The year 2015 marked a noteworthy 12-month period for oncology drugs approved by the US Food and Drug Administration (FDA). The Center for Drug Evaluation and Research, which reviews the approval of antibodies and small molecules, approved a total of 45 new drugs in 2015; 15 of which are indicated for the treatment of cancer.1

According to the FDA’s drug approval database, there were 34 new FDA-approved indications in the general field of hematology/oncology in 2015.2 Although many of these indications are expansions on previously approved therapeutics,2 17 represent new molecular entities (NMEs) containing active drug moieties not previously approved by the FDA.3

In particular, disease states for which multiple NMEs were approved included non−small-cell lung cancer (NSCLC), with 3 new drug approvals (alectinib, necitumumab, osimertinib), as well as multiple myeloma, with 4 new drug approvals (elotuzumab, daratumumab, ixazomib, panobinostat).1,2,4 Also included in this list of 2015 FDA approvals were filgrastim-sndx (Zarxio injection), the first biosimilar approved in the United States, and talimogene laherparepvec (Imlygic), the first US-approved oncolytic viral therapy.2

**Dominance of Immunotherapy Approvals**

The subspecialty of oncology that has dominated the list of recently approved therapeutics is immuno-oncology.4 Medicines for this subfield work by activating T-cells to target cancer, or inhibiting tumor antigens that allow cancer cells to evade the immune system (eg, checkpoint inhibitors).4

Two of the unique aspects of immunotherapies include their ability to achieve relatively high response rates in pretreated patients, as well as the potential for durable remissions in patients who respond to therapy. Currently, several of these agents have achieved FDA approval for use in patients with metastatic melanoma or NSCLC.4 In addition, there are a multitude of ongoing clinical trials evaluating the activity of checkpoint inhibitors in a variety of different malignancies.5

The 17 hematology/oncology NMEs approved in 2015 represent a significant upward trajectory from the 2 previous years—9 oncology NMEs were approved in 2014, and 7 were approved in 2013.1,4,6 Although it may seem that this accelerated rate of drug approvals is unsustainable, there is reason to believe that this trend will continue. The American Association for Cancer Research (AACR) estimates that there are more than 836 vaccines and medications for targeting cancer currently being tested in clinical trials, or awaiting FDA approval.7 In addition, the AACR estimates that approximately 80% of these medicines in the pipeline have the potential to become first-in-class therapies, and 73% will potentially be personalized medicines.

Although the AACR has continued to invest heavily in the research and development of innovative oncology drugs, recent legislation indicates that Congress has also recognized the need for additional cancer research funding. In December 2015, Congress passed a bill to increase the budget of the National Institutes of Health by 6.6%; this amounts to a total of $32.1 billion, $5.2 billion of which is designated for the National Cancer Institute.4,8

In the first 3 months of 2016, the FDA already approved 3 hematology/oncology NMEs (Table 1), and 6 new indications for previously approved drugs.2,9-11 In addition to these approvals, we estimate that there could be ≤18 new NMEs and 1 new biosimilar approved during the remainder of 2016 (Table 2).12-40 Below we provide a brief review of select agents with potential for FDA approval in 2016.

**Andexanet alfa**

Andexanet alfa is an intravenous recombinant being developed by Portola Pharmaceuticals, Inc, to reverse
bleeding in patients anticoagulated with factor Xa inhibitors.\(^\text{12,13}\) Currently, there are no FDA-approved medications specifically indicated for the reversal of factor Xa inhibitors; thus, andexanet alfa would represent a first-in-class medication for this indication.

Investigators from 2 randomized, double-blind, placebo-controlled trials (ANNEXA-R and ANNEXA-A) have reviewed the safety and efficacy of andexanet alfa use in healthy volunteers. The results, published in the New England Journal of Medicine\(^\text{13}\), demonstrated that andexanet alfa reversed the anticoagulant effects of apixaban and rivaroxaban within minutes of administration, without causing adverse events.

Portola Pharmaceuticals, Inc, submitted a rolling biologics license application (BLA) to the FDA in early 2016, which was accepted under the accelerated approval pathway. Currently, andexanet alfa has a goal date of August 17, 2016, for the FDA to complete its review of the BLA.\(^\text{12}\)

**Advanced bladder cancer is a disease with limited treatment options, and atezolizumab would represent a first-in-class PD-L1 inhibitor for the treatment of this disease.**

Atezolizumab

Genentech, Inc, is currently in the late stages of developing an immunotherapy agent for patients with previously treated metastatic urothelial bladder cancer.\(^\text{15}\) Atezolizumab, an intravenous monoclonal antibody designed to directly bind with the programmed death-ligand 1 (PD-L1), has a slightly different mechanism of action than the previously approved checkpoint inhibitor, because it targets the PD-L1 tumor antigen rather than the PD-1 receptor on T-cells.\(^\text{15}\) Advanced bladder cancer is a disease with limited treatment options, and atezolizumab would represent a first-in-class PD-L1 inhibitor for the treatment of this disease.

In a phase 2, open-label, single-arm study (IMvigor 210), atezolizumab demonstrated an objective response rate of 27% in patients with metastatic urothelial carcinoma whose disease had medium/high levels of PD-L1 expression.\(^\text{16}\) Importantly, responses were still ongoing during interim data analysis, and median duration of response has not yet been established.\(^\text{16}\) In addition to this study, Genentech, Inc, is currently conducting a phase 3 clinical trial comparing atezolizumab to standard-of-care chemotherapy in patients with metastatic urothelial carcinoma that worsened after treatment with ≥1 platinum-containing regimens.

Genentech, Inc’s BLA submission for atezolizumab was granted priority review in March 2016; the company has a goal date of September 12, 2016, for the FDA’s decision on approval of the drug.\(^\text{15}\)

**Rociletinib**

Clovis Oncology, headquartered in Boulder, CO, is a biopharmaceutical company with several cancer treatments in their pipeline. Their most advanced-stage product is rociletinib, which is being developed for the treatment of NSCLC in patients with initial activating epidermal growth factor receptor (EGFR) mutations, including the T790M mutation.\(^\text{41}\) Rociletinib is a novel, oral, mutation-selective inhibitor of EGFR forms known to be present in 15% to 35% of white and East Asian patients with NSCLC.

Last year, the first therapy (osimertinib) was approved for treatment of patients with T790M gatekeep-

### Table 1: New Hematology/Oncology Drugs Approved by the FDA in 2016

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Class</th>
<th>Route</th>
<th>Approval date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihemophilic factor VIII (recombinant; Kovaltry)(^2,9)</td>
<td>Bayer AG</td>
<td>Pediatric and adult patients with hemophilia A</td>
<td>Recombinant human blood coagulation factor</td>
<td>IV</td>
<td>3/15/16</td>
</tr>
<tr>
<td>Coagulation factor IX (recombinant) albumin fusion protein (Idelvion)(^2,10)</td>
<td>CSL Behring LLC</td>
<td>Children and adults with hemophilia B</td>
<td>Recombinant human blood coagulation factor</td>
<td>IV</td>
<td>3/4/16</td>
</tr>
<tr>
<td>Defibrotide sodium (Defitelio)(^2,11)</td>
<td>Jazz Pharmaceuticals, Inc</td>
<td>Patients with hepatic veno-occlusive disease</td>
<td>Oligonucleotide</td>
<td>IV</td>
<td>3/30/16</td>
</tr>
</tbody>
</table>

*a Includes drugs approved as of April 3, 2016.

FDA indicates US Food and Drug Administration; IV, intravenous.
### Table 2  Potential FDA Hematology/Oncology Drug Approvals in 2016

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Class</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andexanet alfa</td>
<td>Portola Pharmaceuticals, Inc</td>
<td>Reversal of anticoagulant effects of factor Xa inhibitors</td>
<td>Modified recombinant derivative of factor Xa</td>
<td>IV</td>
<td>BLA priority review accepted on 2/17/16</td>
</tr>
<tr>
<td>Atezolizumab</td>
<td>Genentech, Inc</td>
<td>Patients with previously treated metastatic urothelial bladder cancer</td>
<td>Human monoclonal antibody against PD-L1</td>
<td>IV</td>
<td>BLA priority review accepted on 3/15/16</td>
</tr>
<tr>
<td>Abemaciclib</td>
<td>Eli Lilly and Company</td>
<td>Patients with refractory hormone receptor–positive advanced or metastatic breast cancer</td>
<td>Cyclin-dependent kinase</td>
<td>Oral</td>
<td>Breakthrough therapy designation granted on 10/8/2015</td>
</tr>
<tr>
<td>Binimetinib</td>
<td>Array BioPharma</td>
<td>Patients with metastatic melanoma with NRAS mutations</td>
<td>Mitogen-activated protein kinase inhibitor</td>
<td>Oral</td>
<td>Phase 3 trials completed; new drug application not yet submitted</td>
</tr>
<tr>
<td>Brigatinib</td>
<td>ARIAD Pharmaceuticals, Inc</td>
<td>Patients with ALK-positive, advanced, NSCLC whose disease is resistant to crizotinib</td>
<td>ALK inhibitor</td>
<td>Oral</td>
<td>Breakthrough therapy designation granted on 10/1/2014</td>
</tr>
<tr>
<td>CRLX101</td>
<td>Cerulean Pharma Inc</td>
<td>Patients with relapsed ovarian cancer</td>
<td>Nanoparticle-drug conjugate</td>
<td>IV</td>
<td>Orphan drug designation granted on 5/26/2015</td>
</tr>
<tr>
<td>Evofosfamide</td>
<td>Threshold Pharmaceuticals</td>
<td>Patients with previously untreated metastatic or locally advanced, unresectable pancreatic tumors</td>
<td>Hypoxia-activated prodrug of alkylating mustard</td>
<td>IV</td>
<td>Fast track approval granted on 5/12/2015</td>
</tr>
<tr>
<td>Fostamatinib</td>
<td>Rigel Pharmaceuticals, Inc</td>
<td>Patients with immune thrombocytopenic purpura</td>
<td>Spleen tyrosine kinase inhibitor</td>
<td>Oral</td>
<td>Orphan drug designation granted on 9/8/2015</td>
</tr>
<tr>
<td>Kevetrin</td>
<td>Cellceutix Corporation</td>
<td>Patients with ovarian and pancreatic cancers</td>
<td>p53 activator</td>
<td>IV</td>
<td>Orphan drug designation granted on 7/15/2015 and 1/21/2016</td>
</tr>
<tr>
<td>Neratinib</td>
<td>Puma Biotechnology, Inc</td>
<td>HER2-positive breast cancer</td>
<td>HER2 tyrosine kinase inhibitor</td>
<td>Oral</td>
<td>NDA filing expected in 2016</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Sandoz Inc</td>
<td>All approved indications for Neulasta (pegfilgrastim)</td>
<td>Biosimilar leukocyte growth factor</td>
<td>Subcutaneous</td>
<td>BLA filing accepted on 11/18/2015</td>
</tr>
</tbody>
</table>

*Continued*
Table 2  Potential FDA Hematology/Oncology Drug Approvals in 2016 (Continued)

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Manufacturer</th>
<th>Indication</th>
<th>Class</th>
<th>Route</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKC41229 (midostaurin)</td>
<td>Novartis AG</td>
<td>Patients with newly diagnosed AML with FMS-like tyrosine kinase mutations who are eligible to receive standard induction and consolidation chemotherapy</td>
<td>Multitargeted kinase inhibitor</td>
<td>Oral</td>
<td>Breakthrough therapy designation granted on 2/19/2016</td>
</tr>
<tr>
<td>Pracinostat42</td>
<td>MEI Pharma, Inc</td>
<td>Patients with myelodysplastic syndrome</td>
<td>Histone deacetylase inhibitor</td>
<td>Oral</td>
<td>Orphan drug designation granted on 2/28/2014</td>
</tr>
<tr>
<td>Rociletinib31</td>
<td>Clovis Oncology</td>
<td>Patients with NSCLC with T90M mutations, after disease progression with EGFR-directed therapy</td>
<td>EGFR inhibitor</td>
<td>Oral</td>
<td>Breakthrough therapy designation granted in May 2015</td>
</tr>
<tr>
<td>Tazemetostat32,33</td>
<td>Epizyme, Inc</td>
<td>Patients with malignant rhabdoid tumors</td>
<td>Histone methyltransferase EZH2 inhibitor</td>
<td>Oral</td>
<td>Orphan drug designation granted on 2/8/2016</td>
</tr>
<tr>
<td>TRC10534,35</td>
<td>TRACON Pharmaceuticals, Inc</td>
<td>Patients with soft tissue sarcoma</td>
<td>Chimeric anti-CD105 (endoglin) monoclonal antibody</td>
<td>IV</td>
<td>Orphan drug designation granted on 1/25/2016</td>
</tr>
<tr>
<td>VAL-08336,37</td>
<td>DelMar Pharmaceuticals, Inc</td>
<td>Patients with medulloblastoma</td>
<td>Bifunctional alkylating agent</td>
<td>Oral; IV</td>
<td>Orphan drug designation granted on 3/15/2016</td>
</tr>
<tr>
<td>Venetoclax31,38</td>
<td>AbbVie Inc; E Hoffmann-La Roche Ltd; Genentech, Inc</td>
<td>Patients with chronic lymphocytic leukemia who have received ≥1 prior therapies, including those with 17p deletion</td>
<td>B-cell lymphoma 2 inhibitor</td>
<td>Oral</td>
<td>NDA accepted and priority review status granted on 1/12/2016</td>
</tr>
<tr>
<td>Vyxeos39,40</td>
<td>Celator Pharmaceuticals, Inc</td>
<td>Elderly patients with secondary AML</td>
<td>Liposomal formulation of cytarabine and daunorubicin</td>
<td>IV</td>
<td>Fast track designation granted on 1/20/2015</td>
</tr>
</tbody>
</table>

ALK indicates anaplastic lymphoma kinase; AML, acute myeloid leukemia; BLA, biologics license application; EGFR, epidermal growth factor receptor; FDA, US Food and Drug Administration; HER2, human epidermal growth factor receptor 2 ; IV, intravenous; NDA, new drug approval; NSCLC, non–small-cell lung cancer; PD-L1, programmed death-ligand 1; TNF, tumor necrosis factor.

er mutation, which can result in patients developing resistance to first- and second-line EGFR inhibitors. Updated results from Clovis Oncology’s phase 2 trial demonstrated that rociletinib produced an objective response rate in 60% of patients with the T790M mutation, 37% with T790M-negative disease, and was relatively well-tolerated.42,43

In May 2014, rociletinib was granted breakthrough therapy designation by the FDA for the treatment of patients with NSCLC and the T790M mutation, after their disease progressed on EGFR-directed therapy.41 Most recently, the FDA has extended the review period...
Venetoclax

In partnership with AbbVie Inc, F. Hoffmann-La Roche Ltd is developing venetoclax, a new, targeted agent for the treatment of patients with relapsed or refractory chronic lymphocytic leukemia (CLL).31 Venetoclax is an oral, bioavailable, highly selective inhibitor of the B-cell lymphoma 2 (BCL-2) protein. BCL-2, which is expressed in various types of leukemia and lymphoma, confers that an antipapoptotic signal when constitutively active leads to long-lived malignant lymphocytes that are highly resistant to apoptosis.31

The advancement in our understanding of tumor biology has paved the way for future cancer treatments that are more effective, less toxic, and personalized to each patient’s specific disease state.

Results from a phase 1, dose-escalation study demonstrated that venetoclax was highly active against CLL, and that it was able to produce an overall response rate of ≥71%, with 20% of patients achieving complete remissions.38 Venetoclax was granted breakthrough therapy designation in April 2015 for the treatment of patients with previously treated (relapsed or refractory) CLL, including those with 17p deletion.

In January 2016, the FDA granted venetoclax priority review; the companies anticipate a final decision on approval of the drug in mid-to-late 2016.

Conclusion

The information provided in this pipeline preview sheds light on some of the unique characteristics of select emergent therapies expected to receive approval in 2016. The advancement in our understanding of tumor biology has paved the way for future cancer treatments that are more effective, less toxic, and personalized to each patient’s specific disease state. In projecting the 2016 hematology/oncology drug pipeline, we can clearly see continued trends in targeted therapies, as well as immunotherapy. Along with these potential new drug approvals will come continued emphasis on identifying patients who will benefit most from these emerging therapies, as well as determination of where these drugs fit into existing oncology treatment pathways. Although there remain many unanswered questions about the state of cancer treatment, we anticipate that the current pipeline of oncology therapeutics will provide evidence-based solutions that will continue to advance the standard of care across all types of cancers.

Author Disclosure Statement

Dr Beechler reported no conflicts of interest. Dr Valgus is on the Advisory Boards for Genentech, Inc, Sandoz, and Taiho Oncology, Inc.

References


