GI Cancer
Locally Advanced Rectal Cancer, What is the Standard of Care? Mehmet Sitki Copur, MD, FACP, Whitney Wedel MD, Pornchai Jonglertham MD, Thomas Zusag MD, Adam Horn

Lung Cancer
A Patient with Newly Diagnosed Advanced **EGFR** Mutated Non-Small Cell Lung Cancer
Luis Lara-Mejía, MD; Roberto Sánchez-Reyes, MD; Alejandro Avilés-Salas, MD; Oscar Arrieta-Rodríguez, MD

Hematologic Malignancies
**CAR T-Cell Therapy Shows Promise**
Kristie L. Kahl

Breast Cancer
**The Impact of PI3K Inhibitors for the Treatment of Patients with Breast Cancer**
Tiffany A. Traina, MD

GU Cancer
**FDA Approves First Agent to Treat Locally Advanced, Metastatic Urothelial Cancer**
Kristie L. Kahl
A diagnosis of prostate cancer was life-changing news for over 170,000 people per year.

Cutting edge treatments that are noninvasive so he can enjoy a life-changing trip around the world.
IN THIS ISSUE

12 IMMUNOTHERAPY: Cover
Finding the Next Line of Treatment in Melanoma
Jeffrey Weber, MD
ONCOLOGY recently sat down with the NYU Langone Health expert on the highs and lows of discovering new treatment options for patients with melanoma.

7 Sarcoma: Review
Location, Location, Location: Approaches to Retroperitoneal Vascular Leiomyosarcoma
Jason T. Wiseman, MD, MSPH, and Valerie Grignol, MD
Experts describe the approach to treating leiomyosarcoma, one of the most common soft tissue sarcomas.

11 GU CANCER: New Drug Approval
FDA Approves First Agent to Treat Locally Advanced, Metastatic Urothelial Cancer
Kristie L. Kahl

Table of Contents continued on page 4

Visit CancerNetwork.com, home of the journal ONCOLOGY and a web destination for oncolgists seeking expert peer perspectives, podcasts, and other clinically practical features.

FEATURED VIDEO
Megan Kruse, MD, Discusses the Use of Biosimilars in Breast Cancer Treatment

cancernetwork.com/Kruse

NEWS
Cancer Mortality Rates Decline Suggesting Notable Gains in Common Cancer Types

cancernetwork.com/ACS-Update-2020

GUIDELINES
NCCN Publishes Updated Genetic Risk Assessment Recommendations

cancernetwork.com/Genetic-Risk-Assessment
GI CANCER: Case Study
16 Locally Advanced Rectal Cancer, what is the standard of Care?
Mehmet Sitki Copur, MD, FACP, Whitney Wedel MD, Pornchai Jonglertham MD, Thomas Zusag MD, Adam Horn

A medical oncologist/hematologist discusses the case of a 39-year-old man with locally advanced rectal cancer.

LUNG CANCER: Clinical Quandary
21 A patient with Newly Diagnosed Advanced EGFR Mutated Non-Small Cell Lung Cancer
Luis Lara-Mejia, MD; Roberto Sanchez-Reyes, MD; Alejandro Aviles-Salas MD; Oscar Arrieta-Rodriguez MD

HEMATOLOGIC MALIGNANCIES: Medical Conference Review
20 CAR T-Cell Therapy Shows Promise
Kristie L. Kahl

BREAST CANCER: Continuing Medical Education
28 The Impact of PI3K Inhibitors for the Treatment of Patients with Breast Cancer
Tiffany A. Traina, MD

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<table>
<thead>
<tr>
<th><strong>Position</strong></th>
<th><strong>Name</strong></th>
<th><strong>City</strong></th>
<th><strong>State</strong></th>
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<tbody>
<tr>
<td><strong>BREAST CANCER</strong></td>
<td>Apar K. Ganti, MD, MS, FACP</td>
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<td><strong>COLORECTAL/GASTROINTESTINAL CANCER</strong></td>
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Dear Reader,

While the development of immunotherapy and targeted agents has advanced treatment options for a variety of malignancies, there is still the reminder that not all regimens work in treating cancer.

The melanoma field, in particular, has seen the ups and downs over the years. Earlier in the decade, oncologists felt the excitement of initial data being presented on drugs like nivolumab (Opdivo), pembrolizumab (Keytruda), and ipilimumab (Yervoy). However, in recent years, researchers have struggled while investigating combination therapies to treat the disease.

In this issue of ONCOLOGY, we spoke with Jeffrey Weber, MD, deputy director of the Perlmutter Cancer Center and the codirector of the Melanoma Research Program at NYU Langone Health, on these ups and downs in the field, and newer phase II and III studies in the pipeline. Moreover, the expert is hopeful and had one piece of advice for his peers: “Be open-minded and nimble and agile on your feet. And as soon as the data look really promising, adopt new ideas. Be open to new ideas, no question about it.”

Also in this issue, you will read of 2 patient scenarios: a 39-year-old male demonstrating symptoms of locally advanced rectal cancer and a 40-year-old woman with newly diagnosed, advanced EGFR-mutated non–small cell lung cancer. How do we treat them? Keep reading to find out. In addition, we feature a review article on approaches to retroperitoneal vascular leiomyosarcoma, one of the most common soft tissue sarcomas where location is key.

Within these pages, you will also find highlights from the 61st American Society of Hematology Annual Meeting & Exposition, and a breakdown of the FDA’s recent approval of enfortumab vedotin for the treatment of patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1/PD-L1 inhibitor and platinum-containing chemotherapy.

I hope you find our journal helpful in caring for your patients through what is likely one of the most challenging times in their lives. As always, thank you for reading.

- Mike Hennessy, Sr.
Chairman and Founder of ONC’s parent company, MJH Life Sciences
Location, Location, Location: Approaches to Retroperitoneal Vascular Leiomyosarcoma

Jason T. Wiseman, MD, MSPH, and Valerie Grignol, MD

ABSTRACT: Leiomyosarcoma, one of the most common soft tissue sarcomas, can occur anywhere in the body, but it is frequently found in the abdomen and retroperitoneum. When arising in the retroperitoneum, anatomic constraints can have a profound effect on treatment, particularly when these tumors abut or involve the inferior vena cava. Although there have been improvements in systemic and locoregional therapies for leiomyosarcomas, surgery remains the mainstay for management. Herein describes our approach to these tumors.

Introduction
Sarcomas are relatively rare malignant tumors that arise from mesenchymal cells and therefore encompass a variety of histologies and can occur in any anatomic compartment. The incidence of sarcoma is estimated at 1% of all new cancer diagnoses in the United States annually.1 Approximately 15% of soft tissue sarcomas occur in the retroperitoneum, with about 1600 new retroperitoneal sarcoma cases diagnosed in the United States each year.2

Leiomyosarcoma
Leiomyosarcomas, a subset of soft tissue sarcomas, are malignant smooth muscle neoplasms that account for approximately 5% to 10% of all sarcomas. Natural history is dependent on the anatomic location in which they arise. About 50% arise in the retroperitoneum/abdomen and these include visceral, uterine, and retroperitoneal, with the uterus being the most common location. Given the frequent large size and location of these tumors, abdominal pain, nausea, vomiting, anorexia, weight loss, fatigue, and malaise are common presenting symptoms.3 At the time of diagnosis, leiomyosarcomas were likely present for a period of weeks to years. Incidence is most common during adulthood and in women, particularly when the tumor is located in the retroperitoneum.3,4 Grossly, they appear as firm, nodular masses with a scar-like consistency and usually have sharply demarcated borders. Histologically, they are ordinarily composed of spindled cells. Tumor grade is a significant prognostic factor, with higher tumor grade being associated with progression to both metastasis and death.4 Metastases are most common to the lungs and liver and develop in an estimated 50% of patients.

Leiomyosarcomas of the Inferior Vena Cava
Vascular leiomyosarcomas are derived from smooth muscle cells within the medial layer of blood vessels. These tumors more commonly occur within veins rather than arteries and most often originate from the inferior vena cava (IVC).6 Leiomyosarcomas originating from the IVC account for approximately 0.5% of soft tissue sarcomas; about 300 of these tumors have been reported in this location in the literature.6 As with leiomyosarcoma in general, leiomyosarcoma of the IVC typically manifests during middle adulthood, predominantly in women.

Patient symptoms vary with the location of the tumor in the IVC. Leiomyosarcomas arising in the middle portion of the IVC (ie, infrahepatic, suprarenal) are the most frequent at about 40%, and symptoms may include a palpable abdominal mass, abdominal or visceral pain, and bilateral lower extremity edema. High suspicion is warranted for tumor extension with associated partial or complete thrombosis of the renal vein(s) in patients with renal dysfunction. Leiomyosarcomas involving the lower portion of the IVC (ie, infrarenal) are the second most common in frequency at approximately 30%. Patients present with similar symptoms of an abdominal mass and lower extremity edema, but they may also have flank pain. Patients with leiomyosarcoma of the superior portion of the...
the IVC (ie, suprahepatic), which has an estimated frequency of 25%, can present with symptoms of the Budd-Chiari syndrome such as jaundice, ascites, and hepatomegaly.

Vascular IVC leiomyosarcomas are relatively slow-growing tumors that are typically attached to the wall of the vena cava and exhibit extraluminal growth. Some will project into the vessel lumen, which may ultimately cause vascular thrombosis. Intraluminal tumor thrombi may course along the IVC and extend into the renal veins, hepatic veins, or even extend cephalad to the level of the right atrium. These tumors may also extend outward into the retroperitoneum and involve surrounding structures. Given that many of these tumors have a delayed presentation due to the vagueness of symptoms, they have a wide range in size at diagnosis, with reported cases ranging from 2 to 30 cm and an average size of approximately 10 cm.6

Diagnosis

For imaging, a contrast-enhanced computed tomography (CT) scan of the abdomen and pelvis is preferred to evaluate the primary disease site as and a chest CT to evaluate the presence of metastatic disease to the lungs. CT is advantageous over magnetic resonance imaging (MRI) for the following reasons: it better defines the relationship of the primary tumor to surrounding structures; it can evaluate for the presence of peritoneal or liver metastasis; and most importantly, it provides the appearance of the primary tumor which may suggest histologic subtype and grade. Often a CT or MRI venogram is obtained in addition to standard studies to define the anatomic detail of the tumor for surgical planning. The anatomic structures that are evaluated in particular with this imaging modality are those intimately involved with the IVC, including the aorta, iliac veins, the renal hilum, pedicle, ureter, and other immediately adjacent structures. To evaluate perihepatic structures, an MRI with liver protocol can be a useful adjunct, particularly when tumors involve the retrohepatic IVC. This modality is useful to evaluate the extent of liver and hepatic vein involvement. The role for positron emission tomography with fluorodeoxyglucose in the initial staging evaluation is not clearly established; however, and we do not routinely recommend its use.

Although imaging can be highly suggestive of certain diagnoses, imaging features alone are not adequate to determine histology.7 As the majority of IVC leiomyosarcomas are exophytic, image-guided needle biopsy is safe and should be performed to ascertain diagnosis. Additionally, the information gained can assist in determining multimodal treatment planning and allow for consideration of neoadjuvant therapies and clinical trials. A fear of tumor seeding via core biopsy is unsubstantiated.8

Treatment

To date, the majority of knowledge in treating IVC leiomyosarcoma has come from case reports and case series. Surgical resection offers the best chance at long-term survival and potential for cure.9 Remarkably, 5-year disease-free survival in patients who underwent resection was between 30% and 60%; however, in those who did not undergo surgery, survival was often less than 1 year.6,10,12 Even after surgical resection, recurrence is rather common. Given this and the poor prognosis associated with recurrence, traditional adjuvant chemotherapies are often employed. The efficacy of such chemotherapies, however, has never been shown to definitively lengthen survival. No clear benefit has been established with radiation therapy, although current research is investigating its utilization.14 Nevertheless, even with systemic and locoregional therapy being studied in the adjuvant setting, we tend to favor neoadjuvant chemotherapy with or without preoperative radiation therapy because the risk of metastatic disease is relatively high. This decision is best made by a multidisciplinary tumor board that can consider grade, size, and extent of surgery. We do not recommend adjuvant chemotherapy outside the setting of a clinical trial. To that end, if available, we suggest participation in ongoing clinical trials.

Determining resectability largely depends on the extension of the tumor and what surrounding structures it involves. Classically, findings from imaging that generally deem the tumor unresectable include: diffuse peritoneal implants or distant metastases not able to be completely resected, spinal cord involvement, bilateral renal involvement requiring bilateral nephrectomies, extensive liver hilum involvement, and envelopment of the mesenteric root. A relative contraindication is vascular involvement, because reconstructive options vary given tumor location and tissue involvement.15 Liberal en
bloc resection of adjacent viscera, however, may allow a subset of patients, who might otherwise have been considered unresectable, to achieve wide, macroscopically negative surgical margins.

**Operative Approach**

When proceeding with operative planning, the primary oncologic goal is to obtain a microscopically negative margin (R0) resection. Given the location and sometimes large size of the tumor, it is difficult, if not impossible to obtain wide margins. As the size of IVC leiomyosarcomas can be significant, en bloc resection of surrounding structures may be required to clear all disease. Organs frequently involved include the right kidney, colon, liver, and aorta. Remarkably, several case series have reported relatively low perioperative death rates after surgery for leiomyosarcoma, ranging from 0% to 20%.6,10-15 Leiomyosarcomas can be significant, en bloc resection of adjacent viscera, however, may allow a subset of patients, who might otherwise have been considered unresectable, to achieve wide, macroscopically negative surgical margins.

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When proceeding with operative planning, the primary oncologic goal is to obtain a microscopically negative margin (R0) resection. Given the location and sometimes large size of the tumor, it is difficult, if not impossible to obtain wide margins. As the size of IVC leiomyosarcomas can be significant, en bloc resection of surrounding structures may be required to clear all disease. Organs frequently involved include the right kidney, colon, liver, and aorta. Remarkably, several case series have reported relatively low perioperative death rates after surgery for leiomyosarcoma, ranging from 0% to 20%.6,10-15 Leiomyosarcomas can be significant, en bloc resection of adjacent viscera, however, may allow a subset of patients, who might otherwise have been considered unresectable, to achieve wide, macroscopically negative surgical margins.

The IVC leiomyosarcoma may originate from a narrow pedicle of the IVC allowing primary closure or vein patch for reconstruction. Small segments may be closed primarily or can be patched with a vein patch such as a saphenous or internal jugular vein. Alternatively, the leiomyosarcoma may be firmly attached to a broad section of the IVC, requiring segmental resection and ligation or prosthetic graft interposition of the IVC, depending on the patency of the IVC. Below the renal veins, the vena cava is often amenable to ligation because many patients with IVC leiomyosarcoma have developed extensive venous collaterals. Preoperative CT imaging may be able to suggest the amount of collateralization. Ligation can typically be performed after tumor excision in the setting of preoperative IVC occlusion for the same reason. If flow is present preoperatively, however, IVC repair should be attempted.16-20 Larger segments, whether circumferential or longitudinally oriented, will require IVC reconstruction with a prosthetic tube graft material such as polytetrafluoroethylene. The size of the graft will vary depending on the native IVC, but the most common graft size typically ranges from 16 to 22 mm. Cadaveric tissue and autologous tissue grafting from a variety of donor sites are also possible conduits and may offer advantages if the surgical site is contaminated, as when enteric resection is necessary.18-20

The operative approach depends on which segment of the IVC is affected. The IVC can be divided into 3 segments as described previously: the lower segment (below the renal veins to the origin of the IVC), middle segment (below the hepatic veins to the renal veins), and the upper segment (from the right atrium to the hepatic veins). In middle and lower segment tumors, superior control of the IVC is achieved by mobilizing the right lobe of the liver or via an anterior approach by transecting the caudate lobe. The renal vessels are medically isolated and preserved. In preparation for a segmental IVC resection, the anesthesia team is alerted and the IVC superior to the tumor is clamped to check for hemodynamic response. If the patient tolerates this, the segmental IVC resection can proceed. If the right kidney is being resected, the right renal artery can be divided. The left renal vein should be divided proximal to the left gonadal vein to preserve drainage, but if only 1 kidney is to remain, an interposition graft of the renal vein to the IVC should be considered to preserve optimal function. This can similarly be considered for preservation of 1 or both kidneys if the tumor extends to the os of the vein but does not involve a significant length of vein. Autotransplantation of a kidney can also be utilized to preserve renal function and render a tumor resectable.

IVC leiomyosarcoma in the middle segment extending to the upper segment may require hepatic resection when the tumor involves retrohepatic caval tumors. Techniques often employed include total hepatic vascular exclusion and venovenous bypass.6,21 Total hepatic vascular occlusion can be performed by first creating a plane between the liver and diaphragm. Isolation of the IVC superior to the liver can be done at the junction of the hepatic veins and IVC or via a transdiaphragmatic pericardial window to isolate and loop the infrapercardial IVC. A Pringle maneuver is employed around the hepatoduodenal ligament containing the portal triad. The infrahepatic IVC is also isolated and looped. Total hepatic vascular occlusion can be
completed by clamping of the portal triad, suprahepatic IVC, and infrahepatic IVC.22 The retrohepatic IVC can then be exposed by a liver hanging technique, which allows the IVC to be exposed without complete mobilization of the right liver. This technique consists of lifting the liver during parenchymal transection by an umbilical tape or similar material passed between the anterior surface of the IVC and the posterior surface of the liver. Parenchymal dissection along this plane can proceed in a relatively safe fashion due to the presence of longitudinal avascular compartment guided by the tape.23 Venovenous bypass involves the extracorporeal circulation of blood from the venous system below the IVC isolation clamps (ie, the inferior mesenteric vein and femoral veins) with return to the central veins (ie, the axillary or internal jugular veins). Upper segment tumors may require cardiopulmonary bypass and circulatory arrest.

An example of the extent of dissection and collateral resection needed for extensive IVC leiomyosarcoma tumors in difficult locations is exemplified by the tumor shown in Figure 1. This IVC leiomyosarcoma tumor extended from immediately beneath the hepatic veins along the retrohepatic IVC to the level of the renal veins, involving the left lobe of the liver, caudate lobe, and the right renal vein. After receiving neoadjuvant chemotherapy that led to a decrease in the size of the tumor, this patient underwent exploratory laparotomy, left hepatectomy, right nephrectomy, and resection of the involved IVC with reconstruction using a synthetic interposition graft. The liver hanging technique was utilized to expose the retrohepatic IVC. Preparations for venovenous bypass were made preoperatively by placing appropriate cannulas after the induction of anesthesia; however, it was not necessary to utilize the circuit as there was an adequate cuff of IVC below the hepatic veins for reconstruction. The surgical specimen and the reconstruction are depicted in Figure 2 and Figure 3, respectively. This procedure required collaboration from a surgical team including sarcoma, hepatobiliary, and vascular surgeons.

Conclusions
Leiomyosarcomas of the IVC overall have a more indolent course than other locations of this histology. Many of the usual predictors of prognosis such as size and grade may not apply because the anatomic constraints of location determine surgical resectability, the mainstay of treatment. Careful preoperative planning with imaging and preparation for reconstruction with a surgical team of experts is required. This often requires a multispecialty team of surgeons including those in surgical oncology, vascular surgery, urology, and transplant.

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FIVE KEY REFERENCES

For full reference list, visit cancnetwork.com/ Leiomyosarcoma

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FDA Approves First Agent to Treat Locally Advanced, Metastatic Urothelial Cancer

Kristie L. Kahl

The FDA approved enfortumab vedotin-ejfv (Padcev)—the first drug to treat adult patients with locally advanced or metastatic urothelial cancer who have received prior treatment with a programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy.1,2

“Typically, for this patient population, there really was not anything that was active (in treating patients), and what we have seen is about 12% of patients have a complete tumor disappearance. Overall, about 40% of patients have what is called a partial response and 84% of patients have some form of tumor reduction,” explained Dr Daniel Petrylak, professor of medicine, medical oncology and urology, and co-leader of Cancer Signaling Networks, at Yale Cancer Center. “So, this is really a remarkable finding. To my knowledge, this is the most active single agent (in treating advanced bladder cancer). It is even more active than drugs they have been using in the earlier setting.”

EV-201 Trial
The FDA based its decision on data from the multicenter, single-arm, phase II pivotal EV-201 trial. This study was designed to evaluate enfortumab vedotin in 125 patients with locally advanced or metastatic urothelial cancer who received prior treatment with a PD-1 or PD-L1 inhibitor, including those who were previously treated with platinum-containing chemotherapy (cohort 1) and those who have not received platinum-containing chemotherapy and are ineligible for cisplatin (cohort 2). A total 128 patients were enrolled at multiple centers internationally for cohort 1, in which enfortumab vedotin was given at 1.25 mg/kg intravenously on days 1, 8, and 15 of each 28-day cycle.

The primary end point was confirmed overall response rate (ORR) per blinded independent central review, while secondary end points included duration of response (DOR), disease control rate, progression-free survival (PFS), overall survival (OS), safety, and tolerability. Patients are continuing to be enrolled in cohort 2.

Enfortumab vedotin elicited an overall response rate (ORR) of 44% in patients with locally advanced or metastatic urothelial cancer, which included a 12% complete response rate, and a 32% partial response rate. Additional results showed that the OS was 11.7 months (95% CI, 9.1-not reached), the median PFS was 5.8 months (95% CI, 4.9-7.5), and the median DOR was 7.6 months (range, 0.95-11.30). Responses were observed across all subgroups, irrespective of response to prior PD-1/PD-L1 inhibitors or presence of liver metastases (ORR, 38%; 95% CI, 24.7%-52.8%). The median time to response was 1.8 months (range, 1.2-9.2), with 44% of responses ongoing.

Regarding safety, the most common treatment-related adverse events (TRAEs) of any grade were fatigue (50%), alopecia (49%), and decreased appetite (44%), while TRAEs of interest included any case of rash (all grades, 48%; grade ≥3, 12%), any peripheral neuropathy (all grades, 30%; grade ≥3, 3%), and any hyperglycemia (all grades, 11%; grade ≥3, 6%).

Accelerated Approval
The first-in-class antibody-drug conjugate, which is directed against nectin-4, a protein located on the surface of cells and highly expressed in bladder cancer, is approved under the FDA’s Accelerated Approval Program. In this instance, the accelerated approval was based on tumor response rate, the study’s primary end point.

Continued approval of enfortumab vedotin will be contingent upon further evaluation to verify and describe the clinical benefit of the drug in a confirmatory trial. “There are a lot of next steps. This is an exciting drug, and it has a tremendous amount of activity,” Petrylak said. “We are looking to move this up earlier, in the course of disease. There is a trial being done in patients who have had frontline chemotherapy, and we are looking to [add enfortumab vedotin] in the neoadjuvant setting prior to [a patient] having their bladder taken out. And so the thought is that perhaps we will have more activity earlier.” Petrylak added that researchers are also looking to add the agent to other combinations, like checkpoint inhibitors.

For references visit cancernetwork.com/Enfortumab-Approval
Jeffrey Weber, MD

Finding the Next Line of Treatment in Melanoma

Seven years of famine and 7 years of feast in melanoma breakthroughs

For those with early-stage melanoma, surgery may be the only treatment needed. However, when melanoma has spread beyond the skin, additional treatments before or after surgery may be necessary. Multiple lines of therapy are also considered.

With the development of immunotherapy and targeted agents, the treatment landscape for melanoma has changed immensely over the years. ONCOLOGY recently sat down Jeffrey Weber, MD, to discuss the successes and failures in developing new treatments for patients, whether they be alone or in combination, to ultimately prevent relapse. Although there have been many highs and lows, Weber is enthusiastic as to what is to come in the future.

Q: What are the major trends in melanoma treatment right now?

DR. WEBER: Well, the field is obviously moving to detecting the optimal combination. The late 2000s to 2013 saw a whole variety of trials evaluating nivolumab (Opdivo), pembrolizumab (Keytruda), ipilimumab (Yervoy) plus nivolumab, and ipilimumab plus pembrolizumab, and in 2013 it was an absolute big deal because all the initial data that were presented sparked a lot of excitement. Then by 2014 to 2015, those drugs were all approved and they were used in the adjuvant setting. What is happening now is people are interested in neoadjuvant approaches which is not a new drug development issue, it is just how we reuse old drugs.

Looking at new combinations, the first of the new combination trials was Incyte’s indoleamine 2,3-dioxygenase (IDO) inhibitor plus pembrolizumab, that was a complete bust. That was a little worrisome, but then there were 6 or 7 large phase III trials that came in the next year, like the MASTERKEY-265 trial and the trial evaluating an anti-lymphocyte-activation gene 3 (LAG-3) monoclonal antibody and nivolumab. There are also trials evaluating SD-101, CMP-001, and ipilimumab plus IMO-2125, so we have all these trials of mostly programmed cell death protein 1 (PD-1) blockades but at least 1 ipilimumab phase III trial that will be complete and the data will mature in the next year and a half. And we hope that at least some of them will be positive.

My concern is [that] a lot of them were embarked upon without adequate randomization, without an adequate phase II randomized experience, so there is a risk and the risk is that these may not be positive trials. And that is going to hurt the field. For example, the IMO-2125 trial, I believe, was a phase III trial embarked upon with having treated 26 patients. That is a very aggressive drug development pathway.

But everything that is happening is about combinations and what will the best combination be—a direct injection of the toll-like receptor (TLR) agonist? Is it going to be anti–LAG-3? Is it going to be anti–mucin domain-containing protein 3 (TIM-3)? Is it going to be a new checkpoint inhibitor? Nobody knows, and we are not going to know until we see the results of these phase III studies. The best-case scenario is all of them are positive and then we will have a wealth of options to choose from. But where the field is going is toward optimal combinations of new drugs with PD-1 blockade that would not significantly improve or worsen the toxicity, so you would no longer have to use ipilimumab/nivolumab, which frankly is a pretty toxic combination. Right now, that is the regimen to beat, at least in the United States. The best long-term survival data come with ipilimumab and nivolumab, no question.

The original question was where is the field going. The field is going toward defining optimal combinations of checkpoint inhibition to try to keep the toxicity at a reasonable level or certainly not more than what you see with anti–PD-1 agents alone.

And then there is Iovance’s tumor-infiltrating lymphocytes (TIL) trial. TIL therapy has been
around for 30 years, and it is finally going to get its turn with the FDA to see whether they will be able to register it. I would say the initial data that have been made public suggest you are looking at a 30-plus percent response rate in all-comers that grow cells, which is almost all the patients. It looks interesting and promising. We will see whether that pans out. It depends on the duration of response, and the progression-free survival, and ultimately the overall survival. We will know that soon [from results] in a large phase II study. There is a lot of excitement about these bispecific T-cell enhancers. I think they will come along in melanoma and other tumors. So, it is just a variety of things, almost all of which depend on [if]...novel new drugs [can be] almost all of which depend on melanoma and other tumors.

Q: What are the most exciting trials?

DR. WEBER: The studies that are probably furthest along would be the direct injectables, things like SD-101, CMP-001, and T-VEC. Those are all [being investigated] in randomized trials that are large, definitive registration phase III trials. I think MASTERKEY-265 probably will read out among the earliest. So those are all TLR agonists that are involved in large phase III trials. I think they have probably accrued most, if not all, of their patients already. They are probably close to complete accrual. There is also an anti–LAG-3/niivolimumab trial. There is a phase II anti–TIM-3 trial. There are several vaccines... that are in phase II [trials], but [they] are not yet in phase III trials. Those are the [most exciting trials with data] that will be mature the [earliest].

Then there is the IMO-2125 ipilimumab trial. That is a separate trial with ipilimumab. So, we are looking at nivolumab/anti–LAG-3 and direct injectables. The idea of niivolimumab/anti–LAG-3 is that LAG-3 is a checkpoint that inhibits T-cell reactivity in addition to PD-1 blockade, especially in the PD-1 refractory population. And by blocking it you will overcome resistance which is a reasonable hypothesis.

And the idea of using a direct injectable like T-VEC, or TLR-9, or other agonists is that too many of the tumors have an immunologically privileged tumor microenvironment. We do not have enough... T cells. It is not a so-called inflamed tumor microenvironment, so the direct injection will inflame the tumor microenvironment, attract T cells, and try to induce a stronger immune response in the tumor microenvironment. And those T cells can then exit the tumor and be disseminated elsewhere into distant tumors. And, if that works out, that is a good idea.

There is 1 more phase III trial that started that is going to take a while to accrue [patients] other than [those with] metastatic disease, and that is the neoadjuvant ECOG SWOG trial of neoadjuvant pembrolizumab. There is the CheckMate 915 trial, an adjuvant trial of ipilimumab/nivolumab versus nivolumab alone. All... patients were accrued as of 6 months ago, and we will probably need to wait another year to see any information. [Also,] there is a stage II... pembrolizumab versus placebo trial, and... a nivolumab versus placebo trial for resected stage IIIB and IIC melanoma. So these will be adjuvant/neoadjuvant trials.

Q: In lung cancer, if you have a druggable, targetable mutation, the patient does not seem to respond well to immunotherapy. Is there worry that it will be the same situation in melanoma?

DR. WEBER: Well, it has been kind of a bust so far. I mean, there is this Novartis phase III trial, called COMBI-i which will read out very soon, in the next 3 to 6 months. That [trial assessed] ...the combination of dabrafenib (Tafinlar) plus trametinib (Mekinist) plus PDR001 versus dabrafenib/trametinib alone. And, if that is a negative study that is going to really kill the targeted plus immunotherapy field.

There was a randomized phase II trial of dabrafenib/trametinib/pembrolizumab versus dabrafenib/trametinib alone. And, if that is a negative study that is going to really kill the targeted plus immunotherapy field.

Q: What research are you working on right now?

DR. WEBER: We have submitted a manuscript showing that a resulting (C-reactive protein) and other acute phase reactants are immunosuppressive. So, the best way to suppress them is [by] blocking interleukin-6 (IL-6), and there is such an antibody called tocilizumab (Actemra), from Genentech. Also, I have an investigator-sponsored trial with [Bristol-Myers Squibb; BMS] to look at ipilimumab/nivolumab plus tocilizumab to potentially reduce toxicity and increase effectiveness or both.

Obviously, if neither works it is a bust of a trial, but that trial is ready to go. It is going to be done here at Dana Farber. It is a phase II designed trial. I like
the idea that there are correla-
tive markers built into it. And I 
think it will be a very interesting 
trial. So, I like that idea. I also 
like the idea of IDO or histone 
deacetylase (HDAC) inhibition, 
and there are a couple of trials 
out there looking at PD-1 plus 
HDAC, and we have a trial that 
we are going to try and get together 
of ipilimumab plus nivolumab plus 
HDAC inhibition which I think 
has some promise.

Q: If this is successful, it could increase 
the response rate pretty significantly?

DR. WEBER: If we see an increased 
response rate, I will be tickled 
pink. You evaluate 18 patients 
in the first stage and you then 
move on to 49 in the second 
stage. So, if we see a promising 
response rate, we will go up to 
67 patients. If it still looks 
that promising, I am sure that 
it is going to become a corpo-
rate-sponsored trial, and it will 
just be an expanded, maybe 
a randomized phase II trial. If I 
were BMS and I saw promising 
data in a 67-patient phase II study, I 
would want to do a 
randomized phase II trial and 
really decide whether the idea 
of tocilizumab plus ipilimumab/ 
nivolumab is promising. I would 
say it is probably more likely 
that we are going to see reduc-
tion in toxicity than increased 
response rate. But I would be 
ticked pink if we saw both. 
We will see. Obviously, the worst-
case scenario is you see neither, 
and after 18 patients you 
declare it a busted trial and you 
move on and do something else.

Q: What is the theory on 
why it would reduce 
the toxicity or the adverse 
events?

DR. WEBER: Oh, there is already 
ample evidence in the litera-
ture that patients who have 
steroid-refractory colitis and 
other immune-related adverse 
events respond to tocilizumab. 
Tocilizumab is an IL-6 recep-
tor blocking antibody that is 
approved for arthritis of 
different types, and it is used 
to block the cytokine release 
syndrome in patients getting 
CAR T-cell therapy, so there 
is ample evidence that it can 
reduce immune toxicity in cer-
tain scenarios. This will be the 
first time we use it preventively 
try to block the possibility of 
the side effects occurring. 
And it would make sense be-
cause it seems unlikely that it 
would have a negative impact 
on efficacy. In fact, it would 
 promote efficacy because we 
have data submitted showing 
that high levels of IL-6 are 
 associated with bad outcomes 
with immunotherapy and che-
motherapy. So, it is a negative 
prognostic marker.

Q: Among patients who 
are not responding to 
 ipilimumab plus nivolumab, 
how many have the 
mutation that you were just 
talking about that you are 
going to try and suppress?

DR. WEBER: BRAF is probably 
present in about half the pa-
tients who do not respond 
 to ipilimumab/nivolumab, 
and then they would go to 
dabrafenib/trametinib or en-
corafenib (Braftovi)/binimetinib 
(Mektovi), or vemurafenib 
(Zelboraf)/cobimetinib (Co-
telic) as their second choice if 
they [have the mutation]. If they 
do not have the mutation], that 
is a difficult situation. Those 
patients almost all go on trials, 
or if they are at an institution 
that does not have trials, they 
may go on chemotherapy, or 
if they are lucky and near an 
institution that does high-dose 
interleukin-2 or TIL [therapy], 
they’ll go on high-dose IL-3 or 
a TIL trial. That would be the 
perfect thing for such a patient.

Q: What other work is 
being done in trying 
to figure out who does and 
who does not respond to 
checkpoint inhibitors, either 
alone or in combination?

DR. WEBER: Oh, there are many, 
many studies going on currently 
to assess whether biomarkers 
can be defined, both for im-
une-related adverse events and 
 efficacy… People are looking at 
the genome, RNA expression 
peripherally in the tumor. So, 
people are looking in the tumor, 
in the periphery. They are look-
 ing at proteomics, epigenomics, 
genomics, expression, tumor mi-
 croenvironment by microscopy, 
 phenotyping, high-resolution 
phenotyping in the periphery 
and in the tumor.

There is just huge amount of 
efforts going on to define 
biomarkers because everybody 
wants to be able to tell you who 
not to treat or who to treat 
with these expensive therapies. 
Keep in mind, in the adjuvant 
mode, you are treating 4 pa-
tients to benefit 1, right? In the 
adjuvant setting to treat stage 
III patients, you have a 50% 
average risk of relapse, and 
you have a hazard ratio of 0.5. 
So that means that for every 4 
patients, 1 of them is not going 
to relapse. I would rather have 
that be for every 2 patients, 1 
of them will not relapse. But 
treating 4 patients to benefit
1 gets expensive because you know how much these drugs cost? A lot of money, hundreds of thousands of dollars a year to the insurance company. So, it is a big deal. There is a huge effort in biomarkers. We are also doing microbiome work to define biomarkers.

Q: How large of a population should currently be getting adjuvant treatment?

DR. WEBER: Well it is a pretty big chunk. I have a lot of patients who are getting adjuvant therapy, and it has really changed the landscape because it [is associated with] a 50% risk reduction. You have 20,000 stage III patients in the United States per year, and 10,000 of them would have relapsed back in the bad old days, now only 5000 of them are going to relapse. So, you just cut it down by 5000 patients. That is a big diminution. And we are already seeing lowering death rates and lowering rates of development of stage IV melanoma. Probably a bit of it is the useful adjuvant therapy that we have.

Q: Has any of that work come through to the point where we can say patients probably are not going to respond to immunotherapy and you should go on trial with something else?

DR. WEBER: None of it is at the point of clinically impacting care. As you probably remember, when you are defining biomarkers, you have to prove that you have an analytically valid assay. So, analytical validity. First it is a proof of concept, the idea that it might work. Then you have to show that you have analytic validity, that you have a reliable, robust, useful marker. Then you have clinical validity, meaning it seems to be associated with the clinical outcome in question. And then you have clinical utility showing that you can use it to actually impact care. We are working at the analytical validity and clinical validity level, and we are not at the point of proving clinical utility. Clinical utility means you do a trial where you use the biomarker to impact care [decisions]; [for example,] if…[the] biomarker is negative, [the patient] will not get treated. If it is positive, [the patient] will. I do not think there are any valid biomarkers that are quite at that level yet.

So, for example, in our trial, we will look at IL-6 levels. So, let us say we find that in our studies that patients whose IL-6 levels go down the most with tocilizumab [will] benefit. Then we can say, okay, well, IL-6 is an established Clinical Laboratory Improvement Amendments-certified enzyme-linked immunosorbent assay test, we are going to stratify the patients. If somebody has [high] IL-6 [levels], they are going to go on ipilimumab/nivolumab/tocilizumab. If they have low IL-6 [levels], we are just going to give them regular ipilimumab/nivolumab. That is the kind of thing that you could do. But that is clinical utility. That is a couple years away.

Q: When is melanoma usually diagnosed?

DR. WEBER: Most melanomas are diagnosed early in stage I and stage II and cured. If there are 100,000 melanomas a year, I would say 70,000 were caught early, and diagnosed at the earliest possible time, no question about it.

But, that still leaves a significant bunch of patients who will have stage III disease or a high-risk stage II disease or stage IV disease. And the stage III patients are going to have surgery and most of them will require adjuvant therapy because if I had a 50% risk of relapse at 5 years of my melanoma, I would want to do something rapidly.

Q: Is there anything new, interesting, or different along the lines of early prevention or early detection?

DR. WEBER: There is researcher at our institution who just got a Melanoma Research Alliance grant with 1 of the dermatology residents, [and] they are going to do electronic assessment of patients who go to the dermatologist and they are going to have this electronic remote assessment of the way their skin looks to try to make a diagnosis of melanoma, which is kind of a cool thing. I mean, as you know, getting in to see a dermatologist in this country is like pulling teeth; it is not easy.

They are going to try to assist the dermatologist by having this done remotely, digitally, and electronically where you can do this digitized photography and have it sent remotely to a dermatologist sitting at a computer terminal. That is a very good idea and I think one of the directions early detection is moving in. But there are no magic prevention early detection trials going on in melanoma right now.

Q: Are any of the blood biopsies that are hopefully going to be able to detect a number of important cancers early showing promise in melanoma?

DR. WEBER: Ironically, the same researcher is working on circulating tumor DNA, that is not as much for early diagnosis as it is for diagnosis of early diagnosis of relapse. So, again, if [a patient] has a melanoma surgically removed, instead of scanning them or examining them every 3 months, they would just get a blood sample. And you look and see whether there is any evidence of circulating tumor DNA that has arisen or gone up, and if that is the case, then you get worried and you assume that there is an occult tumor lurking somewhere. And that is the patient you then treat, you could potentially treat them in the absence of disease. So, I think that is a very clever idea.

Let us say you will treat them with sort of adjuvant therapy and there you would have to do a randomized trial to decide whether it was useful. But still, I think that is a very good idea. I applaud that idea, I like it a lot, and I think that is something that will get pursued, no question.

Q: What advice would you give to oncologists and hematologists about how to best position themselves to be ready for development in the field?

DR. WEBER: Be open-minded and nimble and agile on your feet. And as soon as the data look really promising, adopt new ideas. Be open to new ideas, no question about it.

FINANCIAL DISCLOSURE: The authors have no significant financial interest in or other relationship with the manufacturer of any product or provider of any service mentioned in this article.
Case
A 39-year-old Hispanic male presented with complaints of mucous stools, loss of appetite, rectal bleeding and a 30-pound weight loss within the past several months. Initial evaluation discovered iron deficiency anemia. A colonoscopy revealed a rectal mass starting 8 cm from the anal verge extending to 10 cm. Staging computed tomography scans revealed no abnormalities in the chest abdomen but an abnormal asymmetric mural thickening involving the rectum in the pelvis. Magnetic resonance imaging (MRI) of the pelvis confirmed a 9.4 x 4.5 x 3.4 cm large circumferential rectal mass involving the mucosa and submucosa with extension through the muscularis layer (Figures 1–3). A biopsy of the rectal mass showed grade 3/4 invasive adenocarcinoma of the rectum with mucinous features (Figure 4 and Figure 5).

Immunohistochemistry stains showed loss of nuclear staining for MLH1 and PMS2 indicative of a mismatch repair-deficient tumor. Additional testing for BRAF V600E mutation and MLH1 promoter hypermethylation was negative suggesting the presence of a germline mutation. After a genetic consultation and an informed consent, germline multigene Lynch syndrome panel testing was performed. Analyzed genes included MLH1, MSH2, MSH6 and PMS2 (sequencing and deletion/duplication), and EPCAM (deletion/duplication only). There were no pathogenic sequence variants or deletions/duplications. The patient is adopted and is not able to provide any detailed medical history for his parents and siblings. He is married and has 2 children.

Introduction
Colorectal carcinoma (CRC) is the second leading cause of cancer-related deaths in the United States, with an estimated 145,600 cases of CRC and an estimated 51,020 deaths in 2019.1 One-third of CRCs occur in the rectum, which starts at a virtual line from the sacral promontory to the upper edge of the symphysis pubis on MRI and ends at the superior border of the functional anal canal. The functional anal canal is defined as the palpable upper border of the anal sphincter and puborectalis muscles of the anorectal ring. The decision-making process for the optimal treatment of a patient with rectal cancer is usually complicated because of the 2 competing major outcome measures. Curative intent of surgery must be balanced against the functional results of treatment, which include the maintenance or restoration of normal bowel function/anal continence and preservation of genitourinary functions. Contrary to colon cancer, treatment of rectal cancer usually requires locoregional treatment due to the high risk of locoregional recurrence. The surgical technical difficulties in obtaining a wide surgical margin, proximity of the rectum to pelvic structures, and the absence of serosa surrounding the rectum makes rectal cancer a high-risk disease for local recurrence. Historically, radiation therapy has been a crucial part of rectal cancer treatment and has helped decrease the rates of local recurrence but with increased toxicity.2–4

Combined modality therapy consisting of concurrent fluoropyrimidine-based...
chemoradiation, surgery, and adjuvant chemotherapy has been utilized for the majority of patients with stage II or stage III rectal cancer. The National Comprehensive Cancer Network (NCCN) guidelines recommend trimodality treatment with neoadjuvant chemoradiotherapy, surgical resection with total mesorectal excision (TME), plus additional chemotherapy, most commonly in the adjuvant setting. Advances in all 3 treatment modalities (ie, the adoption of the TME surgical technique, optimized timing and dosimetry of radiotherapy, and the incorporation of modern chemotherapy drugs) have led to a marked reduction in local recurrence rates—from as high as 25% to less than 5% to 10% in the contemporary literature. Unfortunately, an estimated 5-year distant relapse rate of 35% remains as one of the main causes of death in this population. Suboptimal delivery of existing treatments due to poor patient compliance has stimulated the development of novel approaches in sequencing and effective utilization patterns.

Chemoradiation Therapy: Adjuvant Versus Neoadjuvant and Long Course Versus Short Course

The benefits of chemoradiation in stage II/III rectal cancer were originally established in the adjuvant setting by 2 prospective randomized trials demonstrating that postoperative chemoradiation significantly decreased local recurrence rate compared with observation or either modality alone. The German Rectal Cancer Study Group trial (CAO/ARO/AIO-94) compared neoadjuvant chemoradiation therapy to adjuvant chemoradiation. Pelvic relapse rates at 5 and 10 years were significantly lower in the neoadjuvant chemoradiation group compared with the adjuvant group (6% vs 13%; P = .006 and 7% vs 10%; P = .048, respectively). Although no significant differences in disease-free survival (DFS) or overall survival (OS) were apparent between the 2 groups, patients receiving neoadjuvant chemoradiation experienced considerably less acute and chronic greater than grade 3 toxicities (14% vs 24%; P = .01). These long-term follow-up results established the current standard role of neoadjuvant chemoradiation in stage II and III rectal cancer. Two different neoadjuvant chemoradiation approaches have been validated in randomized trials to be equally effective in reducing the risk of local disease recurrence in stage II/III rectal cancer compared with surgery alone. One approach, short-course radiotherapy, consists of 1 week of radiation (25 gray [Gy] in 5 fractions) typically followed by surgery in 1 week. The other approach, long-course chemoradiotherapy, consists of 45 to 50.4 Gy in 25 to 28 fractions with concurrent fluorouracil-based chemotherapy followed by surgery in 4 to 8 weeks. The potential benefits of the short-course regimen may include improved patient convenience, lower rates of acute toxicity and lower cost, long-course chemoradiation has been associated with lower surgical morbidity, increased sphincter preservation, and a lower incidence of positive radial resection margins. Further research is needed to determine whether longer follow-up results will increase the adoption of short-course radiotherapy in the United States.

Systemic Chemotherapy: Adjuvant Versus Neoadjuvant

Systemic chemotherapy in rectal cancer has 2 main purposes; first, it provides a radiation sensitizer effect, and second, it serves to eliminate circulating micrometastases and distant organ involvement.
Current professional consensus guidelines recommend 4 months of adjuvant fluoropyrimidine-based chemotherapy for all patients with rectal cancer who receive neoadjuvant chemoradiation followed by surgical resection.\(^5\) A systematic review and meta-analysis of individual patient data from 4 studies specifically examining the efficacy of adjuvant chemotherapy in rectal cancer showed a significant increase in DFS in a subgroup analysis of patients with proximal tumors (10-15 cm above the anal verge) and fewer distant recurrences.\(^18\)

A recent National Cancer Database analysis investigating NCCN guideline adherence and associated survival benefit for adjuvant chemotherapy revealed improved OS across all pathologic stages, with the greatest survival benefit among patients with a pathologic complete response after surgery (hazard ratio, 0.40; 95% CI, 0.23-0.67). However, the reported rates of patients receiving adjuvant chemotherapy were remarkably low (32%), highlighting the poor compliance rate with planned chemotherapy.\(^19\)

Several small studies have tested the utility of neoadjuvant chemotherapy before chemoradiation and surgery. In the Spanish GCR-3 randomized phase II trial, capecitabine and oxaliplatin (CAPOX) chemotherapy before chemoradiation or after surgery provided similar pathologic complete response (pCR) rates; however, patients in the neoadjuvant chemotherapy group experienced less toxicity.\(^20,21\) Another phase II trial randomized patients to neoadjuvant folinic acid, fluorouracil, and oxaliplatin (FOLFOX) chemotherapy prior to chemoradiation or chemoradiation alone followed by surgery. There were no differences in clinical outcomes with more toxicities in the neoadjuvant FOLFOX group.\(^22\) The phase II AVACROSS study assessed the safety and efficacy of adding bevacizumab to induction therapy with CAPOX prior to chemoradiation and surgery. This regimen was well tolerated with a pCR rate of 36%.\(^23\)

Current national practice guidelines continue to recommend a 4-month systemic chemotherapy course before or after surgical resection for all patients, regardless of neoadjuvant chemoradiation.\(^5,24\)

Total Neoadjuvant Therapy: Chemoradiation Followed by Systemic Chemotherapy Versus Systemic Chemotherapy Followed by Chemoradiation

Historically, treatment for clinical stage II or III locally advanced rectal cancer (T3/4, N0, or node-positive) consisted of preoperative chemoradiotherapy followed by TME and postoperative adjuvant chemotherapy with fluorouracil and oxaliplatin.\(^25\) A pragmatic approach to optimize delivery of trimodality therapy is the incorporation of systemic chemotherapy before or after neoadjuvant chemoradiation. This induction or consolidation chemotherapy with chemoradiation prior to surgery for stage II/III rectal cancer has been called total neoadjuvant therapy (TNT). Among several reported advantages of this approach are improved delivery of planned therapy, increased downstaging, earlier elimination of micrometastatic disease, and an opportunity for in vivo assessment of chemosensitivity. In addition, delivery of all chemotherapy preoperatively obviates the need for postoperative therapy, reducing duration with a diverting ileostomy and saving patients from undergoing chemotherapy with a stoma. Accumulating literature suggests that systemic neoadjuvant chemotherapy is a safe and feasible option. NCCN guidelines now include its use. Optimal scheduling of chemotherapy in relation to chemoradiation with respect to treatment efficacy, toxicity, and compliance has not been well studied; it is the subject of an ongoing randomized clinical trial.\(^26\) Results from the first randomized, phase II trial addressing this very question were recently published.\(^27\) In this study, chemoradiation followed by systemic chemotherapy resulted in higher compliance with chemoradiation but lower compliance with chemotherapy. A pCR in the intention-to-treat population was achieved in 17% of patients treated with systemic chemotherapy followed by
chemoradiation versus 25% in patients treated with chemoradiation followed by systemic chemotherapy. Long-term follow-up will assess whether improved pCRs in the chemoradiation followed by systemic chemotherapy group translates to better outcomes.

Selective Elimination of Surgery Versus Radiotherapy

The efficacy of TNT brings the high possibility of clinical complete response as determined by a combination of physical examination and radiologic and endoscopic surveillance methods. A subset of patients who achieved a complete clinical response will also have a pCR, thus they may not benefit from subsequent surgery. This challenge lies in the accurate determination and definition of a complete clinical response. Available information so far has demonstrated promising outcomes with nonoperative management. While a higher proportion of patients are reported to have local recurrence in the absence of surgical resection, this does not appear to compromise outcomes if salvage surgery was performed. Research is now focusing on improving patient selection, refining noninvasive MRI criteria for response determination, and incorporating more targeted therapies into TNT.

While the incorporation of chemoradiation has dramatically improved local recurrence rates, the impact on OS has been difficult to demonstrate due to relapsing patients dying from systemic metastatic disease. With the improved surgical techniques and widespread utilization of TME, it is tempting to question if potential short- and long-term toxicities of pelvic radiotherapy can be avoided. A subset of patients, indeed, may be eligible for this approach. One particular group of patients are those with proximal tumors who may have a higher likelihood of negative circumferential radial margins at the time of surgery. Several ongoing studies (BACHUS: NCT01650428, FOWARC: NCT01211210, and PROSPECT: NCT01515787) are investigating this strategy. Currently, the selective use of radiation therapy remains an investigational strategy and insufficient data exist to use this method outside of a clinical trial setting.

Conclusions

Outcomes for patients with locally advanced rectal cancer have improved considerably with the availability of combined modality therapy. However, the primary cause of death from locally advanced rectal cancer remains as the distant relapse rate, which far exceeds the rate of local recurrence. The necessity to optimally address micrometastatic disease has led to increasing interest in delivering chemotherapy in the neoadjuvant setting rather than the postoperative or adjuvant setting. As a result, the TNT concept was born, providing a promising platform for novel nonoperative or nonradiation protocols. The promise of this approach has been highlighted by the recent, rapidly increasing TNT literature, which gives additional support for the current NCCN guidelines that categorize TNT as a viable treatment strategy for rectal cancer. Long-term results of ongoing and future trials will continue to refine the role of TNT in providing selective exclusion of radiation and nonoperative management.

Outcome of the Case

The patient was treated with 8 cycles of FOLFOX followed by 6 weeks of chemoradiation followed by surgery. Pathology revealed T3N1M0 disease. He is currently receiving follow-up.

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

FIVE KEY REFERENCES


For full reference list visit cancernetwork.com/RectalCancerSOC
Multiple studies designed to evaluate chimeric antigen receptor (CAR) T-cell therapies in various hematologic malignancies appeared to show promise at the 61st American Society of Hematology (ASH) Annual Meeting & Exposition in Orlando, Florida. “This is a very encouraging space to watch as new agents become available,” Stephen M. Ansell, MD, PhD, from Mayo Clinic, said in an interview with ONCOLOGY. “…I think as a class this is a very promising approach.”

**Anti-BCMA and CD38 Dual-Targeted CAR T-Cell Therapy**

CAR T-cell therapy targeting both B-cell maturation antigen (BCMA) and CD38 induced promising responses among patients with multiple myeloma who were treated with at least 3 prior therapies and whose disease had spread outside of the bone marrow.1 “This is the first clinical trial of anti-BCMA and CD38 dual-targeted CAR T-cell therapy in refractory multiple myeloma. Our study demonstrates improved efficacy and manageable safety,” Yu Hu, MD, PhD, of Union Hospital at Huazhong University of Science and Technology in Wuhan, China, said during a presentation to an audience at the 61st ASH Annual Meeting and Exposition.

The objective response rate was 90.1%, with 12 patients achieving a stringent complete response (sCR) as their best response, meaning that no plasma cells were detected in the bone marrow. Seven patients (31.8%) had a partial response (PR), meaning that the level of M-protein in their blood or urine was reduced but still detectable, with 2 achieving a very good partial response (VGPR). One patient had a minor response. Eighteen patients (81.8%) reached bone marrow minimal residual disease-negative status.

At the cutoff date of October 31, 2019, 19 patients were still alive with 10 still in an sCR, 1 with a VGPR, and 4 with PRs. Three patients experienced a relapse and 1 patient developed progressive disease.

**ZUMA-2 Trial in Mantle Cell Lymphoma**

Results from the ZUMA-2 trial indicated that patients with relapsed/refractory mantle cell lymphoma (MCL) resistant to prior therapies may benefit from treatment with KTE-X19, an autologous CD19-targeting CAR T-cell therapy. In this multicenter phase II study of 74 patients, 93% responded to the CAR T-cell therapy, with 67% of participants achieving a complete response (CR). Currently, this is the highest reported rate of disease response in patients with prior Bruton’s tyrosine kinase inhibitor failure.

“High overall response rates, durable remissions at a year, and without any mortality attributed to the CAR T-cell therapy. This is a big deal. For patients with proliferative mantle cell lymphoma, for patients with p53 variant mantle cell lymphoma, we desperately need active therapies,” Bijal D. Shah, MD, of the Moffitt Cancer Center, said in an interview at the meeting.

Study investigator Michael Wang, MD, professor in the department of lymphoma and myeloma at the University of Texas MD Anderson Cancer Center, noted that responses occurred rapidly after KTE-X19 infusion, with a median time to response of 1 month (range, 0.8-3.1 months). Responses were also durable; the median duration of response had not been reached at the end of follow-up (8.6 months-not estimable). Fifty-seven percent of all evaluable patients, including 78% of those with a CR, remained in remission at data cutoff.

**ZUMA-1 Trial in Refractory B-Cell Lymphoma**

Axicabtagene ciloleucel (axi-cel; Yescarta) demonstrated improved overall survival (OS) for patients with refractory large B-cell lymphoma, according to a 3-year analysis of the pivotal phase II ZUMA-1 trial.3 The CAR T-cell therapy induced a median OS of 25.8 months. At a median follow-up of 39.1 months, the 3-year OS rate was 47% with axi-cel, with approximately 60% of patients having relapsed or progressed. In a previous 2-year analysis of the study data, the objective response rate was 83% and the complete remission rate was 58%. The 2-year OS rate was 51% and the 2-year progression-free survival rate was 39%.

“These data are highly encouraging,” Sattva S. Neelapu, MD, department of lymphoma and myeloma, The University of Texas MD Anderson Cancer Center, said during a presentation of the findings.

For references visit cancernetwork.com/ASH-CAR-T
A Patient With Newly Diagnosed, Advanced EGFR-Mutated Non–Small Cell Lung Cancer

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A 40-year-old woman presented with a productive cough and shortness of breath that limited her regular activities. Her past medical history was relevant for hypertension since 2016; it is well controlled and treated with enalapril 5 mg twice daily. She also revealed a past wood smoke exposure of 2 hours per day for 10 years during her childhood.

A chest computed tomography (CT) scan was performed which showed a 30-mm lung nodule in the lower left lobe and mediastinal and ipsilateral pleural thickening with moderate pleural effusion and several bilateral lung metastases. The patient underwent a CT-guided lung biopsy. The pathology evaluation revealed a well-differentiated lepidic lung adenocarcinoma (positive for cytokeratin 7, thyroid transcription factor 1, and napsin A). Brain magnetic resonance imaging with contrast revealed the presence of 2 occipital metastatic lesions without surrounding edema. She denied headaches, nausea, vomiting, visual alterations or focalization symptoms.

A mutational profile was performed and was positive for the presence of an epithelial growth factor receptor (EGFR) mutation (exon 19 deletion).

Based on the most recent data, which of the following would be the best initial therapy for this patient?

A. First-generation EGFR tyrosine kinase inhibitor (TKI; erlotinib or gefitinib)
B. Dacomitinib
C. Osimertinib
D. Combination therapy with gefitinib and platinum-based chemotherapy
E. Combination therapy with erlotinib and ramucirumab

TURN TO PAGE 22 for the answer and a discussion of this case by experts.
CORRECT ANSWER: C. Osimertinib

Continued from page 21

TABLE 1 Oncological outcomes of first and second-generation TKI’s studies in the first-line setting compared with chemotherapy.

<table>
<thead>
<tr>
<th>Trial</th>
<th>TKI</th>
<th>Chemotherapy</th>
<th>Mutation</th>
<th>mPFS(m)</th>
<th>ORR (%)</th>
<th>OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS [8, 9]</td>
<td>Gefitinib</td>
<td>Carboplatin / Paclitaxel</td>
<td>NSP</td>
<td>9.5 vs 6.3 HR 0.48 P&lt;0.001</td>
<td>71 vs 47</td>
<td>21.6 VS 21.9 NSD</td>
</tr>
<tr>
<td>First signal [10]</td>
<td>Gefitinib</td>
<td>Gemcitabine / Cisplatin</td>
<td>NSP</td>
<td>8.0 vs 6.3 HR 0.54 P&lt;0.001</td>
<td>84.6 vs 37.5</td>
<td>22.3 VS 22.9 NSD</td>
</tr>
<tr>
<td>NEJ-002 [11]</td>
<td>Gefitinib</td>
<td>Carboplatin / Paclitaxel</td>
<td>EGFRm (+)</td>
<td>10.8 vs 5.4 HR 0.32 P&lt;0.001</td>
<td>74 vs 31</td>
<td>27.7 VS 26.6 NSD</td>
</tr>
<tr>
<td>WJTOG 3405 [12, 13]</td>
<td>Gefitinib</td>
<td>Carboplatin / docetaxel</td>
<td>EGFRm (+)</td>
<td>9.2 vs 6.3 HR 0.48 P&lt;0.0001</td>
<td>62 vs 32</td>
<td>34.8 VS 37.3 NSD</td>
</tr>
<tr>
<td>OPTIMAL [14, 15]</td>
<td>Erlotinib</td>
<td>Carboplatin / Gemcitabine</td>
<td>EGFRm (+)</td>
<td>13.1 vs 4.6 HR 0.16 P&lt;0.0001</td>
<td>83 vs 36</td>
<td>22.8 VS 27.2 NSD</td>
</tr>
<tr>
<td>EURTAC [16]</td>
<td>Erlotinib</td>
<td>Cis or carboplatin / docetaxel or gemcitabine</td>
<td>EGFRm (+)</td>
<td>9.7 vs 5.2 HR 0.37 P&lt;0.0001</td>
<td>58 vs 15</td>
<td>22.9 VS 19.6 NSD</td>
</tr>
<tr>
<td>Lux-Lung 3 [17, 18]</td>
<td>Afatinib</td>
<td>Cisplatin / pemetrexed</td>
<td>EGFRm (+)</td>
<td>13.6 vs 6.9 HR 0.47 P=0.001</td>
<td>56 vs 23</td>
<td>28.2 VS 28.2 NSD</td>
</tr>
<tr>
<td>Lux-Lung 6 [19]</td>
<td>Afatinib</td>
<td>Cisplatin / Gemcitabine</td>
<td>EGFRm (+)</td>
<td>11 vs 5.6 HR 0.28 P&lt;0.0001</td>
<td>67 vs 23</td>
<td>23.1 vs 23.5 NSD</td>
</tr>
</tbody>
</table>

Discussion

Lung cancer remains the most common malignancy (11.6% of all cases) and the leading cause of cancer deaths worldwide (18.4%). Non–small cell lung cancer (NSCLC) accounts for approximately 80% to 90% of lung cancer cases, and adenocarcinoma has become the most predominant histotype (45%-55%). The discovery of activating mutations in the EGFR gene led to the development of TKIs and resulted in a paradigm shift in the treatment strategy. The EGFR gene comprises 28 exons, but activating and sensitizing mutations occur in exons 18 through 21, which encode the site for adenosine triphosphate binding within the tyrosine kinase (TK) domain. Somatic activating mutations in the TK domain of EGFR act as oncogenic drivers leading to ligand-independent activation of receptor downstream signaling, favoring cell proliferation, survival, and cell migration. EGFR oncopgenic mutations were found in 32.4% of cases of NSCLC from the worldwide population. Nonetheless, many studies have demonstrated marked variations in prevalence depending on ethnic races. EGFR mutations were reported in approximately 10% to 15% of the Caucasian population and nearly 50% of Asian patients with advanced NSCLC. Three generations of TKIs are approved for frontline treatment in this group of patients based on multiple studies which demonstrated considerable superiority in progression-free survival (PFS) and overall response rate (ORR) with a decrease in the toxicity profile compared with chemotherapy. Answers A and B referred to first and second-generation TKIs that have demonstrated a favorable PFS and an important ORR in numerous phase III trials compared with the historic standard of care (SoC)—chemotherapy (Table). Furthermore, these TKIs were associated with lower rates of adverse events (AEs) and better symptom control. Despite a remarkably high ORR of approximately 60% to 75% to such treatments, all patients will develop secondary resistance, with average median PFS ranging from 9 to 15 months. Additionally, none of the first-generation TKIs have proved an overall survival (OS) benefit, so answer A is not the best answer with the available information. Particularly focusing on answer B, second-generation TKIs (afatinib and dacomitinib) have also demonstrated a PFS advantage compared with chemotherapy and first-generation TKIs in the first-line setting (Figure). These drugs are irreversible inhibitors forming covalent bonds with the kinase domains of EGFR and other human epidermal growth factor receptor family receptors. The first head-to-head comparison between 2 TKIs was conducted in the LUX-Lung 7 trial, a phase IIb study, in first-line advanced EGFR-mutated patients (Del19 or L858R only), that assessed afatinib versus gefitinib. The primary outcome was median PFS, so the study did not have enough power to demonstrate an overall survival difference. Approximately 15% of patients in both arms had controlled brain metastasis before randomization. The median PFS was marginally better in the afatinib arm, 11.0 versus 10.9 months (hazard ratio [HR], 0.73; 95% CI, 0.57-0.95; P = .017), but it was not clinically meaningful. Even though the ORR was higher in the afatinib arm (70% vs 56%; P = .0083), differences in median OS for both arms were not significant, 27.9 months in the afatinib arm versus 24.5 months in the gefitinib arm. Grade 3 to 4 AEs were more common with afatinib than gefitinib, especially rash or acne (9% vs 3%) and diarrhea (13% vs 1%), respectively. Also, a higher rate of serious AEs occurred (11% vs 4%) in the afati-
prognosis than those in the LUX-Lung 7 study. The exclusion of this population may limit the applicability of these results in real-world practice where brain metastases are common in this population. Brain metastasis as the main site of progression occurred in 1 patient in the dacomitinib arm while 11 patients were affected in the gefitinib arm, suggesting a protective effect in dacomitinib. Noteworthy, this was not a preplanned analysis and a small number of patients were involved. Further studies are necessary to establish the CNS activity of dacomitinib.

Less than 50% of patients in the dacomitinib arm received second-line treatment and chemotherapy was the most prescribed therapy in less than one-third of patients. Few patients in both arms received osimertinib, 9.7% in the dacomitinib group and 11.1% in the gefitinib group. Median OS was 36.7 months in the group of patients who received dacomitinib followed by osimertinib, the ideal sequence in patients who started with a second-generation TKI. Thus, the results should be interpreted with caution considering the low number of patients that underwent the ideal sequence, as AURA3 study results do not represent the real-world practice nowadays. Noteworthy, the percentage of patients who developed an EGFR T790M mutation was not reported in ARCHER 1050.

On the other hand, tolerability is essential for any treatment, and dacomitinib was often associated with significantly more toxic AEs than gefitinib. Grade 3 to 4 AEs were 53% with dacomitinib versus 32% with gefitinib; AES of note with dacomitinib were dermatitis acneiform (14%), diarrhea (8%) and paronychia (7%). Serious AEs were twice as high with dacomitinib compared with gefitinib (9% vs 4%) and 2 treatment-related deaths occurred in the dacomitinib group. Dose reductions (66% vs 38%), temporary discontinuations (78% vs 54%) and permanent discontinuations (10% vs 7%) were more common with dacomitinib than gefitinib, respectively. Finally, among the 66% of patients given dacomitinib who needed a dose reduction, almost 30% of them received the lowest permitted dose of 15 mg per day. Surprisingly, results from a subanalysis presented at the ESMO Asia Congress 2019, revealed that the best OS outcomes occurred in the populations who received the lowest doses. The exclusion of patients with CNS disease, limited access to second-line treatment in more than a half of the patients, and remarkable toxicity and low tolerability with the initial dose does not support dacomitinib to be the best available option. Thus, answer B is not the best considering the CNS affection in our clinical case.

Some physicians have argued the benefit of combination strategies, answers D and E. First-generation TKIs (gefitinib with pemetrexed-based chemotherapy and erlotinib with an antiangiogenic) represent the most robust available information of combination treatments in the first-line setting. In a preclinical study, simultaneous treatment with gefitinib and pemetrexed favored cell growth inhibition, death, and prevented the appearance of resistance mediated by the EGFR T790M mutation. Moreover, it appears that combination therapy prevents epithelial-to-mesenchymal transition, suggesting a positive synergistic effect on the tumor’s microenvironment. In another study, thymidylate synthase levels were decreased with the use of an oral TKI, which may enhance pemetrexed efficacy.

NEJ009 was an Asian, open-label, phase III trial, that evaluated the efficacy of gefitinib, carboplatin, and pemetrexed (GCP)
for up to 6 cycles followed by pemetrexed and gefitinib maintenance versus gefitinib alone in 345 patients harboring EGFR-activating mutations (Del19, L858R, and uncommon mutations). A total of 25% of patients with asymptomatic brain metastases were included in this analysis. Median PFS, progression-free survival following initiation of second-line therapy (PFS2), and OS were analyzed as primary end points according to a hierarchical sequential testing method. Median PFS was superior in the combination arm, with an absolute benefit of 9 months (20.9 vs 11.9 months) (HR, 0.493; 95% CI: 18.0, 24.2; P < .001). The ORR rate was significantly higher in the combination group (84% vs 67%; P < .001) with complete responses of 4%. PFS2 showed a nonsignificant difference (20.9 vs 18.0 months; HR, 0.81; P = .092). Even though median OS was much longer in the combination arm (52.2 vs 38.8 months; HR, 0.722; P = .021), the study was not sufficiently powered to test these differences. In general, this combination strategy was much more toxic than gefitinib alone. The rate of grade 3 to 4 AEs with the combination was more than double that with gefitinib (65% versus 31%) and one death was reported associated with combination treatment. Osimertinib was received as a second-line treatment in 19% of the patients in the overall population, 23% in the gefitinib arm and 22% in the combination arm. The long-term quality of life analyses was not different, even after 36 months of follow-up.

An Indian phase III study evaluated the same combination (GCP vs gefitinib alone) in patients with advanced NSCLC harboring an EGFR-sensitizing mutation (Del19, L858R, and exon 18 mutations). Chemotherapy in the combination arm was administered for 4 cycles followed by maintenance pemetrexed and gefitinib until progression. A total of 18% of patients had brain metastases and 21% had a performance status of 2. The radiologic response rate was superior in the combination group (75% vs 63%) (P = .01), almost reaching 3% of complete responses. The estimated median PFS and PFS2 were doubled in the combination therapy arm, 16 months versus 8 months (HR, 0.51; 95% CI, 0.30 to 0.66; P < .001) and 23 months versus 14 months (HR, 0.69; 95% CI, 0.53 to 0.92; P < .001), respectively. Also, median OS was not reached in the combination group, it was estimated to be significantly longer compared with gefitinib monotherapy (17 months; HR, 0.45; 95% CI, 0.31 to 0.65; P < .001). Additionally, the rate of grade 3 or higher AEs was 75% versus 49% in the combination arm and gefitinib arm, respectively, and serious adverse events occurred in 50.6% versus 25.3% (P < .001). Quality of life reports are not presented in this publication and will be reported in the future.

The combination strategy with gefitinib and chemotherapy emerged as an interesting frontline strategy based on the PFS and OS outcomes that consistently demonstrated a delay in the appearance of secondary resistance. However, these findings need to be explored in a future confirmatory analysis. A considerable limitation of these studies is that the strongest evidence comes from specific populations, Asians and Indians, respectively. In the case of the Indian study, the evidence came from a single institution, so extrapolation of this benefit to other races is not advised. Until now, we did not have a clear OS benefit with the combination strategy of chemotherapy and a TKI. Premature results need to be confirmed from the Indian study with a longer follow-up. Additionally, the NEJ009 study is a negative trial for OS based on its hierarchical design. Moreover, the Indian study showed a median PFS and OS inferior to that of historical records in previous trials with gefitinib monotherapy in first-line setting. The study investigators justify these results with the inclusion of patients with more aggressive disease, including 18% of patients with brain metastases and 21% of patients with a performance status of 2. A higher toxicity profile must be assumed with a combination strategy. The rate of grade 3 or higher AEs was higher in the combination arm, especially hematologic toxicities. More multicentric clinical trials are needed to clarify the role of combination therapy with chemotherapy and a TKI, so answer D cannot be considered as the correct answer with the available information.

Preclinical studies have demonstrated increased signal transducer and activator of transcription 3 (STAT3) mediated by interleukin-6 in NSCLC with both activating-EGFR and T790M mutations. STAT3 has been correlated with an upregulation of VEGF expression by an independent way of the mitogen-activated protein kinase and AKT pathway. Thus, there is good rationale to try a combination therapy in EGFR-mutated NSCLC with an antiangiogenic. A European phase II study (BELIEF) reported a median PFS in the whole cohort of 13.2 months with the combination of erlotinib and bevacizum-
ab (E+B) at a 15 mg/kg dose. The study met its end point only in the pretreatment T790M mutation-positive population, with a median PFS of 16 months compared with 10.5 months in the T790M-negative patients (HR, 0.52; 95% CI, 0.30-0.88; \( P = .016 \)). Patients with CNS metastases were not allowed in the study.31

The first phase III trial to evaluate the combination of erlotinib with bevacizumab compared with erlotinib monotherapy was NEJ026, a Japanese, open-label trial in patients with EGFR-mutated (del 19 and L858R). The median PFS benefit in the first interim analysis (16.9 vs 13.3 months; HR, 0.605; 95% CI, 0.417-0.877; \( P = .016 \)) favored the combination arm. The ORR was not different between strategies (72% vs 66%; \( P = .31 \)). Noteworlhily, 88% and 46% of grade 3 or higher AEs occurred in the combination and monotherapy groups, respectively.31

The RELAY study is a worldwide, phase III trial designed to explore the combination of erlotinib and ramucirumab versus erlotinib alone in the EGFR-mutated (del19 or L858R) population. Patients with brain metastases were excluded from the study. Median PFS was considerably higher in the combination group compared with erlotinib alone, 19.4 months versus 12.4 months (HR 0.59; 95% CI, 0.46-0.76; \( P <.0001 \)). ORR was similar between groups, 76% with ramucirumab plus erlotinib and 75% with erlotinib alone. OS analysis was immature at data cutoff. More than half of the patients per arm received subsequent medication. An increase in grade 3 to 4 AEs and serious AEs predominated in the erlotinib and ramucirumab arm compared with the erlotinib arm (72% vs 54%). The most common grade 3 to 4 AEs in the combination group were hypertension (24%) and dermatitis acneiform (15%). Serious AEs were more common in the combination arm compared with erlotinib alone (29% vs 21%) and 1 treatment-related death occurred in the combination group.22

Considerable toxicity is a major problem with combination therapies and is was common in the 5 studies previously mentioned. Both combination strategies (chemotherapy and antiangiogenic combinations) are pending from a quality of life analysis, which should be considered, based on the approval of other options with much fewer adverse events. Despite the exciting results in the RELAY study, patients with brain metastases were excluded and the benefit cannot be extrapolated to the real-world population. Presence of CNS metastases is an adverse prognostic factor, thus this trial may have been enriched with patients with a better prognosis. A longer follow-up is needed than in the RELAY study for the combination of erlotinib and ramucirumab to be considered a standard of treatment. Nevertheless, the improvement in terms of PFS, especially for the L858R-mutated population, is noteworthy. This mutation is historically associated with poorer outcomes compared with the exon 19 deletion. A resistance mechanism after combination therapy is not well defined, but the number of patients with a T790M mutation after progression was similar between groups in the RELAY study. More multicentric evidence is necessary, ideally, to make head-to-head comparisons with a third-generation TKI (eg, osimertinib), which recently demonstrated an OS benefit compared with a first-generation EGFR-TKI (gefitinib or erlotinib) with an improvement in the toxicity profile. In conclusion, Answers D and E are not the best options with the available information.

Osimertinib is a third-generation EGFR-TKI that binds selectively and irreversibly to the tyrosine-kinase domain (C797 residue), blocking the downstream proliferation signal. Osimertinib inhibits both EGFR-TKI-sensitizing and T790M resistance mutations and has shown eficacy in patients with CNS metastases. Osimertinib was approved based on data from the AURA3 trial, in the second-line setting after progression with a first-generation TKI (gefitinib or erlotinib), exclusively in the EGFR-mutated population with the T790M positive mutation. Median PFS was longer in the osimertinib group compared with the platinum-based chemotherapy group, 10.1 months versus 4.4 months (HR, 0.30; 95% CI, 0.23-0.41; \( P <.001 \)), with an absolute benefit of 5.7 months.34 Recently, at the ESMO Asia Congress 2019, OS results did not confirm the PFS benefit seen in the first publication. The median OS in the osimertinib group was 26.8 months compared with 22.5 months in the chemotherapy group (HR, 0.87; 95% CI, 0.67-1.12; \( P = .227 \)). The percentage of patients who crossed over to osimertinib as a third-line therapy was 86% of those randomized to the chemotherapy arm. Meanwhile, 59% of patients in the osimertinib arm received a third-line therapy; for most of them (65%), chemotherapy was the preferred line.

Subsequently, the FLAURA trial evaluated osimertinib in the first-line setting in pa-

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**Table 2: PFS & OS depending on initial therapy in EGFR mutated NSCLC (mos)**

<table>
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<tr>
<th>Therapy</th>
<th>PFS</th>
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<tr>
<td>First generation TKI</td>
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<td>Osimertinib FLAURA</td>
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<td>Dacomitinib ARCHER 1050</td>
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<td>Comb. w/ ramucirumab RELAY</td>
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*Immature OS analysis **OS not powered

Direct comparison between now available strategies of upfront treatment in advanced NSCLC based on phase 3 trials.
patients with EGFR mutation-positive (exon 19 deletion or L858R) advanced NSCLC. Osimertinib demonstrated a greater benefit in terms of median PFS compared with a first-generation EGFR-TKI (erlotinib or gefitinib) (18.9 vs 10.2 months; HR, 0.46; 95% CI, 0.37-0.57; P <0.001). This difference was significant independent of other clinical factors (eg, EGFR mutation, CNS disease, race, or age). 35 No significant difference in ORR was observed but it was numerically higher in the osimertinib arm (80% vs 76%). The median OS was presented at the ESMO Congress 2019, and the median OS was 38.6 months in the osimertinib group and 31.8 months in the comparator group (HR, 0.799; 95.05% CI, 0.641-0.997; P = .0462), an absolute benefit of almost 7 months.23 Moreover, osimertinib was well tolerated, with fewer grade 3 or higher AEs compared with first-generation EGFR-TKIs (42% vs 47%), the most common being rash, diarrhea, and dry skin. Rates of drug interruptions, drug reductions, and permanent discontinuation of treatment because of AEs were very similar between the groups.23

It is noteworthy that among all the patients who underwent randomization, 31% of patients in FLAURA study did not receive a second-line treatment in the osimertinib group and 30% in the comparator group, most of them because of deaths in approximately 22% of patients in both groups. In real-world data presented at the ESMO Congress 2019, about 25% of patients died without receiving subsequent therapy after progression with a first- or second-generation EGFR-TKI. These data were supported last year in the Flatteron Health electronic health records database, where 22% and 40% of patients died before receiving a second- or third-line treatment, respectively. EGFR T790M mutation is the most common mechanism of acquired resistance for a first- or second-generation EGFR-TKI in 50% of the patients, whereas MET amplification, human epidermal growth factor receptor 2 amplification, and small cell transformation occur less frequently.37

As a result, one-third of the patients who started with a first- or second-generation EGFR-TKI and develop a T790M mutation will be candidates to receive the best drug in this scenario. For a majority of patients, the first-line option would be the only shot they have in the course of their disease, supporting the idea to use the best drug as an up-front treatment.

Referring to second-line treatments, 48% of patients in the osimertinib group and 65% in the comparator group received subsequent therapy. Chemotherapy was the most frequent second-line treatment in the osimertinib group (68%). Otherwise, osimertinib was administered to 27% of the those who received a subsequent treatment in the comparator group (65% of patients). Thus, just 17.5% of the total cohort in the comparator group received osimertinib as a first subsequent therapy.23 This percentage of osimertinib crossover in the first subsequent therapy was less than expected, considering the historical one-third of patients that develop a T790M mutation and receive osimertinib as a second-line treatment. Nevertheless, the investigators argued a 31% crossover considering the additional number of patients who received osimertinib as a second subsequent anticancer therapy.

Many questions remain to be solved. One is the biological response of the tumor microenvironment and clinical behavior (secondary resistance to osimertinib) after first-line osimertinib. Plasma genotyping analyses have highlighted differences in the frequency and preponderance of resistance mechanisms depending on the line of osimertinib therapy, underlying the discrepancies in selection pressure and clonal evolution. Approximately 15% of patients will develop MET amplification as the most common resistance mechanism for osimertinib in the up-front setting. Meanwhile, C797S mutation is the most common when osimertinib is followed by a first- or second-generation TKI.37 In a FLAURA post-progression analysis at the first data cutoff, 26% of patients had second progressions. The median PFS2 was not reached in the osimertinib arm and it was 20 months in the SoC EGFR-TKI (HR, 0.58; 95% CI, 0.44-0.78; P = .0004), suggestive of no aggressive biological change or resistance to subsequent therapies that would lead to rapid disease progression.24

Brain metastases are a poor prognostic factor in the course of the disease, and it is known to confer a deterioration in the quality of life. Particularly in EGFR-mutated patients, the CNS is involved in 20% to 25% of patients at the diagnosis of advanced disease.39 However, CNS progression occurs in approximately 35% to 50% of patients treated with a first- or second-generation EGFR-TKI.40 Data from preclinical and large-scale studies support the ability of osimertinib to cross the blood-brain barrier and penetrate CNS.41 In a pooled analysis of data from 2 AURA (extension trial and phase 2 trial)

![Figure 4 Evaluation of response. Thoracic Computed Tomography](image) After three months a CT scan was performed and a 68% reduction size in target lesions, compatible with partial response by RECIST criteria.
studies the ORR was 59% in patients with CNS involvement, with a median PFS of 8.2 months versus 12.4 months in those without brain metastases. The AURA 3 study randomized 34.5% of patients with CNS metastases. In those with CNS involvement, the ORR was 7% and the median PFS was longer among patients receiving osimertinib than chemotherapy (8.5 vs 4.2 months; HR, 0.32; 95% CI: 0.15-0.69; \( P = 0.004 \)). Finally, the FLAURA study included 21% of patients with controlled CNS metastases. Among patients with documented CNS metastases, median PFS was 9.6 months with standard EGFR-TKIs and 15.2 months with osimertinib (HR: 0.47; 95% CI: 0.30-0.74; \( P < 0.001 \)), reflecting good penetration in patients with CNS affection at diagnosis. A total of 6% of patients without brain metastases at diagnosis had CNS progression in the osimertinib arm, compared with 15% in the control arm, suggesting a preventive effect in patients with no CNS involvement at diagnosis.\(^{15}\)

In conclusion, there are 2 accepted sequences in the use of osimertinib. Nonetheless, upfront osimertinib has demonstrated an OS benefit, but not in the second-line setting. A prespecified subanalysis of OS in the FLAURA study showed scarce benefit in Asian patients [HR: 1.0 (95% CI: 0.75-1.32)] and L858R mutation carriers [HR: 1.0 (95% CI: 0.71-1.40)]. Despite this emergent information, these subgroup analyses were not sufficiently powered to show statistical differences. Nevertheless, it generates an interesting hypothesis about how to individualize available treatment options in a short future. On the other hand, the higher expression of commutation drivers could be a theoretical explanation of the absence of benefit in L858R carriers. Surprisingly, no differences have been reported between these 2 populations with other treatment strategies, like those in the RELAY study.

First-line therapy with osimertinib targeted the total population with EGFR-sensitive or resistant mutations. Future cost-effectiveness analyses are appropriate. This is especially needed for developing countries, where up-front treatment with osimertinib for a median of almost 19 months will triple the costs compared with sequential treatment. Interesting recent data were published from the GioTag study. This observational study with real-world data analyzed patients with EGFR mutation-positive NSCLC who received sequential treatment with afatinib and then osimertinib in those with a T790M mutation. The exploratory median OS was 41.3 months in the entire cohort (n = 203) and 45.7 months in patients with exon 19 deletion (n = 149). It seems proper to establish with future prospective studies which patients are going benefit the most with osimertinib as frontline therapy and which patients can be treated with a sequential strategy of a first- or second-generation TKI followed by osimertinib.

Results reported in the FLAURA study are some of the most relevant from the last decade for patients with advanced EGFR-mutated NSCLC. The benefit with osimertinib has been observed in a multicenter, phase III trial compared with the SoC (a first- or second-line EGFR-TKI), with a positive impact in PFS, OS, and CNS activity, and less toxicity despite more exposure to the drug. Undoubtedly, the study findings are practice changing, and it is already approved for first-line treatment in 78 countries worldwide. Special considerations and individualized recommendations are necessary for low-income or developing countries, which most of the time have limited access to novel drugs, where social and economic barriers exist. So, until now and if medication is available, it seems secure to bet for osimertinib as the best first-line option (Answer C), especially for patients with brain metastases. Real-life data about osimertinib in the frontline setting is necessary and may reinforce the benefit reported in controlled clinical trials. One question is for the Asian population and L858R-mutated carriers, which in the subgroup analyses do not have the same benefit as other populations. These populations must be studied in future trials with different treatment strategies. A combination of treatments are being tested in many trials. In a first analysis of data from the RELAY study, differences in the type of mutation and race were not observed, and erlotinib and ramucirumab represent a promising strategy. Many unanswered questions about combination therapy have arisen and will probably guide the future clinical practice in this disease.

**Outcome of the Case**

The patient started treatment with osimertinib 80 mg per day. After 2 weeks of treatment, a significant improvement of symptoms was achieved with good treatment tolerability.

At the last follow-up, the patient continues with a good functional status and is tolerating the treatment properly with a PFS of 17 months.\(^{27}\)

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

For full reference list, visit cancernetwork.com/EGFR-NSCLC
CONTINUING MEDICAL EDUCATION

The Impact of PI3K Inhibitors for the Treatment of Patients with Breast Cancer

LEARNING OBJECTIVES

Upon successful completion of this activity, you should be better prepared to:

• Explain the rationale for the use of PI3K inhibitors to treat patients with breast cancer.
• Outline the most important results from clinical trials exploring the use of PI3K inhibitors alone or in combination with other therapies for the treatment of patients with breast cancer.
• Implement strategies to identify and monitor adverse events associated with PI3K inhibitors to improve the outcome of patients with breast cancer.

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This activity is funded by PER®.
Phosphatidylinositol-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling is 1 of the most important intracellular pathways, which can be considered as a master regulator for cancer. It regulates cell growth, motility, survival, metabolism, and angiogenesis. Activation of the PI3K/AKT/mTOR pathway contributes not only to the development of tumor but is also involved in resistance to anticancer therapies. In estrogen receptor–positive (ER+) breast cancer, mutations in PIK3CA represent the most common genetic events, occurring at a frequency of 30% to 50%. Less commonly observed are mutations in PTEN (2% to 4%), AKT1 (2% to 3%), and phosphatidylinositol-3-kinase regulatory subunit alpha (PIK3R1: 1% to 2%). Similar findings were observed in HER2-positive breast cancer. The frequent occurrence of PI3K pathway activation makes it an attractive therapeutic target in breast cancer.

PI3K inhibitors are subdivided into dual PI3K/mTOR inhibitors, pan-PI3K inhibitors and isoform-specific inhibitors. Promising results with these agents have been observed in the treatment of advanced ER+ breast cancer. Preclinical data demonstrated that the presence of PIK3CA mutations in human epidermal growth factor receptor 2–positive (HER2+) breast cancer uncouples HER2 and PI3K signaling, rendering tumor cells resistant to HER2-targeted agents such as trastuzumab, while dual targeting of the HER2 and PI3K pathways was effective in overcoming trastuzumab resistance.

Several clinical trials have proved the potential of targeting PI3K/AKT/mTOR in breast cancer. The phase III BOLE-RO-2 study of the addition of everolimus to exemestane in the treatment of postmenopausal hormone receptor–positive (HR+) advanced breast cancer showed that the combination of everolimus with exemestane had increased efficacy compared with exemestane plus placebo with respect to progression-free survival in the range of 4 to 6 months in a patient population of postmenopausal, hormone receptor–positive, advanced breast cancer patients, suggesting that the addition of everolimus to exemestane is a potential viable treatment option for this patient population. However, increased toxicity profile was observed in the combination arm of exemestane plus placebo with respect to hyperglycemia, gastrointestinal toxicity, rash, fatigue, transaminitis, and skin rash. Hyperglycemia is an on-target side effect of PI3K inhibition and is often manageable with metformin. It remains to be determined whether isoform-specific inhibitors are more advantageous in widening the therapeutic window of PI3K inhibitors.

In clinical trials of PI3K inhibitors, common adverse events included hyperglycemia, gastrointestinal toxicity, fatigue, transaminitis, and skin rash. Hyperglycemia is an on-target side effect of PI3K inhibition and is often manageable with metformin. It remains to be determined whether isoform-specific inhibitors are more advantageous in widening the therapeutic window of PI3K inhibitors. Strategies that combine PI3K pathway inhibitors with inhibitors against receptor tyrosine kinases, or inhibitors against MEK, MYC, PARP, or STAT3 pathways, or agents that activate autophagy and apoptosis machineries, are being explored and there is continued effort to identify resistance mechanisms and predictors of therapeutic response.

Dr Tiffany Traina, MD reviews the role of the PI3K pathway in tumor development, clinical trials studying PI3K inhibitors for the treatment of patients with breast cancer, and how to manage and mitigate adverse events associated with PI3K inhibitors. Traina also discusses candidate partners for PI3K inhibitors and the future of PI3K clinical research.

Q: What is the rationale for the use of PI3K-targeted therapies to treat patients with breast cancer?

Dr Traina: The rationale for using PI3 kinase-targeted therapies in treating patients particularly with hormone receptor-positive advanced breast cancer, really dates to the fact that despite significant improvement in the management of ER-positive advanced disease with anti-estrogen therapies and CDK4/6 inhibitors, resistance to the therapies remains a problem in the setting of metastatic disease. And when you look at the literature, activation of growth factoring signaling pathways is one of the well described mechanisms of resistance to endocrine therapy.

Alterations in HER2, FGFR, and PI3 kinase can lead to estrogen independent signaling. The literature has shown, that using a next-generation sequencing platform called IMPACT, about 40% of the patients who had hormone receptor–positive/HER2-negative metastatic breast cancer had PI3 kinase mutations. And the patients in that series, tended to be young women with advanced disease, and about half of those had prior treatment with endocrine therapy and a median of about three prior lines of therapy. And so, you can see that PI3 kinase pathway activation...
is a common mechanism for escape from endocrine-targeted therapies. So up until now, for progression after first line therapy, we’ve had options like single agent aromatase inhibitors, or aromatase inhibitors with mTOR inhibitor everolimus. Otherwise, patients were progressing onto chemotherapy or, or clinical trials. But, unfortunately, the median progression for survival in that sort of second/third line base with agents like exemestane and everolimus was about seven-eight months. That was in the BOLERO-2 study. So, clearly, there was opportunity for targeting other pathways that were important as mechanisms of escape from endocrine-targeted therapies and PI3 kinase alterations are one of the most prevalent in this mechanism.

Q: Can you tell us about the identification of genetic predictors of response to PI3K inhibitors and some of the most important trials studying targeting PI3K pathway in breast cancer?

Dr Traina: One of the first trials that was important as more of a proof of concept for the relevance of the PI3 kinase pathway was BOLERO-2, and that was a study in post-menopausal women with ER-positive metastatic breast cancer that had progressed on nonsteroidal aromatase inhibitors. And in that setting, adding an mTOR inhibitor everolimus to the aromatase inhibitor exemestane improved median progression-free survival from about three months to almost eight months. And that significant about 55% improvement in progression-free survival. I think, more recently, the interesting and compelling studies that we’ve seen for PI3 kinase inhibitors include SANDPIPER and SOLAR-1. SANDPIPER was presented as an ASCO [The American Society of Clinical Oncology Annual Meeting] about a year ago, now, and this was a phase III trial of fulvestrant with or without the PI3 kinase inhibitor taselisib in women with the ER-positive/HER2-negative metastatic breast cancer, and they had recurred after or on aromatase inhibitor therapy. And, here, the most compelling signals of benefit came in patients who had PI3 kinase mutations, where median progression-free survival increased from about 5.5 months to 7.4 months. And that was about a 30% improvement in progression-free survival that meant significant. But that benefit appeared to be in PI3 kinase mutant patients, or tumors, I should say. The most exciting contemporary data that we have and that led to FDA approval of the PI3 kinase inhibitor comes from the SOLAR-1 data, and that was just published in the New England Journal of Medicine earlier this year.8 So alpelisib is unique in that it is an alpha-specific PI3 kinase inhibitor. This is the study of almost 600 women that were postmenopausal with ER-positive/HER2-negative metastatic breast cancer. They needed to have knowledge of the tumor’s PI3 kinase status that lead into categorization either for PI3 kinase mutant tumors with a randomization to fulvestrant with or without alpelisib, or a cohort of patients with kinase wild-type tumors, again, randomized to fulvestrant with or without alpelisib. Alpelisib was dosed at 300 mg oral daily continuous dosing and the primary end point of the study was specifically progression-free survival in those patients with PI3 kinase mutant tumors, as we’ve seen from now 2 prior trials having a PI3 kinase mutation. And this could be detected either in-tumor or even through cell-free DNA technology and that seemed to be the predictor for benefit from the PI3 kinase inhibitor. So, in SOLAR-1, the patients, who had PI3 kinase mutant ER-positive breast cancer, had an improvement in median progression-free survival from 5.7 months to about 11 months and that was about 35 percent improvement in median progression-free survival. And this is considered a positive study and led to FDA approval of alpelisib in those patients who have tumors that are PI3 kinase altered or mutant.

I think that when we see such compelling benefit from an agent like a PI3 kinase inhibitor in later line ER-positive advanced disease, it makes us wonder if we may have greater benefit moving this up earlier in the disease journey.

-Tiffany A. Traina, MD

Q: What are the adverse events associated with PI3K inhibitors?

Dr Traina: I think that the efficacy of these agents is quite compelling, and we, as oncologists, need to be aware of some of the unique, essentially, class-specific toxicities that come from PI3 kinase inhibitors. The top adverse events that are associated with these drugs include hyperglycemia, rash, fatigue, and a bit of diarrhea. And if we look specifically at the SOLAR-1 study, hyperglycemia of all grades was quite high at almost 64 percent, and significant grade 3 or 4 hyperglycemia occurred in about 37% of patients. We, as oncologists, need to be aware of how to manage this and counsel our patients. Often, we can begin with recommending low carbohydrate diets; diet that would follow ADA recommendations. We do recommend monitoring of blood glucose and even checking hemoglobin A1C at baseline. And then really having conversations with our endocrinologists and use an oral hypoglycemic, such as metformin, to help mitigate and manage the
hyperglycemia. Probably the second most common adverse event to be aware of that's treatment-related is rash. The rash of any grade occurred in about 36% of patients and significant grade 3 or 4 treatment-related rash occurred in ten percent of patients. In subsequent experience, it appears that you can prophylaxis for this rash with these antihistamines and even topical hydrocortisone. And so, I think it's important to educate our patients about potential for these adverse events and be able to mitigate and manage with supportive regimes. In SOLAR-1, about a quarter of patients discontinued PI3 kinase inhibitor because of adverse events and even despite that, we see that significant improvement in medium progression-free survival of nearly a doubling.

**Q:** What are some of the potential candidate partners of PI3K inhibitors, and what are some of the promises and challenges encountered with these combinations?

**Dr Traina:** I think that when we see such compelling benefit from an agent like a PI3 kinase inhibitor in later line ER-positive advanced disease, it makes us wonder if we may have greater benefit moving this up earlier in the disease journey. So, there are triplet strategy trials going on and planned to look at endocrine therapy plus CDK4/6 inhibitor, plus a PI3 kinase inhibitor in earlier metastatic breast cancer. All the CDK4/6 inhibitors are being explored in this space. And studies are looking at not just PI3 kinase inhibitors, but also other inhibitors of that pathway. There are AKT inhibitors in development, as well as, mTOR inhibitors. I think that one of the interesting areas is a combination of investigational oral agents plus PI3 kinase inhibitors so that we could, you know, hopefully move away from the intramural injection and see benefit from all-oral regimen, but that is very early on in development right now. So, there are a lot of interesting strategies to combine these pathway inhibitors earlier on with various endocrine therapies, as well as CDK4/6 inhibitors.

**Q:** How do you see PI3K's targeting strategies impacting the treatment of patients with breast cancer, and how do you see the future of PI3K clinical research heading in the future?

**Dr Traina:** So those are great questions. I think, foremost, in the short term for physicians and our patients, we're seeing the introduction of PI3 kinase inhibitors as a powerful option for women with endocrine-positive advanced disease to really see clinically meaningful prolongation and progression-free survival in that second line setting. Now, meaningful to be able to be on combination treatment for a year as opposed to less than half a year. And so, that is quite impactful for women living their lives with metastatic breast cancer. As we look towards the future, I think there are a lot of things to still figure out. Particularly, I think that we have a genomic predictor of benefit from the PI3 kinase inhibitor by having next-generation sequencing to enrich for which patients are going to benefit with PI3 kinase mutations. But we would love to be able to better understand now the mechanisms of resistance from PI3 kinase inhibitors. And also wonder about other interesting agents in development such as FGFR inhibitors, on how these may combine with other later-generation cell cycle inhibitors. You know, immunotherapy has been quite exciting in the space of triple negative breast cancer. But we wonder could there be opportunity for turning cold tumors hot and combining immunotherapy with these other PI3 kinase inhibitors. And, lastly, really in the future the ER-positive metastatic breast cancer, there's some exciting antibody drug conjugates coming into this space for when women have ultimately progressed through the endocrine therapy to have novel agents to move on to outside of traditional cytotoxic chemotherapy. So, there are a lot of exciting things on the horizon for this very large group of women that had advanced disease.

**REFERENCES**


For full reference list, visit cancerrnetwork.com/PI3K-Inhibitors
Physician-scientist Dr. Dennis Slamon has been studying cancer for over forty years. His dedication led to the development and approval of Herceptin, a revolutionary treatment designed to target cancers that stem from the HER2+ gene mutation. Dr. Slamon and his research partners, Axel Ullrich and H. Michael Shepard, have been awarded the 2019 Lasker-DeBakey Clinical Medical Research Award for their discovery.

Herceptin: A Decades-Long Journey

The road to Herceptin began in 1986, when Dr. Slamon met Axel Ullrich, a German scientist who was researching a new oncogene, HER2, that produces a protein—a receptor that tells cells when to grow and divide. Dr. Slamon hypothesized that HER2 alteration could be tied to aggressive breast malignancies. Together, he and Ullrich discovered that when present, the HER2 gene alteration is associated with an early relapse of the disease and a shortened survival.

After identifying a link between the HER2+ gene mutation and aggressive breast cancer, Dr. Slamon developed a theory suggesting that if researchers could identify what was broken in a tumor cell, and target only the broken parts, it could be possible to treat cancer without damaging healthy tissue.

According to Dr. Slamon: “I’d love to tell you it was some really sophisticated a-ha moment but it was pretty logical. If cancer is an abnormality in the regulation of growth, why not look at the genes and pathways that regulate growth and find out if they’re altered or broken? It’s that simple...and so that’s what drove our research questions that ultimately led to the development of Herceptin.”

But simple problems don’t always have simple answers. In fact, many members of the medical community initially doubted Dr. Slamon’s concepts. “There were a lot of preconceived notions that this approach couldn’t work because prior antibody therapies in cancer had failed,” Slamon said. “However, we had clear data to back us up and we really stuck to pursuing it. I grew up being told that I was only limited by my own ability. That always stayed with me. You have to be very careful and critical of your data, but if it looks correct, believe it and chase it despite what others may think.”

Beating the Odds

Slamon’s persistence paid off, and after several successful trials in mice, his revolutionary gene therapy was approved for human trials. In the early 1990s, women with the HER2+ subtype had an average life expectancy of three to five years following their diagnosis. Today, thanks to Herceptin, that average post-diagnosis life expectancy has more than doubled. Globally, an estimated 2.7 million to 3 million women with the HER2+ subtype have been treated with Herceptin with an average disease-free survival rate of seven to ten years.

A Continued Dedication to Care

Dr. Slamon currently serves as director of Clinical/Translational Research and director of the Revlon/UCLA Women’s Cancer Research Program at UCLA Health’s Jonsson Comprehensive Cancer Center. As the head of the division of hematology/oncology at UCLA Health, Dr. Slamon has continued to drive progress for targeted cancer therapies. In 2015, the FDA approved palbociclib (Ibrance), for women with advanced estrogen receptor-positive, HER2-negative breast cancer.

Slamon has been a member of the UCLA research community for over 40 years. His research has received multiple national and international awards, including the 2019 Sjöberg Prize from the Royal Swedish Academy of Sciences and Sweden’s Sjöberg Foundation; the Medal of Honor for Clinical Research, the American Cancer Society’s highest honor; and the Gairdner Foundation International Award.