2017–2018 Drug Approvals in Solid Tumors

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Recent approvals for solid tumors by the US Food and Drug Administration (FDA) have not included new classes of agents, but new uses for existing drugs. These include cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors, poly (ADP-ribose) polymerase (PARP) inhibitors, tyrosine kinase inhibitors with various targets, antiandrogens, and others.

"New oncology approvals from 2017 to 2018 have mostly been for additional indications, with many agents moved up to first-line therapy. We are in the era of incremental improvement," said Patrick Kiel, PharmD, BCPS, BCOP, of the Indiana University Simon Cancer Center, at JADPRO Live 2018.

Dr. Kiel summarized the key changes during his presentation:

- CDK4/6 inhibitors are now the first-line standard of care for hormone receptor–positive, HER2-negative breast cancer
- PARP inhibitors are now available for breast cancer patients with germline *BRCA* mutations
- Immunotherapy, especially in combination, is expanding to many tumor types
- Tyrosine kinase inhibitors continue to be approved for non–small cell lung cancer (NSCLC) and renal cell carcinoma
- In melanoma, immunotherapy and BRAF inhibitors have moved into the adjuvant setting
- Prostate cancer is becoming a more complex malignancy, and treatments are evolving to address changing needs

ANTI–PD-1 AGENTS

Investigators continue to find new uses for antibodies targeting programmed cell death protein 1 (PD-1) and ligand 1 (PD-L1). Nivolumab (Opdivo) has new indications in metastatic small cell lung cancer, in combination with ipilimumab (Yervoy) in previously treated microsatellite-high (MSI-H) or mismatch repair-deficient (dMMR) colorectal cancer, and in intermediate/poor-risk untreated renal cell carcinoma. Nivolumab was also approved as adjuvant treatment in node-positive or metastatic resectable melanoma.

Pembrolizumab's (Keytruda) new indications are for metastatic PD-L1 cervical cancer, and in combination with platinum/pemetrexed in first-line NSCLC. Durvalumab (Imfinzi) was approved for stage III NSCLC.

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NEW IMMUNOTHERAPY COMBINATION IN RENAL CELL AND COLORECTAL CANCER

The combination of nivolumab and ipilimumab as first-line treatment for intermediate/poor-risk renal cell carcinoma was approved based on Checkmate 214 and has "quickly been developing" as a standard of care, said Dr. Kiel. The study found large differences in response rates, progression-free survival, and even overall survival in comparison with sunitinib (Sutent; Motzer et al., 2018).

In previously treated MSI-H or dMMR metastatic colorectal cancer, nivolumab/ipilimumab led to a 71% progression-free survival and 85% overall survival at 1 year, vs. 50% and 73%, respectively, for nivolumab alone in CheckMate 142 (Overman et al., 2018). Quality of life was as good on the combination as with the single agent, although the grade 3/4 toxicity rate was 32%. "Part of the challenge is selecting the ideal patient for combination therapy," he said. "We're seeing several combinations emerging, and we still don't know who will benefit most...We need to better communicate with patients and mitigate treatment toxicities, because new drugs are leading to advances in overall survival."

APPROVALS FOR IMMUNOTHERAPY IN NSCLC

In the frontline setting, KEYNOTE-047 evaluated pembrolizumab in combination with carboplatin and paclitaxel, vs. carboplatin/paclitaxel alone, in treatment-naive patients with metastatic squamous NSCLC. Patients receiving the combination were 44% less likely to die or progress ($p < .001$; Paz-Ares et al., 2018).

The PD-L1 blocker durvalumab moved into stage III NSCLC, given after radiation in the PACIFIC trial (Antonia et al., 2017). Progression-free survival in the durvalumab arm was 16.8 months vs. 5.6 months with placebo ($p < .0001$). "Uniquely, for stage III NSCLC, curves separated and stayed separated. This was a practice-changing study," Dr. Kiel commented.

With the PD-1/PD-L1 antibodies, fatigue is the most common toxicity, while infusion reactions are rare. Table 1 shows the general safety profiles of the approved agents.

APPROVALS FOR TARGETED THERAPY IN NSCLC

Also in the first-line setting, several targeted agents were approved: alectinib (Alecensa) for *ALK*-positive NSCLC, and afatinib (Gilotrif) and osimertinib (Tagrisso) for NSCLC that harbors epidermal growth factor receptor (*EGFR*) mutations. Osimertinib is already FDA approved in the relapsed setting for *EGFR* T790M–positive patients (T790M confers resistance to other tyrosine kinase inhibitors). It is now approved in the first line for tumors with EGFR exon 19 deletions or exon 21 L858R mutations. Afatinib is now approved in the first line for nonresistant *EGFR* mutations.

Osimertinib was approved in the first line based on the FLAURA trial, which evaluated osimertinib vs. gefitinib (Iressa) or erlotinib (Tarceva) in patients with the previously mentioned *EGFR* mutations (Soria et al., 2018). Median progression-free survival was 18.9 months with osimertinib vs. 10.2 months with standard therapy, a 54% reduction in risk ($p < .001$). Median overall survival was not reached in either arm.

"We don't exactly know why osimertinib was so much better, but it does have high penetration of the blood-brain barrier so you might get more coverage for the central nervous system," Dr. Kiel suggested, noting that 20% of the study population had stable brain metastases. "When patients progress on EGFR inhibitors, they can be switched to osimertinib."

CDK4/6 INHIBITORS IN BREAST CANCER

After their initial approvals in the relapsed setting for hormone receptor–positive metastatic breast cancer, the CDK4/6 inhibitors ribociclib (Kisqali) and palbociclib (Ibrance) have moved up to front-line endocrine treatment for hormone receptor–positive, HER2-negative advanced or metastatic disease.

Ribociclib was approved in combination with an aromatase inhibitor for pre/perimenopausal or postmenopausal patients as initial endocrine-based therapy, and in combination with fulvestrant for postmenopausal women, either as initial therapy or following disease progression on endocrine therapy. Abemaciclib (Verzenio) was approved in combination with an aromatase inhibitor as ini-

Table 1. General Safety: PD-1/PD-L1 Comparison

	Avelumab		Durvalumab		Pembrolizumab		Nivolumab		Atezolizumab	
Adverse reaction	**All grades**	**Grades 3/4**	**All grades**	**Grades 3/4**	**All grades**	**Grades 3/4**	**All grades**	**Grades 3/4**	**All grades**	**Grades 3/4**
Fatigue	50%	2%	39%	6%	28%	< 1%	17%	2%	52%	6%
Infusion reaction	25%	< 1%	1.80%	< 1%	< 1%	–	–	–	1.70%	–
Arthralgia	16%	–	6%	–	18%	< 1%	–	–	14%	1%
Diarrhea	23%	–	13%	1%	26%	–	9%	2%	18%	1%
Rash	22%	–	11%	1%	24%	< 1%	21%	< 1%	15%	< 1%
Decreased appetite	20%	2%	19%	1%	16%	< 1%	8%	–	26%	1%
Dyspnea	11%	–	13%	2%	11%	< 1%	4%	1%	16%	4%
Hypertension	13%	6%	–	–	–	–	–	–	–	–

Note. Information from AstraZeneca Pharmaceuticals LP (2017); Bristol-Myers Squibb Company (2014); EMD Serono, Inc. (2017); Genentech, Inc. (2016); Merck Sharp & Dohme Corp. (2016).

tial endocrine-based therapy for postmenopausal women.

The pivotal trials leading to the approvals in the first-line setting were MONALEESA-3 for ribociclib in postmenopausal patients (Slamon et al., 2018), MONALEESA-7 for ribociclib in pre/perimenopausal patients (Tripathy et al., 2018), and MONARCH 3 for abemaciclib in postmenopausal patients (Goetz et al., 2017). While the endpoint numbers varied somewhat among these pivotal trials, all studies showed an approximately 40% reduction in risk of progression and essentially a doubling in progression-free survival time. Based on these outcomes, CDK4/6 inhibitors plus endocrine therapy have become standard first-line therapy.

The three approved agents—palbociclib, ribociclib, and abemaciclib—have different selectivity for CDK 4 vs. CDK 6. Abemaciclib is dosed continuously (twice daily), while palbociclib and ribociclib are administered (once daily) for 3 weeks on, with one week off. The toxicity profiles for the three agents also differ somewhat, but all can interact with CYP3A.

Since there are no comparative trials for superiority, selecting one drug over another often hinges on their side effect profiles (Tables 2 and 3). Hepatic toxicity and neutropenia can occur with all three agents. QT interval prolongation is most likely with ribociclib. Diarrhea and venous thromboembolism can be problematic with abemaciclib, while ribociclib and palbociclib carry more risk for high-grade neutropenia.

Appropriate monitoring for these toxicities is important, and patients on abemaciclib should start antidiarrheal treatment at the first sign of loose stools. It is advised that abemaciclib be avoided in patients with underlying gastrointestinal disorders.

PARP INHIBITORS ENTER BREAST ARENA

For patients with a deleterious or suspected deleterious germline *BRCA*-mutated HER2-negative metastatic breast cancer who have received chemotherapy in the neoadjuvant, adjuvant, or metastatic setting, the PARP inhibitor olaparib (Lynparza) became approved in 2018. The phase III OlympiAD trial evaluated olaparib in patients with HER2-negative, hormone receptor–positive or –negative breast cancer who had received at least one hormonal therapy (if appropriate) and no more than two lines of chemotherapy (Robson et al., 2017). Approximately 50% of the study population had a *BRCA1* mutation and were hormone receptor–positive. The single agent was compared to standard-of-care choices, including capecitabine, eribulin, and vinorelbine. A significant 42% reduction in risk of progression was observed with olaparib ($p < .001$).

Table 2. Safety Information for Ribociclib, Abemaciclib, and Palbociclib

	Ribociclib[a]			Abemaciclib[b]			Palbociclib[b]		
Adverse reaction	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**
Fatigue	37%	2%	–	37%	3%	–	36%	2%	–
Nausea	29%	–	–	42%	3%	–	29%	–	–
URI	19%	< 1%	–	11%	–	–	19%	< 1%	–
Diarrhea	19%	–	–	73%	13%	–	19%		–
Arthralgia	13%	< 1%	–	11%	< 1%	–	13%	< 1%	–
Stomatitis	11%	< 1%	–	15%	< 1%	–	12%	< 1%	–
Abdominal pain	7%	1%	–	33%	3%	–	–	–	–
Decreased appetite	12%	1%	–	25%	1%	–	13%	< 1%	–

Note. URI = upper respiratory infection. Information from Cristofanilli et al. (2016); Sledge et al. (2017); Turner et al. (2015).
[a]With letrozole.
[b]With fulvestrant.

Table 3. Laboratory Abnormalities for Ribociclib, Abemaciclib, and Palbociclib

	Ribociclib[a]			Abemaciclib[b]			Palbociclib[b]		
Adverse reaction	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**	**Grade 1/2**	**Grade 3**	**Grade 4**
Neutropenia	14%	50%	10%	20%	24%	3%	16%	55%	10%
Anemia	17%	< 1%	< 1%	22%	7%	< 1%	25%	3%	–
Thrombocytopenia	28%	1%	< 1%	14%	2%	1%	19%	2%	1%
QT prolongation	3%	< 1%	–	–	–	–	–	< 1%	–
Increased ALT	36%	8%	2%	9%	4%	< 1%	4%	2%	–
Increased creatinine	19%	1%	–	11%	1%	–	–	–	–
Hypokalemia	9%	1%	1%	27%	7%	< 1%	–	< 1%	–
Hyponatremia	–	–	–	31%	–	–	1%	1%	–
Febrile neutropenia	–	< 1%	–	–	< 1%	–	–	1%	–

Note. Information from Cristofanilli et al. (2016); Lilly USA, LLC (2017); Novartis (2017); Pfizer (2015); Sledge et al. (2017); Turner et al. (2015).
[a]With letrozole.
[b]With fulvestrant.

Rucaparib (Rubraca), niraparib (Zejula), and olaparib have similar safety profiles across the board. Practitioners should watch for signs of pneumonitis, bone marrow suppression, cardiovascular effects, myelodysplastic syndrome, and acute myeloid leukemia.

Regarding other PARP inhibitor approvals, rucaparib was approved in ovarian cancer as maintenance treatment following a response to a platinum-based regimen. The next frontier for this class is prostate cancer. A number of trials are evaluating olaparib alone and in combination with anti–PD-1/PD-L1 antibodies, abiraterone (Zytiga), and other drugs in this tumor.

APPROVALS IN MELANOMA

In melanoma, dabrafenib (Tafinlar) plus trametinib (Mekinist) is now an approved combination as adjuvant treatment in *BRAF*-mutated melanoma. Another BRAF inhibitor/MEK inhibitor combination, encorafenib (Braftovi) plus binimetinib (Mektovi), is approved in unresectable advanced *BRAF*-mutated disease based on results of the three-arm COLUMBUS trial (Dummer et al., 2018), which compared the combination to encorafenib alone and to vemurafenib (Zelboraf) alone.

The combination led to an overall response rate of 63% and reduced the risk of progression by 46% over vemurafenib ($p < .0001$). Toxicities were as expected for BRAF/MEK inhibition, and generally occurred less with the combination than with the single agents.

APPROVALS IN PROSTATE CANCER

"Prostate cancer has been evolving in complexity and drugs are meeting these needs. We've gone from antihormonal therapies to docetaxel, to now having more agents targeting testosterone, which is still the main target in this disease," Dr. Kiel said.

Three new drugs were approved in prostate cancer: abiraterone, in combination with prednisone for metastatic high-risk castration-sensitive prostate cancer, and apalutamide (Erleada) and enzalutamide (Xtandi) for nonmetastatic castration-resistant prostate cancer.

LATITUDE evaluated androgen deprivation therapy (ADT) with and without abiraterone/prednisone in newly diagnosed high-risk castrate-sensitive men (Fizazi et al., 2017). An overall survival advantage, a 48% reduction in risk ($p < .001$), was seen with abiraterone, as well as a 53% reduction in the risk of progression ($p < .001$), vs. placebo.

In a similar study, SPARTAN, apalutamide in nonmetastatic castration-resistant prostate cancer produced a 72% reduction ($p < .001$) in the

risk of metastasis or death (metastasis-free survival) vs. ADT alone (Smith et al., 2018).

Enzalutamide was evaluated in combination with ADT vs. ADT alone in the PROSPER trial (Hussain et al., 2018), producing a median metastasis-free survival of 36.6 months vs. 14.7 months, a 71% reduction in risk ($p < .0001$).

"Apalutamide and enzalutamide offer an impressive 2-year median metastasis-free survival improvement," Dr. Kiel noted.

BEVACIZUMAB IN OVARIAN CANCER

In an approval that "threw some for a loop," Dr. Kiel commented, bevacizumab (Avastin) became available as first-line ovarian cancer treatment based on GOG-0218 (Burger et al., 2013, 2018). Patients received carboplatin/paclitaxel plus bevacizumab for 6 cycles or bevacizumab continuously for 15 months. "Regardless of how you look at this, there was a benefit for bevacizumab with maintenance," he said, citing a 6-month advantage in progression-free survival and a 3-month increase in overall survival.

OTHER DRUG APPROVALS

Dr. Kiel also noted the following approvals:

- In the first-line setting, lenvatinib (Lenvima) for unresectable hepatocellular cancer
- In the first-line setting, cabozantinib (Cabometyx) for advanced renal cell carcinoma
- In early breast cancer, pertuzumab (Perjeta) in combination with trastuzumab (Herceptin) as adjuvant therapy in HER2-positive disease
- For *BRAF*-mutated anaplastic thyroid cancer, dabrafenib plus trametinib
- The biosimilar trastuzumab-dkst (Ogivri)
- FoundationOne CDx as a next-generation diagnostic panel.

Disclosure

Dr. Kiel has served on speakers bureaus for Celgene, Genentech, Gilead, and Takeda, and has received consulting fees from Takeda.

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