, which might play a role in tumor inhibition.[11]

Donald Abrams, MD, an integrative oncologist and professor of medicine at the University of California San Francisco’s Osher Center for Integrative Medicine, noted research published in *JAMA Oncology* in October of this year that made waves in the field—but in a much more negative light. Conducted by Johnson et al of Yale School of Medicine, researchers found that cancer patients who utilized complementary medicine were more likely to refuse conventional treatment, and therefore had a higher risk of death compared with those who did not use complementary medicine.[12] According to Abrams, the study was unbalanced in that it compared a significantly smaller cohort of patients utilizing complementary therapies (258) compared with control (1,901,557), and the results thus “suggested that it [complementary medicine] was detrimental.”

**Lung Cancer**

The combination of either pembrolizumab or atezolizumab with chemotherapy made waves in the treatment of lung cancer in 2018, according to Apar K. Ganti, MD, an associate professor in the Department of Internal Medicine, Division of Oncology/Hematology, at the University of Nebraska Medical Center in Omaha.
With respect to metastatic non-squamous non–small-cell lung cancer (NSCLC), a global randomized controlled trial conducted by Paz-Ares et al found that adding pembrolizumab to chemotherapy (pemetrexed and carboplatin) nearly doubled the objective response rate (ORR) in patients. They also concluded that this combination offers a tolerable safety profile.[13]

In the Hoffman-La Roche phase III IMpower132 study, researchers showed that the combination of atezolizumab plus chemotherapy (cisplatin or carboplatin plus pemetrexed) reduced the chances of disease progression or death vs sole chemotherapy in frontline treatment of advanced NSCLC.[14]

Prostate Cancer

Tomasz M. Beer, MD, deputy director, Grover C. Bagby Endowed Chair for Prostate Cancer Research, and professor of medicine at OSHU Knight Cancer Institute in Portland, Oregon, told ONCOLOGY that the introduction of two new agents for the treatment of high-risk, non-metastatic, castration-resistant prostate cancer was particularly important. Apalutamide and enzalutamide were approved by the FDA based on the findings of the SPARTAN[15] and PROSPER[16] trials, respectively.

In the SPARTAN trial, apalutamide decreased the risk of developing metastasis and death by 72% vs placebo.[15] In the PROSPER trial, enzalutamide lowered the chances of metastasis or death by 71% vs placebo.[16] In both studies, men were treated with ongoing androgen deprivation therapy.[15,16] On a historical note, the FDA approval of apalutamide was a first for patients with non-metastatic, castration-resistant prostate cancer.

Radiation Oncology

“For me, the big story in radiation [in 2018] was the emerging use of radiotherapy—most often SBR [stereotactic body radiation therapy] for the treatment of oligometastatic disease,” James Yu, MD, MHS, director of Yale Medicine’s Prostate & Genitourinary Cancer Radiotherapy Program, told ONCOLOGY. “Several major studies presented at [the] ASTRO [American Society for Radiation Oncology meeting] or ESMO [the European Society for Medical Oncology meeting] are starting to validate the idea that aggressive treatment of disease with radiation and other local therapy such as surgery—even when [the cancer is] metastatic—may potentially improve outcomes.”

Yu specifically cited a phase II randomized controlled study in which Gomez et al found that local consolidative therapy plus or minus maintenance therapy for patients with three or fewer metastases from NSCLC that did not progress following initial systemic therapy enhanced PFS vs maintenance therapy alone. These findings indicate that aggressive local therapy has the potential to become a standard treatment alternative for these patients.[17]

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/YIR-2018
Dr. Crowther expressed intrigue in novel precision therapies for acute myeloid leukemia (AML). In an abstract titled “Initial Report of the Beat AML Umbrella Study for Previously Untreated AML: Evidence of Feasibility and Early Success in Moleculary Driven Phase 1 and 2 Studies,” [1] Burd and colleagues presented data that bolstered the feasibility of an algorithm strategy for the treatment of AML in older patients who were previously untreated. “The Beat AML trial is a model for dynamic, mechanism-based clinical trials in blood cancers where genomic analysis may inform, accelerate, and improve drug development,” wrote the authors.

Chimeric antigen receptor (CAR) T-cell therapy was a focus of the conference as well. Julie Vose, MD, the Division of Hematology/Oncology Chief at University of Nebraska Medical Center, noted the significance of the five CAR T-cell therapy studies, which offer long-awaited hope for patients with several different types of aggressive blood cancers, including diffuse large B-cell lymphoma.[2-5]

Important discussions about brentuximab vedotin also took place at the conference. “Clearly, Steve Horwitz’s presentation on ECHELON-2 was a highlight,” said Bruce Cheson, MD, Deputy Chief, Division of Hematology/Oncology at Georgetown University. This study showed that adding brentuximab vedotin to chemotherapy resulted in a clinically significant improvement in progression-free and overall survival in patients who have CD30-expressing peripheral T-cell lymphoma (PTCL).[6]

“Also, the ALLIANCE and ECOG chronic lymphocytic lymphoma trials[7,8] are practice changing,” he added. Results of these trials support the use of ibrutinib as standard-of-care or first-line treatment in elderly patients with chronic lymphocytic lymphoma.

**SIO 2018**

The SIO 2018 annual conference continued SIO’s mission of advancing the field by focusing on findings that can guide strategy in the clinical practice of oncology. “Many interesting studies were presented,” said Santosh Rao, MD, medical director of integrative medicine at Banner MD Anderson Cancer Center and co-chair of SIO 2018.

One of the most important goals of integrative oncology, especially in light of the opioid crisis, has been nonpharmacologic approaches to cancer pain. Acupuncture, in particular, has garnered attention. In a presentation on this discipline, Puislon and colleagues provided evidence of its safety in the treatment of lymphedema in breast cancer survivors.[9] Yoga may enhance certain functions in the frontal and temporal lobes.

In another important presentation, Romero et al identified potentially beneficial genotypes involved in neurotransmission, thermo-regulation, and inflammation that may predict response to acupuncture for hot flashes in breast cancer survivors.[10] “If confirmed by future studies, these findings can inform the development of personalized acupuncture for managing hot flashes in BC breast cancer survivors,” the authors concluded.

Deleemans et al presented research on bright white light therapy, offering evidence that it may reduce cancer-related fatigue in patients.[11] In particular, an ANOVA analysis revealed a significant effect of time on cancer-related fatigue, as scores on measures of fatigue decreased from pre- to post-intervention.

Two other important studies presented at the meeting—one by Chen et al on Quxie capsules,[12] and one by Deng et al on yoga and cognitive function[13]—are summarized in more detail in the “Integrative Oncology” section on page 7 of this issue.

**SABCS 2018**

The San Antonio Breast Cancer Symposium (SABCS) is, by its own description, “designed to provide state-of-the-art information on the experimental biology, etiology, prevention, diagnosis, and therapy of breast cancer and premalignant breast disease, to an international audience of academic and private physicians and researchers.” To this end, there was no shortage of excellent studies presented.

Melanie Royce, MD, PhD, Director of the Multidisciplinary Breast Cancer Clinic and Programs at UNMCC, highlighted several studies of interest from SABCS.

In a study titled “Development and validation of a chemotherapy toxicity risk score for older patients with breast cancer receiving adjuvant/neoadjuvant treatment,” Magnuson and colleagues developed and validated a novel chemotherapy toxicity risk score (CARG-BC), which predicts toxicity for older patients with stage I, stage II, and stage III breast cancer. The CARG-BC score is linked to dose reduction, delay, hospitalizations, and so forth, and could play a role in adjuvant decision-making.[14] “Use of this tool may help identify which older patients are at higher risk for developing toxicities with neo/adjuvant chemotherapy and thus can be more carefully monitored for toxicities,” said Royce.

Turner NC et al discussed the PALOMA-3 trial in “Overall Survival with Palbociclib and Fulvestrant in Advanced Breast Cancer,” which found that palbociclib-fulvestrant resulted in longer overall survival than treatment with placebo...
fulvestrant among patients who had sensitivity to previous endocrine therapy.[15]

In their presentation on “PHARE randomized trial: final results comparing 6 to 12 months of trastuzumab in adjuvant early breast cancer,” Pivot and colleagues found that 6 months of trastuzumab is non-inferior to 12 months of trastuzumab as adjuvant treatment in early breast cancer. “The findings are very similar to PERSEPHONE in design but opposite conclusions,” said Royce, “mainly due to predefined statistical boundaries of non-inferiority for each trial – the HR [hazard ratio] for both trials were similar: 1.08 vs. 1.07 for PHARE and PERSEPHONE, respectively.”[16]

Presenting on “Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer,” Francis PA et al referenced the SOFT and TEXT trial, which found that the addition of ovarian suppression to tamoxifen resulted in significantly higher 8-year rates of both DFS and OS compared with tamoxifen alone. The use of exemestane plus ovarian suppression resulted in even higher rates of freedom from recurrence. The frequency of adverse events was higher in the two groups that received ovarian suppression than in the tamoxifen-alone group.[17] “This gives us a good idea on what to do with patients with the intermediate range recurrence scores; should we recommend chemo or not? This study at least suggests that worry probably should be more focused on the younger (age 50 or under) patients,” said Dr. Royce.

Finally, Dr. Royce pointed out a notable novel biomarker presented at SABCS. In a study titled “Clinical utility of Circulating Tumor Cells (CTC) count to choose between 1st line hormone therapy & chemotherapy in ER (estrogen receptor)+ HER2- metastatic breast cancer: Results of the phase III STIC CTC trial,” Bidard et al found that CTC is a clinically reliable and reproducible biomarker in women with estrogen receptor–positive, human epidermal growth factor receptor 2–negative disease, although more research needs to be conducted. Specifically, the researchers found that in patients with > 5 CTC/7.5mL, chemotherapy outperforms single agent endocrine therapy.[18] ■

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**For references visit cancernetwork.com/2018-Q4-conf**

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Current and Future Landscape of Immune Checkpoint Inhibitors in Urothelial Cancer

Omar Alhalabi, MD*, Amishi Y. Shah, MD*, Emily A. Lemke, DNP, AGPCNP-BC, AOCNP, and Jianjun Gao, MD, PhD

*Contributed equally to manuscript.

ABSTRACT: Immune checkpoint inhibitors have revolutionized the field of oncology, providing a novel mechanism for anticancer therapy. Programmed death 1–targeting antibodies pembrolizumab and nivolumab and programmed death ligand 1 (PD-L1)–targeting antibodies atezolizumab, durvalumab, and avelumab have been approved for use in advanced urothelial cancer in the post-platinum setting or in the upfront setting in platinum-ineligible patients. While this represents a significant step forward in management of urothelial cancers, most patients do not have an objective response to these therapies. PD-L1 expression is not a consistently predictive biomarker, but is recommended for checkpoint utilization in select circumstances. We report here a summary of known data and the differences between these agents, as well as future avenues to explore with immuno-oncologic agents in urothelial cancer. Much work is ongoing to better understand resistance mechanisms, to maximize efficacy with combination strategies, to find improved predictive biomarkers, to assess curative-intent strategies, and to better manage toxicity with these agents.

Introduction
Bladder cancer (synonymously referred to as urothelial carcinoma) is the 4th most common cancer occurring in men and the 12th in women, with an estimated US incidence of 81,190 cases and an estimated 17,240 deaths in 2018.[1] While 75% of new urothelial cancer cases are non-muscle-invasive, 25% are muscle-invasive or metastatic at presentation.[2] Traditionally, outcomes have been poor in metastatic disease, with a 5-year survival rate of 4.8% in the distant metastatic setting, compared with 68% for localized disease.[3] Prior to the development of immunotherapies, the median overall survival (OS) for metastatic urothelial cancer patients was 13.8 to 15.5 months when using standard-of-care platinum-based therapies.[2,4] For those who are ineligible for treatment with cisplatin, carboplatin-based regimens are available and provide modest activity, with an historic median OS of approximately 9 months.[5] Following platinum chemotherapy, patients who receive second-line chemotherapies have a lower median OS of approximately 7 months.[6,7] The past few years have brought the introduction of immune checkpoint inhibitors, which have led to an upsurge in effective treatments for previously refractory metastatic cancers.[8]

Cancer Immune Response and Checkpoint Inhibition
Antitumor immunity is dependent on a complex series of events that involve antigen
Immune checkpoint inhibitors have substantially impacted the treatment of metastatic urothelial carcinoma, as very well outlined in the review article by Alhalabi et al. We should celebrate the US Food and Drug Administration’s approval of five new agents in this setting. Despite this clear progress, however, it is apparent that there is still a great unmet clinical need. The current response rate to therapy in urothelial carcinoma remains low, even in biomarker-selected populations.

Two main approaches can increase patient response to these agents: combination therapy with other immune modulators or the addition of immune checkpoint inhibitors to cytotoxic/targeted agents, as well as better patient selection. Many trials examining combination treatments in urothelial carcinoma are currently underway. One challenge resulting from the dramatic increase in the number of agents available in this setting is completing the large number of active trials. Regrettably, the development of biomarkers for these agents has been individualized to each drug, with different assays and thresholds. This makes it difficult to define the best approach to utilize predictive biomarkers in urothelial carcinoma and to gain generalizable knowledge to advance the field. Other emerging biomarker approaches, including tumor mutational burden and molecular subtypes, may provide additional information to improve patient selection.

In many ways, this is an optimistic time for patients with advanced urothelial carcinoma. Compared with just a few years ago, we are now in a much stronger position in terms of improving medical treatment options. Today, we are now concerned about successful trial completion—not because of poor general accrual/ pharmaceutical engagement, but due to the high number of trials and promising agents. To benefit patients and to continue to maximize clinical benefit, we need to find ways to share data, and even samples, from past and future trials. Doing so will help us reach our goals of improving our basic understanding of advanced urothelial carcinoma, thereby establishing a consensus on the use of predictive biomarkers in this realm.

**FINANCIAL DISCLOSURE:** Dr. Flaig receives clinical trial support from Agensys, Astellas, AstraZeneca, Bristol-Myers Squibb, Janssen, Merck, Pfizer, Roche/Genentech, and Seattle Genetics. He is also a founder and holds intellectual property for Aurora Oncology.

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**An Optimistic Time for Patients With Advanced Urothelial Carcinoma**

**Immune Checkpoint Inhibitors for Metastatic Urothelial Carcinoma After Frontline Platinum Therapy**

Two monoclonal antibodies targeting PD-1 (nivolumab and pembrolizumab) and three antibodies targeting PD-L1 (atezolizumab, avelumab, and durvalumab) have changed the treatment landscape of metastatic urothelial carcinoma. **Table 1** has further details on outcomes with each of these immune checkpoint inhibitors. These agents have demonstrated clinical activity following platinum-containing chemotherapies in metastatic urothelial carcinoma, with objective response rates (ORRs) ranging from 15% to 25%.11-16 Of note, investigators have historically relied on Response Evaluation Criteria in Solid Tumors (RECIST) to evaluate antitumor responses to chemotherapeutic agents. However, the responses that are seen with immunotherapeutic agents may extend beyond those of cytotoxic agents and could include responses that are not captured by RECIST. The immune-related response criteria (irRC) can better capture the response patterns for immunotherapeutic agents.17

**Atezolizumab**

Atezolizumab is an anti-PD-L1 monoclonal antibody and was the first immune checkpoint...
inhibitor to be approved by the US Food and Drug Administration (FDA) for locally advanced or metastatic urothelial carcinoma patients who progressed during or after platinum therapy. In a large phase I trial that enrolled 68 patients with previously treated disease, atezolizumab had an ORR ranging from 11% to 43%.

[15] The higher ORR was seen in tumors expressing high levels of PD-L1, defined as ≥ 5% on tumor cells or tumor-infiltrating immune cells. These exciting results led to the IMvigor210 trial, a phase II trial that included two cohorts (previously treated and treatment-naive patients). PD-L1 expression on immune cells determined stratification of patients with the following thresholds: IC0 (< 1%), IC1 (≥ 1% but < 5%), and IC2/3 (≥ 5%). The ORR to second-line cytotoxic chemotherapy in all-comers was 15% vs 10% in historical controls. However, higher IC score led to higher response, with an ORR of 18% for IC1/2/3 and 27% for IC2/3.[13] This provided the basis for the FDA to approve atezolizumab in May 2016.

IMvigor211 followed IMvigor210 and randomized patients who progressed after platinum therapy to receive either atezolizumab or chemotherapy (physician’s choice between taxanes or vinflunine). Similarly to IMvigor210, PD-L1 on immune cells was used to stratify patients. The primary endpoint of OS was tested in hierarchical fashion: first in the IC2/3 population, followed by the IC1/2/3 population, and then the intention-to-treat population. The IC2/3 population failed to show improved survival; therefore, the other populations were not evaluated.[18]

**Avelumab**

Avelumab is a fully human anti–PD-L1 monoclonal antibody that has the additional ability to lyse PD-L1–expressing tumor cells by antibody-dependent cell-mediated cytotoxicity.[19] In a phase Ib trial, avelumab showed an ORR of 18.2% in post-platinum metastatic urothelial carcinoma, with a tolerable safety profile (grade 3/4 adverse events, 6.8%). In a pooled analysis of two cohorts (both post-platinum therapy and cisplatin-naive) from the phase I dose-expansion JAVELIN Solid Tumor study, avelumab showed a similar safety profile to the phase Ib data. Antitumor activity was analyzed in the post-platinum cohort and demonstrated an ORR of 17%. Patients in the JAVELIN trial were not selected based on PD-L1 expression.

The ongoing phase III JAVELIN Bladder 100 trial (ClinicalTrials.gov identifier: NCT02603432) is examining avelumab as a maintenance therapy in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum-containing chemotherapy. GCISAVE (NCT03324282) is a study that will assess the efficacy and safety of the combination of gemcitabine, cisplatin, and avelumab in the first-line treatment of locally advanced or metastatic urothelial carcinoma patients.

**Durvalumab**

Durvalumab, another anti–PD-L1 monoclonal antibody, was evaluated in a phase I trial and showed an ORR of 46.4% in a PD-L1–positive (defined as ≥ 25% on tumor cells or tumor-infiltrating immune cells) subgroup and 0% in a PD-L1–negative subgroup.[20] These results were further assessed in a phase II trial of metastatic urothelial carcinoma patients who progressed on, were ineligible for, or refused prior chemotherapy. The majority (95.3%) of enrolled patients had failed platinum therapy. The ORR was 17.8% across all patients.[12] In May 2017, based on these results, the FDA granted accelerated approval for the use of durvalumab in the second-line setting for metastatic urothelial cancer refractory to first-line cisplatin-based chemotherapy.

### Table 1: Checkpoint Inhibitors Approved for Use in Urothelial Carcinoma

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Phase</th>
<th>Patients (N)</th>
<th>Mechanism of Action</th>
<th>ORR (95% CI)</th>
<th>Median PFS (95% CI)</th>
<th>Median OS (95% CI)</th>
<th>Approved in First Line, Cisplatin Ineligible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atezolizumab</td>
<td>IMvigor210</td>
<td>II</td>
<td>310</td>
<td>Anti–PD-L1</td>
<td>15% (11–20)</td>
<td>2.1 mos (2.1–2.1)</td>
<td>9 mos (7.1–10.9)</td>
<td>Yes</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>CheckMate 275</td>
<td>II</td>
<td>270</td>
<td>Anti–PD-1</td>
<td>19.8% (15.0–24.9)</td>
<td>2 mos (1.27–2.63)</td>
<td>8.74 mos (6.05–NR)</td>
<td>No</td>
</tr>
<tr>
<td>Pembroliuzumab</td>
<td>KEYNOTE-045</td>
<td>III</td>
<td>266</td>
<td>Anti–PD-1</td>
<td>21.1% (12.9–32.7)</td>
<td>2.1 mos (2.0–2.2)</td>
<td>10.3 mos (8–11.8)</td>
<td>Yes</td>
</tr>
<tr>
<td>Avelumab</td>
<td>JAVELIN Solid Tumor</td>
<td>Ib</td>
<td>44</td>
<td>Anti–PD-L1</td>
<td>18.2% (8.2–32.7)</td>
<td>11.6 wks (6.1–17.4)</td>
<td>13.7 mos (8.5–NE)</td>
<td>No</td>
</tr>
<tr>
<td>Durvalumab</td>
<td>Study 1108</td>
<td>I/II</td>
<td>191</td>
<td>Anti–PD-L1</td>
<td>17.8% (12.7–24)</td>
<td>1.5 mos (1.4–1.9)</td>
<td>18.2 mos (8.1–NE)</td>
<td>No</td>
</tr>
</tbody>
</table>

NE = not estimable; NR = not reported; ORR = objective response rate; OS = overall survival; PD-1 = programmed death 1; PD-L1 = programmed death ligand 1; PFS = progression-free survival.
**Nivolumab**

Nivolumab is an anti–PD-1 monoclonal antibody that was first assessed in CheckMate 032, a phase I/II single-arm trial. It showed an ORR of 24.4% in patients with locally advanced or metastatic urothelial cancer who progressed after platinum-based therapy. When stratified by PD-L1 expression, the response rate was similar for the PD-L1–high (≥ 1% on tumor cells) and PD-L1–low (< 1% on tumor cells) groups (24% vs 26%). However, median OS was 16.2 months for PD-L1–high patients compared with 9.9 months in the PD-L1–low group.[14]

The phase II single-arm CheckMate 275 trial followed, which evaluated nivolumab for metastatic disease after platinum therapy.[21] The primary endpoint was ORR by tumor PD-L1 expression (both ≥ 5% and ≥ 1%) and ORR in all treated patients. The ORR was 19% for all patients, regardless of PD-L1 expression. However, when analyzed by PD-L1 expression, the ORR was 28.4% when PD-L1 expression was ≥ 5%, 23.8% when PD-L1 expression was ≥ 1%, and 16.1% when PD-L1 expression was < 1%. Nivolumab was well tolerated, with only 18% of patients experiencing grade 3/4 adverse events. Based on these results, in February 2017, the FDA granted approval to nivolumab for second-line use in metastatic urothelial carcinoma patients following progression on cisplatin chemotherapy.

**Pembrolizumab**

Pembrolizumab is an anti–PD-1 monoclonal antibody that was studied in the phase Ib KEYNOTE-012 trial.[22] This study required at least 1% PD-L1 expression detected on the tumor cells or in tumor stroma, as determined by immunohistochemistry. Overall response was achieved in 26% of patients. Grade 3 adverse events occurred in 15% of patients. Following KEYNOTE-012, KEYNOTE-045 was a phase III trial that investigated pembrolizumab in patients with metastatic urothelial carcinoma that recurred or progressed after platinum-based chemotherapy.[23] Patients received either pembrolizumab at 200 mg every 3 weeks or the investigator’s choice of chemotherapy with docetaxel, paclitaxel, or vinflunine.

In this trial, the concept of combined positive score (CPS) was used after being introduced in the KEYNOTE-052 trial.[24] CPS is defined as the percentage of PD-L1–expressing tumor cells and infiltrating immune cells relative to the total number of tumor cells. The OS was longer for the pembrolizumab group vs the chemotherapy group for all patients (10.3 vs 7.4 months) and for those with CPS ≥ 10% (8.0 vs 5.2 months). The ORR was 21% for pembrolizumab vs 11% for chemotherapy. Based on these results, in May 2017, the FDA approved pembrolizumab for patients with metastatic urothelial cancer who have disease progression during or following platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant treatment.

**Immune Checkpoint Inhibitors for Metastatic Urothelial Carcinoma in the Frontline Setting**

**Atezolizumab**

Cohort 1 of the IMvigor210 trial used atezolizumab in treatment-naïve metastatic urothelial carcinoma patients who were ineligible for treatment with cisplatin.[25] Stratification was again based on PD-L1 expression (IC0, IC1, and IC2/3). The ORR in all patients was 23%, and in contrast to prior results, the ORR did not correlate with PD-L1 expression. In April 2017, the FDA accelerated the approval of atezolizumab for the first-line treatment of cisplatin-ineligible patients with metastatic disease.

IMvigor130 is an ongoing phase III trial to further study the treatment-naïve cohort, but it was amended to include all platinum-eligible patients. It is randomizing patients to three arms: atezolizumab and platinum-based chemotherapy, atezolizumab alone, or chemotherapy alone. Stratification is similar to the IMvigor210 and IMvigor211 trials. In June of this year, the FDA announced that treatment-naïve patients with low PD-L1 status (IC0/1) have a lower OS with the use of atezolizumab monotherapy compared with platinum-based chemotherapy alone. Therefore, the FDA revised the indication label for atezolizumab to include cisplatin-ineligible patients, as long as they are categorized as IC2/3 as determined by an FDA-approved test. However, if patients are cisplatin and carboplatin ineligible, then atezolizumab is still indicated regardless of PD-L1 status. The FDA has not changed the indications for disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment.

**Pembrolizumab**

The phase II KEYNOTE-052 trial studied pembrolizumab as first-line treatment for 370 cisplatin-ineligible patients with metastatic urothelial carcinoma.[24] There was a 24% ORR in all patients who received at least one dose of pembrolizumab. The ORR was higher—38%—in patients with a CPS of 10% or more. The ongoing phase III KEYNOTE-361 trial (NCT02853305) is randomizing treatment-naïve metastatic urothelial cancer patients 1:1:1 to receive pembrolizumab, pembrolizumab plus investigator’s choice
of chemotherapy (containing cisplatin), or chemotherapy alone. Patients who are cisplatin-ineligible are randomized to a carboplatin-based regimen. In June, the FDA announced that treatment-naive patients with a low CPS (< 10%) have a lower OS with the use of pembrolizumab monotherapy compared with platinum-based chemotherapy alone. Therefore, the FDA revised the indication label for pembrolizumab to include cisplatin-ineligible patients, as long as they have a CPS ≥ 10% by an FDA-approved test. In fact, the data monitoring committee for the IMvigor130 and the KEYNOTE-361 trials stopped enrolling patients with PD-L1–low status to the immunotherapy-only arms. Similar to atezolizumab, if patients are ineligible for cisplatin and carboplatin, then pembrolizumab is still indicated regardless of PD-L1 status. The FDA has not changed the indications for disease progression during or following chemotherapy (containing cisplatin), or chemotherapy alone. Patients who are cisplatin-ineligible are randomized to a carboplatin-based regimen. In June, the FDA announced that treatment-naive patients with a low CPS (< 10%) have a lower OS with the use of pembrolizumab monotherapy compared with platinum-based chemotherapy alone. Therefore, the FDA revised the indication label for pembrolizumab to include cisplatin-ineligible patients, as long as they have a CPS ≥ 10% by an FDA-approved test. In fact, the data monitoring committee for the IMvigor130 and the KEYNOTE-361 trials stopped enrolling patients with PD-L1–low status to the immunotherapy-only arms. Similar to atezolizumab, if patients are ineligible for cisplatin and carboplatin, then pembrolizumab is still indicated regardless of PD-L1 status. The FDA has not changed the indications for disease progression during or following any platinum-containing chemotherapy, or within 12 months of neoadjuvant or adjuvant treatment.

**Predictive Biomarkers for Response and Resistance to Immune Checkpoint Inhibitors**

Blocking the PD-1 checkpoint or its ligand PD-L1 has revolutionized the management of patients with metastatic urothelial carcinoma. However, a large majority of patients do not respond to these agents. Consequently, there have been several efforts to identify biomarkers to predict response and tackle this challenge.

**PD-L1 as a prognostic and predictive marker**

Early experiments showed PD-L1 expression in urothelial cancer to be associated with a higher grade of tumor,[26] worse clinical outcomes, and decreased postoperative survival.[27] Therefore, it seemed obvious to use it as a predictive biomarker for patient selection. However, as previously mentioned and outlined further in Table 2, PD-L1 status is not always predictive of response. In the IMvigor210 trial, a higher score for PD-L1 expression was associated with a higher response rate.[13] In contrast, the CheckMate 275 trial showed clinically meaningful responses to nivolumab irrespective of PD-L1 expression.[21] Several explanations for this discrepancy exist. First, staining and interpreting PD-L1 expression by immunohistochemistry assays is not yet reproducible. For example, the IMvigor210 trial used the Ventana PD-L1 (SP142) assay to measure PD-L1 on tumor-infiltrating immune cells, the durvalumab trial utilized the Ventana PD-L1 (SP263) assay to measure PD-L1 on tumor cells only.[13,20,21]

### Table 2: Status of Programmed Death Ligand 1 (PD-L1) Positivity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Definition of PD-L1–Positive</th>
<th>Percent (N) of Pts With PD-L1–Positive Status</th>
<th>ORR in PD-L1–Positive Pts (95% CI)</th>
<th>ORR in PD-L1–Negative Pts (95% CI)</th>
<th>PD-L1 Testing Sample</th>
<th>PD-L1 Testing Assay Used</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Atezolizumab</strong></td>
<td>IC1: ≥ 1% but &lt; 5% IC2/3: ≥ 5%</td>
<td>IC1: 35% (107) IC2/3: 32% (100)</td>
<td>IC1: 10% (5–18) IC2/3: 26% (18–36)</td>
<td>8% (3–15)</td>
<td>Tumor</td>
<td>IHC with SP142 assay (HistoGeneX)</td>
</tr>
<tr>
<td><strong>Nivolumab</strong></td>
<td>PD-L1 ≥ 1% PD-L1 ≥ 5%</td>
<td>PD-L1 ≥ 1%: 45% (122) PD-L1 ≥ 5%: 30% (81)</td>
<td>PD-L1 ≥ 1%: 23.8% (16.5–32.3) PD-L1 ≥ 5%: 28.4% (18.9–39.5)</td>
<td>16.1% (10.5–23.1)</td>
<td>TC PD-L1 membrane expression</td>
<td>Dako PD-L1 IHC 28-8 pharmDx kit</td>
</tr>
<tr>
<td><strong>Pembrolizumab</strong></td>
<td>PD-L1 ≥ 10%</td>
<td>28% (74)</td>
<td>21.6% (12.9–32.7)</td>
<td>NR</td>
<td>Tumor</td>
<td>Dako PD-L1 IHC 22C3 pharmDx assay</td>
</tr>
<tr>
<td><strong>Avelumab</strong></td>
<td>PD-L1 ≥ 5%</td>
<td>29.5% (13)</td>
<td>53.8% (25.1–80.8)</td>
<td>4.2% (0.1–21.1)</td>
<td>Tumor</td>
<td>IHC via proprietary assay on the basis of anti–PD-L1 rabbit monoclonal antibody clone (73–10), under license to Merck KGaA</td>
</tr>
<tr>
<td><strong>Durvalumab</strong></td>
<td>PD-L1 ≥ 25% on TC or IC</td>
<td>51.3% (98)</td>
<td>27.6% (19.0–37.5)</td>
<td>5.1% (1.4–12.5)</td>
<td>TCs and ICs</td>
<td>Ventana SP263 assay optimized for use on the automated BenchMark ULTRA platform</td>
</tr>
</tbody>
</table>

IC = immune cell; IHC = immunohistochemistry; NR = not reported; ORR = objective response rate; TC = tumor cell.
the percentage cutoffs used to define high and low expression were not uniform. Third, PD-L1 expression is dynamic, and a single biopsy is unlikely to provide a complete assessment of status for the entire duration of disease.

Tumor interferon-γ signaling correlates to response/resistance to immune checkpoint inhibition

In the aforementioned CheckMate 275 trial, higher values of the 25-gene interferon-γ (IFN-γ) signature were associated with a greater proportion of responders to nivolumab and higher PD-L1 expression. [21] Genomic defects in IFN-γ pathway genes have been described in patients who do not respond to anti–CTLA-4 treatment. [28,30] Anti–PD-1 therapy in melanoma was reported to induce JAK1 and JAK2 truncating mutations, a genomic evolution that would lead to PD-1 resistance. [29] This is thought to be due to ineffective IFN-γ signaling and insensitivity to its antiproliferative effects on cancer cells. Some proposed that these mutations result in lack of reactive PD-L1 expression and response to IFN-γ. [30,31] In a CRISPR-Cas9 screening effort to identify the genes essential for the tumor effector function of T cells, APLNR gene mutations were found in melanoma tumors refractory to PD-1 blockade. [32] Again, APLNR interaction with JAK1 was essential for IFN-γ responses. These data collectively suggest that tumor IFN-γ pathway signaling deficiency predicts both primary and secondary resistance to immune checkpoint inhibitor therapy.

Transforming growth factor β attenuates tumor response to PD-L1 blockade

The role of transforming growth factor β (TGFβ) in the tumor microenvironment is complex. High preoperative plasma levels of TGFβ1 are associated with poor clinical outcomes in patients with urothelial carcinoma. [33] In addition, decreased expression of TGFβ receptor 1 in bladder cancer biopsies is associated with poor prognosis. [34] Tumor samples from the IMvigor210 trial, studied by RNA sequencing, showed that TGFβ attenuates tumor response to PD-L1 blockade by contributing to exclusion of T cells. [35]

Tumor mutational burden in urothelial carcinoma

An exploratory subgroup analysis of cohort 2 of the IMvigor210 trial that evaluated 315 cancer-related genes showed a significant increase in mutation load in responding patients relative to non-responding patients (12.4 per megabase vs 6.4 per megabase). [13] Smoking status and the Cancer Genome Atlas (TCGA) subtype did not correlate with mutational burden, suggesting that it may be a more reliable predictor of response to PD-L1 blockade in urothelial cancer. Significant challenges confront the use of tumor mutational burden as a predictive biomarker for immunotherapy. First is the challenge of unifying and standardizing the definition of mutation burden relative to the depth of sequencing performed. Second, targeted sequencing panels may not adequately cover gene fusions, truncations, and translocations. Third, germline variants may not be silenced by informatics techniques that filter common germline single-nucleotide polymorphisms.

Clustering by TCGA subtype

Other possible biomarkers include the four microRNA subtype clusters I–IV (luminal I, luminal II, basal I, and basal II) elucidated by the TCGA project. [36] In cohort 2 of IMvigor210, responses to atezolizumab were higher in the luminal cluster II subtype. [13] A similar trend was noted in cohort 1 as well. By contrast, the CheckMate 275 study showed basal I subtype tumors to have higher ORRs. [21] These discrepancies might be related to two factors. First, both IMvigor210 and CheckMate 275 allowed biopsy specimens from the primary tumor, lymph nodes, or metastatic lesions for TCGA subtyping, which may lead to inappropriate tumor classification. Second, the criteria for molecular subtyping differs in each study, highlighting a challenge in standardizing TCGA classification. Until further details emerge, TCGA subtype is not likely to prove to be a strong predictive biomarker for immunotherapy at this time.

CTLA-4 Blockade in Urothelial Cancer

Ipilimumab is an anti–CTLA-4 monoclonal antibody that has been tested in urothelial cancer. In a clinical trial at MD Anderson Cancer Center, 12 patients with localized disease received 2 doses of ipilimumab prior to undergoing cystectomy.

Six patients received 3 mg/kg/dose and were analyzed for safety before 6 additional patients were enrolled to receive 10 mg/kg/dose. [37,38] Eight out of 12 patients were found to have a lower stage of disease on their surgical specimen, and 4 out of 12 had a change from positive urine cytology and/or fluorescence in situ hybridization (FISH) analysis to negative urine cytology and/or FISH. Despite the limitations, these data suggest that CTLA-4 blockade leads to a therapeutic effect in urothelial cancer.

IN PRACTICE

Despite its limitations, data suggest that CTLA-4 blockade leads to a therapeutic effect in urothelial cancer.

Recognizing and Managing Toxicity From Immune Checkpoint Inhibitors

Most of the adverse events experienced by
patients receiving checkpoint inhibitors (immune-related adverse events [irAEs]) are inflammatory in nature and usually occur during the first 3 months of therapy. [39] Table 3 summarizes the common irAEs, which include hypophysitis, pneumonitis, hepatitis, colitis, dermatitis, and other less common conditions. The types of irAEs also vary with the type of checkpoint inhibitor. For example, PD-1 inhibitors are associated with higher rates of pneumonitis; conversely, diarrhea/colitis is a more common complaint in patients receiving therapy with a CTLA-4 inhibitor. The combination of PD-1 and CTLA-4 inhibitors has led to higher rates of grade 3/4 toxicity. There are minimal published data on irAEs from combination immune checkpoint inhibitor treatment in urothelial cancer. However, in melanoma, a phase III trial using the combination of nivolumab and ipilimumab showed grade 3 or higher toxicity at a rate of 55%. [40] Similar frequency was noted in renal cell carcinoma, at 46%. [41] Because many of these toxicities can present subtly but then become refractory to treatment, cancer care providers are urged to take detailed histories and have a low threshold to work up and treat immune checkpoint inhibitor–mediated events.

### Immune Checkpoint Inhibitors in Upper Tract Urothelial Cancer

Upper tract urothelial carcinoma (UTUC) makes up roughly 5% of all urothelial carcinomas. [42,43] UTUCs are reported to have higher frequencies of mutations in mismatch repair genes, resulting in higher microsatellite instability (MSI). [44,45] This includes patients with both germline and somatic mutations, potentially representing up to 30% of the total UTUC population. It is recommended that patients with UTUC be screened for MSI. In a colon cancer study, there was an ORR of 71% with pembrolizumab in a cohort of seven patients with high MSI. [46] Although the response rate is not defined for immune checkpoint inhibitors in patients with UTUC, most patients should be considered for treatment with checkpoint blockers.
Combinations of immuno-oncologic agents with other agents that target the immune microenvironment, such as the IDO inhibitor epacadostat, may have synergy and increase response rates. This possibility is being investigated in KEYNOTE-698/ECHO-303 (NCT03374488), a randomized phase III study of pembrolizumab and epacadostat vs pembrolizumab and placebo in metastatic urothelial carcinoma patients in the second-line setting.

It should be noted that it is not likely that immune checkpoint inhibitors will replace the current standard-of-care chemotherapy, but rather augment it. Currently, IMvigor130 and KEYNOTE-361 are addressing whether combination immunochemotherapy will be more effective than immunotherapy alone. Interestingly, cohort 2 of the IMvigor210 study demonstrated that high PD-L1 expression corresponded with a higher ORR, while in cohort 1 there was no correlation between PD-L1 expression and ORR. The major difference between cohorts was the exposure of cohort 1 patients to chemotherapy prior to receiving atezolizumab.[13] This suggests that prior chemotherapy can modulate the immune microenvironment and expression of PD-L1. Indeed, a recent retrospective study demonstrated that PD-L1 expression was significantly higher on post-neoadjuvant chemotherapy specimens than on matched pre-neoadjuvant chemotherapy specimens, supporting this premise.[47]

M7824 is a novel first-in-class bifunctional fusion protein consisting of the extracellular domain of the TGFβ receptor 2, which functions as a “trap” for all three TGFβ isoforms, covalently linked to the C-terminus of the heavy chain of the anti–PD-L1 antibody derived from avelumab.[48] Preliminary data from a phase I dose-escalation study suggest that M7824 has clinical activity and a manageable safety profile in patients with heavily pretreated advanced solid tumors,[49] and this is being further explored in urothelial cancer.

**Conclusion**

Immune checkpoint inhibitors are a remarkable development that have brought new treatment options to patients with metastatic urothelial carcinoma, whether in the second-line setting or the first-line setting when they are ineligible for or refractory to cisplatin. However, response rates with immune checkpoint inhibitor monotherapy remain low, and it is important to further understand mechanisms of resistance, identify biomarkers to guide therapy, and develop novel combination therapies. PD-L1 is a controversial marker, with no consensus method to assess its validity. Furthermore, understanding toxicity mechanisms for better management of side effects from immunotherapy is also essential to maximize the benefit of this therapy.

**FINANCIAL DISCLOSURE:** Dr. Gao serves on the scientific advisory committee for ARMO Biosciences and Jounce Therapeutics; he is also a consultant for AstraZeneca. The other 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.
Current Strategies for the Management of Locoregional Breast Cancer Recurrence

Irene L. Wapnir, MD, and Atif Khan, MD, MS

ABSTRACT: Advances in the treatment of breast cancer have decreased the rate of isolated locoregional recurrences (ILRRs) over time. Surgery, radiation therapy, and systemic therapies are used to manage these failure events and their associated poor prognosis. Operable ipsilateral breast tumor recurrences (IBTRs) are treated by either salvage mastectomy or, in select cases, repeat lumpectomy. Axillary nodal recurrences and postmastectomy chest wall relapses are commonly amenable to surgical resection, too. Repeat sentinel node mapping may be undertaken after IBTRs and chest wall recurrences. Aberrant lymphatic drainage, especially after previous mastectomy, is frequently observed. Adjuvant radiation is recommended for most ILRR cases; the dose and volume must be adjusted for prior to receipt of therapy. Implementation of adjuvant systemic therapies after ILRR should be based on the expression of molecular markers in the recurrent tumor. Administration of chemotherapy for estrogen receptor–negative ILRR is indicated, since it significantly decreases the rate of distant metastases.

Introduction
Much of the available data on the long-term risks of isolated locoregional recurrences (ILRRs) in breast cancer are derived from studies carried out in the 1980s and 1990s, when first-line primary interventions consisted of modified radical mastectomy or lumpectomy and axillary node dissection followed by whole-breast radiation therapy.[1-6] Significant advances have occurred since then, changing the landscape in which an ILRR occurs. Implementation of sentinel lymph node biopsy (SLNB), routine use of systemic therapies, and the adoption of partial breast irradiation (PBI) after lumpectomy are foremost. Additionally, downstaging with neoadjuvant chemohormonal regimens, in combination with increasing use of postmastectomy radiation therapy (PMRT) and regional nodal irradiation (RNI), have enhanced the effectiveness of locoregional treatments, while limiting the use of more extensive surgery.

In this review, we focus primarily on describing locoregional and systemic management strategies for ILRRs manifesting as isolated first-failure events following mastectomy or breast-conserving therapy. Over the last 3 decades, findings from only two prospective randomized trials—the Swiss Group for Clinical Cancer Research (SAKK) 23/82 trial and the Chemotherapy as Adjuvant for Locally Recurrent breast cancer (CALOR) trial—have provided information on the benefits of adjuvant systemic therapies after ILRR.[7,8] The National Comprehensive Cancer Network (NCCN) classifies ILRRs into three groups based on prior therapy: 1) recurrences that occur after breast-conserving surgery plus radiotherapy, 2) those that occur after mastectomy and level I/II axillary lymph node dissection (ALND) with PMRT, or 3) those that occur after mastectomy and level I/II ALND without PMRT.[9] Given current clinical practices regarding the extent of nodal surgery and RNI, it is perhaps more practical to discuss the management of the breast separate from the nodes.
Clinical Scenarios

An ILRR represents the reappearance of breast cancer in the region of the ipsilateral breast/chest wall or the draining regional lymph node basins. The majority are isolated first-failure events, with the remainder accompanying or following distant metastases.[4] Most ILRRs are locally limited and operable. Historically, recurrences after mastectomy were discovered on clinical examination as skin changes, palpable masses, or lymphadenopathy. Many recurrences can be asymptomatic, appearing as a subtle change in skin color. Others may be more symptomatic, with a fullness or mass in the operative field, increasing discomfort, and limited or painful range of motion of the upper extremity. However, diffuse skin involvement or invasion into surrounding structures, such as the periosteum, intercostal muscles, or brachial plexus, at the time of recurrence can render patients inoperable, irrespective of the primary cancer type.

ILRR after breast conservation therapy

Local relapses after breast-conserving surgery can occur within the breast tissue itself or the chest wall, nodal basins, or skin. Most ipsilateral breast tumor recurrences (IBTRs) are detected on physical exam or by routine mammographic or MRI surveillance. Surgery- and radiation-induced changes in the breast may decrease the reliability of the physical exam. Over 90% of IBTRs after breast-conserving surgery for invasive breast cancer are invasive again, irrespective of radiation therapy. The majority are localized within 3 cm to 5 cm of the tumor bed.[10-13] In contrast, only 50% of IBTRs after ductal carcinoma in situ (DCIS) are invasive. [14] The location of the IBTR; time to recurrence; and prior treatment, such as PBI, are some of the factors that define the biological significance of the recurrence. IBTRs occurring in another quadrant or exhibiting different histology may represent a new primary tumor rather than a true recurrence or growth of persistent disease, especially if they appear after a long interval.[13,15-19] Diffuse skin involvement can be the only manifestation of relapse and is analogous to the same presentation in mastectomy-treated patients (Figure 1).[20]

ILRR after mastectomy

Postmastectomy recurrences involve the chest wall, skin, or regional lymph nodes. Invasive recurrences can be localized or diffuse and involve the skin, subcutaneous tissues, chest musculature, or extranodal soft axillary tissue. Invasive recurrences rarely occur after mastectomy for DCIS. [21] Invasion into the ribs or sternum is considered largely inoperable and has a poor prognosis, similar to distant metastases.[22] Prosthetic and autologous tissue breast reconstruction can theoretically interfere with the detection of small recurrences. However, mammographic screening of the reconstructed breast after mastectomy is not superior to physical exam.[23] Although annual PET or CT scans may detect nodal recurrences before they are palpable, there are no data to support routine implementation after primary treatment.[24]

Risk Factors for Developing Locoregional Recurrence

Over the last decade, tumor biology has emerged as one of the most powerful

FIGURE 1 Inoperable Locoregional Recurrences. (A) Rash-like skin recurrence after breast-conserving surgery. (B) Fixed infiltrated breast with raised skin tumor nodules and exophytic mass at the lateral edge of the nipple areolar complex.

ILRR as regional nodal recurrences

Nodal recurrences most commonly manifest in the ipsilateral axilla on physical exam or radiologic tests.[25] In current practice, most patients will have had only sentinel node resection for their primary cancer surgery, with the exception of clinically node-positive patients, who may have also received regional and axillary irradiation. The biological significance of nodal recurrences may not all be the same, and the approaches to these failures must be tailored to prior interventions as we detail below.

Relapses in the interpectoral, internal mammary node, and infraclavicular (level III axillary node) basins are uncommon.[26] Inclusion of supraclavicular nodal failures in the ILRR classification has been controversial, but is currently classified as N3c disease.[22,27,28] The contralateral axilla may be considered an area for ILRR, a consequence of postoperative aberrant lymphatic drainage following a SLNB or complete lymphadenectomy.[29]
determinants of locoregional recurrence. The incidence of IBTRs and chest wall or regional node recurrences varies based on the stage of disease at presentation and adjuvant treatments.[5,6] Young age, nodal positivity, larger tumors, and hormone receptor–negative tumors have been associated with a higher risk of recurrence.[30-34] However, this rate has been dropping.[35] Tumor biology impacts the interval to ILRR; the median time to ILRR is longer for estrogen receptor (ER)-positive (6.8 years) vs ER-negative (3.6 years) cancers. [8] Triple-negative breast cancers have a higher early local failure rate compared with ER-positive cancers, with a 5-year cumulative incidence of 4.2% and 5.4% for lumpectomy and mastectomy, respectively.[36,37] Notably, ILRR events among patients with ER-positive cancers continue over a 20-year period.[38]

The molecular profiling of tumors has shed further light on the biological behavior of breast cancer, including the risk of locoregional recurrence.[39,40] A high Oncotype DX Recurrence Score, indicative of a patient’s risk for distant metastases in ER-positive carcinomas, is also associated with a higher risk of locoregional recurrence.[41-43]

**Lumpectomy margins and radiotherapy**

Many studies have described the relationship between lumpectomy margins and local recurrence. [44-46] This was verified in a systematic review of 33 trials encompassing 28,162 patients. Those with close/positive margins had an odds ratio for IBTR of 1.96 compared with 1.0 for those with negative margins (defined as no tumor on ink). [47] Wider negative margins were not associated with superior local control. In this same analysis, a radiation boost to the lumpectomy cavity reduced IBTR rates, but it did not completely overcome the effect of microscopic positive margins.

Omission of breast irradiation is associated with higher rates of locoregional recurrence and earlier manifestation of recurrence.[48] In a pooled analysis of 15 trials, the annual risk of IBTR ranged from 0.4% to 2.1% with radiation therapy compared with 1.4% to 5.7% without radiation therapy.[49] The Early Breast Cancer Trials’ Collaborative Group (EBCTCG) conducted a meta-analysis of 17 randomized trials involving 10,801 women. A 10-year reduction in the risk of IBTR, from 35% to 19.3%, was seen with breast radiation therapy.[50]

The management of locoregional recurrence (LRR) in breast cancer remains a challenge, as it requires input from multiple disciplines: surgery, radiation oncology, and medical oncology. In breast oncology, we have grown accustomed to making decisions regarding adjuvant therapy based on clinical trials that enroll and collect data from thousands of patients. However, clinical trials studying LRR in breast cancer have been difficult to perform due to the heterogeneity of the patient population.

In this issue, Wapnir and Khan review the current literature that can be used to guide clinical decisions, including results from the only two prospective randomized trials on LRR conducted in the past 3 decades. They found that the literature supports excision of recurrent disease, when possible. Patients should receive radiation therapy, if not already performed, and be considered for re-irradiation based on the individual clinical scenario.

As the authors noted, the Swiss Group for Clinical Cancer Research (SAKK) trial evaluated the benefit of tamoxifen after excision and radiation among 167 patients with postmastectomy LRR. Adding to the evidence is the Chemotherapy as Adjuvant for Locally Recurrent breast cancer (CALOR) trial, which evaluated the benefit of chemotherapy amongst 162 patients with isolated LRR. Patients who experience LRR have an increased chance of developing distant metastatic disease, and both of these trials showed that additional systemic therapy can reduce this risk. Regarding recurrent disease that is hormone receptor (HR)-negative, results from the CALOR trial show that systemic chemotherapy, preferably doublet therapy, provides a clear benefit. Although a statistically significant improvement in disease-free survival after systemic chemotherapy was not seen amongst HR-positive patients, we cannot draw a firm conclusion from such a small patient sample.

Decisions regarding the role of systemic chemotherapy should take into consideration many factors, including HR status and other characteristics of the tumor, timing of the recurrence after initial treatment, prior response to systemic therapy, and the patient’s tolerability of therapy. There is no “one size fits all” approach to the management of LRRs in breast cancer, and the challenge of conducting clinical trials in this setting still remains. Thankfully, improvements in therapy have reduced the rate of LRRs so that fewer patients have to face this challenge.

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

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**Amelia B. Zelnak, MD, MSc**

No “One Size Fits All” Approach Exists

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**Nodal involvement**

The risk of ILRR is related to the extent of initial nodal involvement. Thus, patients with more positive nodes experience higher rates of locoregional failure. The rate of nodal recurrence for patients who have negative sentinel nodes or low-burden nodal involvement is less than 2%. Systemic therapy has been instrumental in enhancing local control of disease, which is exemplified by the decreasing trends in 10-year cumulative risks observed in the National Surgical Adjuvant Breast and Bowel Project (NSABP) trials. Targeted therapies—such as the anti–human epidermal growth factor receptor 2 (HER2) agent trastuzumab—have greatly contributed to reducing locoregional recurrences in both lumpectomy- and mastectomy-treated populations. Use of neoadjuvant chemotherapy is linked to a complete pathologic response in triple-negative and HER2-positive breast cancers, but not necessarily in endocrine-responsive cancers.

**Prognosis After ILRR**

ILRRs are associated with an unequivocal high risk of developing distant metastases and, consequently, poor survival. For example, 50% of mastectomy-treated patients in Danish Breast Cancer Group trials who experienced an ILRR then developed distant metastases within 2 years. In 1990, Halverson et al treated postmastectomy ILRRs with radiation therapy and reported 5-year and 10-year survival rates of 43% and 26%, respectively. IBTRs, too, have been largely viewed as indicators of future risk for distant metastases. The 5-year distant disease–free survival (DDFS) after an IBTR was 67% in node-negative patients vs 51.4% for node-positive patients in pooled analyses of NSABP trials. Strikingly worse was the 5-year DDFS for non-IBTR ILRR—28% in node-negative patients and 19% in node-positive patients. Among nodal recurrences, the 5-year DDFS rates were 31.5% for axillary recurrences and 12.1% for supraclavicular events. Globally, early recurrences, defined as within 24 months, have a far worse prognosis than those occurring after more than 48 months.

Second ILRRs are common after treatment of an ILRR, only exceeded by distant failures. In the CALOR trial, these second relapses occurred at a median interval of 1.6 years, and prognosis after this event was poor compared with those experiencing distant metastases.

**Diagnosis and Management of ILRR**

The type of biopsy performed to diagnose a recurrence depends on the location of the recurrence. Internal mammary or supraclavicular recurrences are safer to sample via fine needle aspiration, whereas other sites are amenable to core needle biopsy sampling. Metastatic disease must be ruled out concurrently with a diagnosis of ILRR via CT or PET/CT scans. Obtaining an updated family history and considering genetic testing or re-testing, given the more informative multigene panels available today, are equally important. Hormone receptor and HER2 testing should be repeated for any recurrence, so that systemic therapies are guided by the molecular characteristics of the recurrence rather than the primary occurrence.

Salvage strategies for any ILRR should account for the index cancer presentation, pattern, and location of the recurrence, as well as prior therapies. Clinical management of an ILRR has been focused on surgical removal of recurrent disease whenever possible, selective use of radiotherapy, and systemic treatments. Outside of systemic therapy, no prospective randomized clinical trial data exist to ascertain the benefit of local treatment strategies. We address this discussion in four broad categories of recurrences: post–breast-conserving therapy, postmastectomy, nodal recurrences, and inoperable recurrences.

**ILRR after initial breast conservation therapy**

Mastectomy as a strategy. Salvage mas-
tectomy remains the standard of care for an IBTR after initial lumpectomy and whole-breast adjuvant radiotherapy (Figure 2 and Figure 3). Concerns about skin viability and the time interval following radiation treatments must be considered when selecting a postmastectomy breast reconstruction procedure. Nipple-sparing salvage mastectomies have recently been reported with satisfactory technical and oncologic results.[61-64]

The reported locoregional control rates after salvage mastectomy are highly variable; they range from single digits to as high as 30% to 50%.[65-67] Therefore, PMRT should be considered, even though there are no high-level data on its use in the salvage setting after initial breast-conserving therapy with whole-breast radiation therapy. In cases with positive mastectomy margins, PMRT is likely beneficial.[59] Because the majority of irradiated tissue is removed during a salvage mastectomy, and the remnant chest wall and skin have a relatively high tolerance for radiotherapy, re-irradiation is feasible and can also be considered for patients whose index cancer was associated with biologically more aggressive cancers (eg, multiple positive nodes). The IBTR may be accompanied by concurrent nodal relapse, necessitating the inclusion of nodal basins, which is further complicated if the initial adjuvant radiotherapy for breast-conserving therapy included RNI. In these patients, the brachial plexus constrains the re-irradiation dose, posing significant morbidity risks. Still, with today’s highly conformal radiotherapy techniques, brachial plexus dose carve-outs can be attempted for women with particularly high-risk presentations that warrant re-irradiation to the regional nodal basins. This should be considered only after a multidisciplinary consensus, with documentation of patient consent after a thorough discussion of the inherent risks.

Repeat breast-conserving therapy as a strategy. Kurtz and colleagues first described the use of repeat lumpectomy for IBTR in 1989.[10] In a nonrandomized comparison, without the routine benefit of systemic therapies, the locoregional failure rate was 36% compared with 12% after salvage mastectomy. Others have reported a wider range of second ILRR rates, from 7% to 38% at 51 to 120 months of median follow-up.[68-73] In contrast, Gentilini et al found that recurrent tumors measuring < 2 cm that recurred 48 months or later had low subsequent second ILRR rates with repeat lumpectomy alone.[72]

Re-irradiation of the breast has been reported by several groups.[74] Most of these series used PBI as a method to limit the volume being irradiated.[75,76] Of note, in the CALOR trial, 16 of 89 IBTR cases (18%) received repeat lumpectomy, and only 2 reported breast re-irradiation.[60] During a median follow-up of 5 years, a second ILRR occurred in 2 repeat lumpectomies (12.5%) compared with 6 of 73 salvage mastectomies (8.2%).

Clinical management of an ILRR has focused on surgical removal of recurrent disease when possible, selective use of radiotherapy, and systemic treatments. Outside of systemic therapy, no prospective randomized clinical trial data exist to ascertain the benefit of local treatment strategies.

Three noteworthy studies involving breast re-irradiation provide insight into this topic. One study by Hannoun-Levi et al is significant for its large size (N = 69) and long follow-up (median of 50 months); the second is a prospective series by Chadha et al.[77,78] Both were done with low-dose-rate multicatheter implants at centers with considerable brachytherapy experience, and both reported excellent outcomes in terms of local control and toxicity. A third study by Arthur et al—considered the current highest level of evidence for repeat breast-conserving therapy—is the Radiation Therapy Oncology Group (RTOG) 1014 trial, which utilized external-beam conformal PBI.[79] Treatment was completed in 58 of the 65 accrued patients, and systemic therapy was administered in 51.7%. There were two local recurrences, for a 3-year estimate of 3.7% and a breast preservation rate of 94.8%. At a median follow-up of 3.64 years, there were 4 patients (6.9%) with late grade 3 treatment-related adverse events. A larger follow-up trial is now being developed by NRG Oncology to build on the experience of RTOG 1014.

ILRR after initial mastectomy

The local salvage strategy for ILRR after mastectomy is guided by the extent of recurrence and prior radiotherapy. In general, the aim is to attempt removal of all gross disease, understanding that microscopically negative margins are not applicable posteriorly on the chest wall.
ogous tissue offers better coverage and aesthetically superior reconstruction re-
sults. Either pedicled or free tissue flaps are commonly used. Administration of
radiation therapy after reconstruction can aggravate skin changes, contracture,
and fibrosis of soft tissue flaps. In general, reconstructions in a previously irra-
diated field are associated with a higher complication rate.

**Nodal ILRR**

Axillary recurrences most commonly involve remaining nodes, but can also appear within the fat or connective tissue of the axilla. Ascertainment of prior nodal involvement and the extent of axillary node surgery for the index cancer is key. If a level I and II ALND was performed during the initial cancer operation, then surgery is aimed at resection of the recurrent tumor only. Con-
versely, if SLNB or limited lymphadenectomy (defined as fewer than 6 to 8 nodes) was performed, then a completion ALND is indicated. 
Exploration of the inter-
pectoral and level III nodes should be included. Nodal recurrences fixed to the chest wall, axillary vein, or brachial plexus are not considered operable. A minority of supraclavicular recurrences can be treated surgically, but systemic therapy and radiation therapy are the preferred approach.[81]

Axillary reoperations, even after a prior SLNB, may increase the likelihood of arm and breast lymphedema. Reverse mapping of arm-draining lymphatics has been described in the context of routine nodal staging as a means of identifying and sparing lymphatics and nodes draining the arm.[82,83] This approach may be considered as an adjunct to re-operation for limited nodal recurrences.

**Nodal restaging.** The merit of repeat sentinel node mapping after postmaste-
tomy recurrences or IBTRs is debated. [29,84,85] The controversy rests on whether this procedure unmasks unsuspected disease, aids in maintaining locoregional control if positive nodes are discovered, or influences the choice of systemic therapy. Moreover, the proponents of repeat SLNB argue that decisions regarding the use of regional irradiation may be directed by these findings. Maaskant-Braat et al conducted a meta-analysis of published studies reporting repeat lymphatic mapping and SLNB among 692 patients with a locoregional recurrence.[85] Sentinel nodes were successfully identified in 65.5% and 68.9% of patients who underwent lumpectomy and mastectomy, respectively. Aberrant drainage patterns, namely to the contralateral axilla, have been found in 17.4% of cases with a prior SLNB compared with 69.2% after ALND. Overall, the success rate of repeat SLNB after a previous SLNB for a primary cancer was 81% compared with 52.2% (P < .0001) if performed after a prior ALND. Contralateral axillary sentinel nodes can be resected when repeat mapping drains to that basin. Although controversial, if positive, completion ALND and/or RNI could be considered. However, long-term outcome data are unavailable with respect to local control and subsequent distant metastases.

**Inoperable locoregional recurrences**

Systemic therapy is indicated for inoperable ILRR at presentation. Diffuse erythema; papular, rash-like skin changes; and thickened, edematous-appearing skin are akin to an inflammatory presentation of cancer. Large, bulky recurrences of the chest wall may appear amenable to surgical resection if not fixed, but should preferably be downstaged with systemic therapy first. Extensive chest wall resections and complex reconstructions are possible, but have fallen out of favor over time.[86,87] Recurrences that invade musculoskeletal or neurovascular structures are challenging. Typically, the prognosis of these patients is poor; thus, surgery should be undertaken as a palliative measure and with consideration of the presence of distant disease.

Supraclavicular or internal mammary lymph node recurrences can be difficult to resect. Hence, the preferred treatment approach has shifted to the use of adjuvant treatments. Pedersen et al reported outcomes for 305 patients with supraclavicular recurrences, including 38% with synchronous sites of locoregional recurrence treated between 1977 and 2003.[81] Combination locoregional and systemic therapy and locoregional therapy alone resulted in remission rates of 67% and 64%, compared with 40% for systemic therapy alone. However, the 5-year rates of progression-free survival and overall survival were poor: 15% and 24%, respectively. In a multivariate analysis, the type of treatment and the histologic grade of differentiation were the only independent prognostic factors. Current practice favors neoadjuvant sys-
temic therapy followed by consolidation with radiation at the point of maximal response. These approaches have limited the role of surgical intervention, but resection can be considered on a case-by-case basis.

**Postoperative radiotherapy**

For patients who did not receive PMRT during initial management, the general consensus is that comprehensive radiation should be administered to the chest wall and draining lymph node basins in the axilla and supraclavicular and infraclavicular regions, and to the internal mammary nodes after an ILRR. Patients who received chest wall radiation therapy only for a postmastectomy chest wall recurrence had inferior outcomes.
compared with patients treated comprehensively to the chest wall and regional lymphatics. Long-term local control rates, in the range of 40% to 80%, attest to the efficacy of radiation therapy in the salvage setting. Willner et al reported a 5-year overall survival rate of 42% among 145 patients with an ILRR after a modified radical mastectomy. The 5-year overall survival rate for those with an isolated axillary recurrence was 50%. On multivariate analysis, the site of recurrence and number of recurrent chest wall nodules had the strongest influence on survival. Additional variables influencing survival included time to recurrence, age at recurrence, sustaining local control at the sites of recurrence and of the primary tumor, and the presence of tumor necrosis in the primary tumor. As previously discussed, re-irradiation of patients who received PMRT may be warranted, and it is feasible in certain situations with the appropriate technology and expertise.

### Systemic therapy

The high likelihood of developing metachronous distant metastases after an ILRR mandates consideration of systemic therapy. The long-term prognosis for these patients is affected by the time interval between the index cancer and ILRR, as well as the stage of disease at presentation. Two major trials have addressed the concept of systemic therapy after a locoregional recurrence. First, SAKK studied the use of tamoxifen in 167 postmastectomy ER-positive recurrences. A statistically significantly improved 5-year disease-free survival (DFS) rate was observed favoring tamoxifen over placebo (61% vs 40%). Second, the CALOR trial recruited 162 patients between 2003 and 2010 with ILRRs and randomly assigned patients to the physician’s choice of chemotherapy. Chemotherapy significantly improved the 10-year DFS rate, from 34% for the no-chemotherapy subgroups to 70% for the chemotherapy subgroups; the hazard ratio (HR) was 0.29 (95% CI, 0.13–0.67). No benefit of chemotherapy could be ascertained in the ER-positive cohort (10-year DFS rate, 50% vs 59%, respectively; HR, 1.07; 95% CI, 0.57–2.00). In multivariable analyses, the hormone receptor status of the ILRR was the best predictor of a chemotherapy benefit, underscoring that the receptor status of the recurrence should always be evaluated and utilized as a guide in the selection of systemic therapy.

### Conclusion

Locoregional control of breast cancer has improved in both mastectomy- and lumpectomy-treated populations, resulting in fewer locoregional recurrences. Management should be largely individualized and tailored to the extent of disease, the molecular profile of the recurrence, and prior adjuvant treatments. Moreover, for most clinical scenarios of ILRR, there may be multiple reasonable salvage strategies that multidisciplinary teams should carefully discuss and present to the patient. Finally, surgical excision and locoregional radiation should be considered in nearly all subgroups of patients, along with recommendations for systemic therapy.

**FINANCIAL DISCLOSURE:** Dr. Wapnir served on a one-time Advisory Board for Amgen, Cardinal Health, Genomic Health, and Tolmar. Dr. Khan 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/ILRR-breast-cancer

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Introduction
Cyclin-dependent kinase (CDK) 4/6 inhibitors are a class of anticancer medications that can reduce or eliminate endocrine resistance when used in combination with endocrine therapy for the treatment of hormone receptor–positive (HR+) breast cancer. Currently, three CDK4/6 inhibitors are approved for the initial treatment of HR+ advanced breast cancer in combination with an aromatase inhibitor (AI): abemaciclib,[1] palbociclib,[2] or ribociclib.[3] Additionally, ribociclib can be used in the first-line setting in combination with fulvestrant, and abemaciclib is appropriate as monotherapy for disease progression, following both endocrine therapy and chemotherapy. The addition of CDK4/6 inhibitors to endocrine therapy presents new challenges for providers, particularly regarding laboratory monitoring for neutropenic toxicities.[4]

Association Between CDK4/6 Inhibitors and Neutropenia
In the PALOMA-2 and PALOMA-3 trials, neutropenia was the most common adverse effect seen in patients receiving ribociclib (all grade, 74%; grade > 3, 58%). The median time to onset of neutropenia (grade > 2) was 16 days with an average duration of 12 days.[7-9]. The efficacy and safety of abemaciclib was evaluated in the MONARCH trial series. Rates of neutropenia in patients receiving abemaciclib were 41% (22%, grade > 3) in MONARCH-3, 46% (32%, grade > 3) in MONARCH-2, and 37% (27%, grade > 3) in MONARCH-1. Median time to first episode of neutropenia was 29 to 33 days with a duration of 11 to 15 days [10-12]. Despite the higher rates of grade > 3 neutropenia reported in the trials evaluating CDK4/6 inhibitors, the incidence of febrile neutropenia was relatively low (palbociclib, 1.8%; ribociclib, 1%; abemaciclib, < 1%), suggesting CDK4/6

When to Dose Reduce?
Kristina Frinzi Byers, PharmD, BCOP

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<th>TABLE</th>
<th>Additional Considerations for CDK4/6 Inhibitors</th>
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<td>Coadministration with grapefruit/grapefruit juice increases the serum concentration of CDK4/6 inhibitors. Patients should be advised to avoid grapefruit/grapefruit juice due to the potential for increased toxicity.</td>
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<tr>
<td>CDK4/6 inhibitors are major cytochrome P450 3A4 (CYP3A4) substrates. Coadministration with CYP3A4 inducers should be avoided due to the potential for diminished efficacy, and dose reductions should be considered if coadministration with CPY3A4 inhibitors is unavoidable.</td>
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<td>Additional adverse effects that should be monitored include fatigue, headache, alopecia, skin rash, diarrhea, nausea, and abnormal liver function tests.</td>
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CDK = cyclin-dependent kinase.

In contrast to chemotherapy, CDK4/6 inhibitor–associated neutropenia is rapidly reversible.

inhibitor–induced neutropenia rarely leads to infection.

**Mechanism of Action**
Mechanistically, CDKs regulate cell cycle progression from the G1 to the S phase. CDK6 is particularly involved in the differentiation of hematologic precursor cells. Inhibition of this pathway leads to senescence of hematologic precursor cells, resulting in the neutropenia associated with CDK4/6 inhibitors. For palbociclib and ribociclib, cell arrest does not lead to the apoptosis seen with cytotoxic chemotherapy, and intermittent dosing allows for neutrophil recovery. However, abemaciclib has greater selectivity for CDK4 than CDK6, which likely accounts for the lower rates of neutropenia reported in clinical trials. Instead, diarrhea and fatigue are more commonly associated with abemaciclib than palbociclib and ribociclib.[13]

**Monitoring Parameters and Dose Modifications**
As seen in the clinical trials, onset of neutropenia occurred most commonly in the first 2 weeks of treatment. As a result, strict monitoring is recommended during the first 2 cycles of treatment for all three CDK4/6 inhibitors. For palbociclib and ribociclib, a complete blood count (CBC) with differential should be obtained prior to treatment initiation every 2 weeks for the first 2 cycles, then monthly for the next 4 cycles. If neutropenia remains < grade 2 during the first 6 months, CBC with differential can be extended to once every 3 months at the discretion of the prescriber. For abemaciclib, CBC with differential should also be obtained prior to treatment initiation and every 2 weeks for the first 2 cycles. Due to lower rates of neutropenia seen with abemaciclib, CBC with differential should continue monthly for 2 additional cycles, and then at the discretion of the provider thereafter. No dose adjustments are required for grade < 2 neutropenia (absolute neutrophil count [ANC], 1.0 × 10⁹ /L [lower limit of normal]). Grade 3 neutropenia (ANC range, 0.5–1.0 × 10⁹ /L) requires treatment interruption until neutrophil recovery is < grade 2, with resumption at the same dose level. Recurrent grade 3 neutropenia, grade 3 neutropenia with fever (> 101.3°F), and grade 4 neutropenia (ANC < 0.5 × 10⁹ /L) all require dose interruption until neutrophil recovery is < grade 2, with resumption at the next lower dose level.[1-3].

For references visit cancernetwork.com/managing-neutropenia

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Immunotherapy has become a major pillar of oncology therapy, with more than 20 approvals by the US Food and Drug Administration (FDA) for both solid tumors and hematologic malignancies in the last few years. There are two distinct approaches to immunotherapy in leukemia treatment: 1) antibody-drug conjugates that target leukemia-specific antigens, such as CD33, CD123, and CLL1, in AML and deliver a toxic payload (bacterial or chemical) into the leukemic blasts, resulting in cytotoxic cell death; and 2) T-cell–based therapies that seek to enhance T-cell responses to leukemia blasts, such as bispecific T-cell engagers, immune checkpoint antibodies, and CAR T cells. These therapies are distinct in their mechanism of action, efficacy, and toxicities.

Q: For patients with AML, what is the rationale for using immunotherapy? Are there specific characteristics of AML that make it amenable to immunotherapy approaches?

DR. DAVER: AML is one of the first diseases for which we used immunotherapy in the form of allogeneic stem cell transplant. For almost 4 decades we have been using this modality to replace the patient’s immune system with a donor immune system, and we have seen that it is quite an effective approach for treating AML. In addition, in the last 4 to 5 years, my colleagues and I in the immunotherapy group at MD Anderson, including Drs. Padmanee Sharma and James Allison, have been interrogating AML patients’ blood and bone marrow samples to try to understand the nature of T cells in AML, and our data were published recently in the journal Cancer.[1]

What we found when we looked at more than 100 patients with AML is that the T-cell population, both in the absolute numbers and the percentage, was quite preserved compared with healthy donors who had no disease. Additionally, we saw that there was an upregulation of multiple different immune checkpoint co-receptors, the most striking being PD-1 [programmed cell death 1] and OX40. This upregulation was highest in patients with relapsed AML compared with new AML, but both sets of patients had higher expression of PD-1 and OX40 compared with healthy donors. This suggested that there is a favorable T-cell profile, as well as expression of inhibitory immune checkpoint receptors, in the setting of AML, which may be one of the ways that AML tries to escape from being killed by the host defense immune system.
We could potentially activate these T cells by blocking the inhibitory immune checkpoint receptors, allowing them to fight the leukemia. This form of immunotherapy—T-cell-specific immunotherapy, which includes immune checkpoint antibodies, bispecific antibodies, and CAR [chimeric antigen receptor] T cells—enhances the patient’s own immune system.

Antibody-drug conjugates are also frequently used in patients with AML, targeting leukemia-specific antigens, most commonly CD33 and CD133, as well as newer antigens like CLL1 (CLEC12a). We usually develop an antibody that also carries a toxic payload that is bacterial or chemical, and these are delivered directly to the leukemia cells. It is important to note the difference between T-cell–based and antibody-based immunotherapy, but both types seem to have preclinical and clinical efficacy in AML and are being extensively evaluated.

Q: In regard to T-cell–based immunotherapy, your recently published study in Cancer Discovery[2] tested the combination of azacitidine, a chemotherapy agent, and nivolumab, an anti–PD-1 checkpoint inhibitor, in patients with relapsed or refractory AML. Can you tell us about this trial and the results? Is this among the first positive immunotherapy clinical trials in AML?

DR. DAVER: This trial was developed a few years ago as part of an ongoing strategic alliance collaboration between MD Anderson Leukemia Department chairman Dr. Hagop Kantarjian and Bristol-Myers Squibb to evaluate multiple immunotherapy combinations in different types of leukemias, with the best combinations being further studied in larger registrational trials. The conception of this trial came from preclinical data that our colleagues at MD Anderson had generated that showed that azacitidine—which we have used for many years both in frontline and relapsed AML, as well as in myelodysplastic syndromes (MDS)—upregulated the expression of PD-1 and its ligand PD-L1.

DR. DAVER: We are conducting a number of different immune checkpoint inhibitor trials. We have a parallel MDS study ongoing, looking at the combination of azacitidine and nivolumab, but also azacitidine with the anti–CTLA-4 antibody immune checkpoint inhibitor ipilimumab in both frontline high-risk MDS patients with high blasts and in MDS patients who have failed hypomethylating agents. My colleague, Dr. Guillermo Garcia-Manero, presented these data last year as an oral abstract at the 2017 American Society of Hematology (ASH) Annual Meeting,[4] and presented updated data at the 2018 meeting as well.[5] What we are seeing overall is that in the frontline setting, the combination of azacitidine with ipilimumab showed very encouraging response rates and survival. Even in patients who have failed azacitidine and decitabine (so-called post–hypomethylating agent MDS), who historically have dismal response rates and survival, we see that azacitidine with ipilimumab showed interesting activity, with response rates of about 30% to 40%, as well as a signal for improved survival. We believe there may be a role for ipilimumab in MDS, and potentially in AML, since ipilimumab, but not nivolumab, seems to have both single-agent and combination activity with azacitidine.

Learning from this experience, we are also evaluating ipilimumab in AML. We have an ongoing study that is combining azacitidine with nivolumab and now adding ipilimumab at a low dose of 1 mg/kg, which is one-third of the standard dose and given every 6 weeks; an update on this triplet therapy was also presented at ASH.[6] Just as has been seen in solid tumors, in which the combination of these two immune checkpoint inhibitors usually doubled or tripled response rates, we are hoping that this combination will further improve response rates and may even work in patients who have lower CD3 infiltration in the bone marrow, thereby overcoming the impact of low CD3 as a negative predictive biomarker. There are also a number of other company-sponsored and institutional phase I/II studies with other immune checkpoint inhibitors, such as pembrolizumab, pidilizumab, and durvalumab, most in combination with azacitidine.

One approach that I think will be very interesting, and first shown by our colleagues at the Dana-Farber Cancer Institute, is using an immune checkpoint inhibitor after a stem cell transplant. It was shown that this is quite an efficacious approach in patients who have relapsed AML post-transplant: single-agent ipilimumab showed complete remission in 5 of 12 patients, including skin and lymph node clearance of disease. We have an ongoing trial looking at the safety and efficacy of combining ipilimumab and nivolumab in patients who have either relapsed disease or have high-risk features before or after transplant, including adverse cytogenetics, TPS3 mutation, and minimal residual disease positivity (ClinicalTrials.gov identifier: NCT03600155). We believe that in the setting of a transplant, enhancing immune surveillance with these drugs could potentially improve relapse-free and overall survival in high-risk patients who often do poorly even with transplant.
The development and approval of immunotherapeutic agents have revolutionized the treatment of patients with solid malignancies. In 2018 alone, the US Food and Drug Administration (FDA) approved more than a dozen new indications for these therapies. While immune checkpoint inhibitors are not currently approved for acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), several trials are ongoing or have been completed.

In this interview, Dr. Daver, who has led and participated in several immunotherapy trials, provides useful insights related to the use of immunotherapy in leukemia. In a phase II trial of relapsed/refractory AML, Dr. Daver and colleagues demonstrated a promising response rate and survival with a combination of azacitidine and nivolumab, particularly in the absence of prior exposure to a hypomethylating agent. Although immune-related adverse events, such as pneumonitis or nephritis, were largely grades 1–2, they resulted in drug discontinuation and deaths in some instances. It is important to note that a prior trial using atezolizumab in higher-risk MDS was prematurely stopped because of high early mortality.[1] The combination of azacitidine and nivolumab is being tested as part of a four-arm, larger phase II/III trial led by the Southwest Oncology Group (ClinicalTrials.gov identifier: NCT03092674). This study is temporarily closed to enrollment. While excess toxicities and deaths were previously seen with immune checkpoint inhibitors in solid malignancies, high vigilance and early interventions have allowed for the safe use of these effective drugs. Our ability to safely manage adverse events in ongoing and future trials of immune checkpoint inhibitors in AML and MDS will be important. In the last 2 years, the FDA has approved 8 new drugs for AML. This remarkable feat is the result of collaboration between multiple stakeholders. Such collaborative spirit will certainly lead to the development of strategies to safely and effectively incorporate immune checkpoint inhibitors into therapy to improve the health and life expectancy of our patients with leukemia.

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**For references visit cancernetwork.com/daver-AML-interview**

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on the surface of T cells in patients with AML and MDS.[3] We believed we could use azacitidine as an immune modulator in this situation and combine it with an anti–PD-1 antibody, which was nivolumab in our study.

The study was designed in the same way as most initial first-in-human trials in any given malignancy, to see if the combination was safe and effective. We enrolled a total of 70 relapsed AML patients, allowing for both de novo and secondary AML and patients with different types of cytogenetics. The study included patients 18 years of age and older, but the median age of patients in the trial was 69 years. This was due to the fact that many physicians tend to favor hypomethylating-based treatment approaches, whether in the frontline or relapsed setting, in elderly patients. One-third of patients had adverse cytogenetics, and about 22% had TP53 mutations. The primary endpoint of this study was to assess the response rate, which was defined by the European LeukemiaNet (ELN) criteria, and included complete remission (CR) and complete remission with incomplete blood count recovery (CRi), as well as partial response and hematologic improvement.

The overall response rate was 33% in all relapsed AML patients. What was interesting was that the CR/CRi rate was 23%, but we had a number of nontraditional CR/CRi responses, including hematologic improvements in 10% and stable disease in 10%. Hematologic improvement and stable disease are not typically responses we consider when we use high-dose intensive cytotoxic therapies in AML, but these responses have been shown to be meaningful and important for quality of life, survival, and transfusion independence in elderly AML patients treated with agents such as azacitidine or IDH [isocitrate dehydrogenase] inhibitors. With immunotherapy for solid tumors, we know that a number of responses could occur in the form of stable disease and par-
At the end of the day, the most important thing we discovered was that it was specific subsets that seemed to have what we would consider the most clinically important benefit.

Q: Are there other important immunotherapy modalities that are now being tested for AML patients that we haven’t discussed yet?

DR. DAVER: There are a number of other immunotherapy modalities that have been gaining traction in the last 3 to 4 years. In fact, at the 2018 ASH meeting, a number of studies were presented on immunotherapies such as bispecific antibodies, CAR T cells, monoclonal antibodies, and, of course, immune checkpoint inhibitor antibodies. I think we are seeing what was seen with solid tumors, such as lung cancer, renal cancer, and melanoma a few years ago—initially the targeted approaches took precedence and these were developed and became mainstream, but now there are a large onslaught of immunotherapy approaches that are becoming a major part of therapy.

One approach that is going to be important in hematologic malignancies is treatment with monoclonal antibodies. There will be updates on trials of monoclonal antibodies targeting CD33 (IMGN779; ClinicalTrials.gov identifier: NCT02674763), as well as a CD123 antibody (IMGN632; NCT03386513), that we are working on at MD Anderson. Both of these are antibody-drug conjugates that carry a potent toxin on the antibody, and both have shown single-agent complete responses in patients with AML who are relapsed after failing standard therapy. IMGN632 appears especially active, with a CR/CRi rate of 26% as a single agent in all evaluable relapsed AML patients in the phase I study. We believe that when we combine these antibodies with azacitidine, venetoclax, or other therapies, we could enhance their activity even more.

The other group of drugs to look out for are the bispecific antibodies. Blinatumomab was approved by the FDA for acute lymphocytic leukemia (ALL). Blinatumomab links to CD3 on T cells and to CD19 antigen on the blast cell, and by doing that, brings the T cell in close proximity to the ALL blast cell, resulting in T-cell mediated death of the blasts. Based on this concept, many companies have started developing bispecific antibod-
ies for AML, including Amgen’s AMG 330, Xencor’s XmAb CD3-CD133 antibody, and MacroGenics’ CD3-CD133 antibody. We are seeing that they have single-agent activity in the relapsed AML setting. However, thus far the response rates have been lower than what we have seen with blinatumomab in ALL patients. The responses seem to be best in patients with low-burden disease, so we believe they may actually play a role in this setting, which is also where they happen to work best in ALL patients.

Lastly, there is early development of CAR T cells in AML, although the datasets are not large or quite yet clear. In ALL and lymphoma, we have data on CAR T cells that show high response rates. There are some early signals in AML, including a City of Hope study that showed responses with CD123 CAR T-cell therapy in multiply relapsed AML.[7] However, I think CAR T-cell therapy is about 4 to 5 years away from being mainstream in this setting. It is more likely that immune checkpoint inhibitors, bispecific antibodies, and monoclonal antibodies will be commercialized in the near future for the treatment of AML.

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For references visit cancernetwork.com/daver-AML-interview
**Pathologic Hip Fracture in a 49-Year-Old Man With Widespread Metastatic Sclerotic Bone Lesions**

Mehmet Sitki Copur, MD, Adam Horn, MD, and Pornchai Jonglertham, MD

**THE CASE**

A 49-year-old Caucasian man with back, rib, hip, and leg pain that has persisted for several months presents to the emergency department with severe right hip pain. He reports that he heard a popping noise and felt a sudden, sharp, severe pain in his right hip joint when he tried to stand up from the toilet seat. An initial plain x-ray revealed a right femoral intertrochanteric/neck fracture and sclerotic appearance of the proximal femur. Further workup with 3-view x-rays of the lumbar spine demonstrated lytic lesions throughout the bony structures, suggesting metastatic disease. The patient was admitted to the hospital and underwent internal fixation of the femur.

On physical examination, decreased motor function in both the upper and lower (more pronounced on the lower) extremities was noted. Blood work was obtained and was significant for anemia, leukopenia, and thrombocytopenia (white blood cell count, 3.9 × 10⁹ μl; hemoglobin level, 7.8 g/dL; platelet count, 77 × 10⁹ L), with a normal peripheral differential. Levels of alkaline phosphatase and lactic acid dehydrogenase, as well as the erythrocyte sedimentation rate, were elevated, at 578.0 mm/h, 488.0 mm/h, and 50.0 mm/h, respectively. Renal function was normal.

**FIGURE 1 CT Scan Results.** Multiple osteolytic bony lesions are visible in nearly all the bony structures, along with bulky retroperitoneal and iliac chain lymphadenopathy, in CT scans of the chest (A), abdomen (B), and pelvis (C).

**What is the patient’s diagnosis?**

- A. Multiple myeloma
- B. Non-Hodgkin lymphoma
- C. Metastatic urothelial carcinoma
- D. Metastatic prostate cancer
- E. Metastatic testicular cancer

TURN TO PAGE 34 for the answer and a discussion of this case by experts.
The total protein level was 6.6 g/dL, and the albumin level was 3.7 g/dL. Tumor markers were ordered.

CT scans of the chest, abdomen, and pelvis revealed multiple osteolytic bony lesions in nearly all the bony structures, along with bulky retroperitoneal and iliac chain lymphadenopathy (Figure 1). An MRI of the spine confirmed multilevel spinal metastases and extradural spinal masses at the T5 and L3 levels, causing severe spinal stenosis. A surgical specimen from an internal fixation operation was sent to pathology.

Soon after internal fixation of his femur fracture, the patient developed further loss of motor strength in all four extremities. While waiting for pathology results of the surgical specimen, the result of his serum prostate-specific antigen (PSA) test came back, at 8,972 ng/mL. Blood work for coagulation tests was performed in contemplation of spinal decompression surgery, revealing abnormal coagulation parameters consistent with early disseminated intravascular coagulation (DIC).

The patient was started on degarelix with close monitoring of his neurologic symptoms and coagulation parameters. Within 48 hours of the degarelix injection, his PSA level decreased to 650 ng/mL, and his coagulation test results normalized. He underwent spinal decompression surgery at the T5 and L3 levels, without major complications. Physical therapy was initiated as tolerated. Four weeks after admission, the patient was discharged to the rehabilitation unit to continue physical therapy and recovery from his hip surgery. He regained full upper extremity function and 80% of his lower extremity function.

**Discussion**

This 49-year-old, otherwise healthy, man presented with high-volume metastatic hormone-sensitive prostate cancer. In addition to bulky retroperitoneal lymphadenopathy, his widespread osteolytic bony metastatic disease was concerning for early spinal cord compression, the signs and symptoms of which occurred soon after his hospitalization. Blood work revealed early findings of DIC. While bulky retroperitoneal lymphadenopathy and lytic bone metastases made the initial differential diagnosis challenging, the early finding in his blood work of a very high PSA level of 8,972 ng/mL led to a quick diagnosis of metastatic prostate cancer. This diagnosis was later confirmed by the pathology of the surgical specimen (Figure 2).

Based on the early signs of spinal cord compression in this case, immediate androgen deprivation therapy (ADT) without any testosterone flare was critical. Thus, administration of a luteinizing hormone-releasing hormone (LHRH) antagonist was an appropriate first step. While orchectomy may otherwise have been a reasonable approach, the patient’s early DIC picture and low platelet count rendered this option less favorable. Similarly, spinal decompression surgery would not be possible without reversal of DIC blood picture. DIC is the most frequent coagulation disorder in patients with prostate cancer. It may occur as a result of the introduction of thromboplastic substances into the bloodstream after a biopsy of the primary tumor or a metastatic site; as in the case presented here, it may also develop as a manifestation of advanced disease.[1] Optimal management of DIC associated with prostate cancer requires treatment of the underlying prostate cancer, in combination with supportive measures to control the abnormal coagulation. Within 48 hours of the start of ADT, the patient’s DIC picture improved enough that he was able to undergo spinal decompression surgery.

Of note, this patient presented with diffuse osteolytic metastases. A widely metastatic osteolytic presentation as in this case requires a thorough evaluation to rule out other malignancies, including multiple myeloma, lymphoma, and solid tumors such as urothelial cancer or breast cancer. An early diagnosis based on a highly elevated PSA level is very helpful. Recent research studies have focused on the pathogenesis of bone metastases to identify potential targets for therapeutic interventions. Metastatic tumor cells from various cancers in the bone dysregulate the coordinated relationship between osteoclastic and osteoblastic functions, promoting tumor cell proliferation while causing bone destruction aided by various cytokines and growth factors. The pathologic dominance of different cytokines determines the common radiographic pattern of bone lesions, which may vary from predominantly osteolytic, as commonly seen in breast cancer and multiple myeloma, to predominantly osteoblastic, as commonly seen in prostate cancer. On radiographs, the bone metastases from prostate cancer typically have the characteristic osteoblastic appearance.

Diffuse osteolytic metastases from prostate cancer, as seen in this case, are quite rare, with few cases reported in the literature.[2,3] Prostate cancer cells
promote both osteoblastic and osteolytic activity through production of factors that have direct or indirect osteogenic properties. \[4\] Factors such as bone morphogenetic proteins, endothelin 1, PSA, and parathyroid hormone-related protein promote osteoblastic activity. The receptor activator of nuclear factor kappa-B ligand (RANKL)—and its receptor, RANK—promote osteoclastic activity, while osteoprotegerin (OPG) protects the skeleton from excessive bone resorption by binding to RANKL and preventing it from binding to RANK. \[5\] Prostate cancer cells express both OPG and RANKL. \[6\] The RANKL-to-OPG ratio determines bone mass, with a decrease in OPG resulting in excessive bone resorption. It is possible that, in some patients with predominantly osteolytic bone lesions, the RANKL-to-OPG balance is altered, resulting in the appearance of osteolytic bone lesions, as seen in this case.

Docetaxel is included as an upfront treatment option for men with metastatic hormone-sensitive prostate cancer based on the results of two phase III trials. \[7,8\] The survival benefit of this agent is more pronounced in patients with high-volume disease, as shown in the subgroup analyses of these trials. In this case, adding 6 cycles of docetaxel to continued ADT would be appropriate since the patient has high-volume metastatic hormone-sensitive prostate cancer. Previous studies have reported that LHRH agonists and LHRH antagonists are generally well tolerated, with the exception of reactions at the injection site with LHRH antagonists; most adverse events that do occur are consistent with androgen suppression or the underlying condition. Some insurance plans may prefer leuprolide due to its reduced cost. Since some evidence on the efficacy, safety, and potential cost savings of switching from an LHRH antagonist to an LHRH agonist has been reported, \[9,10\] switching from degarelix to leuprolide plus bicalutamide would be a reasonable option for this patient.

Finally, ADT increases bone turnover and decreases bone mineral density, leading to a greater risk of skeletal-related events. Zoledronic acid every 3 to 4 weeks or denosumab every 4 weeks is recommended for men with prostate cancer and bone metastases to prevent or delay disease-associated skeletal-related events. However, the optimal duration of zoledronic acid or denosumab remains unclear. A multiinstitutional, open-label, randomized trial in patients with bone-metastatic prostate cancer, breast cancer, or multiple myeloma found that zoledronic acid every 12 weeks was non-inferior to zoledronic acid every 4 weeks. \[11\]

### Outcome of This Case

After a month of degarelix, the patient’s PSA level decreased to 52.0 ng/mL. Following the addition of docetaxel, his PSA level went down to 0.5 ng/mL within 2 months. He is currently on his fourth cycle of docetaxel, and his PSA level is 0.2 ng/dL. He is able to walk with a walker and continues physical therapy at home.

**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/bony-lesions-case

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**FIGURE 2** Pathology of the Surgical Specimen. The pathology of the surgical specimen revealed metastatic adenocarcinoma as found via a hematoxylin and eosin stain (A); positive immunohistochemical prostatic acid phosphatase stain (B); and a positive immunohistochemical prostate-specific antigen stain (C).

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Vitamin D and Omega-3 Supplements for Preventing Cancer and Other Chronic Diseases

Dr. Manson discusses the results of the recently published VITAL study that tested whether vitamin D or omega-3 supplements could be effective for primary prevention of cancer and cardiovascular disease.

Q: What are the questions that the VITAL study intended to address?

DR. MANSON: Most previous studies of these dietary supplements have been observational, and we were interested in testing, in a large-scale randomized clinical trial setting, the effects of vitamin D and omega-3 fatty acid (FA) supplements on the risks of major chronic diseases, including cancer and cardiovascular disease. We wanted to have a “usual risk” population that was representative of the general public, age 50 and older and at typical risk of cancer and cardiovascular disease. All of the participants were free of these conditions at baseline.[1,2]

Q: Could you tell us about the details of the study design?

DR. MANSON: The study included nearly 26,000 US men and women. The men were age 50 and older and the women were 55 and older, with racial and ethnic diversity. As I mentioned, the participants were free of cardiovascular disease and cancer at baseline. The duration of the trial was a median of 5.3 years, so this trial was longer than many of the previous randomized trials with these supplements. We used what is called a factorial design, which enabled us to look at the independent and joint effects of the two dietary supplements. Vitamin D was given at a dose of 2,000 international units (IUs), and the omega-3 FAs (which were in the form of a prescription medication called Lovaza in the United States) had 1 gram a day of the marine omega-3 FAs EPA [eicosapentaenoic acid] and DHA [docosahexaenoic acid].

Q: What’s next for this study? You mentioned further follow-up. Are there additional analyses that you and your colleagues are now conducting, and are the participants still being followed to track outcomes?

DR. MANSON: We will be continuing to follow the participants for at least 2 years post-intervention. The treatment period ended December 31, 2017, and we will follow for an additional 2 years to see if any of these signals, such as the trend for a reduction in cancer death with vitamin D, will become stronger or weaker over time. We will also see if a significant reduction in cancer incidence emerges over time. Additionally, we will keep an eye on the omega-3 findings in relation to cancer. We plan to apply for a renewal grant and follow the participants for even longer, hopefully for at least 4 to 5 more years after this 2-year period.
time point, allowing us to account more fully for latency of cancer and to have greater statistical power to look at the relationship between these dietary supplements and cancer.

We also have several ancillary studies that may help to inform the benefit-risk profile of these supplements. For example, we are looking at effects on diabetes, cognitive function, depression, and autoimmune diseases, and also testing their effect on numerous biomarkers, including telomere length and metabolomics, that may be of relevance to cancer, cardiovascular disease, and other chronic diseases.

**Q:** How do you interpret the VITAL study results and are there other similar trials that are ongoing or being planned, or is this trial unique?

**DR. MANSON:** There are other trials on vitamin D, but most are smaller or have tested lower doses. There is a large trial in Australia that has close to 20,000 participants, and the results should be reported over the next 2 years. Smaller trials on these supplements will report results over the next few years. Overall, the randomized clinical trials on vitamin D analyzed in meta-analyses have not suggested a reduction in the incidence of cancer, but have suggested a reduction in cancer mortality, so our findings are consistent with these meta-analyses. As the largest vitamin D trial, we should be able to contribute to additional meta-analyses and the updated results are likely to suggest an even stronger signal regarding cancer death. The longer follow-up of our study will be of great benefit. With the omega-3 FAs, there have been very few long-term randomized trials looking at cancer as a prespecified endpoint, so I think we will have important information from the longer follow-up of the VITAL trial.

**Q:** What are the clinical implications of these results?

**DR. MANSON:** In terms of guidance regarding who should take supplements and who should not, we feel that we were able to demonstrate the safety over 5.3 years of this dose of vitamin D (2,000 IU per day) and 1 gram per day of omega-3 FAs. We did not see significant side effects—there was no increased risk of hypercalcemia with this dose of vitamin D and no increased risk of bleeding with the omega-3 FAs. For patients who are already taking these supplements in similar doses, we don’t think the VITAL trial provides a strong reason...
Reducing Cancer Risk Through Diet

Ms. Anselmo has specialized in oncology nutrition since 2007. She is a Registered Dietitian Nutritionist at the Evelyn H. Lauder Breast Center of Memorial Sloan Kettering Cancer Center, New York, New York.

We feel that we were able to demonstrate the safety over 5.3 years of a dose of 2,000 IUs per day of vitamin D and 1 gram per day of omega-3 fatty acids, with no significant side effects.

For references visit cancernetwork.com/vitD-omega3-supplements

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

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Cara Anselmo, MS

INTEGRATIVE ONCOLOGY INTERVIEW

for stopping these dietary supplements. However, we do think that it is important to caution against mega-dosing on these supplements because much higher doses of vitamin D have been linked to hypercalcemia and higher doses of omega-3 FAs can increase bleeding risk. This is an important warning, because there are individuals taking extremely high doses of these supplements.

For the omega-3 FAs, we did find that those who had lower fish consumption tended to benefit the most in terms of cardiovascular disease and heart attack risk. So, if someone has a very low fish intake despite encouragement to increase their consumption, and they’re at elevated risk for heart disease, they may be a candidate for an omega-3 FA supplement. However, we are not encouraging routine use of these supplements. Mostly we’re saying, stay tuned and we will have additional results in the next 6 to 12 months from several ancillary studies, as mentioned earlier, and we’ll have longer-term follow-up of the cohort. Some of the signals we saw may strengthen or weaken with longer follow-up. Both the longer-term follow-up and the ancillary studies will be very helpful in informing decision making. We expect that medical and public health authorities, over time, may look at the results from VITAL and other recent randomized trials, and assess whether the clinical guidelines for the use of these dietary supplements should be updated.

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