Cancer Drug Approvals: A Tale of 2 Views

By Sharon Donovan

Following a year in which approximately 2 dozen cancer drugs were approved by the FDA, approvals in 2016 decreased by approximately 50% compared with 2015.[1] This tally comes on the heels of a relatively light year of approvals in 2014, when only 10 cancer drugs were approved.[1]

However, a year-end review of the FDA's 2016 cancer drug approvals points to 5 new molecular entities and 17 efficacy supplements. This also includes 6 accelerated approvals, 17 priority reviews, and 11 approvals of breakthrough-designated therapies.[2] The review was co-authored by Richard Pazdur, MD, Director, FDA's Oncology Center of Excellence, which oversees the FDA's regulatory scientists and reviewers with expertise in drugs, biologics, and devices. His work expedites the development of novel cancer products as part of the National Cancer Moonshot Initiative.

Parsing through the focus and rates of FDA cancer drug approvals over several years tells just one side of the story. Out of the gate so far this year, the only approved cancer drug has been to treat diarrhea caused by carcinoid syndrome. Of the 11 cancer drugs approved by the FDA in 2016, 2 target advanced renal-cell carcinoma, 2 treat head and neck squamous-cell carcinomas, and 2 treat nausea and vomiting associated with cancer chemotherapy.[2] In 2015, when 21 cancer drugs were approved by the FDA, 5 drugs focused on metastatic non–small-cell lung cancers versus 4 for myeloma and 2 for melanoma.[1] Of the 10 cancer drugs approved in 2014, 2 drugs were approved for melanoma, 2 for leukemia, and 2 for lymphoma, whereas non–small-cell lung, ovarian, and gastric cancers were the focus of 1 drug approval each.[3] A drug to prevent chemotherapy-induced nausea was also approved in 2014.[3] Although 2013 scored 12 FDA cancer drug approvals,[4] in 2012 the FDA approved 21 cancer drugs.[5]

The decline of FDA cancer drug approvals from 2015 to 2016 has some industry observers concerned. They point out that the oncology arena may be experiencing some weakness. Still, others believe that cancer treatment innovation will accelerate in the coming years, and that drug approvals will rise to meet the previous averages of 30 drugs annually.

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Many theories are circulating as to the reasons behind the seemingly erratic rise and fall of the FDA approvals. One suggestion is that, in part, it had to do with the FDA's approval of several drugs in late 2015 that were expected in 2016. Had they been approved in 2016, the decrease would not seem as dramatic.

Of note, too, is that the FDA delayed approval of some cancer drugs in 2016 until pharmaceutical companies' plants were in compliance with the FDA's standards of Good Manufacturing Practices.

Bernard Munos, Founder, InnoThink Center for Research in Biomedical Innovation, Indianapolis, IN, voiced concern that the decrease may be a "reflection of the inherent softness in the [drug] pipeline." He added that the situation "does not bode well" for the sustainability of the industry.[6]

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But many experts are encouraged by the FDA's direction—noting that quality, not quantity is the main goal.

The year-end review, with its emphasis on checkpoint inhibitors, shows that the FDA has been responsive in the immunotherapy field, and open to a combination of other therapies "to make the system work faster," observed Jill O'Donnell-Tormey, PhD, Chief Executive Officer and Director, Scientific Affairs, Cancer Research Institute, New York.

"We all want safe [treatments], but done in a timely manner. I think this trend will continue and more checkpoint [inhibitors] will get approved as first-line treatment for more cancers. In other cancers, I think you will see combinations of checkpoints with other immunotherapies, targeted therapy, chemo[therapy], and radiation," she said. Checkpoint inhibitors are already the standard of care for the indications approved by the FDA.

Does the focus on immunotherapy and checkpoint inhibitor innovation mean that they will eventually replace chemotherapy?

"Chemotherapy may remain the standard in other cancers. Immunotherapy may replace chemo[therapy] in certain cancers in the near future, but it will not be 100%," Dr O'Donnell-Tormey said.

The FDA approvals show that a move toward precision medicine may have slowed the process somewhat, requiring extra oversight to get the "right drug to the right person at the right time," said Peg Ford, Patient Advocate and Co-Founder/President, Ovarian Cancer Alliance of San Diego, CA.

"The direction toward precision medicine is heartwarming. The FDA's changes in design amount to a quantum shift," she said, adding that this effort includes crucial input from oncology nurses, nurse navigators, and patients themselves.

Like Ms Ford and Dr O'Donnell-Tormey, many observers are encouraged by the aggressive progress and numerous innovative steps outlined by Dr Pazdur, who forecasts that "real-world evidence" will play a significant role outside of clinical trials. Electronic health records, patient registries, mobile health applications, and social media will be among multiple resources, whereas more emphasis on data sharing across the biomedical community will "rapidly translate basic and clinical observations to improve patient care."[2] ■

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IN THE LITERATURE

Venetoclax plus Rituximab Improves Outcomes in Chronic Lymphocytic Leukemia

In preclinical models of B-cell malignancy, researchers observed synergy when the BCL2 inhibitor venetoclax (Venclexta) was combined with the anti-CD20 monoclonal antibody rituximab (Rituxan). This led researchers to conduct a phase 1b dose-escalation study that assessed the safety, pharmacokinetics, and activity of venetoclax in combination with rituximab in patients with relapsed or refractory chronic lymphocytic leukemia (CLL), the results of which were recently published in *Lancet Oncology* (Seymour JF, et al. *Lancet Oncol*. 2017;18:230-240).

The phase 1b dose-escalation study included 49 patients with relapsed or refractory CLL or small lymphocytic lymphoma. The patients received daily doses of venetoclax that were escalated to a target dose of 200 mg to 600 mg, followed by monthly rituximab at 375 mg/m^2 in month 1 and 500 mg/m^2 in months 2 to 6. Researchers permitted drug cessation for patients with a complete response (including complete response with incomplete marrow recovery) or negative bone marrow minimal residual disease. At the time of analysis, patients were still receiving treatment, with ongoing follow-up.

The primary end points were to assess the safety profile of the combination to determine the maximum tolerated dose, and to establish the recommended phase 2 dose of venetoclax when combined with rituximab. The secondary end points included overall response rate (ORR), duration of response, and time to tumor progression.

Of the 49 patients who received the combination treatment, 42 (86%) achieved ORR, including a complete response in 25 (51%) patients, and 28 (57%) patients attained negative marrow minimal residual disease. The

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