2017 notches up some landmark approvals

David M Mintzer, MD

Section of Hematology and Medical Oncology, Abramson Cancer Center of Pennsylvania Hospital, Philadelphia

With advances in the understanding of cellular pathways, molecular genetics, and immunology, new drugs for cancer are being released at an increasing rate. A variety of novel agents have recently become available for use, generating excitement for patients and oncologists. Keeping track of all of these new agents is increasingly challenging. This brief review will summarize some of the newest drugs, their indications, and benefits (see also pp. e283-e290).

Therapies by tumor

Breast cancer

CDK4/6 inhibitors. The CDK4/6 inhibitor palbociclib was approved in 2015 for the treatment of estrogen-positive, HER2-negative advanced breast cancer, and this year, two more drugs in this class – ribociclib and abemaciclib – were approved for the treatment of hormone receptor–positive breast cancer.

Ribociclib (Kisqali) 600 mg daily (3 weeks on, 1 week off) is approved for use in combination with an aromatase inhibitor. In the study on which the approval was based, there was a response rate of 53% for patients in the study group, compared with 37% for those who received aromatase inhibitor alone (progression-free survival (PFS), not reached vs 14.7 months for single-agent aromatase inhibitor).[1] The occurrence of neutropenia seemed to be similar to that in patients receiving palbociclib. However, unlike with palbociclib, ribociclib requires ECG monitoring for QTc prolongation as well as monitoring of liver function tests.

Abemaciclib (Verzenio) has been approved in combination with fulvestrant as well as a monotherapy.[2] PFS was 16.4 months for abemaciclib (150 mg bid in combination with fulvestrant), compared with 9.3 months for fulvestrant alone, with corresponding response rates of 48% and 21%. As monotherapy, abemaciclib 200 mg bid had a response rate of 20% with a duration of response of 8.6 months.

Tyrosine kinase inhibitors. The tyrosine kinase inhibitor **neratinib** (Nerlynx) was approved for extended adjuvant treatment of HER2-positive breast cancer after 1 year of adjuvant trastuzumab.[3] Given at 240 mg (6 tablets) daily for a year, compared with a no-treatment control arm, it demonstrated an improvement in invasive disease-free survival (DFS) at 2 years from 91.9% to 94.2%, with no difference in overall survival yet noted. It is associated with diarrhea and also requires hepatic function monitoring.

Acute myelogenous leukemia

Multiple new agents were recently approved for use in acute myelogenous leukemia (AML), after decades of slow advance in new drug development.

Midostaurin (Rydapt) is an FLT3 inhibitor approved for use in combination with daunorubicin and Ara-C (cytosine arabinoside) for newly diagnosed AML with *FLT3* mutations, which occur in about 30% of AML patients.[4] It is given orally on days 8-21 at 50 mg bid with induction and consolidation.

In the study on which the approval was based, there was a 10% improvement in overall survival for this subset of AML patients who have a typically a worse prognosis. Event-free survival in patients in the study group was 8.2 months, compared with 3 months in the control arm patients, who did not receive the agent. The drug was also approved for aggressive systemic mastocytosis.

Enasidenib (Idhifa) has been approved for AML with an *IDH2* mutation in the refractory/relapsed settings.[5] *IDH2* mutations are present in about 20% of patients with AML. Given orally at 100 mg daily as a single agent, enasidenib was associated with a 19% complete remission rate. Patients need to be monitored for differentiation syndrome, somewhat similar to what is seen with ATRA with acute promyelocytic leukemia.

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Liposomal daunorubicin and cytarabine (Vyxeos) was approved for newly diagnosed therapy- or myelodysplasia-related AML.[6] This novel liposomal formulation combines two standard agents and is given intravenously on days 1, 3 and 5 over 90 minutes as daunorubicin 44 mg/m^2 and cytarabine 100 mg/ m^2. (For a second induction and in lower dose on consolidation cycles, it is given only on days 1 and 3). The liposomal formulation achieved a superior complete response rate compared with the standard 7+3 daunorubicin plus cytarabine regimen (38% vs 26%, respectively) and longer overall survival (9.6 versus 5.9 months) in these generally poor prognosis subsets.

Gemtuzumab ozogamicin (Mylotarg) was initially approved in 2000 but withdrawn from use in 2010 after trials failed to confirm benefit and demonstrated safety concerns. It has now been re-released in a lower dose and schedule from its original label.[7] This immunoconjugate of an anti-CD33 bound to calicheamicin is approved for CD33-positive AML. Given at 3 mg/m^2 on days 1, 4, and 7 in combination with standard daunorubicin–cytarabine induction chemotherapy, it improved event-free survival from 9.5 to 17.3 months. When administered as a single agent (6 mg/m^2 on day 1 and 3 mg/m^2 on day 8) in patients who were unable or unwilling to tolerate standard chemotherapy, it improved overall survival (4.9 months versus 3.6 months for best supportive care). As a single agent in relapsed AML, given at 3 mg/m^2 days 1, 4, and 7 and followed by cytarabine consolidation, it was associated with a 26% complete response rate, with a median relapse-free survival of 11.6 months.

Ovarian/fallopian tube cancers

PARP inhibitors. For patients with ovarian/fallopian tube cancer, there are new indications and agents for PARP inhibition, including for patients with *BRCA* mutations (both somatic and germline) and those without *BRCA* mutations.

Olaparib (Lynparza) was previously approved only in a fourth-line setting for germline *BRCA*-mutated patients with advanced ovarian cancer, with a response rate of 34% with a median duration of 7.9 months. Given at 300 mg orally bid, it is now approved for use in maintenance in recurrence after response to platinum-based chemotherapy after 2 or more lines of therapy regardless of *BRCA* status. In this setting, progression-free survival increased to 8.4 months, compared with 4.8 months for placebo.[8]

Rubicarib (Rubraca) is approved for *BRCA*-mutated patients (either germline or somatic) with advanced ovarian cancer after two or more lines of chemotherapy.[9] At 600 mg orally bid, results from phase 2 trials noted a 54% response rate, with a median duration of 9.2 months.

Niraparib (Zejula) is approved for use in maintenance in recurrent epithelial ovarian, fallopian tube, and primary peritoneal cancers after platinum-based chemotherapy.[10] In patients with germline *BRCA* mutations, niraparib at 300 mg orally daily resulted in a PFS of 21 months, compared with 5.5 months with placebo; PFS in patients with nongermline *BRCA* mutations was 9.3 versus 3.9 months, respectively.

Non-small cell lung cancer with EML-4 alk translocation

Crizotinib (Xalkori) has been the mainstay for treatment of for EML4-alk translocated non-small cell lung cancer. However, **alectinib** (Alcensa), previously for predominantly second-line use, seems more active than crizotinib in the first-line setting, particularly in the treatment and prevention of CNS metastases.

In addition, **brigantinib** (Alunbrig) has been approved for patients who are intolerant/refractory to crizotinib.[11] At 90 mg once daily for 7 days, then escalating to 180 mg daily, it was noted to have a 50% response rate in crizotinib failures, including in the CNS.

Ceritinib (Zykadia) was approved at 750 mg once daily for EML4 alk positive NSCLC.[12] In first line it had a response rate of 73% (versus 27% for chemotherapy) with a remission duration of 23.9 months (versus 11.1 months for chemotherapy).

Therapies by drug class

PD-1/PD-L1 antibodies

Anti-PD-1 antibodies **nivolumab** (Opdivo) and **pembrolizumab** (Keytruda) are widely used for a range of tumor types. Newer approvals for pembrolizumab are for adenocarcinoma of the stomach/gastro-esophageal junction with at least 1% PD-L1 expression, and in any tumor demonstrated to be MSI-high. Newer indications for nivolumab are for bladder cancer, MSI-high colon cancer, and for hepatoma previously treated with sorafenib. The anti-PD-L1 antibody **atezolizumab** (Tencentriq) is now approved for platinum-resistant metastatic lung cancer, in addition to platinum-ineligible and platinum-resistant urothelial cancer.

Avelumab (Bavencio) is an anti-PD-L1 approved for both Merkel cell and previously treated urothelial cancers at a dose of 10 mg/kg every 2 weeks.[13] It demonstrated a 33% response rate for Merkel cell and a 16% response rate for urothelial cancer.

Durvalumab (Imfinzi) is another anti PD-L1 antibody approved at 10 mg/kg every 2 weeks for previously treated urothelial cancer with a 17% response rate (RR: PD-L1 high, 26%; low, 4%).[14]

PI3K kinase inhibitors

Copanlisib (Aliqopa) is a PI3K inhibitor approved for relapsed follicular lymphoma in patients who have progressed after two previous lines of therapy.[15] It is a 60-mg, 1-hour infusion given on days 1, 8, and 15 every 28 days. In a phase 2 trial, it had a 59% response rate (14% complete response) and a median response duration of 12.2 months.

BTK inhibitors

Acalabruitnib (Calquence) is approved for adults with previously treated mantle cell lymphoma. In a phase 2 trial at 100 mg orally bid, it achieved an 80% overall and 40% complete response rate.[16] These response rates are higher than were seen for ibrutinib in its original phase 2 trial. The spectrum of toxicities seems similar to ibruitinib and includes bleeding, cytopenias, infection, and atrial fibrillation.

CD19 CAR-T cells

Perhaps the most exciting and novel new agents are genetically engineered autologous T cells. **Tisagenlecleucel** (Kymriah), a chimeric antigen receptor T cell (CART) that targets CD19 is approved for refractory B cell precursor acute lymphoblastic leukemia (in patients under 25 years) where the complete response rate was 83% (including patients with incomplete blood count recovery).[17]

Axicabtagene ciloleucel (aci-cel; Yescarta), also CD19-directed CART, is approved for adults with relapsed or refractory non-Hodgkin lymphoma after two lines of previous therapy (specifically large-cell lymphoma, primary mediastinal large B-cell lymphoma, and transformed follicular lymphoma). Response rate was 72% (complete, 51%; partial, 21%), with a median duration of response of 9.2 months.[18]

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