Before we discuss the new indications for oncology therapies approved in 2018, a word about the novel drugs entering the market is in order, considering the new record set last year in drug approvals in the United States. The number of novel biologic drugs and new small-molecule drugs approved by the US Food and Drug Administration (FDA) reached a new record in 2018. According to the FDA, it approved a total of 59 new molecular entities (NMEs) and new biologic license applications (BLAs)1 (which includes the approval of the combination of fosnetupitant and palonosetron [Akynzeo] for intravenous use; this drug was initially approved by the FDA in 2014 as oral capsules that combine netupitant and palonosetron). This new record represents the greatest number of new drugs approved by the FDA in 1 year in the past decade (Figure).1

Many of the new drugs approved in 2018, especially among oncology drugs, represent new targeted therapies approved for a specific biologic marker or a new mutation, or drugs approved for the first time for a rare type of cancer, such as mogamulizumab-kpc (Poteligeo), a novel monoclonal antibody approved for relapsed or refractory mycosis fungoides or Sézary syndrome, which is also the first treatment approved by the FDA for Sézary syndrome.

“Mycosis fungoides and Sézary syndrome are rare, hard-to-treat types of non-Hodgkin lymphoma, and this approval fills an unmet medical need for these patients,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence.

Another novel medicine approved in 2018, iobenguane I 131 (Azedra), an intravenous radioactive therapy, is the first medicine approved by the FDA for the treatment of iobenguane scan–positive advanced or metastatic, unresectable rare adrenal gland tumors (ie, pheochromocytoma or paraganglioma). As a novel radioactive therapy and not an NME or a BLA, the FDA did not include iobenguane I 131 in its count of 59 novel agents approved in 2018, which includes NMEs and BLAs only.

“We’re at a critical point for the future of biosimilars in the U.S. Millions of American patients stand to benefit from increased utilization of these lower-cost, high-quality products. At the FDA, we’re committed to helping patients realize the public health benefits of a robust, competitive market for biosimilars.”

—Scott Gottlieb, MD

For a complete and detailed update of the novel NMEs, BLAs, and new biosimilars approved by the FDA in 2018, see page 14.

In all, 43 of the new drugs were designated by the FDA for a priority review, supporting the FDA’s increasing efforts to expedite the approval process to further encourage innovation in drug development.1 Of the newly approved agents, 19 were first-in-class medicines (which included 5 for cancer), and 34 were for rare or
orphan diseases that affect fewer than 200,000 people in the United States.

**BIOSIMILARS**

Furthermore, in 2018 the FDA approved 7 new biosimilars, 6 of which were for cancer (see page 17), using the FDA’s definition of a biosimilar having to demonstrate a high level of similarity to the originator drug but not being interchangeable with that reference drug.

In the FDA’s March 7, 2019, statement regarding the naming of biologics, then-FDA Commissioner Scott Gottlieb, MD, highlighted the need to increase access to biosimilars for the benefit of patients. “We’re at a critical point for the future of biosimilars in the U.S.,” Dr Gottlieb said. “Millions of American patients stand to benefit from increased utilization of these lower-cost, high-quality products. At the FDA, we’re committed to helping patients realize the public health benefits of a robust, competitive market for biosimilars.”

Dr Gottlieb further clarified the new naming convention for all biologic drugs by adding an arbitrary 4-letter suffix that is now being used not only for biosimilars but for all new biologic agents entering the market, and this suffix will remain the same for any future biosimilars for that originator drug, to enhance the understanding of the high pharmacologic similarity between the originator drug and the biosimilar agent.

In addition, the FDA is going to address the issue of interchangeability between a biosimilar and the originator drug. If biosimilars are considered interchangeable with the reference drug, it would allow the pharmacy to exchange a prescription for a reference drug with a biosimilar without the approval from the prescribing physician. Many states have enacted rules to disallow that practice, and the FDA has indicated it would issue an update on this topic sometime in 2019.

**ONCOLOGY OVERVIEW**

Continuing the trend from the recent past, oncology remains a key focus for drug manufacturers, as is evidenced by the 18 new oncology drugs (in addition to the 6 new biosimilars) approved by the FDA in 2018 for different types of cancer, as well as the many new indications approved for various oncology drugs already on the market, as featured in this article.

In light of the prominent role that oncology/hematology has in drug development today, the goal of this article is to provide a quick overview of the many new indications approved by the FDA in 2018 for different anticancer drugs, including the new indications for drugs already on the market.

As is reflected in this article, the majority of the new indications approved in 2018 in oncology are centered around several clinical areas, including breast and gynecologic cancers; genitourinary cancers; hematologic malignancies; and lung cancer.

The majority of the new indications approved in 2018 in oncology are centered around several clinical areas, including breast and gynecologic cancers, genitourinary cancers, hematologic malignancies, and lung cancer.

1. **Breast Cancer New Indications**

**KISQALI.** On July 18, 2018, the FDA approved 2 new indications for ribociclib (Kisqali; Novartis), an oral inhibitor of cyclin-dependent kinase (CDK)4/CDK6. One indication was for the treatment, in combination with an aromatase inhibitor, as initial endocrine-based therapy for pre-, peri-, or postmenopausal women with hormone receptor (HR)-positive, HER2-negative advanced or metastatic breast cancer. This approval was based on MONALEESA-7, a randomized, placebo-controlled clinical trial that demonstrated a progression-free survival (PFS) advantage for patients who received ribociclib plus an aromatase inhibitor and goserelin versus patients who received an aromatase inhibitor plus goserelin alone.

The second new indication for ribociclib was, in combination with fulvestrant, as an initial endocrine-based therapy or after disease progression while receiving endocrine-based therapy, for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer. This approval was based on the MONALEESA-3 study, a randomized, placebo-controlled study demonstrating a significant, an almost 8-month PFS advantage with ribociclib versus placebo in this patient population.

These 2 new indications were the first time the FDA used its Real Time Oncology Review program and the Assessment Aid program—2 pilot programs that enable the FDA to begin analyzing trial data before the drug application is submitted by the manufacturer. In this case, this early analysis enabled the FDA to approve the drug application within less than 1 month after it was submitted.

Ribociclib was previously approved, in combination with an aromatase inhibitor, as initial endocrine therapy for postmenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer.
LYNPARZA. On January 12, 2018, the FDA approved a new indication for olaparib (Lynparza; AstraZeneca), an oral poly (ADP ribose) polymerase (PARP) inhibitor, for the treatment of patients with deleterious or suspected deleterious germline BRCA-positive, HER2-negative metastatic breast cancer who have received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting.

This marks the first approval of a PARP inhibitor for the treatment of breast cancer. Concurrently, the FDA approved the BRACAnalysis CDx test to identify patients with deleterious or suspected deleterious germline BRCA-positive breast cancer who may be eligible for olaparib therapy.

“This class of drugs has been used to treat advanced, BRCA-mutated ovarian cancer and has now shown efficacy in treating certain types of BRCA-mutated breast cancer. This approval demonstrates the current paradigm of developing drugs that target the underlying genetic causes of a cancer, often across cancer types,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence.

“This approval demonstrates the current paradigm of developing drugs that target the underlying genetic causes of a cancer, often across cancer types.”

—Richard Pazdur, MD

Olaparib was granted this approval based on data from the randomized open-label clinical trial OlympiAD, which demonstrated a significant PFS advantage for olaparib compared with chemotherapy alone in this patient population.

Olaparib was previously approved for the treatment of patients with advanced ovarian cancer and a BRCA mutation who have received ≥3 chemotherapy treatments, and for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer whose tumors had a complete or partial response to chemotherapy. See also page 9.

VERZENIO. On February 26, 2018, the FDA approved abemaciclib (Verzenio; Eli Lilly), an oral inhibitor of CDK4/CDK6, in combination with an aromatase inhibitor, as initial endocrine-based therapy for postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer.

This approval was based on MONARCH 3, a randomized, placebo-controlled study that demonstrated a PFS advantage for the abemaciclib-containing combination treatment compared with letrozole or with anastrozole alone.

Abemaciclib was previously approved, in combination with fulvestrant, for the treatment of patients with HR-positive, HER2-negative metastatic breast cancer whose disease progressed after receiving endocrine therapy, and as monotherapy for adults with HR-positive, HER2-negative metastatic breast cancer whose disease progressed after endocrine therapy and chemotherapy.

2. Genitourinary Cancers New Indications

OPDIVO & YERVOY. On April 16, 2018, the FDA approved a new indication for the combination of the 2 immunotherapies, nivolumab and ipilimumab (Opdivo and Yervoy; Bristol-Myers Squibb), for the first-line treatment of patients with intermediate- or poor-risk advanced renal-cell carcinoma. The combination of nivolumab, a programmed death (PD)-1–blocking antibody, and ipilimumab, a human CTLA-4–blocking antibody, is the first immunotherapy combination regimen to be approved by the FDA for the treatment of patients with renal-cell carcinoma.

This approval was based on the open-label CheckMate-214 clinical trial, which demonstrated significant improvements in overall survival (OS) and response rates for nivolumab plus ipilimumab versus nivolumab plus sunitinib (Sutent).

This combination is also approved for the treatment of patients with unresectable or metastatic melanoma, and for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer. See also page 13.

XTANDI. On July 13, 2018, the FDA approved a new indication for enzalutamide (Xtandi; Astellas Pharma), an oral androgen receptor inhibitor, for the treatment of castration-resistant prostate cancer. This approval expands the treatment population for enzalutamide therapy to include patients with nonmetastatic prostate cancer. Enzalutamide is the first oral FDA-approved drug for the treatment of nonmetastatic or metastatic castration-resistant prostate cancer. This new indication was based on the placebo-controlled clinical trial PROSPER, which demonstrated that enzalutamide plus androgen-deprivation therapy increased metastasis-free survival compared with androgen-deprivation therapy alone.

Enzalutamide was previously approved for the treatment of patients with metastatic castration-resistant prostate cancer who had received chemotherapy with docetaxel, and for the treatment of chemotherapy-naive men with metastatic castration-resistant prostate cancer. Patients receiving enzalutamide should contin-
ue to receive concurrent gonadotropin-releasing hormone (GnRH) analog therapy or who have had bilateral orchiectomy.

**ZYTIGA.** On February 7, 2018, the FDA approved a new indication for abiraterone acetate (Zytiga; Janssen Biotech), an oral cytochrome P17 inhibitor, in combination with prednisone, for the treatment of patients with metastatic, high-risk, castration-sensitive prostate cancer. This was the first FDA approval of a treatment for this type of prostate cancer.

The approval of this new indication was based on data from LATITUDE, a randomized, placebo-controlled clinical trial that demonstrated an OS advantage in patients who received abiraterone acetate plus prednisone compared with those who received placebo.

Abiraterone acetate was already approved for the treatment of patients with metastatic, castration-resistant prostate cancer, including those who had previously received chemotherapy. Patients receiving abiraterone acetate should also receive a GnRH concurrently or should have had bilateral orchiectomy.

**3. Gynecologic Cancers New Indications**

**AVASTIN.** On June 13, 2018, the FDA approved a new indication for bevacizumab (Avastin; Genentech), a vascular endothelial growth factor (VEGF)-directed antibody, administered by IV infusion, in combination with carboplatin and paclitaxel, for the treatment of patients with stage III or stage IV epithelial ovarian, fallopian tube, or primary peritoneal cancer, followed by single-agent bevacizumab, after surgical resection.

This new approval was granted based on data from the double-blind, placebo-controlled GOG-0218 clinical trial, which demonstrated improvement in PFS for the bevacizumab-containing arm of the study compared with the placebo arm.

Bevacizumab was previously approved for the treatment of specific subsets of patients with metastatic colorectal cancer, cervical cancer, metastatic renal-cell carcinoma, non–small-cell lung cancer (NSCLC), or glioblastoma.

**KEYTRUDA.** On June 12, 2018, pembrolizumab (Keytruda; Merck), a PD-1–blocking antibody administered via IV infusion, was approved for the treatment of patients with recurrent or metastatic cervical cancer expressing PD ligand 1 (PD-L1), as determined by an FDA-approved test, whose disease progressed during or after chemotherapy.

This approval was based on response rate data from the nonrandomized, open-label, multicohort KEYNOTE-158 trial showing improved response rate with pembrolizumab in this patient population.

Pembrolizumab is approved for specific subgroups of adults with metastatic NSCLC, squamous-cell carcinoma of the head and neck, urothelial cancer, gastric cancer, hepatocellular carcinoma, Merkel-cell carcinoma, all solid tumors with the MSI-H biomarker (in adults and children), primary mediastinal large B-cell lymphoma, and classical Hodgkin lymphoma (in adults and children). See also pages 10, 12.

**LYNPARZA.** On December 19, 2018, the FDA approved a new indication for olaparib (Lynparza; AstraZeneca), an oral PARP inhibitor, for the maintenance treatment of adults with deleterious or suspected deleterious germline or somatic BRCA mutation–positive advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer whose disease had a complete or partial response to first-line platinum-based chemotherapy. The FDA concurrently approved the BRACAnalysis CDx test to identify patients with germline BRCA mutation and 1 of the 3 types of cancer.

The FDA approved this indication based on results of the SOLO-1 randomized, double-blind, placebo-controlled clinical trial, which demonstrated a significant PFS improvement with olaparib compared with placebo.

Olaparib was previously approved for the treatment of patients with advanced ovarian cancer and a BRCA mutation who have received ≥3 chemotherapy treatments, and for the maintenance treatment of patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer whose tumors had a complete or partial response to chemotherapy. See also page 8.

**RUBRACA.** On April 6, 2018, rucaparib (Rubraca; Clovis Oncology), an oral PARP inhibitor, was approved by the FDA for the maintenance treatment of adults with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who have had a complete or partial response to platinum-based chemotherapy.

Concurrently, the FDA approved FoundationFocus CDx (BRCA LOH), a next-generation sequencing assay, for the identification of homologous recombination deficiency (HRD) status in tumor samples. HRD is a new somatic mutation found in less than 10% of ovarian cancers.

This approval was based on results from the randomized, double-blind, placebo-controlled ARIEL3 clinical trial, which showed significant improvement in PFS with rucaparib compared with placebo.

Rucaparib was previously approved for the treatment of women with deleterious BRCA mutation (germline and/or somatic)-associated epithelial ovarian, fallopian tube, or primary peritoneal cancer who have received ≥2 chemotherapies.
4. Hematologic Malignancies New Indications

**ADCETRIS.** In 2018, the FDA approved 2 new indications for brentuximab vedotin (Adcetris; Seattle Genetics), an IV antibody-drug conjugate that targets CD30.

On March 20, 2018, the FDA approved brentuximab vedotin, in combination with chemotherapy, for the first-line treatment of adults with untreated stage III or stage IV classical Hodgkin lymphoma. This approval was based on the ECHELON-1 clinical trial, which showed an improvement in modified PFS for the brentuximab vedotin–containing arm versus a chemotherapy-only regimen.

“Today’s approval represents an improvement in the initial treatment regimens of advanced Hodgkin lymphoma that were introduced into clinical practice more than 40 years ago,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence.

On November 16, 2018, brentuximab vedotin received a second new indication as the first drug approved, in combination with chemotherapy, for the first-line treatment of patients with systemic anaplastic large-cell lymphoma or other CD30-expressing peripheral T-cell lymphomas, including angioimmunoblastic T-cell lymphoma and peripheral T-cell lymphoma not otherwise specified. This approval was based on data from the phase 3 ECHELON-2 clinical trial, which showed PFS and OS advantages with brentuximab vedotin plus chemotherapy versus chemotherapy alone.

“Today’s approval represents an improvement in the initial treatment regimens of advanced Hodgkin lymphoma that were introduced into clinical practice more than 40 years ago.” —Richard Pazdur, MD

Brentuximab vedotin was previously approved for the treatment of patients with classical Hodgkin lymphoma who are at high risk for disease relapse or progression, as autologous hematopoietic stem-cell transplantation consolidation, and after nonresponse to stem-cell transplantation or at least 2 previous chemotherapy regimens; and for the treatment of primary cutaneous anaplastic large-cell lymphoma or CD30-expressing mycosis fungoides in patients who have received systemic therapy.

**BLINCYTO.** On March 29, 2018, the FDA approved a new indication for blinatumomab (BlinCyto; Amgen), a bispecific CD19-directed CD3 T-cell engager administered by IV infusion, for the treatment of adults and pediatric patients with B-cell precursor acute lymphoblastic leukemia (ALL) who are in first or second complete remission, with minimal residual disease (MRD) of ≥0.1%. Blinatumomab is the first treatment approved by the FDA for patients with ALL and MRD.

“This is the first FDA-approved treatment for patients with MRD-positive ALL. Because patients who have MRD are more likely to relapse, having a treatment option that eliminates even very low amounts of residual leukemia cells may help keep the cancer in remission longer,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence.

“Today’s approval represents an improvement in the initial treatment regimens of advanced Hodgkin lymphoma that were introduced into clinical practice more than 40 years ago.” —Richard Pazdur, MD

This approval was based on data from the BLAST trial, which showed the achievement of undetectable MRD within 1 cycle of blinatumomab treatment and the extension of hematologic relapse-free survival. Blinatumomab was previously approved for the treatment of patients with relapsed or refractory B-cell precursor ALL.

**KEYTRUDA.** On June 13, 2018, pembrolizumab (Keytruda; Merck), a PD-1 inhibitor administered via IV infusion, was approved for the treatment of adults and pediatric patients with refractory primary mediastinal large B-cell lymphoma or in patients whose disease has relapsed after 2 or more previous lines of therapy.

This approval was based on results from an open-label, single-arm trial known as KEYNOTE-170, which demonstrated an overall response rate of 45% with pembrolizumab among this patient population.

Pembrolizumab is also approved for specific subsets of adults with metastatic NSCLC, recurrent or metastatic squamous-cell carcinoma of the head and neck, urothelial cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel-cell carcinoma, all solid tumors with the MSI-H biomarker (in adults and children), and classical Hodgkin lymphoma (in adults and children). See also pages 9, 12.
KYMRIAH. On May 1, 2018, the FDA approved a new indication for tisagenlecleucel (Kymriah; Novartis), a CD19-directed chimeric antigen receptor (CAR) T-cell genetically modified immunotherapy, for the treatment of adults with relapsed or refractory large B-cell lymphoma who have received 2 or more lines of systemic therapy, including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma, and DLBCL resulting from follicular lymphoma.

This new indication was based on data from the open-label, multicenter phase 2 JULIET trial, which showed an overall response rate of 50% with tisagenlecleucel among patients with relapsed or refractory DLBCL, and with DLBCL transformed from follicular lymphoma.

Tisagenlecleucel was previously approved for young patients aged <25 years with relapsed or refractory B-cell precursor ALL. Tisagenlecleucel was first approved by the FDA in 2017 as the first CAR T-cell therapy to receive approval in the United States. It is not indicated for the treatment of patients with primary central nervous system lymphoma.

TASIGNA. On March 22, 2018, nilotinib (Tasigna; Novartis), an oral tyrosine kinase inhibitor, was approved by the FDA for the first- and second-line treatment of pediatric patients aged ≥1 year with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in the chronic phase (CML-CP).

This new indication approval for nilotinib was based on the results of 2 open-label, multicenter trials, CAMN107A2120 and CAMN107A2203, that used major molecular response rate as the primary efficacy end point.

Nilotinib was previously approved by the FDA for the treatment of pediatric patients aged ≥1 year with Ph+ CML-CP that is resistant to or who are intolerant of tyrosine kinase inhibitor therapy, as well as adults with Ph+ CML-CP or Ph+ CML in the accelerated phase that is resistant to or who are intolerant of therapy that included imatinib.

VENCLEXTA. In 2018, the FDA approved 2 new indications for venetoclax (Venclexta; AbbVie/Genentech), an oral BCL-2 inhibitor.

On June 8, 2018, the FDA granted approval to venetoclax for the treatment of adults with chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL), with or without 17p deletion, who have received 1 or more previous therapies. This approval was based on data from the multicenter, open-label phase 3 MURANO study, which showed that a fixed duration of the combination of venetoclax plus immunotherapy with rituximab (Rituxan) in patients with CLL or SLL significantly increased PFS compared with the combination of chemotherapy with bendamustine (Bendeka) plus rituximab.

On November 21, 2018, the FDA granted accelerated approval to venetoclax, in combination with chemotherapy (with azacitidine or decitabine or low-dose cytarabine), for the treatment of newly diagnosed acute myeloid leukemia (AML) in older patients aged ≥75 years or in patients who have comorbidities that preclude the use of intensive induction chemotherapy.

This approval was based on 2 open-label, nonrandomized trials, Study M14-358 and Study M14-387, of patients aged ≥75 years with newly diagnosed AML or patients with AML and comorbidities that precluded the use of intensive induction chemotherapy. Venetoclax improved the rate of complete remissions and the duration of complete remissions compared with chemotherapy.

Venetoclax was previously approved for the treatment of patients with CLL and 17p deletion who received at least 1 previous therapy.

5. Lung Cancer New Indications

GILOTRIF. On January 12, 2018, the FDA approved a new indication for afatinib (Gilotrif; Boehringer-Ingelheim), an oral tyrosine kinase inhibitor that inhibits the epidermal growth factor receptor (EGFR), for first-line treatment of patients with metastatic NSCLC associated with a nonresistant EGFR mutation, as detected by an FDA-approved test.

This approval was based on the demonstration of durable responses to afatinib in patients with metastatic NSCLC that harbors nonresistant EGFR mutations other than exon 19 deletions or exon 21 L858R mutations (S768I, L861Q, and/or G719X) and were enrolled in 1 of 3 clinical trials. The safety and efficacy of afatinib have not been established in patients with resistant EGFR mutations.

Afatinib was previously approved by the FDA for the treatment of patients with metastatic squamous NSCLC that progressed after platinum-based chemotherapy.

IMFINZI. On February 16, 2018, the FDA approved a new indication for durvalumab (Imfinzi; AstraZeneca), a PD-L1–blocking antibody that is administered via IV infusion, for the treatment of patients with unresectable stage III NSCLC whose disease has not progressed after concurrent platinum-based chemotherapy and radiation therapy.

This approval was supported by interim data from the placebo-controlled PACIFIC trial, which demonstrated a significant improvement in PFS with durvalumab therapy compared with placebo.

Durvalumab was previously approved for the treatment of patients with locally advanced or metastatic
urothelial carcinoma whose disease progressed during or after platinum-containing chemotherapy or within 12 months of neoadjuvant or adjuvant platinum-based chemotherapy.

**KEYTRUDA.** On August 20, 2018, the FDA approved a new indication for pembrolizumab (Keytruda; Merck), a PD-1–blocking antibody administered by IV infusion, in combination with pemetrexed and platinum, for the first-line treatment of patients with metastatic nonsquamous NSCLC without EGFR or ALK mutations.

This approval was based on data from the CheckMate-032 clinical trial, which showed durable overall response rate in patients who received pembrolizumab plus chemotherapy compared with patients who received placebo plus chemotherapy.

Pembrolizumab is also approved for other subsets of patients with metastatic NSCLC, as well as specific subsets of adults with metastatic squamous-cell carcinoma of the head and neck, urothelial cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, Merkel-cell carcinoma, all solid tumors with the MSI-H biomarker (in adults and children), primary mediastinal large B-cell lymphoma, and classical Hodgkin lymphoma (in adults and children). See also pages 9, 10.

**OPDIVO.** On August 16, 2018, the FDA approved a new indication for nivolumab (Opdivo; Bristol-Myers Squibb), a PD-1–blocking antibody that is administered by IV infusion, for the treatment of patients with metastatic small-cell lung cancer that progressed after platinum-based chemotherapy and ≥1 other lines of therapy. This approval was based on data from the CheckMate-032 clinical trial, which showed durable overall response rates and increased duration of response with nivolumab after platinum-based therapy in patients with small-cell lung cancer.

Nivolumab is the first immunotherapy to receive approval for metastatic small-cell lung cancer, and the first new treatment in the past 20 years approved for this patient population.

Nivolumab was previously approved for subsets of patients with metastatic NSCLC; melanoma; advanced renal-cell carcinoma; metastatic squamous-cell carcinoma of the head and neck; hepatocellular carcinoma; locally advanced or metastatic urothelial carcinoma; MSI-H or dMMR metastatic colorectal cancer in adults and children; and classical Hodgkin lymphoma. See also pages 8, 13.

**TAGRISSO.** On April 18, 2018, the FDA approved a new indication for osimertinib (Tagrisso; AstraZeneca), an oral EGFR kinase inhibitor, for the first-line treatment of patients with metastatic NSCLC whose tumors have specific subtypes of EGFR mutations (ie, exon 19 deletions or exon 21 L858R mutations), as detected by an FDA-approved test. The approval of this new indication was based on the FLAURA study, which demonstrated a significant PFS advantage for osimertinib compared with gefitinib (Iressa) or erlotinib (Tarceva) in patients with metastatic NSCLC and EGFR exon 19 deletions or exon 21 L858R mutations.

Osimertinib was previously approved for the treatment of metastatic NSCLC with an EGFR T790M mutation, as detected by an FDA-approved test, in patients whose disease progressed during or after receiving EGFR tyrosine inhibitor therapy.

**TECENTRIQ.** On December 6, 2018, the FDA approved a new indication for atezolizumab (Tecentriq; Genentech), a PD-L1–blocking antibody administered by IV infusion, in combination with bevacizumab (Avastin), paclitaxel, and carboplatin, for first-line treatment of patients with metastatic nonsquamous NSCLC without EGFR or ALK gene mutation. This approval was based on the IMpower150 clinical trial, which demonstrated an OS advantage for patients who received the atezolizumab-containing 4-drug regimen compared with patients who received carboplatin, paclitaxel, and bevacizumab.

Atezolizumab was previously approved for the treatment of patients with metastatic NSCLC whose disease progressed during or after platinum-containing chemotherapy, as well as for the treatment of patients with locally advanced or metastatic urothelial carcinoma who are ineligible for cisplatin-containing chemotherapy and whose tumors express PD-L1.

### 6. Other Tumor Types New Indications

**KEYTRUDA.** On December 19, 2018, pembrolizumab (Keytruda; Merck), a PD-1–blocking antibody administered by IV infusion, received a new indication for the treatment of adults and pediatric patients with recurrent locally advanced or metastatic Merkel-cell carcinoma.

This approval was based on the nonrandomized, open-label KEYNOTE-017 clinical trial, which showed durable and complete responses in patients with recurrent, locally advanced or metastatic Merkel-cell carcinoma who had not received systemic therapy for their advanced disease.

Pembrolizumab is approved for specific subsets of patients with melanoma, metastatic NSCLC, recurrent or metastatic squamous-cell carcinoma of the head and neck, urothelial cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, all solid tumors with the MSI-H biomarker (in adults and children),
primary mediastinal large B-cell lymphoma, and classical Hodgkin lymphoma (in adults and children). See also pages 9, 10.

**LENVIMA.** On August 16, 2018, the FDA approved a new indication for lenvatinib (Lenvima; Eisai), an oral VEGF receptor kinase inhibitor, for the first-line treatment of patients with unresectable hepatocellular carcinoma.

This approval was based on the randomized, open-label, noninferiority clinical trial REFLECT, which compared lenvatinib with sorafenib. The study results demonstrated that lenvatinib was noninferior (but not superior) to sorafenib (Nexavar) in OS, and that lenvatinib therapy resulted in a significant improvement in PFS compared with sorafenib.

Lenvatinib was previously approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, and in combination with everolimus (Afinitor), for the treatment of patients with advanced renal-cell carcinoma after 1 antiangiogenic therapy.

**OPDIVO & YERVOY.** On July 10, 2018, the FDA approved a new indication for the combination of the 2 immunotherapies, nivolumab (Opdivo), a PD-1–blocking antibody, and ipilimumab (Yervoy), a human CTLA-4–blocking antibody, for the treatment of patients aged ≥12 years with MSI-H or dMMR metastatic colorectal cancer that progressed after a chemotherapy regimen with a fluoropyrimidine, or irinotecan.

This approval was based on results from the open-label, multicenter clinical trial CheckMate-142 of patients with MSI-H or dMMR metastatic colorectal cancer that progressed after a chemotherapy regimen with a fluoropyrimidine, oxaliplatin, and irinotecan.

This approval was based on the randomized, open-label, noninferiority clinical trial REFLECT, which compared lenvatinib with sorafenib. The study results demonstrated that lenvatinib was noninferior (but not superior) to sorafenib (Nexavar) in OS, and that lenvatinib therapy resulted in a significant improvement in PFS compared with sorafenib.

Lenvatinib was previously approved for the treatment of patients with locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer, and in combination with everolimus (Afinitor), for the treatment of patients with advanced renal-cell carcinoma after 1 antiangiogenic therapy.

**TAFINLAR & MEKINIST.** In 2018, the FDA approved 2 new indications for the combination of the 2 oral tyrosine kinase inhibitors, dabrafenib capsules and trametinib tablets (Tafinlar and Mekinist; Novartis).

On April 30, 2018, the FDA approved a new indication for the combination of dabrafenib and trametinib for the adjuvant treatment of patients with melanoma and a BRAF V600E or V600K mutation associated with lymph-node involvement after complete resection. This approval was based on the COMBI-AD study, a randomized, double-blind, placebo-controlled clinical trial that demonstrated a significant reduction in death or in disease relapse with the combination of dabrafenib plus trametinib compared with placebo.

On May 4, 2018, the FDA approved yet another indication for the dabrafenib plus trametinib combination, for the treatment of patients with locally advanced or metastatic unresectable anaplastic thyroid cancer and a BRAF V600E mutation, representing the “first FDA-approved drug for the treatment of patients with this aggressive form of thyroid cancer,” said Richard Pazdur, MD, Director of the FDA’s Oncology Center of Excellence. This approval was based on a multicenter, nonrandomized, open-label study demonstrating a high response to treatment with this drug combination in patients with locally advanced or metastatic unresectable anaplastic thyroid cancer and a BRAF V600E mutation.

This drug combination was previously approved by the FDA for the treatment of patients with unresectable metastatic melanoma and a BRAF V600E or V600K mutation, and for the treatment of patients with metastatic NSCLC and a BRAF V600E mutation.

References

