Insights from an Oncology Pharmacist
Managing Steroid Refractory Immune Related Adverse Events
Marley L. Watson, PharmD, BCOP; Tyler Beardslee, PharmD, BCOP

Clinical Quandaries
Metastatic Lung Adenocarcinoma
Yuly A. Remolina-Bonilla, Raul R. Trejo-Rosales, Bruno Saladivar-Oviedo, Alejandro Gabutti, MD, Maria T. Bourlon, MD

Also in This Issue
Pediatric ALL, Thyroid Cancer, Gilteritinib, Atezolizumab, Clinical Trials in Prostate Cancer, Genetic Testing for Breast Cancer
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IN THIS ISSUE

308 Cover I Review Article
Targeting the Sanctuary Site: Options When Breast Cancer Metastasizes to the Brain
Mridula Krishnan, MD, Jairam Krishnamurthy, MBBS, and Nicole Shonka, MD
PERSPECTIVE: Jaleh Fallah, MD, and Manmeet Ahluwalia, MD
University of Nebraska oncologists discuss novel treatments for brain mets, as well as molecular subtypes and treatment options.

304 Insights From an Oncology Pharmacist
Management of Steroid Refractory Immune Related Adverse Events
Marley L. Watson, PharmD, BCOP, and Tyler Beardslee, PharmD, BCOP
PERSPECTIVE: Ninh M. La-Beck, PharmD
Oncology pharmacists present clinical strategies for managing the serious potential corollaries of checkpoint inhibitors.

316 Interview
Pediatric ALL and the Role of CAR-T Cells
Susan Reingold, MD
PERSPECTIVE: Pat Brown, MD
Pennsylvania hematologist-oncologist Susan Reingold explores therapeutic strategies for acute lymphocytic leukemia in the pediatric population.
Interview
321 Monitoring Recurrence of Differentiated Thyroid Cancer
Alan Peiris, MD

PERSPECTIVE:
Nazanene Esfandiari, MD

Review Article
337 Universal Genetic Testing in Breast Cancer
Mehmet Sitki Copur, MD, FACP

Clinical Quandaries
325 Metastatic Lung Adenocarcinoma
Yuly A. Remolina-Bonilla, MD, Raul R. Trejo-Rosales, MD, Bruno Saldivar-Oviedo, Alejandro Gabutti, MD, and Maria T. Bourlon MD, MS

Oncologists present strategies for treating a case of metastatic lung adenocarcinoma response patterns.

Also in this Issue:
330 Clinical Trials in Prostate Cancer
332 Drug Profile: Gilteritinib
334 New Drug Use: Atezolizumab

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Management of Steroid-Refractory Immune-Related Adverse Events

Marley L. Watson, PharmD, BCOP, and Tyler Beardslee, PharmD, BCOP

Introduction
The development of immune checkpoint inhibitors (ICIs) has led to an instrumental transformation in the treatment of cancer. The only US Food and Drug Administration (FDA)-approved ICIs include cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4)-CD28, programmed death 1 (PD-1), and programmed death ligand 1 (PD-L1) inhibitors. The ever-increasing utilization of these agents including combination regimens (CTLA-4 and PD-1 inhibitors) has presented a novel set of immune-related adverse events (irAEs) that have proven to be extremely challenging to manage in some cases. Based on the mechanism of ICIs, irAEs can affect any organ system in the body at any time during treatment with varying grades of severity. Due to the complexity of these toxicities, an experienced multidisciplinary team is critical to provide optimal treatment recommendations.

Current guidelines have assisted in standardizing the approach to managing irAEs, accentuating the importance of early recognition and preventing delays by initiating immunosuppressive treatment prior to ruling out other potential diagnoses. For more severe irAEs, the guidelines generally recommend initiating corticosteroids (prednisone 1–2 mg/kg/d or equivalent) as first-line treatment. If no improvement is observed after 2 to 3 days, then the irAE may be considered steroid refractory and require increased immunosuppression with other medications. Due to the limited number of clinical trials focusing on steroid-refractory irAEs, most of the data supporting the use of additional immunosuppressive agents are provided by case series, case reports, and expert opinions. This article will focus on three of the most common irAEs seen in clinical practice including immune-related colitis, hepatitis, and pneumonitis.[1–6]
Immune-Related Colitis

Gastrointestinal toxicities are one of the most common irAEs reported in patients receiving ICIs. A systematic review reported the incidence of immune-related colitis among solid tumor patients receiving ICIs and found the overall incidence with CTLA-4 inhibitor ipilimumab was 9.1% for all-grade colitis.[7] Monotherapy PD-1/PD-L1 inhibitors had the lowest incidence at 1.3% for all-grade colitis, while combination CTLA-4/PD-1 inhibition had the highest incidence of all-grade colitis at 13.6%.[7] Symptoms of colitis include watery diarrhea, cramping, urgency, abdominal pain, blood and mucus in the stool, and fever.[1–3,8] The onset of these symptoms more commonly occurs 5 to 10 weeks after ICI initiation. These symptoms, however, can occur or even reoccur months after ICI discontinuation and can sometimes emulate inflammatory bowel disease.[1,3,9]

High-dose corticosteroids are the initial treatment recommendation for high-grade colitis. If no response is seen to corticosteroids after 2 to 3 days, then gastroenterology should be consulted and escalating drug immunosuppression utilizing a tumor necrosis factor inhibitor should be considered. Current guidelines suggest the initiation of infliximab at 5 to 10 mg/kg. The duration of treatment is not well defined, but most patients require only 1 dose [1–3]. If a second dose is required, it should be administered 2 weeks after infliximab initiation. For patients deemed infliximab refractory or who have a contraindication to infliximab (perforation, sepsis, tuberculosis, New York Heart Association class III/IV congestive heart failure), recent case reports have suggested utilizing vedolizumab, an integrin antagonist targeting α4β7 integrin. Due to vedolizumab’s more direct immune suppression to inflamed gastrointestinal mucosa, there is speculation it may not induce systemic immunosuppression, thus potentially improving long-term morbidity and preserving the antitumor immune responses. [2–4,10–12] Mycophenolate mofetil and tacrolimus have also been reported as potential treatment options for steroid-refractory colitis.[4]

Immune-Related Hepatitis

Hepatic toxicity related to immune therapy is slightly less common than immune-related colitis and is often less severe.[13] The incidence of immune-related hepatitis is highest in combination therapy with dual CTLA-4/PD-1 inhibition. With combination therapy, 29% of patients experienced all-grade hepatitis and 17% experienced severe hepatitis. Ipilimumab monotherapy results in immune-related hepatotoxicity in 3% to 9% of patients, and immune-related hepatotoxicity is less prevalent in PD-1/PD-L1 monotherapy with just 0.7% to 1.8% of patients experiencing all-grade hepatitis.[2] The typical case of immune-related hepatitis occurs 5 to 6 weeks after initiation of ICIs, but immune-related hepatitis can occur at any time during ICI therapy. Other medications that have the potential to cause hepatotoxicity should be stopped in a patient experiencing hepatitis on ICIs. Histologic features are different in autoimmune hepatitis and drug-induced hepatitis, however, and imaging may also help distinguish this difference.[2,14]

As with other irAEs, high-dose corticosteroids are indicated in patients with immune-related hepatitis of grade 2 or greater. Early initiation of corticosteroids is key, and consultation with a gastroenterology specialist may be indicated for patients with irAEs that worsen or do not demonstrate improvement within 2 to 3 days of high-dose corticosteroid initiation. Infliximab should be avoided in this setting due to concern about liver toxicity. Mycophenolate mofetil dosed at 0.5 to 1 g every 12 hours is the recommended drug of choice in steroid-refractory immune-related hepatitis. Case reports and small studies have shown that calcineurin inhibitors may also be used in steroid-refractory immune-related hepatitis.[15,16]

Immune-Related Pneumonitis

Pneumonitis related to ICI therapy is relatively rare compared to immune-related hepatitis or immune-mediated colitis, but it carries a higher risk of fatality. Unlike with most other irAEs, the incidence of immune-related pneumonitis is less common with ipilimumab monotherapy than with PD-1/PD-L1 inhibitors, with 1% or fewer of patients experiencing immune-related pneumonitis with ipilimumab.[17] All-grade immune-related pneumonitis occurs in 5% or fewer of patients, and only 1% of patients experience severe immune-related pneumonitis with PD-1/PD-L1 inhibitors.[18] Up to 10% of patients receiving combination therapies can sometimes emulate inflammatory symptoms, however, can occur or even reoccur months after ICI discontinuation and can sometimes emulate inflammatory bowel disease.[1,3,9]

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T he rapidly expanding repertoire of immune checkpoint inhibitors approved for the treatment of various cancers now include ipilimumab, nivolumab, pembrolizumab, atezolizumab, durvalumab, avelumab, and cemiplimab. In addition to activating antitumor immune responses, “One concern with all of these drugs is that they can allow the immune system to attack some normal organs in the body, which can lead to serious side effects in some people. Common side effects of these drugs can include fatigue, cough, nausea, loss of appetite, skin rash, and itching. Less often they can cause more serious problems in the lungs, intestines, liver, kidneys, hormone-making glands, or other organs.” — American Cancer Society

Immune checkpoint inhibition can lead to activation of autoreactive T-cells resulting in unique immune-related adverse events (irAEs). Corticosteroids are the mainstay for treating irAEs, although a portion of patients are refractory to corticosteroids, and Drs. Watson and Beardslee summarize the immunosuppressive drugs that can be used in this scenario. As they have pointed out, there have been no prospective randomized trials comparing the efficacy of immunosuppressive therapies in mitigating irAEs and the current approach is largely based on case reports and expert opinions. One imperative question that is not addressed is whether corticosteroids and other immunosuppressive drugs can oppose the immunostimulatory activity of immune checkpoint inhibitors. A retrospective study in 604 non-small cell lung cancer patients treated with PD-1 or PD-L1 inhibitors found that progression-free survival and overall survival were significantly lower in those with baseline corticosteroid use > 10 mg, even after adjusting for smoking history, performance status, and history of brain metastases. While these results should be confirmed prospectively and in a larger cohort of patients, they support a potential pharmacodynamic drug interaction that may adversely impact clinical outcomes. Perhaps it is time to reassess when and how we use immunosuppressive drugs in the setting of concurrent immunotherapy aimed at stimulating antitumor immunity.

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

Dr. La-Beck is an Associate Professor, Department of Immunotherapeutics & Biotechnology, Department of Pharmacy Practice, Texas Tech University Health Sciences Center, School of Pharmacy, Abilene, Texas.
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Targeting the Sanctuary Site: Options when Breast Cancer Metastasizes to the Brain

Mridula Krishnan, MD, Jairam Krishnamurthy, MBBS, and Nicole Shonka, MD

ABSTRACT: Brain metastasis is a poor prognostic factor in breast cancer progression, and traditional treatment options have shown minimal response with overall low median survival rates. The incidence of brain metastasis has been increasing despite and, in part, due to advancements in treatment as a result of prolongation of survival. Targeted therapy such anti-HER2 agents have a lower efficacy in this setting compared to metastases elsewhere; however, novel therapies are emerging in this regard. In this comprehensive review, we discuss risk per subtype, special considerations for therapy selection, current focal and systemic treatments, and recent advancements and potential future targets for success. We present our treatment paradigm and multidisciplinary approach to brain metastases arising from breast cancer based on the available evidence, incorporating molecular characteristics.

Introduction
Breast cancer has the second highest incidence of brain metastasis among all malignancies. There are few systemic therapies that penetrate the blood-brain barrier (BBB).[1,2] Brain metastasis carries a very poor prognosis, is often associated with a decline in cognition, and may affect sensory and motor function.[3] In this review, we discuss the current management of breast metastasis in breast cancer including focal therapies as well as systemic options for specific populations, including emerging and novel therapies.

Risk per subtype
The risk of developing brain metastases arising from breast cancer varies by subtype as a result of the natural history of each. Basal tumors (estrogen receptor [ER]/progesterone receptor [PR]-/anti-human epidermal growth factor receptor 2 [HER2]-) and HER2-positive tumors (ER/PR-/HER2+) have an increased risk of developing brain metastases ranging from 25% to 27% and 11% to 20%, respectively. Luminal tumors are least likely to metastasize to the brain, with luminal A (ER/PR+/HER2-) at lowest risk of 0.7%, while luminal B (ER/PR+/HER2+ or ER/PR+ or /HER2-) is slightly higher at 12%, due to the HER2 positivity.[4–6] Figure 1 demonstrates the risk of developing brain metastasis in accordance with the subtype of breast cancer.[6] The recognition of molecular subtypes has improved the understanding of the genomic landscape and heterogeneity of the disease, which has been and continues to be one of the important obstacles to advancements in the prognosis and treatment of the disease.

Special/molecular considerations for therapy selection
HER2 positive breast cancer
Approximately 25% of patients with HER2-positive breast cancer will develop brain metastases.[7] Those with HER2-positive disease have demonstrated a significant survival benefit with the use of systemic anti-HER2 therapy.[8] One proposed mechanism behind the propensity of HER2-positive disease to metastasize to the brain is the inability of trastuzumab to cross the BBB.[9] HER2-directed therapies for breast
cancer can be classified into three subgroups: monoclonal antibodies such as trastuzumab and pertuzumab, small-molecule tyrosine kinase inhibitors (TKIs) such as lapatinib and neratinib, and the antibody-drug conjugate ado-trastuzumab emtansine (T-DM1). The American Society of Clinical Oncology has recommendations on disease management for advanced HER2-positive breast cancer and brain metastases, which we have outlined in Table 1.[10]

Trastuzumab was the first developed recombinant monoclonal antibody directed against the HER2 oncoprotein. Like most other monoclonal antibodies, it is too large to cross an intact BBB, making the brain a safe haven or “sanctuary site” for any cells able to hematogenously disseminate there. The brain is increasingly reported as the first site of distant relapse in HER2-positive patients, especially those who are treated with trastuzumab. The exact mechanism is unclear but is possibly linked to the increased survival in this subset of patients since the emergence of HER2-targeted therapy. It is speculated that there is sufficient opportunity to develop brain metastasis as a result of prolongation of survival.[11,12]

Although pertuzumab is also unable to cross the BBB, dual HER2 targeting appears to delay the onset of brain metastases. Table 2 highlights some of the key clinical trials upon which systemic therapy recommendations for the treatment of brain metastases in breast cancer are based.[12–21] The CLEOPATRA trial demonstrated a significant increase in time to development of brain metastases with the addition of pertuzumab to trastuzumab and docetaxel from 11.9 months to 15 months (P = .0049).[8] The current standard clinical practice is to combine 2 anti-HER2 agents with a taxane for patients with untreated HER2-positive disease who did not receive adjuvant treatment at diagnosis.

The role for TKIs for use in brain metastases is of interest due to their increased BBB permeability. Lapatinib is a dual TKI of the HER1 and HER2 receptors. It was analyzed with capecitabine in a phase II trial in the first-line setting to delay whole-brain radiotherapy (WBRT). This study enrolled 45 patients with metastatic breast cancer and brain metastases; 29 patients had a partial response to treatment. The most common grade 3 or 4 toxicities included diarrhea and hand-foot syndrome.[9] Single-agent lapatinib has some activity in patients with progressive HER2-positive brain metastases after progression from radiation and trastuzumab; however, it is traditionally used along with capecitabine due to increased response rates (RR) of 21.4% for the combination compared to lapatinib alone with an RR of 7.2%.[13,15]

Lapatinib with capecitabine is considered a treatment option for progressive brain metastasis (after trastuzumab and T-DM1 failure) and when local therapy has failed, or re-radiation is not feasible, especially when an oral systemic treatment option is preferred. More recently, the TKI neratinib was studied in a phase II trial among 40 patients with HER2-positive breast cancer with brain metastases who had progressed after at least one line of therapy. The intracranial response rates were modest at 8% with this agent.[12]

T-DM1 is an antibody-drug conjugate of trastuzumab and a cytotoxic agent, DM1.[22,23] In an exploratory analysis of the EMILIA trial, median overall survival (OS) with T-DM1 was significantly higher compared to lapatinib with capecitabine in those with brain metastases (26.8 months vs 12.9 months; P = .008).[23] In a subgroup analysis, the incidence of CNS progression was comparable with the lapatinib-capecitabine combination; however, T-DM1 patients had a longer OS.[23] In the randomized phase III TH3RESA trial, 602 patients with locally advanced or metastatic breast cancer, pretreated with at least 2 anti-HER2 agents, were randomized to either T-DM1 or physician’s choice.

**FIGURE 1 Risk of Brain Metastases By Subtype.** [6]
Crossover was allowed. This study demonstrated a significant improvement in the T-DM1 arm in terms of median progression-free survival (PFS) (6.2 months vs 3.3 months; stratified hazard ratio [HR], 0.53; 95% CI, 0.42–0.66) and median OS (22.7 months vs 15.8 months; stratified hazard ratio [HR], 0.68; 95% CI, 0.54–0.85). [24] Currently, we use this active agent for patients who progress after initial trastuzumab and taxane or following both trastuzumab and lapatinib/capecitabine regimens.

**Triple-negative breast cancer (TNBC)**
The backbone of therapy in this subset of triple-negative breast cancer (TNBC) is cytotoxic chemotherapy, as there are no targetable receptors. There is some evidence of CNS response with chemotherapy. Agents demonstrating efficacy include cisplatin-based regimens and single-agent capecitabine.[25,26] Rosner et al in 1986 described various regimens combining cyclophosphamide, methotrexate, anthracyclines, and fluorouracil.

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**WBRT Alone or With Lapatinib?**

In a single-arm phase 2 clinical trial of the combination of lapatinib plus capecitabine in patients with untreated breast metastases due to HER2+ breast cancer 66% response rate was achieved. [5]. However the limitation of this approach is that durability of response was approximately 6 months. The combination of neratinib plus capecitabine was studied in a single-arm phase 2 clinical trial in 49 patients with progressive brain metastases due to HER2+ breast cancer. In this study, there was an objective response in 49% of the patients who had no prior treatment with lapatinib and in 33% of those previously treated with lapatinib [6]. The combination of tucatinib with capecitabine and/or trastuzumab was investigated in a phase 1 clinical trial of patients with HER2+ BMBC which resulted in objective response in at least 40% of the patients with less treatment-related toxicity compared to lapatinib and neratinib [7].

In our experience, in patients with newly diagnosed HER2+ BMBC, SRS plus concurrent lapatinib was associated with higher intracranial disease control compared to SRS alone. In this retrospective study of 84 patients with 487 brain metastases, complete response rate with SRS plus concurrent lapatinib was 35% compared to 11% in patients treated with SRS alone without concurrent lapatinib.[8] The RTOG 1119 is an ongoing randomized phase 2 clinical trial investigating the efficacy of WBRT alone versus WBRT plus lapatinib in patients with HER2+ BMBC (NCT01322868).

Future studies are needed to identify the best approach for HER2+ breast cancer and BM using these new targeted therapies with better BBB either alone or in combination with chemotherapy and/or SRS.
for objective responses up to 50%.\[27\] Temozolomide, an oral alkylating agent, has shown activity in brain metastases arising from breast cancer in combination with other chemotherapy such as cisplatin, capecitabine, or etoposide.\[25,28\]

Although recent developments in the field have shown promising results, there is a need for new therapeutics with BBB penetration to improve CNS control. In Figure 2 and Figure 3, we outline our recommendations on systemic therapy for the various subgroups.

**BRCA mutated breast cancer**

BRCA mutations, particularly BRCA1, increase the likelihood of developing brain metastases. Up to 5% of patients with breast cancer harbor a germline BRCA mutation.\[31\] Poly (ADP-ribose) polymerase (PARP) inhibitors that disrupt DNA repair mechanisms have been developed as an effective therapy in germline BRCA-mutated breast cancers.\[32\] The OlympiAD and EMBRACA trials for PARP inhibition in patients with germline BRCA mutation demonstrated a significant survival advantage with olaparib and talazoparib, respectively. Olaparib was studied in first or second progression, compared with standard therapy. Median PFS benefit was 2.8 months with a decrease of 42% in disease progression and a more favorable safety profile.\[33\] Similarly, talazoparib was shown to have a 3-month PFS benefit compared to standard therapy.\[34\] Another indication for PARP inhibition in most malignancies includes a germline deficiency or somatic loss of function of genes responsible for DNA repair. Repair of both single-strand and double-strand DNA breaks can be blocked using PARP inhibitors, making them particularly useful in those with homologous recombination deficiency.

**ER/PR expressing breast cancer**

Randomized trials are lacking in this area and only low-level evidence exists in the form of case reports to support the activity of endocrine therapy in brain metastases. The overall incidence of brain metastasis in the hormone receptor (HR) positive subtype is much less frequent. Case report data suggest responses to tamoxifen\[35\] and aromatase inhibition.\[36\] Patients with HR positive brain metastases have shown significant responses to cytotoxic chemotherapy. Niwinska et al. demonstrated an improvement in the median survival ranging from 3-14 months with the addition of chemotherapy in luminal
**Focal treatment of brain metastases**

Focal treatment including surgery, WBRT, and stereotactic radiosurgery (SRS) is indicated for the treatment of intracranial metastases across all intrinsic subtypes of breast cancer. However, the type of focal treatment strategy depends upon the extent of CNS disease and other disease- and patient-specific characteristics. An individualized approach is preferred, assimilating the above variables with clinical presentation. The approach to focal treatment of brain metastases in breast cancer is also based upon the intrinsic subtype of breast cancer and should be decided on a case-by-case basis. For example, salvage radiation is likely a first-line therapy among those with TNBC due to limited systemic options. However, a patient with HER2-positive disease may benefit from aforementioned systemic therapy options and may be able to forgo focal therapy.

**Surgery**

In the case of a solitary brain metastasis, preferred treatment options include surgical resection or SRS, although surgical resection may be limited by anatomic site. Neurosurgical resection is also helpful in relieving mass effect in patients with large symptomatic lesions. Due to the high risk of recurrence after surgery, typically postoperative SRS is offered.

**WBRT**

In recent years, the use of WBRT has decreased due to the development of less neurotoxic treatment options for focal disease. However, WBRT remains the therapy of choice in those with multiple metastases (typically >4–5).

**SRS**

SRS is a noninvasive technique for local control of brain metastasis. The technique of SRS involves intersected beams to deliver a high dose of radiotherapy to a target volume in order to generate a significant local effect while sparing the surrounding normal tissue. It may be delivered in single or multiple fractions. There are no prospective studies comparing surgery with SRS for the treatment of limited brain metastases. SRS is typically performed for a limited number of lesions and is preferred over WBRT to avoid the adverse neurocognitive impact that can be seen after WBRT. SRS is typically used for a limited number of metastatic foci, usually 4 to 5 or fewer, and <3 cm in largest diameter.[39] It is a non-invasive technique for local control of brain metastasis. The technique of SRS involves intersected beams to deliver a high dose of radiotherapy to a target volume in order to generate a significant local effect while sparing the surrounding normal tissue.
TABLE 1 Evidence-Based Guidelines for HER2-Positive Disease With Brain Metastases, American Society of Clinical Oncology Clinical Practice Guidelines[10]

<table>
<thead>
<tr>
<th>HER2-Positive Breast Cancer with Brain Metastases</th>
<th>Number of Brain Metastases</th>
<th>Therapy Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable prognosis</td>
<td>Solitary brain metastasis</td>
<td>Surgerya + postoperative RT, SRS, WBRT, WBRT ± SRS</td>
</tr>
<tr>
<td></td>
<td>Limited number of metastases (2-4 metastases)</td>
<td>Resection+ for large symptomatic lesions plus postoperative RT, SRS, WBRT (± SRS), SRS (± WBRT)</td>
</tr>
<tr>
<td></td>
<td>Size &lt; 3-4cm</td>
<td>Resection + postoperative radiation</td>
</tr>
<tr>
<td></td>
<td>&gt; 4-5 metastatic lesions</td>
<td>WBRT</td>
</tr>
<tr>
<td>Poor prognostic disease</td>
<td></td>
<td>WBRT or best supportive care</td>
</tr>
<tr>
<td>Progressive CNS metastases</td>
<td></td>
<td>SRS, surgery, WBRT, systemic therapy, clinical trial</td>
</tr>
<tr>
<td>Stable extracranial systemic disease at the time of diagnosis of brain metastasis</td>
<td></td>
<td>Continue ongoing systemic therapy</td>
</tr>
<tr>
<td>Progression of extracranial systemic disease at the time of diagnosis of brain metastasis</td>
<td></td>
<td>Anti- HER2 therapy</td>
</tr>
</tbody>
</table>

a. All recommendations for resection are based on size, anatomical location, and clinical presentation.

TABLE 2 Evidence for Systemic/Targeted Therapies for Brain Metastases in Breast Cancer

<table>
<thead>
<tr>
<th>Subgroup/Target</th>
<th>Author</th>
<th>Year</th>
<th>Systemic Therapy</th>
<th>Study Type</th>
<th>N</th>
<th>Median PFS</th>
<th>Median OS</th>
<th>Other Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2 positive</td>
<td>Thein et al[13]</td>
<td>2018</td>
<td>Lapatinib and capecitabine</td>
<td>Systemic review/ meta-analysis</td>
<td>513</td>
<td>CNS OR 26%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lin et al[14]</td>
<td>2009</td>
<td>Lapatinib</td>
<td>Phase II</td>
<td>242</td>
<td>CNS OR 6% (lapatinib)</td>
<td>CNS OR 20% (lapatinib and capecitabine extension)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lin et al[15]</td>
<td>2008</td>
<td>Lapatinib</td>
<td>Phase II</td>
<td>39</td>
<td>OR 2.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fabi et al[16]</td>
<td>2018</td>
<td>T-DM1</td>
<td>Retrospective</td>
<td>3</td>
<td>CNS CR 3.8%</td>
<td>CNS PR 20.7%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jacot et al[17]</td>
<td>2016</td>
<td>T-DM1</td>
<td>Retrospective</td>
<td>39</td>
<td>6.1 mos</td>
<td></td>
<td>CBR 59% PR 44%</td>
</tr>
<tr>
<td></td>
<td>Freedman et al[12]</td>
<td>2016</td>
<td>Neratinib</td>
<td>Phase II</td>
<td>40</td>
<td>1.9 mos</td>
<td></td>
<td>CNS OR 8%</td>
</tr>
<tr>
<td>mTOR</td>
<td>Hurvitz et al[18]</td>
<td>2018</td>
<td>Everolimus (with lapatinib and capecitabine)</td>
<td>Phase Ib/II</td>
<td>11</td>
<td>6.2 mos</td>
<td>24.2 mos</td>
<td>CNS OR 27%</td>
</tr>
<tr>
<td></td>
<td>Swearingen, et al[19]</td>
<td>2018</td>
<td>Everolimus (with trastuzumab and vinorelbine)</td>
<td>Phase II</td>
<td>26</td>
<td>12.2 mos</td>
<td></td>
<td>CNS OR 4% CNS CBR 27%</td>
</tr>
<tr>
<td>VEGF</td>
<td>Lu et al[20]</td>
<td>2012</td>
<td>Bevacizumab (with etoposide and cisplatin)</td>
<td>Phase II</td>
<td>12</td>
<td>6.6 mos</td>
<td></td>
<td>CNS OR 75%</td>
</tr>
<tr>
<td>BRCA mutated</td>
<td>Mehta et al[21]</td>
<td>2015</td>
<td>Veliparib</td>
<td>Phase I</td>
<td>25</td>
<td>Safe and tolerable</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CBR = clinical benefit rate; CNS = central nervous system; CR = complete response; mTOR = mammalian target of rapamycin; OR = objective response; OS = overall survival; PFS = progression-free survival; PR = partial response; T-DM1 = ado-trastuzumab emtansine; VEGF = vascular endothelial growth factor.
It may be delivered in single or multiple fractions. There are no prospective studies comparing surgery with SRS for the treatment of limited brain metastases. SRS is typically performed for a limited number of lesions and is preferred over WBRT to avoid the adverse neurocognitive impact that can be seen after WBRT. SRS is typically used for a limited number of metastatic foci, usually four to five or fewer, and < 3 cm in largest diameter.[39]

**Prognosis**

Development of brain metastases in breast cancer has a poor overall prognosis, with a median survival between 2 and 27 months without treatment.[3,40] In addition, they are often associated with neurocognitive deficits, functional decline, and impaired quality of life. Fortunately, recent advances in the management of brain metastases with systemic therapy have improved this prognosis, particularly for those with targetable mutations.

There are validated prognostic scoring systems for these patients. The most helpful and specific prognostic tool for breast cancer brain metastases is the diagnosis-specific graded prognostic assessment (GPA), which includes age, performance status, and breast cancer subtype. Median survival varies with GPA score, with a score of 0 to 1 predicting a survival of 3.4 months to a score of 3.5 to 4 predicting a median survival of as high as 25.3 months (Table 3).[41]

**Ongoing trials and future prospects**

Current trials include a focus on immunotherapy. From clinical trials in melanoma and lung cancer, we are aware that immunotherapy does have an impact on brain metastases. Hoping to unleash an abscopal effect using radiation in addition to immunotherapy, there are ongoing trials combining the two. Investigators are pursuing a phase II trial with the programmed death ligand 1 inhibitor atezolizumab in combination with SRS in TNBC with brain metastasis (NCT03483012). Another phase II clinical trial is evaluating neratinib with capcetinib in HER2-positive patients. Subsequently, another arm in this trial has been added to include neratinib plus T-DM1 (NCT01494662).

Some of the other noteworthy trials in HER2-positive disease include a phase II randomized controlled trial of a new oral HER2 inhibitor, tucatinib, in combination with trastuzumab and capecitabine (NCT02614794). Some other interesting future prospects include phosphoinositide 3-kinase/mammalian target of rapamycin (PI3K/mTOR) inhibitors and cyclin-dependent kinase (CDK) 4/6 inhibitors.[42]

**Conclusion**

Brain metastasis in breast cancer is a major cause of morbidity and mortality. Increasing evidence supports using an individualized treatment strategy in these patients due to disease heterogeneity. There are a large number of ongoing randomized trials evaluating targeted agents and most recently immunotherapy in the treatment of brain metastasis in breast cancer.

**FINANCIAL DISCLOSURES:** 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.
Using Germline Testing to Inform Treatment Decisions in Breast Cancer
Jennifer K. Litton, MD discusses germline testing and PARP inhibitors in patients with breast cancer.
cancernetwork.com/Litton-germline-BCa

Can a Low-Fat Diet Reduce Breast Cancer Mortality?
The results of the first randomized clinical trial evaluating the link between a low-fat diet and breast cancer incidence and mortality were presented at ASCO 2019.
cancernetwork.com/low-fat-Bca

How to More Effectively Leverage Cancer Genomics Databases as Clinical Decision-Making Tools
Oncologists can leverage genomic data to make treatment decisions.
cancernetwork.com/cancer-genomics-databases

A 41-Year-Old Woman With a Mass in Her Breast
A 41-year-old woman presents with a palpable mass in her left breast. A lumpectomy is performed. What is your diagnosis?
cancernetwork.com/imageIQ-41-breast-mass

Dr. Oratz on PARP Inhibitors to Treat Patients With Breast Cancer
A look at breast cancer treatment with PARP inhibitors.
cancernetwork.com/PARP-inhibitors-BC

KATHERINE Results Back New Adjuvant Standard for HER2+ Breast Cancer
A look at promising findings from the KATHERINE study.
cancernetwork.com/KATHERINE-1

How Various Breast Cancer Screening Guidelines Compare
In this slideshow, various clinical guidelines on breast cancer screening are summarized, including the ACP’s recent recommendations that have come under some scrutiny.
cancernetwork.com/Bca-screen-ss
Meet Our Expert

Dr. Rheingold is the Medical Director of the Oncology Outpatient Clinic, attending physician with the Cancer Center at Children’s Hospital of Philadelphia, and Professor of Clinical Pediatrics at the Perelman School of Medicine in Philadelphia, PA.

Pediatric Acute Lymphoblastic Leukemia
Where We Have Been, Where We Are Now

Recently, ONCOLOGY discussed therapy options, including chimeric antigen receptor (CAR)-T-cell therapies for pediatric acute lymphoblastic leukemia (ALL), with Susan R. Rheingold, MD. Dr. Rheingold is the Medical Director of the Oncology Outpatient Clinic and attending physician with the Cancer Center at Children’s Hospital of Philadelphia. She is also a Professor of Clinical Pediatrics at the Perelman School of Medicine in Philadelphia. Dr. Rheingold specializes in the care of children with hematologic malignancies.

Q: Could you talk about what has been the standard of care as far as initial therapies for pediatric patients diagnosed with ALL?

DR. RHEINGOLD: Over the past 5 to 6 decades, children’s hospitals and pediatric oncologists have created a uniform treatment plan for children and adolescents with ALL. When a child first presents to the hospital and there is concern that the child may have leukemia, what is initially looked at is the age of the child and the white blood cell (WBC) count at presentation. In children with very aggressive leukemia, the leukemia will spill out of the bone marrow where the cancer cells are being made and into the peripheral blood. This causes the child’s WBC count to go very high, sometimes upward of a million, which is well above the normal count of about 7,000 cells.

Using such data, children and adolescents are divided into two groups: those who might get away with basic chemotherapy and those (often including older children) who need a bit more chemotherapy to get to very similar cure rates. These groups are then broken down into what is called the National Cancer Institute (NCI) standard risk, or children younger than age 10 years who have WBC counts less than 50,000, and NCI high risk, or children who are age 10 years or older and have WBC counts over 50,000. That’s really just the starting point to determine the first 4 weeks of therapy. While the child is undergoing the therapy, a lot of background work goes on from which the oncologist and the hematopathologist are assessing the genetic abnormalities in the
leukemia and how well the child is responding to the therapy. At the end of the first month of therapy, they do a very specialized test called the minimal residual disease (MDR) test. This test is looking for 1 in 100,000 leukemia cells still in the child’s bone marrow after just 28 days of therapy.

Oncologists take all that information to decide on the course of therapy. Currently in the United States, girls are treated for about 2¼ years. Boys are treated longer, 3¼ years, although we’re trying to modify that so boys and girls are treated equally. There are biologic reasons for why historically boys have been treated a little longer than girls. But this sets off a whole pattern of looking to see whether any genetic abnormalities might be targeted with a newer agent. So, we have clinical trials in which we are adding some new targeted therapies to our standard chemotherapy backbones. We also have clinical trials in which we are assessing different risk stratifications. This will determine the longer care and treatment plan for a newly diagnosed child.

Q: In 2017, CAR T-cell therapy (tisagenlecleucel) was approved for pediatric ALL patients for refractory disease or following relapse. Can you talk about when this immunotherapy is appropriate, patients are more likely to respond, and then in the context of other treatments that have been previously available for patients who have relapsed refractory disease?

DR. RHEINGOLD: When it was approved in August 2017, it was officially approved up to age 24 years and there was no lower age limit. It was also approved for patients with a second or greater relapse or patients who were refractory to therapy. The definition of refractory is essentially in the eye of the oncologist. Most, however, will say that children who never respond to their initial therapy and may have a positive MDR test months into their therapy or patients who have had a first relapse but don’t respond to relapse chemotherapy are universally considered refractory. So, that is where the US Food and Drug Administration (FDA) approval lies right now.

There are many ongoing clinical trials for both tisagenlecleucel and different versions of the CD19 CAR T-cell therapy at various centers to study whether we can give it earlier to patients who have very early first relapse (they relapse and the leukemia comes back while they are still getting initial therapy) or to patients who don’t respond to therapy in the first course of their treatment. For these children, we want to know if we can do better by getting CD19 CAR T-cell therapy to them earlier. Other groups that teams are looking at to see if the CAR T-cell therapy is appropriate are patients who just relapsed in their spinal fluid or around their brain, which the leukemia does about 20% of the time, and patients who can’t undergo a bone marrow transplant or in whom the toxicity of a transplant would be so significant that it could lead to a child’s morbidity or mortality. The latter would be very high risk and makes people prefer to try something like tisagenlecleucel therapy instead of a bone marrow transplant. Again, these are populations we are studying actively right now and for whom we are hoping to move up CAR T-cell therapy earlier in their treatment course.
**KEY QUESTION**

Is it clear from the studies that have been done whether there are patients who are more likely to respond? Also, can you talk about whether the CAR T-cell therapy is still being done at specific centers that have experience with this treatment?

**Dr. Rheingold:** The only pediatric centers in the United States right now that are participating in CAR T-cell therapy trials are centers with expertise in bone marrow transplant, meaning they have accreditation to collect normal T cells from patients with leukemia through a process called apheresis and they have the ability to give stem-cell infusions. These centers received a lot of the accreditation they need because they are actively doing bone marrow transplants. Other centers are learning how to collect, and we will probably have more centers that have the capability of doing this in the future. Currently, most of the trials are going on in about 40 centers across the United States, but I think that will increase to upward of 60 to 80 centers at which patients will be able to receive CAR T-cell therapy in the next couple of years. There are also more centers that can collect the T cells but don’t actually have experience with infusing them. As long as these centers collect them in the standards required, the patient’s T cells can be frozen and shipped across the country very safely and then either manufactured in a clinical trial site or by the manufacturer of tisagenlecleucel if it’s that product.

What is great about CAR T-cell therapy is it seems that all patients, ages, and genetic subtypes respond. Upward of 90% of patients who actually receive the infusion go into complete remission. We really have not identified any subgroup that does not seem to do as well. Bigger and bigger numbers will allow us to begin to break down genetic subgroups over the next couple of years to see if there is any difference, but the experience right now is as long as it’s a B-cell ALL and it expresses the CD19 protein, most patients have a very good, if not excellent chance of going into complete remission with tisagenlecleucel therapy.

**Q:** In the context of CAR T-cell therapy, which is an immunotherapy, do we have a better understanding now as to how to target and stimulate the immune system to fight pediatric ALL? Are there additional immunotherapies or other CD19 or other CAR T-cell targeted immunotherapies that are being tested for efficacy in ALL?

**Dr. Rheingold:** There are several different CAR T-cell constructs, some of them going against the same CD19 protein that’s almost universally expressed on the outside of pediatric ALL, or pediatric B-cell ALL. There are also what we would call second-generation or humanized versions. Newer versions exist that are trying to stimulate the immune response even further, and CAR-T cell therapies are in clinical trials targeting other proteins on the outside of leukemia cells. Here at the Children’s Hospital of Philadelphia and at the NCI, there is a CAR targeted to CD22, another protein on the outside of B-cell ALL that again is almost universally expressed.

Some centers in the United States right now have adult trials in which they are infusing both CAR CD19 and CAR CD22 simultaneously or they have engineered a CAR that can bind to both CD19 and CD22 simultaneously. Soon, we will be moving down to the pediatric population with the goal to prevent relapse of the child’s leukemia with a leukemia that no longer expresses the protein that the initial CAR T-cell therapy was trying to attack. Leukemia cells can get “smart” and downregulate the CD19 protein on the outside of their cells so that they’re invisible to the CAR T-cells floating around in the patient’s blood and bone marrow. We refer to these as CD19-negative relapses and thus the need for approaches like CD22-targeted therapy. There are also other targets that are actively being investigated. Hopefully in the next couple of years, we will have some targeted to very specific subtypes of protein. A gene called KMT2A seen frequently in infant ALL is of great interest in trying to target some of the abnormalities associated with that particular protein in other types of leukemia such as acute myeloid leukemia.

**Q:** Are there other types of therapies being investigated for pediatric B-cell ALL that you could highlight?

**Dr. Rheingold:** The Children’s Oncology Group currently has a national trial open at over 200 pediatric oncology centers where they’re studying a different means of attacking the CD19 protein with a drug called blinatumomab that is a bispecific antibody. It has one linker that attacks to the CD19 on the B-cell ALL, but as it is bispecific, it has a second linker that attacks to the patient’s T cells floating around in their body. So, with blinatumomab you don’t have to take the T cells out of the child. You can use the T cells that are in the child at the time the drug is actively infusing. The Children’s Oncology Group is studying whether adding that to our traditional relapse chemotherapy is better than just the relapse chemotherapy alone. Early data have shown that the blinatumomab infusions are less toxic than comparable cycles of intensive chemotherapy, but as the study is still accruing we don’t know if adding it in will...
The cure rate for pediatric ALL in the U.S. has risen from 0% in the 1960s to nearly 90% today. This is among the most profound medical success stories in history. A critical contributor to this progress, and progress made in childhood cancer generally, is the comprehensive, collaborative research network that includes the vast majority of hospitals and physicians that treat children, adolescents and young adults with cancer. The improved outcomes in pediatric ALL have been due to a number of factors, including optimizing combinations of chemotherapy, improving supportive care to minimize severe side effects, and incorporating novel diagnostic technologies to guide more personalized, risk-stratified treatment. In addition, pediatric ALL is at the forefront of the development of novel treatments that harness our own immune systems to kill cancer, including chimeric antigen receptor (CAR) T-cells, bispecific T-cell engaging antibodies (BiTEs) and antibody-drug conjugates (ADCs).

Blinatumomab itself was approved on the basis of early phase 1 and phase 2 clinical trials in pediatrics for children with second or greater relapse. It is very actively being used for patients who had relapsed both on that study and then off the study.

A different drug currently being studied in a phase 2 trial is inotuzumab, which is an antibody CD22 attached to a poison packet of calicheamicin. This is FDA-approved in adults, and we pediatric oncologists are actively trying to study it in pediatric and young adult patients as monotherapy. Preliminary data is promising based on some compassionate use reports that have been published. The Europeans as well are studying inotuzumab, which is given once a week for 3 weeks in pediatric patients.

Both of these drugs we hope to move forward in newly diagnosed patients in the next generation of the Children’s Oncology Group trials. This would mean that some children would get standard chemotherapy and some would get standard chemotherapy with blocks of these immunotherapies, either blinatumomab or inotuzumab, added in to their chemotherapy to see if we could increase cure rates and to make sure that when these are added into the regular chemotherapy, we don’t have increased toxicity.

**Q:** Finally, overall on the biology of pediatric B-cell ALL or its treatments, what are the big questions that you and your colleagues are addressing or would like to address as far as improving outcomes for children with this disease?

**DR. RHEINGOLD:** Immunotherapy is great at targeting B-cell ALL. We are not targeting T-cell ALL as well. When you collect the T cells, it’s very hard to get them to kill themselves when you reinfuse them into a patient. So, we are looking and trying to create immunotherapy that would work for T-cell ALL relapses as well as the current armamentarium of immunotherapy that works for B-cell ALL relapses.

The other area we have not discussed is precision medicine or targeted therapy. There are some genetic subtypes of leukemia that we have come to realize will be very responsive to drugs targeted to their genetic abnormality. The classic example of this is Philadelphia chromosome-positive ALL. In this case, there was a translocation and the very first targeted cancer therapy was designed to bind and eradicate the abnormal protein that was being made when the translocation occurred in the leukemia cells. That drug imatinib has now been proven through the Children’s Oncology Group to increase cure rates significantly. Pediatric patients were cured 30% to 40% of the time with bone marrow transplants. By adding a single oral drug the patients took daily to a chemotherapy backbone, now upward of 70% to 80% of children are cured.

Other subtypes of leukemia that people have discovered are now called Philadelphia-like ALL. These respond to the same drug, and we are...
studying whether those subgroups also do better when we use tyrosine kinase inhibitors in combination with standard chemotherapy. So ruxolitinib, dasatinib, and imatinib are all being studied on top of chemotherapy backbones.

That being said, the number of newer targeted agents that are being approved for all types of adult cancers that might work on pediatric leukemia pathways is tremendous. So, we have to figure out the toxicity of these drugs alone and in combination, and how exactly to get them into the appropriate patients who are showing the genetic susceptibility in their specific type of leukemia. It’s an exciting time to be a pediatric leukemia specialist, but we have a lot of work ahead of us to see how much more targeted therapy and immunotherapy we can add to chemotherapy and then begin to study how we can reduce chemotherapy so children don’t have the same amount of long-term effects they have had historically.

FINANCIAL DISCLOSURE:
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For references visit cancernetwork.com/ped-ALL-Rheingold
Monitoring for Thyroid Cancer Recurrence

Alan N. Peiris, MD spoke with ONCOLOGY about guidelines and strategies for treating patients who have had thyroid cancer.

Q: First, could you talk about the importance of monitoring for thyroid cancer recurrence in those patients who have been previously diagnosed and treated for thyroid cancer?

DR. PEIRIS: I think that it is important to monitor for recurrence. To put this in context, we should probably say that there are many different types of thyroid cancer. Some of these are managed more by oncologists. For example, patients with lymphomas generally end up going to oncologists. Whereas most patients with other types of thyroid cancer—certainly the most common ones—come to the endocrinologist.

Monitoring is a huge topic, so I will focus my comments on differentiated thyroid cancers, namely papillary thyroid cancer and follicular thyroid cancer. In other words, they are cancerous but they still process iodine somewhat similarly to normal thyroid tissue. These differentiated thyroid cancers account for the vast majority of thyroid cancers, up to maybe 70% to 80%, so monitoring often comes up in relation to them. It is very important for patients and physicians to consider monitoring. We can always talk about what’s coming down the pipeline, but currently after intervention, we follow these patients carefully with blood work, thyroglobulin measurements, and then consider imaging techniques.

One area of controversy comes from the fact that most of these differentiated thyroid cancers have really good outcomes. Sometimes, the scientific data to back up certain approaches have been hard to validate because people generally do well with these differentiated thyroid cancers and this spills over into monitoring.

The method of monitoring depends on the type of thyroid cancer and the staging. It is difficult to be very specific without having more detailed information. I would say that anyone with thyroid cancer should have some degree of monitoring.

The American Cancer Society estimates that in 2019, there will be 52,070 new cases of thyroid cancer and about 2,170 deaths from thyroid cancer. Women are more likely to get thyroid cancer. It is the most rapidly increasing cancer in the United States, largely due to increase imaging.

There are several forms of thyroid cancer. Moreover, rarely other malignancies can metastasize to the thyroid, so-called secondary involvement of the thyroid gland. In this commentary, we have chosen to focus on the more common thyroid cancers. These more common primary (originating in the thyroid) forms of thyroid cancer are differentiated in cell type and generally have a good prognosis. However, the less common forms such as anaplastic thyroid cancer are undifferentiated and can result in a rapid demise. Treatments vary depending on the type of thyroid cancer. Papillary thyroid cancer along with follicular thyroid cancer account for most thyroid cancers. These differentiated thyroid cancers are generally treated with surgery initially. The extent of the surgery depends on the size of...
here has been a rise in the incidence of thyroid cancer over the last 30 years, especially in small thyroid cancers. Despite the rise in the number of newly diagnosed thyroid cancers, the mortality has relatively remained stable. The rising incidence of thyroid cancer in the United States is predominantly due to the increased detection of smaller papillary cancers; with tumor size ≤ 2cm. Three-fourths of all thyroid cancer diagnoses occur in women. The majority of patients with differentiated thyroid cancer (DTC) have good prognosis. Based on the 2016 American Thyroid Association guidelines for DTC, the risk of recurrence should be categorized as low risk group, intermediate risk group and high risk group, in addition to the American Joint Committee on Cancer (AJCC) tumor, Node, Metastases (TNM) stage. In patients with low risk DTC, the risk of recurrence is a continuum with recurrence occurring in 1-5% and the 10-year disease-specific survival is 95% to 100%. Most of these patients would be classified as stage I or II. Over the last couple of years, the traditional paradigm of “one size fits all” has shifted to more individualized risk assessment. Based on several published studies, low risk group does not benefit from radioactive iodine (RAI) treatment. In contrast, RAI treatment is indicated in patients with distant metastases and evidence of iodine avid disease on radioiodine scan. Some patients in intermediate risk group might require RAI treatment. With the recent shift toward less intensive therapy, there is a need for more studies determining optimal long-term surveillance. As majority of patients with DTC fall within the low risk group, follow up monitoring entails physical exam, neck ultrasound, serum TSH level, plasma thyroglobulin level (Tg), and plasma thyroglobulin antibodies. During the follow up of patients who underwent total thyroidectomy, the rise in thyroglobulin levels or in thyroglobulin antibodies without rise in thyroglobulin levels are usually indicative of recurrence of thyroid cancer. However, the utility of thyroglobulin levels after lobectomy remains unknown. Neck US is the first imaging study to screen for recurrence after total thyroidectomy and the optimal frequency of neck ultrasound after lobectomy is also unknown. Radioiodine scan with radioiodine treatment might be indicated in certain DTC patients after total thyroidectomy with rising Tg levels. Positron emission tomography (PET scan) can detect recurrence in patients with negative RAI scan and rising Tg levels. Further imaging such as CT of neck, chest and abdomen and bone scan might be indicated for further follow up of patients with evidence of recurrence. In patients with evidence of tumor progression and non iodine avid tumor, surgery is the only curative option. However, in case of multiple progressive metastases, recent novel treatment with tyrosine kinase inhibitors, has shown promise in the management of progressive thyroid cancer. These medications are not without serious side effects and they should be recommended after careful consideration. Another option is to enroll these patients into clinical trials. However, the majority of differentiated thyroid cancer has good prognosis and patients live without having much significant morbidity related to their thyroid cancers.

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For references visit cancernetwork.com/mon-thyroid-recurrence

**Dr. Esfandiari** is Associate Professor of Internal Medicine, University of Michigan Medical School, Michigan Medicine Metabolism, Endocrinology and Diabetes Clinic, Ann Arbor, Michigan.

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**Q:** What are the current routine ways to monitor for thyroid cancer recurrence? Specifically, for each subtype, what monitoring is appropriate?

**DR. PEIRIS:** It is helpful to focus on the differentiated thyroid cancers as those account for most of the thyroid cancers. For the most common form of thyroid cancer, we should bear in mind that we do it a couple of ways. We look at thyroglobulin measurements and antithyroglobulin antibody measurement as a blood marker. Then we do imaging, usually a neck ultrasound, to
ensure that there is no recurrence either in the region of the thyroid bed or in the lymph nodes. Most of the recurrences tend to come up in the head and neck area.

For the most common differentiated thyroid (papillary and follicular) cancers, monitoring is done through imaging, including neck ultrasound examinations. Suspicious ultrasound findings can be further evaluated using fine-needle aspiration, with the needle washout fluid also tested for thyroglobulin. Other imaging modalities could include whole body nuclear medicine scans or computed tomography (PET) scans. In differentiated thyroid cancers, we also need to monitor serum thyroglobulin. Imaging may be used to image these cancers but also to treat them if you have proteins or antibodies that bind thyroglobulin, you can have misleading results. How often we do this really depends on the context of the patient. If someone is very stable, if the resection margins of the cancer are free and clear, and if the staging is appropriate and the patient has positive outlook factors, we may not do the monitoring and testing as frequently. If, on the other hand, we see a patient, examine them, and find a lymph node, we need to do it more frequently.

**Q:** Are there other tests that should be done in parallel to thyroglobulin levels in the blood?

**DR. PEIRIS:** Certainly, yes. With the differentiated thyroid cancers, we monitor using a thyroid function test as these patients are normally on thyroxine replacement because they’ve either had their thyroid cancer taken out or were given radioactive iodine. We monitor thyroid function to make sure that the TSH, which is a hormone released from the pituitary, is kept relatively suppressed so it doesn’t stimulate growth of the thyroid. We also monitor for the thyroglobulin with antibodies and imaging, the frequency of which really depends on the individual patient. The imaging may be ultrasound, which is a very easy thing to do. Sometimes (but rarely), imaging involves CT scans, MRIs, or nuclear medicine studies. It is important to remember that these cancers process iodine, so we can use radioactive iodine not only to image these cancers but also to treat them because they are destroyed by radioactive iodine. Now, in some situations these cancers are initially responsive to radioactive iodine. Now, in some situations these cancers also have the ability to make this. Ideally, once the patient has had an intervention for papillary or follicular thyroid cancer, the thyroglobulin level should be really low because there’s no thyroid tissue left, as the patient has had surgery and/or radioactive iodine. The cancer is basically no longer there. If we see a thyroglobulin level, it tells us that there is some normal thyroid tissue or thyroid cancer. And if the level started off low and then starts increasing, that is concerning because the level should be very, very low.

We have a couple of ways that we look at this. We measure the levels of thyroglobulin in the blood through immunoassays. The thyroglobulin levels should always be measured with the antithyroglobulin antibody, because if you have proteins or antibodies that bind thyroglobulin, you can have misleading results. How often we do this really depends on the context of the patient. If someone is very stable, if the resection margins of the cancer are free and clear, and if the staging is appropriate and the patient has positive outlook factors, we may not do the monitoring and testing as frequently.

**KEY QUESTION**

You and your colleagues recently wrote about monitoring by tracking thyroglobulin levels in the blood. Could you talk about the biology of this biomarker and how frequently it should be checked in patients?

**DR. PEIRIS:** Thyroglobulin is found in the normal thyroid and released into the blood. Differentiated thyroid cancers also have the ability to make this. Ideally, once the patient has had an intervention for papillary or follicular thyroid cancer, the thyroglobulin level should be really low because there’s no thyroid tissue left, as the patient has had surgery and/or radioactive iodine. The cancer is basically no longer there. If we see a thyroglobulin level, it tells us that there is some normal thyroid tissue or thyroid cancer. And if the level started off low and then starts increasing, that is concerning because the level should be very, very low.

We have a couple of ways that we look at this. We measure the levels of thyroglobulin in the blood through immunoassays. The thyroglobulin levels should always be measured with the antithyroglobulin antibody, because if you have proteins or antibodies that bind thyroglobulin, you can have misleading results. How often we do this really depends on the context of the patient. If someone is very stable, if the resection margins of the cancer are free and clear, and if the staging is appropriate and the patient has positive outlook factors, we may not do the monitoring and testing as frequently. If, on the other hand, we see a patient, examine them, and find a lymph node, we need to do it more frequently. I would stress that the biggest service we can do for our patients with thyroid cancer is to place their condition in the right context. In other words, not everyone will get the same management and that’s as it should be. Some people are going to be higher risk and need more frequent monitoring, and other people will be at very low risk and their interval for monitoring will be much longer.

Thyroglobulin is produced by normal thyroid tissue and differentiated thyroid cancers and is measured in blood. Thyroglobulin measurement is most useful if done when the TSH is high. A high TSH is seen after thyroid removal if thyroxine replacement is not adequate or from injection of biosynthetic TSH. If thyroglobulin levels are low even in the presence of stimulation by a raised TSH, this is very reassuring and indicates absence of recurrence in papillary and follicular thyroid cancers (differentiated thyroid cancers). More recent sensitive thyroglobulin assays may detect much lower levels of serum thyroglobulin and provide similar information to the values done previously through TSH stimulation. A rising level of serum thyroglobulin may indicate a recurrence, even if imaging is negative. Several steps may occur concurrently in the monitoring for recurrence in differentiated thyroid cancers. These steps include imaging studies and blood work. In order to fully assess the significance of serum thyroglobulin, antithyroglobulin antibodies are requested at the same time. The presence of thyroglobulin antibodies can confound thyroglobulin estimates. Rarely, a rising titer of antithyroglobulin antibodies may indicate a recurrence of differentiated thyroid cancer. The frequency of testing depends on the individual patient and can vary between several months and 6 months or even longer. Periodic risk assessment may allow the change in a patient’s status to higher or lower risk.
iodine but then later become unresponsive to radioactive iodine. At that point, we may use other imaging methodologies like PET-CT scans.

**Q:** Are there additional ways recurrence of thyroid cancer can be detected that are currently being developed?

**DR. PEIRIS:** There are several. I also want to say that although we are very dependent on thyroglobulin measurements and imaging, one should always remember that examining the patient is a time-honored tradition and that should not be de-emphasized. All of the labs and radiology results should be placed in the context of talking to your patients and examining them. As for the question of new markers, we’ve learned a lot over the past few years. We know thyroid cancer is being picked up much more often now, and we’ve also learned that we may have been overly aggressive in treating some forms of differentiated thyroid cancer. The whole purpose is to identify people who are at higher likelihood of recurrence. That’s where the efforts are being focused because it is clear that some patients have greater risks of not only developing differentiated thyroid cancer but also recurrence.

Markers, if they can provide synergy to the current testing, are a very exciting potential future development. There’s a lot there, but these tests have not been fully validated. One is looking at protein, microRNAs, and nucleic acid as markers that may provide some utility in picking up the recurrence. We’ve looked at using ultrasound in different ways. Ultrasound has been used with a technique called elastography for detecting fibrosis in the liver and breast abnormalities. Researchers are looking at that modality to pick up cervical lymph node involvement. Cervical nodes are present in everyone and they often get larger during, for example, a respiratory tract infection. We always have to stop and think whether this enlargement is temporary and related to infection or whether it might mean recurrence of thyroid cancer. In the past, we’ve occasionally had the need to sample these lymph nodes through fine-needle aspiration and measure thyroglobulin in the lymph nodes because normal lymph nodes should not have thyroglobulin. Thyroglobulin is confined to the thyroid gland and thyroid cancer. We are also looking at genetic studies to identify mutations such as the BRAF mutation, which may help risk-stratify papillary thyroid cancer.

A lot of different methods and technologies are being looked at, but I’m not sure they are ready for primetime because they need additional work. But it certainly is a welcome opportunity to improve monitoring of patients. The whole purpose of monitoring is based on an individualized risk assessment. Currently, we could do with some help with newer technologies, but it’s important to realize that not everyone gets the same risk assessment. Therefore, it’s up to the individual clinicians to assess all of the data and determine that risk and then determine how frequent monitoring should be.

Novel markers such as circulating microRNAs and nucleic acids may replace thyroglobulin or have the option of providing additional tests to confirm likelihood of recurrence. However, they need to be standardized after validation. Elevated neutrophil-to-lymphocyte ratio correlates with tumor size and extrathyroidal extension. Elastography, used in liver and breast disease, may offer better ultrasound detection of abnormalities in lymph nodes. Identifying BRAF mutations may help risk-stratify papillary thyroid cancer. Even thyroid cancer rates are increasing, and most new cases are in young adults.
What Are Treatment Options After Progression in PDL-1–Positive Metastatic Lung Adenocarcinoma after Chemo/IO?

Yuly A. Remolina-Bonilla, MD, Raul R. Trejo-Rosales, MD, Bruno Saldivar-Oviedo, Alejandro Gabutti, MD, and Maria T. Bourlon MD, MS

A 49-year-old woman with no smoking history presented to the emergency room with a pathologic left hip fracture. On hip x-ray, a metastatic blastic lesion was found. Workup included a CT scan that detected a primary neoplastic lesion on the left lung. Percutaneous guided biopsy revealed lung adenocarcinoma. Molecular testing of the neoplasm revealed no targetable mutations (EGFR, ALK, ROS) and a programmed death ligand 1 (PD-L1) tumor proportion score of 1%. An F-18-fluorodeoxyglucose (18F-FDG) PET/CT demonstrated metastatic disease to the bone and lymph nodes (Figure 1), and brain MRI revealed multiple brain lesions.

The patient underwent total hip replacement for the hip fracture. She was started on first-line systemic treatment with combination cisplatin, pemetrexed, and pembrolizumab and received whole-brain radiotherapy 30 Gy in 10 daily fractions. Her scans revealed stable disease after the first 3 cycles. After 6 cycles, however, a new PET/CT showed progressive disease with increased size of the primary lung lesion, new bone lesions, new mediastinal lymph nodes, and a new liver lesion (Figure 1).

What is the best treatment option after progression to chemotherapy/immunotherapy (chemo/IO) as first-line treatment for PD-L1–positive lung adenocarcinoma with no sensitizing mutations?

A. Single-agent chemotherapy  
B. Docetaxel with antiangiogenic agent  
C. Clinical trial  
D. All of the above

Discussion

In recent years, the treatment of non-small-cell lung cancer (NSCLC) has changed dramatically and immunotherapy alone or in combination with chemotherapy has become the standard first-line treatment for metastatic lung adenocarcinoma without EGFR or ALK genetic alterations.[1] This recommendation is based on different results of phase III trials that demonstrated an overall survival benefit. Patients with PD-L1 expression of 1% or greater can receive treatment with pembrolizumab as monotherapy.[2,3] Furthermore, immunotherapy plus platinum-based chemotherapy can be used regardless of PD-L1 expression.[4,5] The rationale of
this combination is based on two mechanisms: induction of immunogenic cell death and disruption of the immune-suppressive tumor microenvironment.[6]

Currently, patients with NSCLC PD-L1 of 1% or greater who progress after treatment with checkpoint inhibitors/chemotherapy do not have standard second-line systemic treatment options. National Comprehensive Cancer Network (NCCN) guidelines suggest treatment with chemotherapy alone or in combination with antiangiogenic agents as well as clinical trials and do not recommend routinely switching to another programmed death 1 (PD-1)/PD-L1 inhibitor.[1] However, there are no studies yet that evaluate the appropriate treatment for this scenario. For practical purposes and to facilitate the therapeutic approach, patients who progress after chemo/IO can be classified into two categories: 1) primary resistance (PR) and hyperprogressive disease (HPD); and 2) acquired resistance (AR).

1) Primary resistance (PR) and hyperprogressive disease (HPD)

In this category, both phenomena are indistinguishable and share molecular pathways. Clinically, patients have disease progression in their first image evaluation after treatment initiation. This may be a consequence of an aggressive tumor biology or an immune-related event. PR is characterized by an exhausted T-lymphocyte phenotype, where there is an overexpression of alternative immune checkpoints, which include TIM-3, CTLA-4, LAG-3, and BTLA, as well as the infiltration of immunosuppressive regulatory T cells, which could facilitate the processes of immune escape and tumor progression.[7,8]

HPD is an immune-related progression pattern characterized by an acceleration of tumor growth during treatment with PD-1/PD-L1 inhibitors. There is no consensus for the definition of HPD,[9] but based on the criteria of Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, it can be defined as disease progression on the first CT during treatment with PD-1/PDL-1 inhibitors (Table).[10] The survival curves intersection through the first months of immunotherapy for second-line treatment can be explained by this phenomenon.[11] However, the frequency of HPD in patients receiving chemo/IO as first-line treatment has not been determined.

Studies on HPD have been performed mainly in patients receiving immunotherapy as a second line of treatment. Clinically, patients have disease progression in their first image evaluation after treatment initiation. This may be a consequence of an aggressive tumor biology or an immune-related event. PR is characterized by an exhausted T-lymphocyte phenotype, where there is an overexpression of alternative immune checkpoints, which include TIM-3, CTLA-4, LAG-3, and BTLA, as well as the infiltration of immunosuppressive regulatory T cells, which could facilitate the processes of immune escape and tumor progression.[7,8]

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Studies on HPD have been performed mainly in patients receiving immunotherapy as a second line of treatment. In the retrospective study by Ferrera et al of 406 patients treated with immunotherapy, HPD was more frequent in the group treated with immunotherapy compared to chemotherapy. However, just one case occurred in the first-line setting. It is likely that the use of chemotherapy in combination with PD-1/PD-L1 inhibitors has a favorable impact on decreasing the proportion of patients who have this immune-related phenomenon.[14] The crossing of the Kaplan-Meier curves is not observed in KEYNOTE-189 patients treated with chemo/IO compared with patients treated with pembrolizumab alone, both in first-line settings (Figure 2).[4]

Whether these scenarios represent truly defined clinical entities is controversial. Although HPD is a possibility in cases that show progression in the first months of treatment, primary resistance cannot be ruled out as part of the spectrum of a more aggressive disease.

The best treatment of patients with PR/HPD has yet to be defined. Current information suggests that the use of chemotherapy with docetaxel with or without antiangiogenic agents or pembrolizumab is a reasonable option.[1]

Studies evaluating the effectiveness of chemotherapy after IO mainly include patients treated with IO as monotherapy in second and subsequent lines. These are retrospective and single-institution studies with a limited number of patients.[15-20] They have mostly explored the effectiveness of chemotherapy alone or with antiangiogenic agents after treatment with nivolumab. Park et al compared efficacy of chemotherapy before and after IO in 73 patients. They did not find differences in terms of progression-free survival and overall survival; however, they reported better objective response rates (ORRs) in the group of patients treated with platinum-based combination chemotherapy after IO compared to before IO, 66.7% vs 39.5% ($P = .03$), respectively. ORRs for patients receiving nonplatinum monotherapies were 46.9% vs 25%, respectively ($P = .09$).[20] This trend toward better effectiveness in pa-
Patients treated with chemotherapy after immune checkpoint inhibitors has been reported by other authors in patients treated with docetaxel with or without ramucirumab or docetaxel as monotherapy.[18,21]

2) Acquired resistance (AR)
In this category, patients show disease progression or relapse after an initial stabilization of the disease (ie, partial response or complete response) which had been maintained over a period of several months or years. These patients can be subclassified as oligometastatic vs multi-metastatic progression. Recently, Gettinger et al showed results of 26 patients treated with immunotherapy, 9 of them in the first-line setting. Oligometastatic progression limited to 1 or 2 sites occurred in 8% of cases; exclusive lymph-node involvement occurred in 40% of the entire cohort. Fifty-eight percent of patients received local treatment in the sites of progression, without initiating second-line or later systemic treatment, with a 2-year survival of 92%. After local treatment, 11 patients continued with the same immunotherapy treatment.[22]

Patients with limited progression to 1 or 2 sites may receive local treatment at the site of progression with radiotherapy or surgery, maintaining the same immunotherapy treatment. Cases with multi-metastatic disease can be treated with immunotherapy re-challenge. Treatment with chemotherapy with docetaxel with or without antiangiogenic agent or pemetrexed is also a reasonable option.

The mechanisms associated with acquired resistance include the loss of neoantigens by T-cell-dependent immunoselection processes, mutations in JAK1/JAK2, and mutations in beta-2-macroglobulin.[23-25] Shah et al reported the clinical findings of 57 patients with NSCLC with acquired resistance to immunotherapy. The progression of previously existing lesions occurred in 60.6% of cases, rather than the development of de novo metastatic disease.

FIGURE 2 Overall survival curve in pembrolizumab in combination with chemotherapy vs placebo combination where there is not crossing. Overall survival curve in pembrolizumab alone vs chemotherapy in PD-L1 tumor progression score ≥ 1% population where the intersection is evident.[2,4] PD-L1 = programmed death ligand 1.
In addition, 66.7% of patients had progression in a unique disease site and in 30% the progression was diffuse.[26] Ongoing studies may help select appropriate treatment sequences in NSCLC. The phase III INSIGNA trial (NCT03793179) plans to enroll 846 metastatic nonsquamous NSCLC patients with PD-L1 1% or greater and will be randomized in 3 arms. In arm A, patients will receive upfront pembrolizumab and, at time of disease progression, they will receive pemetrexed and carboplatin. In arm B, patients will receive upfront pembrolizumab and, at time of disease progression, they will receive pembrolizumab beyond progression and pemetrexed and carboplatin combination chemotherapy. In arm C, participants will receive pembrolizumab, pemetrexed, and carboplatin as first-line therapy and pembrolizumab and pemetrexed as maintenance until disease progression. The study plans to end in 2021.

Conclusion

Second-line treatment after progression on chemo/IO in PD-L1–positive lung adenocarcinoma with no sensitizing mutations has not yet been established. Treatment decisions depend on the time to treatment failure and affected sites and may include chemotherapy with or without antiangiogenic agent, local therapy, enrollment in a clinical trial, or reintroduction of immunotherapy.

Algorithm for second line after Chemo/IO in metastatic NSCLC.

Chemo/IO = chemotherapy/immunotherapy; HPD = hyperprogressive disease; NSCLC = non–small-cell lung cancer.
Prostate cancer is the most frequent cancer found in American men, and the second leading cause of cancer death in this population. In 2019 an estimated 174,650 new cases of prostate cancer were diagnosed in the United States, with 31,620 resultant deaths[1]. The incidence of this cancer rises with age. On autopsy about 30% of men aged 60–69 years vs. 67% of men aged 80–89 years are diagnosed with prostate cancer. Risk factors include family history, African American race, and high fat intake.

The majority of prostate cancers are adenocarcinomas, and signs or symptoms can include: focal nodules or induration within the prostate on digital rectal exam, lymph node metastases, lower extremity edema, back pain secondary to pathologic fractures, and urinary obstruction. Prostate cancer can often be found before symptoms start by testing the amount of prostate-specific antigen (PSA) in a man's blood. To help with diagnosis, clinicians perform digital rectal exam, tests for increase prostate specific antigen (PSA) levels, transrectal ultrasound, MRI of the prostate, and more.

For men with newly diagnosed prostate cancer risk stratification in selecting the initial treatment is crucial and include, anatomic extent of disease (tumor, node, metastasis [TNM] stage), histologic grade (Gleason score/grade group) and molecular characteristics of the tumor, serum PSA level, estimated outcome with different treatment options, potential complications with each treatment approach, and the patient's general medical condition, age, and comorbidity, as well as individual preferences. Treatment options include active surveillance, surgical and radiation therapy hormonal treatment with androgen deprivation at the pituitary/hypothalamus, prostate cells, testes and adrenal gland levels, chemotherapy, immunotherapy Active surveillance avoids treatment in men who never experience disease progression, while monitoring and treating men with disease progression. [2]

Currently, scores of reputable clinical trials are underway and recruiting patients.
Dr. Hala Borno on Addressing Disparities in Access to Prostate Cancer Care
Hala Borno, MD, of the University of California, San Francisco, discusses the disparities in access to clinical trials and treatments for patients with prostate cancer. cancernetwork.com/Borno-PCA-Dis

What Is the Optimal MRI-Guided Biopsy Approach in Prostate Cancer?
The PAIREDCAP trial looked at different biopsy approaches to see which has the highest prostate cancer detection rate. cancernetwork.com/PAIREDCAP

Study Explains the Uptick of Prostate Cancer in World Trade Center First Responders
Increased inflammation and immune response may partially explain the excess incidence of prostate cancer among first responders exposed to dust at the World Trade Center after the September 11, 2001 terrorist attacks cancernetwork.com/PCA1stResp

What Is the Ideal Glucocorticoid Regimen Combined With Abiraterone for Prostate Cancer?
Researchers compared several glucocorticoid regimens, given in combination with abiraterone acetate, for metastatic castration-resistant prostate cancer. cancernetwork.com/GC-abiraterone

Visit our site for more research and perspectives on prostate cancer.
Gilteritinib Changes AML Landscape

Naveed Saleh, MD, MS, Clinically reviewed by Mehmet Skitki Copur, MD, FACP

The recent US Food and Drug Administration (FDA) approval of gilteritinib (Xospata), in addition to final trial data from the phase 3 ADMIRAL trial, makes it the new standard of care for acute myeloid leukemia (AML).[1]

**FDA Approval**

On November 28, 2018, the FDA approved gilteritinib for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation per an FDA-approved test. Furthermore, the FDA approved an expanded indication for a companion diagnostic, which was included with the drug. The LeukoStrat CDx FLT3 Mutation Assay is employed to detect FLT3 mutations in AML patients. The approval of gilteritinib was based on an interim analysis of the phase 3 ADMIRAL trial.[2]

**Final Results of the ADMIRAL Trial**

In patients with FLT3 mutation-positive relapsed/refractory acute myeloid leukemia (AML), the potent, selective FLT3 inhibitor gilteritinib yielded significantly longer overall survival (OS), according to study findings presented at the American Association of Cancer Research 2019 Annual Meeting. Gilteritinib also yielded higher response rates vs chemotherapy and was safe.[3]

“These results change the treatment paradigm for salvage therapy of relapsed/refractory FLT3mut+ AML and establish gilteritinib as the new standard of care,” wrote authors led by Alexander E. Perl, MD, a member of the leukemia program in the Abramson Cancer Center and an associate professor in the Division of Hematology/Oncology at the Perelman School of Medicine at the University of Pennsylvania.

In the study, adults with confirmed FLT3 mutation-positive relapsed/refractory AML (FLT3-ITD and/or FLT3-TKD D835/I836 mutations) refractory to induction chemotherapy or in untreated first relapse were randomized (2:1) to receive continuous 28-day cycles of 120 mg/d gilteritinib or prerandomization selected salvage chemotherapy, including low-dose cytarabine, azacitidine, mitoxantrone/etoposide/cytarabine, or fludarabine/cytarabine/ granulocyte colony-stimulating factor/idarubicin.

Perl et al excluded previous FLT3 inhibitor use with the exception of midostaurin or sorafenib. Primary outcomes were OS and the combined rate of complete remission/complete remission with partial hematologic recovery (CR/CRh).

In total, 371 patients (39.4% refractory AML; 60.6% relapsed AML) were included, with 247 on gilteritinib and 124 on salvage chemotherapy. Patients in the experimental group had significantly longer OS (9.3 months) vs salvage chemotherapy (5.6 months; hazard ratio for death, 0.637; \( P \) = .0007). Furthermore, 1-year survival rates were 37.1% in the gilteritinib group vs 16.7% in the
He also noted that testing for FLT3 mutations should become standard for all patients with relapsed/refractory AML.

In an interview with *Cancer Discovery*, Ross Levine, MD, an oncologist at Memorial Sloan Kettering Cancer Center in New York, gave his take on the study: “Gilteritinib went up against investigator/patient’s choice—which included many patients receiving intensive chemotherapy—in the second line and won on all fronts: survival, response rate, toxicity. I think these data and the approval establish this as the treatment of choice for FLT3-mutant AML in the relapsed/refractory setting.”[1]

**More About the Drug**

According to the manufacturer, gilteritinib is a kinase inhibitor used to treat adult patients who have relapsed or refractory AML along with a FLT3 mutation as detected via an FDA-approved test. Dosage for the drug is 120 mg orally once daily, and it comes in 40-mg tablets.[4]

Gilteritinib is a pyrazinecarboxamide derivative that has demonstrated potency, selectivity, and activity against both FLT3-ITD and FLT3-TKD mutations. Gilteritinib also inhibits EML4-ALK and AXL, which is an oncogenic receptor tyrosine kinase believed to play a role in the maintenance of constitutive FLT3-ITD phosphorylation. The activation of AXL has been suggested as a mechanism of secondary resistance to FLT3 inhibitors.

Notably, in vivo models have demonstrated that AXL inhibition diminishes FLT3 phosphorylation and permits myeloid differentiation in FLT3-AML cell lines. In the phase I/II CHRYSALIS trial, investigators studied gilteritinib in patients with relapsed/refractory AML and reported potent FLT3 inhibition with doses 80 mg or more. Antileukemic activity was exhibited regardless of prior tyrosine kinase inhibitor treatment.

During clinical trials, unique adverse effects have been observed including a dose-dependent prolongation of the QTc interval, elevation in creatine kinase, and elevations in liver transaminases. Moreover, a handful of posterior reversible encephalopathy syndrome cases have transpired.

In FLT3-positive patients receiving gilteritinib—including those who were heavily pretreated—administration of the drug led to an OS of about 31 weeks. The single-agent antileukemic activity of gilteritinib has even more potential in patients with FLT3 mutations, according to experts, including those acquired at the FLT3-D835 tyrosine kinase domain.[5]

In clinical trials, the most common adverse reactions (≥ 20%) were myalgia/arthritis, transaminase increase, fatigue/malaise, fever, noninfectious diarrhea, dyspnea, edema, rash, pneumonia, nausea, stomatitis, cough, headache, hypotension, dizziness, and vomiting.

Med-med interactions for the drug occur with combined P-gp and strong CYP3A inducers. Additionally, it’s best to find alternative treatments to strong CYP3A inhibitors. Per the manufacturer, if the concomitant use of strong CYP3A inhibitors is absolutely necessary, patients should be checked more frequently for adverse reactions.

Certain warnings and precautions should be heeded when using gilteritinib. First, the drug should be discontinued in patients who develop posterior reversible encephalopathy syndrome. Second, with prolonged QT interval, drug dosage should be interrupted and reduced in patients who have a QTcF greater than 500 msec. Of note, it’s important to correct hypokalemia or hypomagnesemia prior to and during drug administration. Finally, the dose should also be interrupted and reduced in patients who develop pancreatitis[4]

**Financial Disclosure** Dr. Saleh and Dr. Copur 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/new-gilteritinib

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Atezolizumab is an immune-checkpoint inhibitor, which has been approved by the US Food and Drug Administration (FDA) in various combinations for a number of cancer types in recent years. Here is a closer look at atezolizumab and its expanding uses.

**History of FDA Approvals**

On March 18, 2019, the FDA approved the use of atezolizumab (Tecentriq) in combination with carboplatin and etoposide for first-line treatment of patients with extensive-stage small-cell lung cancer. Results were based on the IMpower133 trial (n = 403). Median overall survival was 12.3 months (10.8, 15.9) for patients receiving atezolizumab with chemotherapy as compared to 10.3 months (9.3, 11.3) for those receiving placebo with chemotherapy (hazard ratio [HR] 0.70; 95% CI, 0.54, 0.91; \( P = .0069 \)). Negative side effects reported in 20% or more of the patient sample included fatigue, nausea, alopecia, constipation, and decreased appetite.[1]

On March 8, 2019, the FDA granted atezolizumab accelerated approval in combination with paxlitaxel protein-bound for the treatment of patients with unresectable or metastatic triple-negative breast cancer with programmed death ligand 1 (PD-L1) tumors. The FDA also approved an accompanying diagnostic assay to identify patients with triple-negative breast cancer.[2]

On December 6, 2018, the FDA approved a new combination of atezolizumab for the treatment of metastatic nonsquamous, non–small-cell lung cancer (NSCLC) that lacks epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) mutations. Specifically, this immune checkpoint inhibitor was approved in combination with a standard regimen of bevacizumab, paclitaxel, and carboplatin.[3]

Atezolizumab plus pembrolizumab and pemetrexed is also FDA approved as first-line treatment for patients with metastatic nonsquamous NSCLC whose tumors lack EGFR or ALK mutations. Importantly, patients with NSCLC without EGFR and ALK mutations—who harbor high PD-L1 levels—have another treatment option: pembrolizumab alone. It remains to be elucidated which option is better because the efficacies of both biologics have not been directly

**Atezolizumab and Its Many Uses**

Naveed Saleh, MD, MS | Clinically reviewed by Mehmet Sitki Copur, MD, FACP

The monoclonal antibody therapy and immunotherapy drug Atezolizumab blocks activity of programmed death ligand 1 (PDL-1).
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Mechanism of Action
Atezolizumab is a humanized monoclonal antibody immune checkpoint inhibitor that selectively binds to PD-L1 to stop the interaction between PD-1 and B7.1 (ie, CD80 receptors). The antibody still allows interaction between PD-L2 and PD-1.

Of note, PD-L1 is an immune checkpoint protein expressed on tumor cells and tumor infiltrating cells that down-regulates antitumor T-cell function by binding to PD-1 and B7.1. Blocking PD-1 and B7.1 interactions returns antitumor T-cell function.

Immune-Mediated Warnings and Precautions
As a biologic agent, atezolizumab can cause a number of immune-mediated complications.

Adrenal insufficiency has been reported with the drug both alone and in combination with other antineoplastic agents. The median time to onset was 5.7 months, and about 25% of patients experienced resolution. With grade 2 or higher adrenal insufficiency, the agent should be withheld and the patient given systemic steroids. Lower grades can be treated with steroids.

Ocular toxicity in the form of uveitis and iritis have been reported in the literature. If uveitis occurs in the presence of other immune-mediated adverse reactions, a Vogt-Koyanagi-Harada-like syndrome should be considered, which may require systemic corticosteroids to decrease the risk of permanent vision loss.

Finally, hypothyroidism, hyperthyroidism, and rarely, acute thyroiditis can arise secondary to the administration of atezolizumab. Thyroid function should be monitored during treatment, and thyroid replacement hormone should be given as needed. With grade 2 or higher hyperthyroidism, one should withhold the agent and administer antithyroid medications.

The most common adverse effect of atezolizumab is urinary tract infection.

Comparison to platinum-based chemotherapy in clinical trials to treat patients with metastatic urothelial cancer who have not received prior therapy and who have low expression of the protein programmed death ligand 1 (PD-L1).
Universal Genetic Testing for All Breast Cancer Patients

Mehmet Sitki Copur, MD, FACP

**ABSTRACT:** Women with pathogenic BRCA1/2 mutations are more likely to develop breast cancer than are women without the mutation and they typically develop cancer at an earlier age. If women are aware of their BRCA1/2 status, however, they can make timely decisions about preventive measures such as chemoprevention with hormonal agents or undergoing prophylactic surgery, all of which have been shown to reduce the risk of cancer and overall mortality. The US Preventive Services Task Force and the National Comprehensive Cancer Network have recommended that women with a family history of breast, ovarian, and certain other cancers consider BRCA1/2 testing. Discovery of additional genes that increase breast cancer risk, coupled with the gradually decreasing cost of performing these tests, has led to the utilization of multigene panels over individual gene testing. Multigene panel testing for hereditary cancer may detect additional mutations that might possibly alter clinical management. Accuracy of current guidelines for genetic testing of breast cancer patients has become a topic of debate due to two studies suggesting these guidelines may miss half the patients with pathogenic variants or genetic mutations. Although the cost of genetic screening has dropped in recent years, there are other costs associated with population screening, including genetic counseling. There is also a lack of evidence in terms of proper procedures and risk management strategies following multigene panel testing, especially when mutations are found in moderate penetrance genes with a high percentage of Variants of Unknown Significance VUS and, if a mutation is discovered regarding the most accurate type of medical care. Universal genetic testing in women with newly diagnosed breast cancer has been proposed by some, stirring up strong views on both sides of the issue.

**Introduction**

Traditionally, healthcare structure has been directed predominantly toward treatment rather than prevention. Advances in genomic medicine offer the opportunity to deliver a new population-based predictive, preventive, personalized, and participatory medicine strategy. Prevention is the key to achieving long-term transformational change and cost effectiveness in cancer care. Approximately 266,120 women are diagnosed with breast cancer every year in the United States. An estimated 5% to 10% of these cancers are likely due to hereditary causes. Individuals with a personal or family history of breast cancer may benefit from genetic evaluation to determine their own and family members’ risk for these and associated cancers. Expertise is required to ensure that genetic testing will be performed on an appropriate population of patients, adequately interpreted, and that results are likely to aid in diagnosis or influence management of the patient or family members at risk for hereditary cancer. The complexity involved in risk assessment underscores the importance of genetic counseling both before and after testing. Guidelines from the American College of Medical Genetics and Genomics (ACMG), the National Society of Genetic Counselors, and the National Comprehensive Cancer Network (NCCN) provide detailed criteria for identifying candidates for genetic counseling and possible testing for hereditary breast cancer. Accuracy of current guidelines for genetic testing of breast cancer patients has been recently challenged by a pair of studies suggesting that these guidelines may miss as many patients with pathogenic variants or genetic mutations. Although the cost of genetic screening has dropped in recent years, there are other costs associated with population screening, including genetic counseling. There is also a lack of evidence in terms of proper procedures and risk management strategies following multigene panel testing, especially when mutations are found in moderate penetrance genes with a high percentage of Variants of Unknown Significance VUS and, if a mutation is discovered regarding the most accurate type of medical care. Universal genetic testing in women with newly diagnosed breast cancer has been proposed by some, stirring up strong views on both sides of the issue.
genetic variants (or genetic mutations) as they may catch. This has led to a call for universal genetic testing in women with newly diagnosed breast cancer, stirring up strong views on both sides of the issue. In one of these two studies, test results from an 80-gene panel in 959 breast cancer patients found no statistically significant difference in the number of pathogenic mutations among breast cancer patients who met the NCCN testing guidelines and those who did not.[8] The other study which involved 4,196 Medicare patients showed that the rate of pathogenic variants for hereditary breast and ovarian cancer patients were similar among patients who qualified for testing under Medicare guidelines and those who did not.[9]

**Background**

Traditionally, breast cancer prevention has been targeted at high-risk individuals such as *BRCA1/BRCA2* mutation carriers. At-risk mutation carriers have been offered MRI and mammography screening, risk-reducing mastectomy, or chemoprevention with hormonal agents.[10,11] Identification of mutation carriers (eg, *BRCA1/BRCA2*) at high risk of breast cancer has involved genetic testing of affected individuals or those from high-risk families in specialized genetics clinics. Clinical-criteria and family-history–based testing have been only moderately effective at identifying mutations, missing more than 50% of affected carriers.[12] Among the newer moderate-risk breast cancer genes, *PALB2* has been shown to grant nonsyndromic quasi-Mendelian susceptibility to disease, for which risk reducing mastectomy or breast MRI has been offered.[13] The mutations of *ATM* and *CHEK2* have lower moderate risks that do not justify risk-reducing mastectomy. Testing for these, though commercially available, is currently not routinely undertaken in clinical practice. [14,15] Manchanda et al addressed the issue of cost effectiveness of a population-based strategy for testing moderate- to high-penetrance ovarian and breast cancer gene mutations in the general population. In their analysis of population–based *BRCA1/BRCA2/RAD51C/RAD51D/BRIP1/PALB2* testing was also found to be more cost effective than *BRCA1/BRCA2* testing alone.[16]

Discovery of additional genes that increase breast cancer risk, coupled with the gradually decreasing cost of these tests, has led to utilization of multigene panel testing over individual gene testing. Multigene panel testing for hereditary cancer may detect additional mutations that might possibly alter clinical management. ACMG and the Association for Molecular Pathology (AMP) recommend categorizing gene variants into five risk levels: pathogenic, likely pathogenic, variant of uncertain significance (VUS), likely benign, and benign. They recommend that VUS should not be used in clinical decision making and, whenever possible, other evidence of disease should be part of a diagnosis.[17] For example, a gene variant deemed “likely pathogenic” might call for additional scans or blood tests to identify specific anomalies. The five categories apply to single-gene diseases like cystic fibrosis and sickle cell disease, but also to cancer risk genes like *BRCA1* and *BRCA2*.

NCCN guidelines recommend germline testing for patients with breast cancer on the basis of age, triple-negative disease, family history, and Ashkenazi Jewish ancestry supported by population-prevalence data.[7] However, research during the past decade has revealed a significant proportion of patients with preventable inherited breast cancer in diverse patient populations. In the United States, fewer than 1 in 5 (an estimated 1.3 million) women with a personal history of breast or ovarian cancer, meeting 2017 NCCN clinical practice criteria for genetic testing, have not been tested for an

As few as **25%** of women with breast cancer undergo testing for known harmful variants in breast cancer susceptibility genes.

inherited susceptibility to cancer.[18] The findings of a recent study on multigene panel testing in a total of 959 patients with breast cancer who did and who did not meet NCCN clinical practice guideline criteria reported similar rates (9.39% vs 7.9%, respectively) of pathogenic/likely pathogenic variants along with a very high (54%) percentage of VUS.[8] Another study reported similar rates of pathogenic variants for hereditary breast and ovarian cancer patients who qualified for testing under Medicare guidelines and those who did not.[9]

Should All Patients With Breast Cancer Be Offered Expanded Panel Testing?
The lowered costs of genomic testing with coverage not infrequently available through health insurance may help facilitate expansion of rather restrictive guideline-based criteria. Removing barriers to testing may increase provider discussions and referrals, reducing the barriers associated with testing.[19] Expanding guidelines may improve support for better management of at-risk populations and their reach to cancer genetic services. Ambiguity of results on moderate penetrance genes and VUS may be alleviated by expanded use of multigene panel testing in diverse populations. Wholesale adoption of universal multigene panel testing in all women diagnosed with breast cancer may help identify many more patients harboring pathogenic variants, which is important for the patients and their families.

Universal multigene panel testing in breast cancer, however, has several limitations. Commercially available tests differ significantly on the number of genes analyzed, turnaround time, insurance coverage, and variant reclassification protocols.[20] Such testing may miss genes that could have been detected with a single-gene analysis test.[21] Mutations identified for more than one gene may complicate risk management recommendations.[22] There is lack of evidence regarding proper procedures and risk management strategies following the testing, especially when mutations are found in moderate penetrance genes with a high percentage of VUS.[23] For example, pathogenic variations in BARD1 are associated with a possible increase in breast cancer risk; however, there is no evidence to support enhanced screening, surveillance, or risk reduction measures. Similarly, pathogenic variants in ATM are associated with an increased risk of breast cancer, but there is insufficient evidence to support risk-reducing breast surgery or bilateral salpingo-oophorectomy.[24] To make matters worse, there are documented discrepancies among laboratories, bringing concerns to the quality of these tests. Testing of more genes also leads to increased detection of VUS. These variants present challenges for both patients and medical providers. It becomes even more complicated in racial and ethnic groups in which such variants are both more common and more poorly characterized. Moreover, before ordering these tests, there must be pretest and post-test counseling by a trained professional genetic counselor. There is already a huge shortage of genetic counselors with the demand to supply ratio expected not to reach equilibrium until 2030.[25] Efforts to Lay the Groundwork for Genetic Screening in Breast Cancer Recent guidelines put forth jointly by the ACMG and AMP have advanced the field, but the degree of subjectivity allowed by these guidelines can still lead to inconsistent classification across clinical molecular genetic laboratories.[17] Concerted efforts, such as those undertaken by the ClinGen [Clinical Genome Resource] Sequence Variant Inter-Laboratory Discrepancy Resolution Working Group are being made to eliminate unwarranted variation in the characterization and reporting of pathogenic/likely pathogenic variants across laboratories and to harmonize the characterization and reporting of variants.[26] Attempts at data sharing through the ClinVar repository offer a unique opportunity to identify interpretation differences among laboratories by providing open access to variant classifications shared from many laboratories.
Clinical laboratories were encouraged to reassess outlier classifications of variants with medically significant differences. These tasks will improve the care of patients with, or at risk for, genetic disorders by providing more consistent variant classifications. Shortage of high-quality genetic counseling on multi-gene panel testing, inequities in access to testing, and the costs of testing to patients and society are being tried to be addressed by using alternative delivery service models such as telemedicine or by training other providers in the field.

Conclusion
Universal multigene panel testing of all women who are diagnosed with breast cancer is not ready for prime time. Pathogenic variations in several moderate penetrance genes without established cancer risk reduction guidelines create more questions (and anxiety) than answers. Many health insurance carriers are requiring a genetic counselor visit before approving payment for genetic testing. Not infrequently, this requirement leads to the cancellation of an ordered genetic test. While Medicare covers BRCA1/2 testing, Medicaid coverage for genetic testing varies by state and 15 states did not cover testing as of January 2018.

Cost barriers to the receipt of genetic testing and counseling cannot be ignored when considering expanding testing to all patients with breast cancer. The current cost of testing ranges from approximately $300 to $5,000, depending on the extent of genes involved. Given the estimated 266,120 new female breast cancer cases per year in the United States, if all women with breast cancer could undergo genetic testing, total charges would range from a low of $80,000,000 to a high of $1,330,600,000. This estimate does not include the cost of pretest and post-test genetic counseling. The value of ordering universal multigene panel testing of all women who are diagnosed with breast cancer should be balanced against the barriers and ambiguity about the interpretation of these results. Priority should be given to improving the frequency of testing in patients who do meet the criteria, improving the quality of multigene sequencing with better-defined test results, and increasing the availability of genetic counselors.

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Dr. Copur is a Medical Oncologist/Hematologist in the Hematology Oncology Department at the Morrison Cancer Center, Mary Lanning Healthcare, in Hastings, Nebraska, and is an Adjunct Professor at the University of Nebraska in Omaha. He is also Editor-At-Large with ONCOLOGY.
a reduced leukocyte telomere length may identify individuals at high risk for papillary thyroid cancer.

**Q:** Finally, in the context of monitoring recurrence, could you briefly highlight advances as far as treatment and diagnosis? What are the prospects for patients who are treated for thyroid cancer?

**DR. PEIRIS:** This discussion has focused mainly on differentiated thyroid cancers, which are basically papillary and follicular variants. I should point out that there are some very aggressive types such as anaplastic thyroid cancers in which the patient is usually dead within 6 months. My comments don’t relate to that type of cancer. There is a saying in endocrinology that if you have to have cancer, have a skin cancer or a differentiated thyroid cancer because many of these patients live a full and unrestricted life span. Differentiated thyroid cancer has a very, very good outlook. Patients can be treated with surgery, radioactive iodine, and very rarely, with external radiation. A new series of drugs is coming out called tyrosine kinase inhibitors. And researchers are working on newer drugs that may help. The traditional standby has been surgery and radioactive iodine and, as I alluded to previously, there’s a consensus that maybe too much therapy was given in the past and we didn’t need to be as aggressive as we were in managing early, limited papillary thyroid cancer. A lot of my patients have a normal life span and they do really very well.

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