A Review of 2014 Cancer Drug Approvals, With a Look at 2015 and Beyond

Taylor Butler, PharmD; Stacey Maravent, PharmD; Jennifer Boisselle; Jose Valdes, PharmD; and Chris Fellner

INTRODUCTION

The number of cancer drugs approved each year by the Food and Drug Administration (FDA) has been growing steadily. From 1998 to 2001, the agency gave the green light to 17 new drugs or additional indications for older drugs in the cancer setting. In contrast, since the beginning of 2011, 55 new cancer drugs or additional indications for older treatments have received regulatory approval.1 With this accelerated entry of new cancer treatments onto the market, health care practitioners may find it difficult to keep abreast of the complex array of mechanisms of action, dosing regimens, monitoring parameters, and drug-preparation requirements.

In addition to the currently available cancer treatments, 771 new agents were reported to be in the pipeline in 2014, with more than 80% of them identified as first-in-class treatments.2 This article provides a concise overview of drugs added to the cancer armamentarium starting at the beginning of 2014 (Table 1); discusses new indications for previously approved cancer treatments; and highlights investigational agents under FDA review or in the oncology pipeline.

RAMUCIRUMAB FOR STOMACH AND LUNG CANCER

Ramucirumab (Cyramza, Eli Lilly) is a recombinant human immunoglobulin G1, monoclonal antibody that specifically binds to vascular endothelial growth factor receptor-2 (VEGFR-2).3 In April 2014, the FDA approved ramucirumab as a single agent or in combination with paclitaxel for the treatment of advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma that has progressed on or after prior fluoropyrimidine- or platinum-containing chemotherapy.4 A few months later, in December 2014, the FDA expanded the labeling for ramucirumab to include its use in combination with docetaxel for the treatment of metastatic non–small-cell lung cancer (NSCLC) with disease progression on or after platinum-based chemotherapy.5

By specifically binding to VEGFR-2, ramucirumab blocks the binding of several VEGF ligands (VEGF-A, VEGF-C, and VEGF-D). As a result, the drug inhibits ligand-stimulated activation of VEGFR2, thereby inhibiting ligand-induced proliferation and migration of human endothelial cells. Ramucirumab has been shown to inhibit angiogenesis in animals.3

Clinical Trial Experience

The FDA’s approval of ramucirumab for the second-line treatment of stomach cancer was supported by data from a phase 3, randomized, placebo-controlled trial involving 355 patients with locally advanced or metastatic gastric cancer (including GEJ adenocarcinoma) who had previously received platinum- or fluoropyrimidine-containing chemotherapy.3,6 The patients received an intravenous (IV) infusion of ramucirumab 8 mg/kg (n = 238) or placebo solution (n = 117) every two weeks. The ramucirumab group received a median of four doses (range, 1–34 doses), and the placebo group received a median of three doses (range, 1–30 doses). The study’s major efficacy outcome measure was overall survival (OS), and the supportive efficacy outcome measure was progression-free survival (PFS).

In the ramucirumab group, median OS was 5.2 months, compared with 3.8 months in the placebo group (P = 0.042). Ramucirumab-treated patients also had significantly longer median PFS compared with those given placebo (2.1 months versus 1.3 months, respectively; P < 0.001).3,6

The median rate of hypertension was notably higher in ramucirumab-treated patients compared with those given placebo (16% versus 8%, respectively). Otherwise, adverse event (AE) rates were mostly similar between the two groups.3,6

The FDA also based its approval on results from a second phase 3 study of ramucirumab in patients with gastric or GEJ adenocarcinoma.3,7 In this randomized, double-blind, placebo-controlled trial, 335 patients were randomly assigned to receive either IV ramucirumab 8 mg/kg or placebo on days 1 to 15, plus IV paclitaxel 80 mg/m² on days 1, 8, and 15, of a 28-day cycle. OS (the study’s primary endpoint) was significantly longer in the ramucirumab/paclitaxel group compared with the placebo/paclitaxel group (median 9.6 months versus 7.4 months; P = 0.017). Median PFS was also significantly longer between the two groups (4.4 months versus 2.9 months; P < 0.001). The overall response rate (ORR) was 28% in patients treated with ramucirumab compared with 16% in those given placebo (P < 0.001).3,7

The most common grade 3 or higher AEs occurring in the ramucirumab/paclitaxel group compared with the placebo/paclitaxel group included neutropenia (41% versus 19%, respectively), leukopenia (17% versus 22%), hypertension (14% versus 2%), fatigue (12% versus 5%), anemia (9% versus 10%), and abdominal pain (6% versus 3%).3,7

Regulatory approval of ramucirumab for the treatment of patients with NSCLC was based on findings from a phase 3, randomized, double-blind trial in which ramucirumab plus docetaxel was compared with placebo plus docetaxel in patients with stage IV lung cancer after progression on platinum-based therapy.3,8 A total of 1,253 patients were randomly assigned to receive either IV ramucirumab 10 mg/kg or placebo in combination with docetaxel 75 mg/m² every 21 days. The study’s major efficacy outcome measure was OS, and the supportive efficacy outcome measures were PFS and ORR.

OS and PFS were significantly improved in patients treated with ramucirumab plus docetaxel compared with those treated...
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## Table 1 Quick Reference for 2014 and Early 2015 Cancer Drug Approvals

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<th>Drug</th>
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<tr>
<td><strong>Blinatumomab</strong>&lt;sup&gt;27&lt;/sup&gt; (Blincyto, Amgen)</td>
<td>• Relapsed or refractory precursor B-cell acute lymphoblastic leukemia</td>
<td>Cycle 1: 9 mcg/D continuous IV infusion (D 1–7), then 28 mcg/D continuous infusion (D 8–28), followed by 14 days off treatment. Cycle 2 and beyond: 28 mcg/D continuous infusion (D 1–28) followed by 14 days off treatment. Premedicate with dexamethasone 20 mg IV. Follow specialized instructions based on dose for admixture. <strong>Boxed warning:</strong> The potential exists for life-threatening or fatal cytokine-release syndrome and life-threatening, severe, or fatal neurological toxicities. Neurological toxicities occurred in 50% of subjects receiving blinatumomab in clinical trials. Serious infections, including sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections, were seen in approximately 25% of patients receiving blinatumomab in studies. Neutropenia and febrile neutropenia, some life-threatening, have been observed. Advise patients to avoid driving and engaging in hazardous activities during administration.</td>
<td>• Infection • Neurological symptoms</td>
<td>-</td>
<td>Cost per cycle (42 days): Cycle 1: $70,946 Cycle 2 onward: $85,440</td>
</tr>
<tr>
<td><strong>Belinostat</strong>&lt;sup&gt;14&lt;/sup&gt; (Beleodaq, Spectrum Pharmaceuticals)</td>
<td>• Relapsed or refractory peripheral T-cell lymphoma</td>
<td>1,000 mg/m² IV daily (D 1–5) of a 21-day cycle. Belinostat has been associated with thrombocytopenia; leukopenia (neutropenia and lymphopenia); anemia; serious and fatal infections, including pneumonia and sepsis; hepatotoxicity and liver-function test abnormalities; tumor lysis syndrome in patients with advanced disease; and embryo-fetal toxicity. In one trial, 97% of patients experienced ADRs; the most common were nausea, fatigue, pyrexia, anemia, and vomiting.</td>
<td>• Infection • GI symptoms • CBC • CMP</td>
<td>-</td>
<td>Cost per cycle (21 days): M: $36,000 F: $32,400&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Ceritinib</strong>&lt;sup&gt;11&lt;/sup&gt; (Zykadia, Novartis)</td>
<td>• Metastatic, anaplastic lymphoma kinase–positive NSCLC</td>
<td>750 mg/D taken orally on an empty stomach. Severe or persistent GI toxicity (often requiring dose modifications) has been reported. In a phase 1 study, diarrhea, nausea, vomiting, or abdominal pain occurred in 96% of ceritinib patients, including severe cases in 14%. Ceritinib can also cause hepatotoxicity, interstitial lung disease or pneumonitis, QT-interval prolongation, hyperglycemia, bradycardia, or fetal harm.</td>
<td>• CBC • CMP • GI symptoms • Pulmonary symptoms • Cardiac function (QTc interval, heart rate)</td>
<td>-</td>
<td>Cost for 28 days: $15,118</td>
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<tr>
<td><strong>Idelalisib</strong>&lt;sup&gt;16&lt;/sup&gt; (Zydelig, Gilead Sciences)</td>
<td>• Chronic lymphocytic leukemia • Follicular B-cell non-Hodgkin’s lymphoma • Small lymphocytic lymphoma</td>
<td>150 mg taken orally twice daily. <strong>Boxed warning:</strong> Idelalisib treatment has the potential for fatal and/or serious hepatotoxicity; fatal and/or serious and severe diarrhea or colitis; fatal and serious pneumonitis; and fatal and serious intestinal perforation. Treatment with idelalisib has also been associated with severe cutaneous reactions, anaphylaxis, neutropenia, and embryo-fetal toxicity. Avoid coadministration with strong CYP3A inducers or substrates.</td>
<td>• CBC • CMP • GI symptoms • Pulmonary symptoms • Dermatological symptoms • Hypersensitivity reactions</td>
<td>-</td>
<td>Cost for 28 days: $8,862</td>
</tr>
<tr>
<td><strong>Lanreotide</strong>&lt;sup&gt;33&lt;/sup&gt; (Somatuline Depot, Ipsen)</td>
<td>• Unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs to improve PFS • Previously indicated for acromegaly</td>
<td>120 mg via deep SC injection once every 4 weeks. Inject in superior external quadrant of buttock, alternating injections between right and left sides. Lanreotide may cause gallstones, hypoglycemia, hyperglycemia, and a decreased heart rate. The most common ADRs in trials included abdominal and musculoskeletal pain, vomiting, headache, injection-site reaction, hyperglycemia, hypertension, and cholelithiasis.</td>
<td>• Gallstones • Glucose metabolism</td>
<td>-</td>
<td>Cost per cycle (28 days): $6,488</td>
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<td>Lenvatinib&lt;sup&gt;41,44&lt;/sup&gt; (Lenvima, Eisai Inc.)</td>
<td>• Locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer</td>
<td>24 mg orally, once daily</td>
<td>Lenvatinib raises the potential for hypertension, cardiac failure, arterial thromboembolic events, hepatotoxicity, proteinuria, renal failure and impairment, GI perforation and fistula formation, QT-interval prolongation, hypocalcemia, RPLS, hemorrhagic events, and embryo-fetal toxicity. Common ADRs included diarrhea, fatigue or asthenia, decreased appetite and weight, and nausea.</td>
<td>• Hypertension</td>
<td>Not available</td>
</tr>
<tr>
<td>Nivolumab&lt;sup&gt;24&lt;/sup&gt; (Opdivo, Bristol-Myers Squibb)</td>
<td>• Unresectable or metastatic melanoma and disease progression after ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor</td>
<td>3 mg/kg IV over 60 minutes once every 2 weeks until disease progression or unacceptable toxicity</td>
<td>Nivolumab has been linked with immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism, and hyperthyroidism, and may also cause embryo-fetal toxicity. The most common ADR was rash.</td>
<td>• Immune-mediated pneumonitis and colitis</td>
<td>Cost per cycle (14 days): M: $7,683 F: $6,475&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td>Olaparib&lt;sup&gt;28&lt;/sup&gt; (Lynparza, AstraZeneca)</td>
<td>• Monotherapy in patients with deleterious or suspected deleterious germline BRCA-mutated advanced ovarian cancer who have been treated with 3 or more prior lines of chemotherapy</td>
<td>400 mg (eight 50-mg capsules) taken orally twice daily for a total dose of 800 mg/D until disease progression or unacceptable toxicity</td>
<td>Myelodysplastic syndrome, acute myeloid leukemia, and pneumonitis—some fatal—have occurred in patients treated with olaparib, which has also been associated with embryo-fetal toxicity. The most common ADRs during ovarian cancer trials included nausea, vomiting, abdominal pain or discomfort, anemia, and diarrhea. Avoid concomitant use of strong CYP3A inhibitors or inducers.</td>
<td>• CBC at baseline and monthly thereafter</td>
<td>Cost for 28 days: $13,440</td>
</tr>
<tr>
<td>Palbociclib&lt;sup&gt;35–39&lt;/sup&gt; (Ibrance, Pfizer)</td>
<td>• ER-positive, HER2-negative advanced breast cancer in post-menopausal women in combination with letrozole as initial endocrine-based therapy</td>
<td>125 mg taken orally once daily for 21 consecutive days followed by 7 days off treatment</td>
<td>The most common ADRs associated with palbociclib in clinical studies included neutropenia, leukopenia, fatigue, anemia, upper respiratory tract infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis. In a phase 2 trial, the most common serious ADRs with palbociclib/letrozole included pulmonary embolism, back pain, and diarrhea.</td>
<td>• CBC at baseline, the beginning of cycles, D 14 of first 2 cycles</td>
<td>Cost per cycle (28 days): $11,820</td>
</tr>
<tr>
<td>Pembrolizumab&lt;sup&gt;20,22&lt;/sup&gt; (Keytruda, Merck)</td>
<td>• Metastatic melanoma with immune-mediated ADRs, including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. It may also cause fetal harm. In a phase 1 study, 79% of patients experienced treatment-related ADRs; the most common were fatigue, rash, pruritus, diarrhea, myalgia, and headache.</td>
<td>2 mg/kg IV once every 21 days</td>
<td>Pembrolizumab has been associated with immune-mediated ADRs, including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. It may also cause fetal harm. In a phase 1 study, 79% of patients experienced treatment-related ADRs; the most common were fatigue, rash, pruritus, diarrhea, myalgia, and headache.</td>
<td>• CMP</td>
<td>Cost per cycle (21 days): M: $9,219 F: $7,769&lt;sup&gt;2&lt;/sup&gt;</td>
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</tbody>
</table>

ADR = adverse drug reaction; CBC = complete blood count; CMP = complete metabolic panel; CYP = cytochrome P450; D = day; ER = estrogen receptor; F = females; GEJ = gastroesophageal junction; GEP-NETs = gastroenteropancreatic neuroendocrine tumors; GI = gastrointestinal; H1 = histamine 1 receptor; HER2 = human epidermal growth factor receptor 2; ILD = interstitial lung disease; IV = intravenous; M = males; NSCLC = non–small-cell lung cancer; PFS = progression-free survival; RPLS = reversible posterior leukoencephalopathy syndrome; SC = subcutaneous

* Assumes a weight of 89 kg for a male and 75 kg for a female

<sup>2</sup> Assumes a body surface area of 2 for a male and 1.8 for a female

<sup>4</sup> Assumes a weight of 89 kg for a male and 75 kg for a female

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| Ramucirumab     | - Advanced gastric cancer  
                 | - Advanced GEJ adenocarcinoma  
                 | - Metastatic NSCLC  | Boxed warning: Ramucirumab increases the risk of hemorrhage, including severe and sometimes fatal hemorrhagic events.  
Serious, sometimes fatal arterial thromboembolic events have been reported in trials. Treatment may also lead to hypertension, infusion-related reactions, GI perforation, impaired wound healing, clinical deterioration in cirrhosis patients, and reversible posterior leukoencephalopathy syndrome. Grade 3 or higher ADRs for ramucirumab combined with paclitaxel included neutropenia, leukopenia, hypertension, fatigue, anemia, and abdominal pain. | Gastric or GEJ: 8 mg/kg IV once every 14 days  
NSCLC: 10 mg/kg IV once every 21 days  
Premedicate with H2-antagonist (add dexamethasone and acetaminophen with previous reaction). | F: $7,344  
M: $8,715  
F: $7,344  
M: $10,894  
F: $9,180 |
| Ceritinib       | - NSCLC = non–small-cell lung cancer  
                 | - ALK = anaplastic lymphoma protein | | | |

ADR = adverse drug reaction; F = females; GEJ = gastroesophageal junction; GI = gastrointestinal; H1 = histamine 1 receptor; IV = intravenous; M = males; NSCLC = non–small-cell lung cancer

a Assumes a weight of 89 kg for a male and 75 kg for a female

b Assumes a body surface area of 2 for a male and 1.8 for a female

c Assumes a weight of 89 kg for a male and 75 kg for a female

with placebo plus docetaxel. Median OS was 10.5 months for the ramucirumab group compared with 9.1 months for the control group (P = 0.023). Median PFS was 4.5 months and 3.0 months in the two groups, respectively (P < 0.0001). The ORR (complete response [CR] plus partial response [PR]) was 23% for ramucirumab plus docetaxel and 14% for placebo plus docetaxel (P < 0.001).3,8

The most common grade 3 or higher AEs were neutropenia (49% of the ramucirumab group versus 40% of the control group), febrile neutropenia (16% versus 10%), fatigue (14% versus 10%), leukopenia (14% versus 12%), and hypertension (6% versus 2%).3

Treatment Considerations

The labeling for ramucirumab includes a boxed warning regarding an increased risk during treatment of hemorrhage, including severe and sometimes fatal hemorrhagic events. Moreover, serious, sometimes fatal arterial thromboembolic events have been reported in clinical trials of ramucirumab. Treatment with ramucirumab may also result in hypertension, infusion-related reactions, gastrointestinal (GI) perforation, impaired wound healing, clinical deterioration in patients with cirrhosis, and reversible posterior leukoencephalopathy syndrome.3

Cost

The average wholesale price (AWP) of Cyramza for a two-week treatment of gastric or GEJ cancer is $8,715 for an 89-kg man and $7,344 for a 75-kg woman. Cyramza is given once every three days for NSCLC; the AWP of the medication during that period would be $10,894 for an 89-kg man and $9,180 for a 75-kg woman.9

CERITINIB FOR LUNG CANCER

Ceritinib (Zykadia, Novartis) is an anaplastic lymphoma kinase (ALK) tyrosine kinase inhibitor that blocks proteins that promote the development of cancerous cells.10,11 It was approved by the FDA in April 2014 for the treatment of patients with metastatic ALK-positive NSCLC who have progressed on or are intolerant of crizotinib (Xalkori, Pfizer), the only other approved ALK tyrosine kinase inhibitor.11,12

The recommended dosage of ceritinib is 750 mg once daily until disease progression or unacceptable toxicity occurs. The capsules should be administered on an empty stomach (i.e., they should not be taken within two hours of a meal).11

Clinical Trial Experience

The antitumor activity of ceritinib was evaluated in a phase 1 trial that included a dose-escalation phase (n = 59) followed by an expansion phase (n = 71), in which all patients received treatment at the maximum dose established in the dose-escalation phase.10 The study’s primary objective was to determine the maximum tolerated dose (MTD) of ceritinib in adult patients with NSCLC tumors harboring an alteration in the ALK gene.

In the dose-escalation phase, patients received ceritinib at daily doses ranging from 50 mg to 750 mg. In the expansion phase, the MTD was determined to be 750 mg.10 A total of 114 patients received ceritinib at a dosage of 50 mg to 300 mg once daily. Of these patients, one (1%) had a confirmed CR; 65 (57%) had a confirmed PR; and 25 (22%) had stable disease. Twelve patients (11%) showed progressive disease, and 11 patients (10%) were not evaluable because of early withdrawal from the study. The ORR was 58%.9 Among 78 patients who received ceritinib at the MTD of 750 mg, 46 had a confirmed PR, for an ORR of 59%.10

Adverse events were primarily GI-related. Approximately half of the patients required dose modifications.9

Treatment Considerations

Treatment with ceritinib has been associated with severe or persistent GI toxicity. Diarrhea, nausea, vomiting, or abdominal
BELINOSTAT FOR ADVANCED LYMPHOMA

Belinostat (Beleodaq, Spectrum Pharmaceuticals), a hydroxamic acid histone deacetylase (HDAC) inhibitor, was approved by the FDA for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL) in July 2014.13

HDACs catalyze the removal of acetyl groups from the lysine residues of histones and some nonhistone proteins. In in vitro studies, belinostat caused the accumulation of acetylated histones and other proteins, thereby inducing cell-cycle arrest and/or apoptosis of some transformed cells. Belinostat showed preferential cytotoxicity toward tumor cells compared with normal cells.14

The recommended dosage of belinostat is 1,000 mg/m² administered over 30 minutes by IV infusion once daily on days 1 to 5 of a 21-day cycle. The cycles may be repeated every 21 days until disease progression or unacceptable toxicity occurs.14

Clinical Trial Experience

Belinostat was evaluated in an open-label, single-arm, nonrandomized trial involving 129 patients with PTCL.14,15 The patients were treated with belinostat 1,000 mg/m² administered over 30 minutes via IV infusion once daily on days 1 through 5 of a 21-day cycle. Treatment was continued in repeat cycles every three weeks until disease progression or unacceptable toxicity occurred. The study’s primary efficacy endpoint was the ORR (i.e., CR plus PR), as assessed by an independent review committee. The key secondary efficacy endpoint was the duration of response.14,15 In evaluable patients (n = 120), the ORR was 25.8%, including CRs in 10.8% and PRs in 15.0%. The median duration of response was 8.4 months, with a median duration of response of 5.6 weeks. Nine patients (7.5%) received a stem-cell transplant after treatment.14,15

Of the 129 enrolled patients, 97% experienced AEs. The most common AEs included nausea (42%), fatigue (37%), pyrexia (35%), anemia (32%), and vomiting (29%). The most common grade 3 or 4 toxicities were thrombocytopenia (13%), neutropenia (13%), and anemia (10%). AEs led to treatment discontinuation in 7% of patients.14,15

Treatment Considerations

Treatment with belinostat has been associated with thrombocytopenia; leukopenia (neutropenia and lymphopenia); anemia; serious and fatal infections, including pneumonia and sepsis; hepatotoxicity and liver-function test abnormalities; tumor lysis syndrome in patients with advanced disease; and embryo-fetal toxicity.14 Because belinostat is primarily (80% to 90%) metabolized by hepatic uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1), clearance of the drug could be decreased in patients with reduced UGT1A1 activity (e.g., patients with the UGT1A1*28 allele). The starting dose of belinostat should be reduced from 1,000 mg/m² to 750 mg/m² in patients known to be homozygous for the UGT1A1*28 allele to minimize dose-limiting toxicities.14

Cost

The AWP of a 28-day supply of Zykadia is $15,118.9

IDELALISIB FOR RELAPSED CLL AND LYMPHOMA

Idelalisib (Zydelig, Gilead Sciences) is a kinase inhibitor indicated for the treatment of three blood cancers: 1) relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other comorbidities; 2) relapsed follicular B-cell non-Hodgkin’s lymphoma in patients who have received at least two prior systemic therapies; and 3) relapsed small lymphocytic lymphoma (SLL) in patients who have received at least two prior systemic therapies.10 The treatment was approved in July 2014.17

Idelalisib achieves its anticancer effects by inhibiting phosphatidylinositol 3-kinase delta (PI3Kδ).18 PI3Kδ promotes the growth and survival of malignant B cells by mediating B-cell receptor signaling. Mutations in B cells have been linked to the development of certain leukemias and lymphomas; as a result, researchers identified the B-cell receptor signaling pathway as a promising target for the treatment of hematological malignancies of B-cell origin.18

The recommended maximum starting dosage of idelalisib is 150 mg twice daily. The tablet can be taken with or without food.16

Clinical Trial Experience

Idelalisib was studied in combination with rituximab in a phase 3, randomized, double-blind, placebo-controlled trial involving 220 patients with relapsed CLL.16,18 Those with decreased renal function, previous therapy-induced myelo-suppression, or major coexisting illnesses were randomly assigned to receive rituximab and either idelalisib (150 mg; n = 110) or placebo (n = 110) twice daily. The patients’ median age was 71 years (range, 47 to 92 years). Nearly all (96%) of the patients had received anti-CD20 monoclonal antibodies. The study’s primary endpoint was PFS.

At 24 weeks, the PFS rate was 93% for idelalisib plus rituximab compared with 46% for placebo plus rituximab (P < 0.001). Median PFS was 5.5 months in the placebo/rituximab group and was not reached in the idelalisib group (P < 0.001).18 Patients treated with idelalisib plus rituximab showed a significantly higher response rate compared with those given placebo plus rituximab (81% versus 13%, respectively; P < 0.001). The idelalisib group also demonstrated a significantly longer OS rate at 12 months (92% versus 80%; P = 0.02).18

Among patients treated with idelalisib plus rituximab, the five most common AEs were pyrexia, fatigue, nausea, chills, and diarrhea. Among patients treated with placebo plus rituximab, the AEs were similar to those in the idelalisib group, with the most common being infusion-related reactions, fatigue, cough, nausea, and dyspnea.18

Idelalisib was also evaluated in a phase 3, open-label study involving 125 patients with indolent non-Hodgkin’s lymphomas...
who had not shown a response to rituximab and an alkylating agent or had experienced a relapse within six months after receipt of those therapies. Subtypes of indolent non-Hodgkin’s lymphoma included SLL, follicular lymphoma, marginal-zone lymphoma, and lymphoplasmacytic lymphoma. The patients’ median age was 64 years (range, 33 to 87 years).

A total of 125 patients received idelalisib 150 mg twice daily until the disease progressed or the patient withdrew from the study. The primary endpoint was the ORR; secondary endpoints included the duration of response, PFS, and safety. The ORR was 57% (71 of 125). Seven patients (6%) had a CR; 63 patients (50%) had a PR; and one patient (1%) had a minor response. Among 120 evaluable patients, 110 (90%) experienced a reduction in the size of their lymph nodes during treatment. The median time to a response was 1.9 months, and the median duration of response was 12.5 months. The median PFS was 11.0 months, with 47% of patients remaining progression-free at 48 weeks. At the time of data cutoff, the median OS was 20.3 months, and OS at 12 months was estimated to be 80%.

The most common AEs included diarrhea (43%), fatigue (30%), nausea (30%), cough (29%), and pyrexia (28%). The most common serious AEs (grade 3 or greater) were diarrhea (13%), pneumonia (7%), and dyspnea (3%). The prescribing information for idelalisib also includes data from a small (n = 26) single-arm trial in patients with relapsed SLL. In this study, all of the subjects had relapsed within six months after treatment with rituximab and an alkylating agent, and had received at least two prior therapies. The patients’ median age was 65 years (range, 50 to 87 years). At baseline, 27% of the patients had extranodal involvement.

The patients received idelalisib 150 mg twice daily until evidence of disease progression or unacceptable toxicity. The study’s primary endpoint was the ORR. Fifteen patients showed a PR to treatment, for an ORR of 58%. The median time to response was 1.9 months, and the median duration of response was 11.9 months.

**Treatment Considerations**

The labeling for idelalisib includes a boxed warning regarding the potential for fatal and/or serious hepatotoxicity; fatal and/or serious and severe diarrhea or colitis; fatal and serious pneumonitis; and fatal and serious intestinal perforation. In addition, treatment with idelalisib has been associated with severe cutaneous reactions, anaphylaxis, neutropenia, and embryo-fetal toxicity. Clinicians should avoid the coadministration of idelalisib with strong cytochrome P450 (CYP) 3A inducers or with CYP3A substrates.

**Cost**

Based on the AWP, a 28-day supply of Zydelig at the maximum starting dose of 150 mg would cost $8,862.

**PEMBROLIZUMAB FOR ADVANCED MELANOMA**

Pembrolizumab (Keytruda, Merck)—formerly known as lambrolizumab—is a human programmed death receptor-1 (PD-1)–blocking antibody indicated for the treatment of patients with advanced (unresectable or metastatic) melanoma and disease progression following treatment with ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor. The drug received FDA approval in September 2014.

Pembrolizumab blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. The binding of these ligands to the PD-1 receptor on cytotoxic T cells inhibits both the proliferation of these cells and the production of cytokines. PD-1 ligands are up-regulated in some tumors, and signaling through the PD-1 pathway may contribute to the inhibition of active T-cell immune surveillance of tumors.

The recommended starting dose of pembrolizumab is 2 mg/kg administered as an IV infusion over 30 minutes every three weeks until disease progression or unacceptable toxicity occurs.

**Clinical Trial Experience**

The safety and antitumor activity of pembrolizumab were evaluated in a phase 1, open-label study involving 135 patients with advanced melanoma. Forty-eight patients (36%) had received ipilimumab, and 87 (64%) had not. Initially, the patients received IV pembrolizumab at a dosage of 10 mg/kg every two weeks. Subsequently, additional patients were enrolled in concurrent cohorts that received pembrolizumab at 10 mg/kg or 2 mg/kg every three weeks. Tumor responses were assessed every 12 weeks.

The ORR across all treatment cohorts, according to immune-related response criteria, was 37%. The highest response rate (52%) was observed in the group that received 10 mg/kg every two weeks. The overall median PFS among the 135 patients was longer than seven months. Of the 52 patients who had shown a response, 42 (81%) were still receiving treatment at the time of the analysis.

Of the 135 patients who received at least one dose of pembrolizumab, 79% experienced treatment-related AEs of any grade, and 13% reported grade 3 or grade 4 drug-related AEs. The most common AEs associated with pembrolizumab included fatigue (41%), rash (28%), pruritus (28%), diarrhea (27%), myalgia (16%), and headache (14%).

In an extension of the previous phase 1, open-label study, the efficacy and safety of pembrolizumab 2 mg/kg was compared with that of pembrolizumab 10 mg/kg in 173 patients with ipilimumab-refractory advanced melanoma. Adult patients whose disease had progressed after at least two doses of ipilimumab were randomly assigned to receive IV pembrolizumab at 2 mg/kg every three weeks (n = 89) or 10 mg/kg every three weeks (n = 84) until disease progression or unacceptable toxicity occurred, or until the withdrawal of consent. The trial’s primary endpoint was the ORR. The median follow-up period was eight months.

The ORR was 26% at both doses: 21 of 81 patients in the 2 mg/kg group, and 20 of 76 patients in the 10 mg/kg group (P = 0.96). Most responses occurred by week 12. A reduction from baseline in the size of the target lesion was experienced by 73% of the 2 mg/kg group. The same result was observed in 68% of the 10 mg/kg group. Median PFS was 22 weeks in the 2 mg/kg group and 14 weeks in the 10 mg/kg.

For both doses, the most common AEs of any grade included fatigue (33% for 2 mg/kg versus 37% for 10 mg/kg), pruritus (26% versus 19%), and rash (18% versus 18%).
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**Treatment Considerations**

Treatment with pembrolizumab has been associated with immune-mediated AEs, including pneumonitis, colitis, hepatitis, hypophysitis, nephritis, hyperthyroidism, and hypothyroidism. The drug may also cause fetal harm.20

No formal drug-interaction studies have been conducted with pembrolizumab.20

**Cost**

A three-week treatment with Keytruda, using the AWP of the powder for solution, would cost $9,219 for an 89-kg man and $7,769 for a 75-kg woman.9

**BLINATUMOMAB FOR ACUTE LYMPHOBlastic LEUKEMIA**

Blinatumomab (Blincyto, Amgen) is a bispecific T-cell engaging (BiTE) antibody that directs cytotoxic T cells to CD19-expressing target cells.24–27 The drug was approved by the FDA in December 2014 for the treatment of patients with relapsed or refractory Philadelphia chromosome–negative (Ph−) precursor B-cell acute lymphoblastic leukemia (ALL), a rare form of ALL.26

In its biphasic mode of action, blinatumomab binds to CD19 expressed on the surface of cells of B-lineage origin and to CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, the up-regulation of cell-adhesion molecules, the production of cytolytic proteins, the release of inflammatory cytokines, and the proliferation of T cells. These activities result in the lysis of CD19-positive cells.24,26

A cycle of treatment with blinatumomab consists of four weeks of continuous IV infusion followed by a two-week treatment-free interval. In cycle 1, blinatumomab is administered at 9 mcg per day on days 1 to 7 and at 28 mcg per day on days 8 to 28 in patients weighing at least 45 kg. A treatment course consists of up to two cycles of blinatumomab for induction followed by three additional cycles for consolidation treatment (up to a total of five cycles).27

**Clinical Trial Experience**

In a pivotal phase 2, open-label study,24,27 the efficacy and toxicity of blinatumomab were evaluated in 185 patients (median age, 39 years; range, 18–79 years) with Ph− relapsed/recurrent ALL. Blinatumomab was administered by continuous IV infusion (four weeks on and two weeks off) for up to five cycles (cycle 1 only: 9 mcg per day on days 1 to 7, then 28 mcg per day). The trial’s primary endpoint was CR or CR with partial hematological recovery (CRh) within the first two cycles.

Sixty patients (32.4%) achieved CR, and 17 patients achieved CRh (9.2%), for an ORR of 41.6%. The median duration of CR was 6.7 months (range, 0.46–16.5 months), and the median duration of CRh was 5.0 months (range, 0.13–8.8 months).27

In a preliminary analysis,24 the most common AEs were pyrexia (59%), headache (35%), and febrile neutropenia (29%). The most common grade 3 or greater AEs included febrile neutropenia (26%), anemia (15%), and neutropenia (15%). The most common grade 3 or greater nervous system disorders were headache (4%), encephalopathy (3%), and ataxia (2%).

In another phase 2, open-label study,23 the efficacy of blinatumomab was evaluated in 21 patients with minimal residual disease (MRD)-positive B-lineage ALL. Patients with MRD persistence or relapse after induction and consolidation therapy were included. Blinatumomab was administered as a four-week continuous IV infusion at a dosage of 15 mcg/m² per day. Sixteen of the 21 patients (76%) became MRD-negative. Of the 16 responders, 12 had been refractory to prior chemotherapy. After a median follow-up period of 405 days, the probability of relapse-free survival was 78%.25

The most common grade 3 or grade 4 AE was lymphopenia, which was completely reversible.25

**Treatment Considerations**

The labeling for blinatumomab includes a boxed warning regarding the potential for cytokine-release syndrome (CRS), which may be life-threatening or fatal, and neurological toxicities, which may be life-threatening, severe, or fatal. Patients should be closely monitored for the signs and symptoms of CRS. Neurological toxicities have occurred in 50% of subjects receiving blinatumomab in clinical trials.27

Serious infections, including sepsis, pneumonia, bacteremia, opportunistic infections, and catheter-site infections, were observed in approximately 25% of patients receiving blinatumomab in clinical studies. During treatment, patients should be monitored for the signs and symptoms of infection.27

Because of the potential for neurological events, including seizures, patients receiving blinatumomab are at risk for loss of consciousness. They should therefore be advised to avoid driving or operating heavy machinery while taking blinatumomab.27

Neutropenia and febrile neutropenia, including life-threatening cases, have been observed during treatment with blinatumomab.27

No formal drug-interaction studies have been conducted with blinatumomab. The initiation of treatment with blinatumomab causes the transient release of cytokines, which may inhibit hepatic CYP450 enzymes.27

**Cost**

Each cycle of Blincyto lasts six weeks, with four weeks of continuous infusion followed by two treatment-free weeks. Based on the AWP and recommended dosing schedule, the first six-week cycle will cost $70,946, while subsequent cycles will cost $85,440.9

**OLAPARIB FOR ADVANCED OVARIAN CANCER**

Olaparib (Lynparza, AstraZeneca) is a poly (ADP-ribose) polymerase (PARP) inhibitor indicated as monotherapy for patients with deleterious or suspected deleterious germline BRCA-mutated (gBRCAm) advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy.28

The drug was approved by the FDA in December 2014.29

PARP enzymes are involved in normal cellular homeostasis, such as DNA transcription and repair. As a PARP inhibitor, olaparib blocks these processes. In vitro studies have shown that olaparib-induced cytotoxicity may involve the creation of PARP-DNA complex, resulting in disruption of cellular homeostasis and cell death.28,29
The recommended dosage of olaparib is 400 mg (eight 50-mg capsules) twice daily, for a total daily dose of 800 mg. Treatment is continued until disease progression or unacceptable toxicity occurs.28

Clinical Trial Experience
The FDA’s approval of olaparib was based on efficacy data from a single-arm, open-label, phase 2 study in patients with deleterious or suspected deleterious gBRCAm-related advanced cancers,20 as well as on safety data from several other olaparib studies, including a placebo-controlled study.

In the open-label, phase 2 study, the efficacy of olaparib was evaluated in 137 patients with measurable gBRCAm-related advanced ovarian cancer treated with three or more prior lines of chemotherapy. All of the patients received olaparib at a dosage of 400 mg twice daily as monotherapy until disease progression or unacceptable toxicity occurred.29,30 The trial results demonstrated an ORR of 34% (CR, 2%; and PR, 32%). The median response duration was 7.9 months.28,30

Among 223 patients with gBRCAm-associated ovarian cancer who received olaparib in clinical studies, the most common AEs (all grades) included nausea (64%), vomiting (43%), abdominal pain or discomfort (43%), anemia (34%), and diarrhea (31%). AEs led to dose interruptions in 40% of patients, to discontinuation in 7%, and to dose reductions in 4%.28

Treatment Considerations
Myelodysplastic syndrome and acute myeloid leukemia have occurred in patients treated with olaparib, and some cases were fatal. Olaparib has also been associated with cases of pneumonitis (some fatal) and embryo-fetal toxicity.28

Olaparib is primarily metabolized by CYP3A4. Clinicians should avoid the concomitant use of strong CYP3A inhibitors or inducers when administering the drug.28

Cost
The AWP for a 28-day supply of the recommended 16 pills a day is $13,440.9

LANREOTIDE FOR NEUROENDOCRINE TUMORS
In December 2014, the FDA approved lanreotide (Somatuline Depot Injection, Ipsen) for the treatment of patients with unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Fifty-five percent of the patients (113 of 204) had neuroendocrine tumors outside the pancreas. The patients were randomly assigned to receive either lanreotide 120 mg (n = 101) or placebo (n = 103) subcutaneously every four weeks. The primary efficacy endpoint was PFS, as determined by independent radiology review.31,33 The trial demonstrated a significant prolongation of PFS in the lanreotide arm (P < 0.001). Median PFS in the lanreotide arm had not been reached at the time of the final analysis and was expected to exceed 22 months. Median PFS in the placebo arm was 16.6 months.31,33

Safety data were evaluated in the 101 patients who received at least one dose of lanreotide 120 mg. The most common AEs included abdominal pain (34%), musculoskeletal pain (19%), vomiting (19%), headache (18%), injection-site reaction (15%), hyperglycemia (14%), hypertension (14%), and cholelithiasis (14%). The most common severe AEs included abdominal pain (6%), musculoskeletal pain (2%), and vomiting (2%).31,33

Treatment Considerations
Gallstones may occur during treatment with lanreotide, and clinicians should consider periodic monitoring. The drug may also cause hypoglycemia and/or hyperglycemia. Glucose monitoring is therefore recommended, and antidiabetic treatment should be adjusted accordingly. Lanreotide may also cause a decrease in heart rate. It should be used with caution in at-risk patients.33

Cost
A four-week supply of Somatuline Depot, using the AWP of a 120-mg/0.5-mL package, costs $6,488.9

NIVOLUMAB FOR ADVANCED MALIGNOMAS
Nivolumab (Opdivo, Bristol-Myers Squibb), a PD-1–blocking antibody, was approved by the FDA in December 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression after treatment with ipilimumab and, if BRAF V600 mutation-positive, a BRAF inhibitor.34,35

Nivolumab is a human immunoglobulin G4 monoclonal antibody that binds to the PD-1 receptor and blocks interactions with its ligands, PD-L1 and PD-L2. This activity releases PD-1 pathway-mediated inhibition of the immune response, including the antitumor immune response. Up-regulation of PD-1 ligands occurs in some tumors, and signaling through this pathway can contribute to the inhibition of active T-cell immune surveillance of tumors. In mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.34

The recommended dosage of nivolumab is 3 mg/kg administered as an IV infusion over 60 minutes every two weeks until disease progression or unacceptable toxicity occurs.34

Clinical Trial Experience
Nivolumab was evaluated in a phase 3, open-label trial that randomly assigned patients with unresectable or metastatic melanoma to receive either IV nivolumab (3 mg/kg every two weeks) or the investigator’s choice of chemotherapy; either single-agent dacarbazine 1,000 mg/m² every three weeks or the combination of carboplatin AUC 6 every three weeks plus paclitaxel.
175 mg/m² every three weeks. The patients were required to have disease progression during or after ipilimumab treatment and, if BRAF V600 mutation-positive, a BRAF inhibitor. Tumor assessments were conducted every nine weeks after randomization, then every six weeks for the first year and every 12 weeks thereafter. The median time on therapy was 5.3 months.34,36

ORR was assessed as planned in the first 120 patients treated with nivolumab. The confirmed ORR by independent radiology review was 32%, consisting of four CRs and 34 PRs. Of the 38 patients with responses, 33 (87%) had ongoing responses, with durations ranging from more than 2.6 months to more than 10 months.34,36 Reductions of 50% or greater in target-lesion burden occurred in 82% (31 of 38) of nivolumab responders. An additional 10 nivolumab-treated patients (8%) showed immune-related response patterns (i.e., a 30% or greater reduction in target-lesion tumor burden).36

Grade 3 or grade 4 drug-related AEs occurred in 9% of the patients treated with nivolumab, and discontinuations due to drug-related AEs (of any grade) occurred in 2%.36

Treatment Considerations
Treatment with nivolumab has been associated with immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism, and hyperthyroidism. Nivolumab may also cause embryo-fetal toxicity.34

Cost
A two-week treatment with Opdivo would cost $7,683 for an 89-kg man and $6,475 for a 75-kg woman based on the AWP.9

PALBOCICLIB FOR ADVANCED BREAST CANCER
In February 2015, the FDA granted accelerated approval to the kinase inhibitor palbociclib (Ibrance, Pfizer), in combination with the aromatase inhibitor letrozole (Femara, Novartis), for the treatment of postmenopausal women with estrogen-receptor–positive (ER+) human epidermal growth factor receptor 2–negative (HER2−) advanced breast cancer as initial endocrine-based therapy for their metastatic disease.37,38

Palbociclib exerts its antitumor effect by inhibiting cyclin-dependent kinase (CDK) 4 and 6. Cyclin D1 and CDK4/6 are downstream of signaling pathways that lead to cellular proliferation. In vivo studies in a patient-derived, ER+ breast cancer model demonstrated that the combination of palbociclib and letrozole increased the inhibition of downstream signaling and tumor growth compared with each drug alone.38

The recommended dosage of palbociclib is a 125-mg capsule taken orally once daily for 21 consecutive days followed by seven days off treatment, comprising a complete cycle of 28 days. Palbociclib should be taken with food in combination with letrozole 2.5 mg once daily given continuously throughout the 28-day cycle.38

Clinical Trial Experience
The FDA’s approval of palbociclib was based on results from an open-label, phase 2 study involving 165 women with ER+, HER2− advanced breast cancer.38,39 The participants were randomly assigned to receive either oral palbociclib (125 mg given once daily for three weeks followed by one week off during 28-day cycles) plus continuous oral letrozole (2.5 mg daily) (n = 84) or continuous oral letrozole alone (n = 81). The patients received treatment until progressive disease, unmanageable toxicity, or consent withdrawal occurred. The study’s primary endpoint was PFS. After a median follow-up period of 29.6 months, 41 PFS events (48.8%) occurred in the palbociclib/letrozole group compared with 59 events (72.8%) in the letrozole group. Median PFS was 20.2 months and 10.2 months in the two cohorts, respectively (P = 0.0004).39

Grade 3 or 4 neutropenia was reported in 45 of 83 patients (54%) treated with palbociclib plus letrozole compared with one of 77 patients (1%) receiving letrozole alone; leukopenia occurred in 19% and 0% of the two groups, respectively. The most common serious AEs in the palbociclib/letrozole group included pulmonary embolism (4%), back pain (2%), and diarrhea (2%). No cases of febrile neutropenia or neutropenia-related infections were reported during the study.39

Treatment Considerations
Decreased neutrophil counts have been observed in clinical trials of palbociclib. In addition, febrile neutropenia was reported during the palbociclib clinical development program. Clinicians should monitor the complete blood count before starting palbociclib therapy and at the beginning of each cycle, as well as on day 14 of the first two cycles and as clinically indicated.38

In the pivotal phase 2 trial, infections and pulmonary embolism were reported at higher rates in patients treated with palbociclib plus letrozole compared with those treated with letrozole alone.38 In clinical studies, the most common AEs associated with palbociclib included neutropenia, leukopenia, fatigue, anemia, upper respiratory tract infection, nausea, stomatitis, alopecia, diarrhea, thrombocytopenia, decreased appetite, vomiting, asthenia, peripheral neuropathy, and epistaxis.38

Based on findings in animals and on its mechanism of action, palbociclib can cause fetal harm.38

Cost
The AWP of a 21-capsule supply of 125-mg Ibrance is $11,820, making this the cost of a 28-day cycle of the medication.9

LENVATINIB FOR THYROID CANCER
February 2015 also saw the approval of lenvatinib (Lenvima, Eisai Inc.) for the treatment of patients with progressive, differ-
entiated thyroid cancer (DTC) whose disease has progressed despite receiving radioactive iodine therapy.40

Lenvatinib is an oral multikinase inhibitor that simultaneously inhibits VEGFR, fibroblast growth factor receptors, and RET, which are involved in tumor angiogenesis and in the proliferation of thyroid cancer.41,42 In addition, lenvatinib is the first compound to demonstrate a new binding mode (type V) to VEGFR-2.43

The recommended dosage is 24 mg (two 10-mg capsules and one 4-mg capsule) taken once daily with or without food. Treatment should continue until disease progression or unacceptable toxicity occurs. In patients with severe renal or hepatic impairment, the recommended dosage is 14 mg once daily.41

Clinical Trial Experience
The efficacy of lenvatinib was demonstrated in the phase 3 SELECT trial (Study of E7080 [Lenvatinib] in Differentiated
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Cancer of the Thyroid), which involved 392 patients with progressive DTC that was refractory to radioactive iodine therapy.41,44

In this randomized, double-blind study, the subjects received either lenvatinib (24 mg per day; n = 261) or placebo (n = 131) in 28-day cycles. The trial’s primary endpoint was PFS. Secondary endpoints included OS, the response rate, and safety.41,44

The median PFS was 18.3 months in the lenvatinib group and 3.6 months in the placebo group (hazard ratio [HR] for progression or death, 0.21; P < 0.001). The lenvatinib-treated patients demonstrated a response rate of 64.8% (four CRs and 165 PRs) compared with a response rate of 1.5% in the placebo group (P < 0.001). The median OS was not reached in either group.41,44

The most common treatment-related AEs in the lenvatinib group included hypertension (67.8%), diarrhea (59.4%), fatigue or asthenia (59.0%), decreased appetite (50.2%), decreased weight (46.4%), and nausea (41.0%). Discontinuations of the study drug because of AEs occurred in 37 patients who received lenvatinib (14.2%) and in three patients who received placebo (2.3%). In the lenvatinib group, six of 20 deaths that occurred during the treatment period were considered to be treatment-related.41,44

Treatment Considerations

The labeling for lenvatinib includes numerous warnings and precautions related to the potential for hypertension, cardiac failure, arterial thromboembolic events, hepatotoxicity, proteinuria, renal failure and impairment, GI perforation and fistula formation, QT-interval prolongation, hypocalcemia, reversible posterior leukoencephalopathy syndrome, hemorrhagic events, impairment of thyroid-stimulating hormone suppression, and embryo-fetal toxicity.41

No dose adjustments are necessary when lenvatinib is coadministered with CYP3A, P-glycoprotein (P-gp), and breast cancer resistance protein (BCRP) inhibitors, or with CYP3A and P-gp inducers.41

Cost

Pricing information is not yet available for Lenvima.

EXPANDED LABELING

In addition to approving the new cancer drugs discussed previously, the FDA has expanded the labeling for several established cancer treatments within the past several months. These expanded indications are discussed below.

Lenvatinib/Dabrafenib for Metastatic Melanoma

In January 2014, the FDA granted accelerated approval to trametinib and dabrafenib (Mekinist and Tafinlar, GlaxoSmithKline) for use in combination to treat patients with unresectable or metastatic melanoma with a V600E mutation-positive or V600K mutation, as detected by an FDA-approved test.45

Trametinib was previously approved in 2013 as a single agent for the treatment of V600E or V600K mutation-positive, unresectable or metastatic melanoma. Dabrafenib was also approved in 2013 as a single agent for the treatment of V600E mutation-positive, unresectable or metastatic melanoma. Trametinib and dabrafenib target two different tyrosine kinases in the RAS/RAF/MEK/ERK pathway.45

Ofatumumab for CLL

In April 2014, the FDA expanded the labeling for ofatumumab (Arzerra injection, GlaxoSmithKline), a monoclonal antibody, by approving it, in combination with chlorambucil, for the treatment of previously untreated patients with CLL for whom fludarabine-based therapy is considered inappropriate. Ofatumumab had already been approved as monotherapy for patients with previously treated CLL in October 2009.46

Ibrutinib for CLL and Waldenström Macroglobulinemia

In February 2014, ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) received accelerated approval to treat CLL in previously treated patients based on its effect on the ORR in clinical trials. In July 2014, ibrutinib’s labeling was expanded to include the treatment of CLL patients who carry a deletion in chromosome 17 (17p deletion), which is associated with poor responses to standard treatment for CLL.47 And in January 2015, ibrutinib became the first therapy specifically approved for patients with Waldenström macroglobulinemia.48

Ibrutinib is a first-in-class oral therapy that inhibits Bruton’s tyrosine kinase, a key signaling molecule in the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells.49 Prior to these approvals, ibrutinib had been used in previously treated patients with mantle cell lymphoma (MCL) since November 2013.47

Enzalutamide for Prostate Cancer

In September 2014, enzalutamide (Xtandi, Medivation/Astellas Pharma) was granted an expanded indication for the treatment of patients with metastatic castration-resistant prostate cancer (CRPC). The FDA initially approved enzalutamide, an oral, once-daily androgen receptor inhibitor, in August 2012 for use in patients with metastatic CRPC who had received docetaxel chemotherapy. The new indication approved the treatment for use in men with metastatic CRPC who had not received chemotherapy.50

Bortezomib for Mantle Cell Lymphoma

In October 2014, the FDA approved bortezomib (Velcade, Millennium/Takeda) for injection for use in previously untreated patients with MCL. This approval extended the use of bortezomib beyond relapsed or refractory MCL, for which it was approved in 2006.51 The antineoplastic agent has also been used in the treatment of multiple myeloma since 2008.52

Bevacizumab for Ovarian, Fallopian Tube, Peritoneal, and Cervical Cancer

In November 2014, bevacizumab solution for IV infusion (Avastin, Genentech) won regulatory approval, in combination with paclitaxel, pegylated liposomal doxorubicin, or topotecan, for the treatment of platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.53 Bevacizumab is a VEGF-specific angiogenesis inhibitor.54

In August 2014, the drug had been approved, in combination with paclitaxel and either cisplatin or topotecan, for the treatment of patients with persistent, recurrent, or metastatic cervical cancer.55

Bevacizumab has been in use for several years for the following indications:54
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• Metastatic colorectal cancer, with IV 5-fluouracil–based chemotherapy, as first- or second-line treatment
• Metastatic colorectal cancer, with fluoropyrimidine-, irinotecan-, or fluoropyrimidine-oxaliplatin–based chemotherapy, for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen
• Non-squamous NSCLC, with carboplatin and paclitaxel, for first-line treatment of unresectable, locally advanced, recurrent, or metastatic disease
• Glioblastoma, as a single agent for adults with progressive disease after prior therapy
• Metastatic renal cell carcinoma, with interferon alfa

Erwinaze for Acute Lymphoblastic Leukemia
In December 2014, the FDA approved the IV administration of Erwinaze (asparaginase Erwinia chrysanthemi). The drug is indicated as a component of a multi-agent chemotherapeutic regimen for the treatment of patients with ALL who have developed hypersensitivity to E. coli–derived asparaginase. Prior to this approval, the only approved route of administration for Erwinaze was intramuscular injection.

Lenalidomide for Multiple Myeloma
In February 2015, the FDA expanded the indication for lenalidomide (Revlimid, Celgene) in combination with dexamethasone to include patients newly diagnosed with multiple myeloma. Lenalidomide plus dexamethasone was approved in June 2006 for multiple myeloma patients who had received at least one prior therapy. In addition, lenalidomide monotherapy is indicated for the treatment of patients with mantle cell lymphoma whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

The new approval was based on safety and efficacy results from phase 3 studies, including the IFStRT2 trial, which evaluated continuous lenalidomide in combination with dexamethasone (continuous Rd) compared with melphalan, prednisone, and thalidomide (MPT) for 18 months as the primary analysis, and a fixed duration of 18 cycles of Rd (Rd18) as a secondary analysis, in 1,623 newly diagnosed patients who were not candidates for stem-cell transplant. PFS, the study’s primary endpoint, was significantly longer for patients receiving continuous Rd than for those treated with MPT (25.5 months versus 21.2 months, respectively; P = 0.0001). Median OS in the two groups was 58.9 months and 48.5 months, respectively. Patients in the continuous Rd arm had a 25% reduction in the risk of death.

ON THE HORIZON

Cancer Drugs Under FDA Review
As of January 2015, the FDA was considering at least 13 applications for new cancer treatments or new therapeutic settings for existing treatments. Potential cancer treatments submitted for FDA review are discussed below.

Cobimetinib for Melanoma
An application has been submitted to the FDA for the use of cobimetinib (GDC-0973, Genentech), a MEK inhibitor, in combination with vemurafenib (Zelboraf, Genentech/Daiichi Sankyo), a BRAF inhibitor, in patients with advanced melanoma that contains a BRAF V600 mutation. In the pivotal phase 3 coBRIM trial, cobimetinib and vemurafenib reduced the risk of disease progression or death by half (HR, 0.51; P < 0.0001), with a median PFS of 9.9 months for cobimetinib plus vemurafenib compared with 6.2 months for vemurafenib alone.

Sonidegib for Basal Cell Carcinoma
An application has been submitted to the FDA for approval of sonidegib (LDE225, Novartis) to treat patients with advanced basal cell carcinoma. Sonidegib is an investigational, selective smoothened inhibitor that regulates the hedgehog signaling pathway, which plays a critical role in stem cell maintenance and tissue repair as well as in advanced basal cell carcinoma. In a pivotal phase 2 trial, patients with locally advanced or metastatic basal cell carcinoma treated with oral sonidegib had “marked and sustained” tumor shrinkage after a median follow-up of 13.9 months.

TAS-102 for Colorectal Cancer
A new drug application for TAS-102 (Taiho Oncology) was completed in December 2014 for the treatment of refractory metastatic colorectal cancer. The drug is a combination of trifluridine (TFD) and tipiracil hydrochloride (TPI). TFD is an antineoplastic nucleoside analog that is incorporated directly into DNA, thereby interfering with the DNA’s function. The blood concentration of TFD is maintained via TPI, an inhibitor of the TFD-degrading enzyme thymidine phosphorylase.

Talimogene Laherparepvec for Metastatic Melanoma
The FDA is reviewing talimogene laherparepvec (T-VEC, Angen) for the treatment of patients with regionally or distantly metastatic melanoma. The regulatory filing for the drug included data from more than 400 patients and was based on positive data from a global, randomized, open-label phase 3 trial that evaluated the safety and efficacy of intralesional T-VEC in patients with stage IIIB, IIIC, or IV melanoma that is not surgically resectable compared with granulocyte-macrophage colony-stimulating factor (GM-CSF). T-VEC, an oncolytic immunotherapy, was designed to work in two complementary ways. First, it is injected directly into tumors, where it replicates inside the tumor cells, causing the cells to rupture and die. In turn, the ruptured cancer cells release tumor-derived antigens, along with GM-CSF, that can stimulate a systemic immune response in which white blood cells are able to target cancer that has metastasized.

Trabectedin for Soft Tissue Sarcoma
The synthetic antitumor agent trabectedin (Yondelis, Janssen) is under review as a treatment for patients with advanced soft tissue sarcoma, including liposarcoma and leiomyosarcoma subtypes, who have received prior chemotherapy, including an anthracycline. The new drug application was submitted in November 2014. Originally derived from the sea squirts Ecteinascidia turbinata, trabectedin works by preventing tumor cells from multiplying.

Cancer Drugs in Late-Stage Clinical Studies
Numerous investigational cancer treatments have reached late-stage clinical trials. Table 2 provides an overview of selected drugs at this level of development. It has been esti-
Table 2  Selected Cancer Treatments Currently in Late-Stage Trials*

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<tr>
<th>Treatment</th>
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<th>Target</th>
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<tr>
<td><strong>Bladder Cancer</strong></td>
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<tr>
<td>Apaziquone (Spectrum Pharmaceuticals)</td>
<td>DNA synthesis inhibitor</td>
<td>Non–muscle-invasive bladder cancer</td>
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<td>CG0070 (Cold Genesys)</td>
<td>Oncolytic virus therapy</td>
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<td><strong>Brain Cancer</strong></td>
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<td>BKM 120 (Novartis)</td>
<td>PI3K inhibitor</td>
<td>Metastatic breast cancer (ER+, aromatase inhibitor-resistant/mTOR-naive)</td>
</tr>
<tr>
<td>BMN-673 (BioMarin Pharmaceutical)</td>
<td>PARP inhibitor</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Etrirototecan pegol (Nektar Therapeutics)</td>
<td>PEGylated irinotecan</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Ethinostat (Syndax Pharmaceuticals)</td>
<td>Histone deacetylase inhibitor</td>
<td>HR+ breast cancer</td>
</tr>
<tr>
<td>LEE011 (Novartis)</td>
<td>Cyclin-dependent kinase 4/6 inhibitor</td>
<td>Breast cancer, first-line</td>
</tr>
<tr>
<td>Niraparib (Tesaro)</td>
<td>PARP inhibitor</td>
<td>BRCA+ breast cancer</td>
</tr>
<tr>
<td>Olaparib (AstraZeneca)</td>
<td>PARP inhibitor</td>
<td>Breast cancer (adjuvant); metastatic breast cancer</td>
</tr>
<tr>
<td>PF-05280014 (Pfizer)</td>
<td>Trastuzumab biosimilar</td>
<td>Metastatic breast cancer</td>
</tr>
<tr>
<td>Veliparib (AbbVie)</td>
<td>PARP inhibitor</td>
<td>BRCA+ breast cancer; triple-negative breast cancer (adjuvant)</td>
</tr>
<tr>
<td><strong>Colorectal Cancer</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BBI608 (Boston Biomedical)</td>
<td>Cancer stemness kinase inhibitor</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>Etrirototecan pegol (Nektar Therapeutics)</td>
<td>PEGylated irinotecan</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>CPP-1X/sulindac (Cancer Prevention Pharmaceuticals)</td>
<td>Eflornithine/sulindac</td>
<td>Colorectal cancer (risk reduction)</td>
</tr>
<tr>
<td>Imprime PGG (Biothera)</td>
<td>Intravenous immunostimulant</td>
<td>Metastatic colorectal cancer, third-line</td>
</tr>
<tr>
<td>MM-398 (Merriamack Pharmaceuticals)</td>
<td>Irinotecan nanotherapeutic</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td>TAS-102 (Taiho Cancer)</td>
<td>Tipiracil/trifluridine</td>
<td>Colorectal cancer</td>
</tr>
<tr>
<td><strong>Hematological Malignancies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CC-486 (Celgene)</td>
<td>Epigenetic agent (oral azacitidine)</td>
<td>Myelodysplastic syndromes; post-induction acute myeloid leukemia maintenance</td>
</tr>
<tr>
<td>Momelotinib (Gilead Sciences)</td>
<td>Janus kinase inhibitor</td>
<td>Myelofibrosis</td>
</tr>
<tr>
<td>Rigosertib (Onconova Therapeutics)</td>
<td>PI3K/Pik1 inhibitor</td>
<td>High- and low-risk myelodysplastic syndromes</td>
</tr>
<tr>
<td><strong>Kidney Cancer</strong></td>
<td></td>
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<tr>
<td>AGS-003 (Argos Therapeutics)</td>
<td>Personalized dendritic cell-based vaccine</td>
<td>Metastatic renal-cell carcinoma</td>
</tr>
<tr>
<td>IMA-901 (Innatics Biotechnologies)</td>
<td>Multiple tumor-associated peptides</td>
<td>Renal cancer</td>
</tr>
<tr>
<td><strong>Leukemia</strong></td>
<td></td>
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<tr>
<td>Alvocidib (Tolero Pharmaceuticals)</td>
<td>Angiogenesis inhibitor</td>
<td>Acute myeloid leukemia, first-line</td>
</tr>
<tr>
<td>HSV-Tk (MoMed)</td>
<td>Thymidine kinase cell therapy</td>
<td>High-risk acute leukemia</td>
</tr>
<tr>
<td>Inotuzumab ozogamicin (Pfizer)</td>
<td>CD22-targeted cytotoxic agent</td>
<td>Acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>IPI-145 (Infinity Pharmaceuticals)</td>
<td>PI3K inhibitor</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Moxetumomab pasudotax (MedImmune)</td>
<td>Anti-CD22 recombinant immunotoxin</td>
<td>Hairy cell leukemia</td>
</tr>
<tr>
<td>PKC412 (Novartis)</td>
<td>Signal-transduction inhibitor</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td>Quizaritnib (Ambit Biosciences)</td>
<td>FMS-like tyrosine kinase-3 inhibitor</td>
<td>Relapsed/refractory acute myeloid leukemia</td>
</tr>
<tr>
<td>Volasertib (Boehringer Ingelheim)</td>
<td>Polo-like kinase-1 antagonist</td>
<td>Acute myeloid leukemia</td>
</tr>
<tr>
<td><strong>Liver Cancer</strong></td>
<td></td>
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<tr>
<td>ADI-PEG 20 (Polaris Pharmaceuticals)</td>
<td>PEGylated arginine deiminase</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>BA-003 (Onexio)</td>
<td>Doxorubicin nanoparticles</td>
<td>Hepatocellular carcinoma, second-line</td>
</tr>
<tr>
<td>E7080 (Eisai)</td>
<td>Multi-targeted kinase inhibitor</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Tivantinib (ArQule/Daiichi Sankyo)</td>
<td>c-Met inhibitor</td>
<td>Hepatocellular carcinoma</td>
</tr>
</tbody>
</table>
A Review of 2014 Cancer Drug Approvals, With a Look at 2015 and Beyond

Table 2  Selected Cancer Treatments Currently in Late-Stage Trials* (continued)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Description</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AZD9291 (AstraZeneca)</td>
<td>EGFR tyrosine kinase inhibitor</td>
<td>Advanced T790M mutation-positive NSCLC</td>
</tr>
<tr>
<td>Custirsen (OXG-111) (OncoGenex/Teva)</td>
<td>Antisense oligonucleotide</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Dacomitinib (Pfizer)</td>
<td>Pan-HER inhibitor</td>
<td>EGFR-mutant NSCLC, first-line</td>
</tr>
<tr>
<td>Ganetesib (Synta Pharmaceuticals)</td>
<td>Heat shock protein 90 inhibitor</td>
<td>NSCLC</td>
</tr>
<tr>
<td>MEDI4736 (MedImmune)</td>
<td>Anti-–PD-L1 monoclonal antibody</td>
<td>Stage III NSCLC; NSCLC, third-line</td>
</tr>
<tr>
<td>Nectatumab (Lilly)</td>
<td>EGFR inhibitor</td>
<td>Squamous NSCLC</td>
</tr>
<tr>
<td>RG7446 (Genentech)</td>
<td>Anti-–PD-L1 monoclonal antibody</td>
<td>NSCLC, second-line</td>
</tr>
<tr>
<td>Selumetinib (Array BioPharma)</td>
<td>MEK inhibitor</td>
<td>KRAF-positive NSCLC, second-line</td>
</tr>
<tr>
<td>TG4010 (Transgene)</td>
<td>MVA-MUC1-IL2 cancer vaccine</td>
<td>Advanced NSCLC</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
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</tr>
<tr>
<td>Alisertib (Millennium Pharmaceuticals)</td>
<td>Aurora A kinase inhibitor</td>
<td>Relapsed/refractory peripheral T-cell lymphoma</td>
</tr>
<tr>
<td>Mogamulizumab (Kyowa Hakko Pharma)</td>
<td>Anti-CD4 humanized antibody</td>
<td>Cutaneous T-cell lymphoma</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ixazomib citrate (Millennium Pharmaceuticals)</td>
<td>Protease inhibitor</td>
<td>Multiple myeloma after autologus-stem-cell transplant</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td></td>
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</tr>
<tr>
<td>MEK162 (Array BioPharma/Novartis)</td>
<td>MEK inhibitor</td>
<td>Low-grade serious ovarian cancer</td>
</tr>
<tr>
<td>MORAb-003 (Eisai)</td>
<td>Immunoglobulin G1 monoclonal antibody</td>
<td>Platinum-sensitive ovarian cancer</td>
</tr>
<tr>
<td>Niraparib (Tesaro)</td>
<td>PARP inhibitor</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Rucaparib (Clovis Cancer)</td>
<td>PARP inhibitor</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Trebananib (Amgen)</td>
<td>Recombinant peptide-Fc fusion protein</td>
<td>Ovarian cancer</td>
</tr>
<tr>
<td>Pancreatic Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T77Lu-Dotatate (Advanced Accelerator Applications)</td>
<td>Somatostatin receptor antagonist</td>
<td>Metastatic GEP-NETs</td>
</tr>
<tr>
<td>Algenpantucel-L (NewLink Genetics)</td>
<td>Cancer immunotherapy vaccine</td>
<td>Pancreatic cancer (resected, borderline resectable, or locally advanced unresectable)</td>
</tr>
<tr>
<td>TH-302 (EMD Serono/Threshold Pharmaceuticals)</td>
<td>Hypoxia-activated prodrug</td>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AdV-IX (Advantgene)</td>
<td>Cancer gene therapy</td>
<td>Newly diagnosed prostate cancer</td>
</tr>
<tr>
<td>Custirsen (OXG-111) (OncoGenex/Teva)</td>
<td>Antisense oligonucleotide</td>
<td>Metastatic castration-resistant prostate cancer, second-line</td>
</tr>
<tr>
<td>JNJ-56021927/ARN-509 (Janssen)</td>
<td>Androgen receptor antagonist</td>
<td>Hormone-refractory prostate cancer</td>
</tr>
<tr>
<td>Oteronel (Millennium Pharmaceuticals)</td>
<td>Lyase inhibitor</td>
<td>Metastatic castration-resistant prostate cancer</td>
</tr>
<tr>
<td>Skin Cancer</td>
<td></td>
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</tr>
<tr>
<td>Cobimetinib (Genentech)</td>
<td>MEK inhibitor</td>
<td>Metastatic melanoma</td>
</tr>
<tr>
<td>LGX181 (Novartis)</td>
<td>BRAF inhibitor</td>
<td>B-RAF-mutant melanoma</td>
</tr>
<tr>
<td>MAGE-A3 (GlaxoSmithKline)</td>
<td>Recombinant antigen-specific cancer immunotherapeutic</td>
<td>Melanoma</td>
</tr>
<tr>
<td>MEK162 (Array BioPharma)</td>
<td>MEK inhibitor</td>
<td>NRAS-mutant melanoma</td>
</tr>
<tr>
<td>MEK162/LGX181 (Novartis)</td>
<td>MEK inhibitor/BRAF inhibitor</td>
<td>B-RAF-mutant melanoma</td>
</tr>
<tr>
<td>POL-103A (Polynoma)</td>
<td>Immunotherapy vaccine</td>
<td>Late-stage malignant melanoma</td>
</tr>
<tr>
<td>Stomach Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BB1608 (Boston Biomedical)</td>
<td>Cancer stem-cell inhibitor</td>
<td>Gastric cancer</td>
</tr>
<tr>
<td>Rilotumumab (Amgen)</td>
<td>Hepatocyte growth factor/scatter factor inhibitor</td>
<td>MET protein receptor-positive gastric cancer</td>
</tr>
<tr>
<td>S-1 (Taiho Cancer)</td>
<td>Gimeracil/oteracil/tegafur fixed-dose combination</td>
<td>Gastric cancer</td>
</tr>
</tbody>
</table>

* This table is not meant to be all-inclusive, but rather to highlight the array of treatment approaches currently under investigation in the oncology setting.

Adapted from Medicines in Development: Cancer—2014 Report.2
A Review of 2014 Cancer Drug Approvals, With a Look at 2015 and Beyond

mated that investigational agents in phase 3 studies have a 20% chance of rejection, as opposed to a 90% chance in phase 1 trials, so many of the drugs listed in Table 2 may be expected to reach the oncology market in 2015.

CONCLUSION

During the past several months, the FDA has rapidly been approving new cancer treatments or expanding the indications for available drugs. Meanwhile, numerous investigational agents have been accepted for regulatory review or are undergoing late-stage clinical trials. This article has provided an overview of current regulatory and investigational activity in the oncology arena, with the aim of helping clinicians to better identify the appropriate available and upcoming treatments for their cancer patients.

REFERENCES


