2016 Oncology Development Review

Oncology developers extend their franchise

Oncology drug developers had another productive year in 2016. However the rewards accrued mainly to companies with new indications for existing drugs, rather than to those which are developing entirely new compounds.

Overall, the regulatory authorities in the US, the European Union, and Japan, approved five new oncology drugs in 2016, down sharply from 13 in 2015. By comparison, the regulators approved 28 new indications for existing drugs, effectively enabling many companies to extend their franchises to new patients. The number of new indications is a record; the previous record was 17, achieved in both 2014 and 2015.

The decline in new oncology drug approvals was part of a trend affecting the broader industry, at least in the US. The Food and Drug Administration's Center for Drug Evaluation and Research authorised 20 new compounds for all disease areas in 2016, down from 45 the previous year. According to John Jenkins, director of the FDA's Office of New Drugs, the decline was mostly due to a drop in applications. Also, the year-to-year comparison was skewed by the fact that at least five new drugs reached the market in 2015, rather than in 2016, because of an accelerated assessment[1].

The oncology sector had its own special features. The global portfolio was robust going into Phase 3. But, as reported in an earlier edition of *MedNous*, 18 candidate drugs failed to meet their endpoints in Phase 3 studies or were abandoned by their developers for safety, efficacy or strategic reasons[2]. This was a high figure by historic standards. In addition, seven candidate drugs received a negative opinion from a regulatory authority, or the sponsor withdrew the application before a formal decision was taken. In at least three cases, developers received complete response letters from the FDA because the candidate compounds failed to show efficacy.

Nevertheless, innovation did reach the market. Of the five new drugs that were approved in 2016, three have entirely new mechanisms of action. They are venetoclax (Venclexta) from Roche and AbbVie Inc, olaratumab (Lartruvo) from Eli Lilly and Company and the cell therapy Zalmoxis, from MolMed SpA.

Venetoclax was approved by both the FDA and the European Commission to treat patients with a specific type of chronic lymphocytic leukaemia (CLL): those with a chromosomal abnormality called 17p deletion. Patients with this mutation lack a portion of the chromosome that acts to suppress cancer growth. Venetoclax targets the B-cell lymphoma 2 (BCL-2) protein that supports this growth. The efficacy of venetoclax was tested in a single-arm trial of 106 CLL patients with the mutation who had received at least one prior therapy. The results showed that 80% of participants experienced a complete or partial remission of their cancer.

Olaratumab, which is a treatment for soft tissue sarcoma, also received both FDA and EU approval. It is the first monoclonal antibody approved to treat the disease, which can start in fat, muscle, nerves or blood vessels. Combined with doxorubicin, the treatment delivered a statistically significant improvement in overall survival in patients with metastatic cancer.

The third new drug, Zalmoxis, is an allogeneic T cell therapy for patients undergoing haematopoietic stem cell transplantation. It was approved in the EU as an adjunct therapy to help transplant patients fight off infection. Table 1 on page 11 gives a full list of the new drug and new indication approvals in 2016. It is interesting to note that four out of the five new drugs and 20 out of the 28 new indications were first issued by the FDA, underscoring that agency's leadership in oncology.

Immuno-oncology therapies

The new immuno-oncology sector continued to expand in 2016. Starting with the approval of ipilimumab (Yervoy) in 2011, this class of drugs has shown remarkable cancer-killing activity in patients. Also known as antibody checkpoint inhibitors, they block certain receptors on T cells, thereby releasing the immune system to fight disease. Two of these receptors are programmed cell death protein 1 (PD-1) and its ligand PD-L1. Four checkpoint antibodies are now on the market, a figure that increased last year with the approval of Roche's atezolizumab (Tecentriq) for urothelial cancer.

As Table 1 illustrates, eight out of the 33 new drug and new indication approvals last year were antibody checkpoint inhibitors. Besides urothelial cancer, the approved indications are head and neck cancer and Hodgkin lymphoma. These augment the marketed indications of melanoma, non-small cell lung cancer and kidney cancer. More recently, Merck KgaA and Pfizer Inc submitted a registration file in the EU and the US for avelumab, an anti-PD-L1 antibody for Merkel cell carcinoma. And AstraZeneca Plc filed an application in the US for its checkpoint antibody durvalumab in urothelial cancer.

Candidate antibodies targeting PD-1 and PD-L1 are also in pivotal clinical trials in 11 other cancers. These are small cell lung cancer, mesothelioma, multiple myeloma, non-Hodgkin lymphoma, colorectal cancer, liver cancer, esophageal cancer, gastric cancer, breast cancer, ovarian cancer and glioblastoma.

FDA and EMA therapy designations

The FDA has been a leader in providing incentives to developers to innovate. In 2012, the agency introduced the 'breakthrough therapy designation (BTD),' which is awarded to companies that are developing drugs for serious or life-threatening diseases. Recipients of this designation get a faster regulatory review. In 2016, the European Medicines Agency introduced a similar incentive called PRIME for priority medicines.

There is no guarantee that products receiving a breakthrough therapy or PRIME designation will be

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approved. However, breakthrough therapy drugs have chalked up some success. In the four years since the policy took effect, 30 designated drugs have been licensed for marketing in the US and six have started the registration procedure. In 2016, 12 of the new drug and new indication approvals in the US were compounds with a breakthrough designation. They included venetoclax, atezolizumab, olaratumab and rucaparib. For a list of BTD and PRIME designated drugs please see Table 2 on page 12.

2016 also saw several drugs with breakthrough status fail in late-stage trials, illustrating the fact that designation doesn't remove the development risk. Three drugs failed to meet their primary endpoints in late-stage trials: Celldex Therapeutics' rindopepimut, a cancer vaccine for glioblastoma; Boehringer Ingelheim's volasertib, a polo-like kinase inhibitor for acute myeloid leukaemia; and Aduro Biotech's CRS-207, an immunotherapy for pancreatic cancer. One breakthrough medicine, Clovis Oncology's lung cancer treatment rociletinib received a complete response letter from the FDA while another, Boehringer Ingelheim's olmutinib for lung cancer was abandoned most likely for reasons of safety.

Overall, our data show that the FDA issued complete response letters to the developers of 13 drugs in the five years through 2016, and four additional registration files were withdrawn. In the same period, the agency approved 122 new oncology drugs and new indications for existing drugs. This gives a failure rate of 12.2% for the period.

Table 1 Worldwide regulatory approvals 2016

Compound	Type	Sponsor	Regulator	Indication
Venetoclax (Venclexta)	ND	Roche Group/AbbVie Inc	US, EU	CLL, second line, with 17p deletion
Rucaparib (Rubraca)	ND	Clovis Oncology Inc	US	Ovarian cancer with BRCA mutation, fourth line
Atezolizumab (Tecentriq)	ND	Roche Group	US	Urothelial cancer, second line
Allogeneic T cells (Zalmoxis)	ND	MolMed SpA	EU	Haploidentical haematopoietic stem cell transplant
Olaratumab (Lartruvo)	ND	Eli Lilly and Company	US, EU	Soft tissue sarcoma, first line
Ofatumumab (Arzerra)	NI	Novartis/Genmab A/S	US, EU	CLL, second line, maintenance
Carfilzomib (Kyprolis)	NI	Amgen Inc	US, EU,JP	Multiple myeloma, second line
Brentuximab vedotin (Adcetris)	NI	Seattle Genetics Inc	EU	HL + anaplastic large cell lymphoma retreatment
Nivolumab (Opdivo)	NI	Bristol-Myers Squibb Company	US, EU	Melanoma, first line with BRAF mutation
Eribulin (Halaven)	NI	Eisai Co Ltd	US, EU	Liposarcoma, second line
Palbociclib (Ibrance)	NI	Pfizer Inc	US, EU	Breast cancer, second line
Afatinib (Giotrif)	NI	Boehringer Ingelheim GmbH	EU	NSCLC, squamous cell type, second line
Obinutuzumab (Gazyva)	NI	Roche Group	US, EU	Follicular non-Hodgkin lymphoma, second line
Everolimus (Afinitor)	NI	Novartis	US, EU, JP	NET, gastrointestinal + lung cancers, second line
Ibrutinib (Imbruvica)	NI	Johnson & Johnson Inc/AbbVie Inc	US, EU	CLL first line
Crizotinib (Xalkori)	NI	Pfizer Inc	US, EU	NSCLC with ROS1 mutation
Enzalutamide (Xtandi)	NI	Astellas Pharma Inc	EU, US	Prostate cancer, first line
Cabozantinib (Cometriq)	NI	Exelixis Inc	US, EU	Kidney cancer, second line
Bevacizumab (Avastin)	NI	Roche Group	EU	NSCLC with EGFR mutation
Ibrutinib (Imbruvica)	NI	Johnson & Johnson Inc/AbbVie Inc	US, EU	CLL, second line
Lenvatinib (Lenvima)	NI	Eisai Co Ltd	US, EU	Kidney cancer, second line
Nivolumab (Opdivo)	NI	Bristol-Myers Squibb Company	US, EU, JP	Hodgkin lymphoma, fourth line
Pembrolizumab (Keytruda)	NI	Merck & Co Inc	EU, US, JP	NSCLC, second line, PD-L1 positive
Pembrolizumab (Keytruda)	NI	Merck & Co Inc	US	Head and neck cancer, second line
Ofatumumab (Arzerra)	NI	Novartis/Genmab A/S	US, EU	CLL, second line
Blinatumomab (Blincyto)	NI	Amgen Inc	US	Paediatric relapsed/refractory ALL
Atezolizumab (Tecentriq)	NI	Roche Group	US	NSCLC, second line
Ibrutinib (Imbruvica)	NI	Johnson & Johnson Inc/AbbVie Inc	EU	Mantle cell lymphoma, second line
Pembrolizumab (Keytruda)	NI	Merck & Co Inc	US, JP	NSCLC, first line, with high PD-L1 expression
Capecitabine (Xeloda)	NI	Chugai Pharmaceutical Co Ltd	JP	Adjuvant for rectal cancer
Nivolumab (Opdivo)	NI	Bristol-Myers Squibb Company	US	Head and neck cancer, second line
Arsenic trioxide (Trisenox)	NI	Teva Pharmaceutical Industries Ltd	EU	Acute promyelocytic leukaemia, first line
Daratumumab (Darzalex)	NI	Johnson & Johnson Inc/Genmab	US	Multiple myeloma, second line

Note: ND=new drug; NI=new indication; CLL=chronic lymphocytic leukaemia; NSCLC=non-small cell lung cancer; NET=neuroendocrine tumour; ALL=acute lymphoblastic leukaemia

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Table 2 Drugs that received FDA breakthrough or EMA PRIME status

Compound	Sponsor	Mode of Action	Status	Indication
Venetoclax	Roche/AbbVie Inc	Targets the BCL2 protein	BTD	Relapsed CLL in combination with rituximab
Venetoclax	Roche/AbbVie Inc	Targets the BCL2 protein	BTD	AML, first line, in elderly patients
Olaparib	AstraZeneca Plc	Inhibits poly ADP ribose polymerase	BTD	Prostate cancer with BRCA1/2 mutation
Sacituzumab govitecan	Immunomedics Inc	Anti-TROP-2 antibody conjugate	BTD	Triple-negative breast cancer
NY-ESO TCR	Adaptimmune Therapeutics Plc	T cell receptor therapy	BTD	Synovial sarcoma
Durvalumab	AstraZeneca Plc	Anti-PD-L1 antibody	BTD	Urothelial cancer with PD-L1 expression
Midostaurin	Novartis	Multi-targeted kinase inhibitor	BTD	AML, first line, with FLT3 expression
Pembrolizumab	Merck & Co Inc	Anti-PD-1 antibody	BTD	Relapsed/refractory Hodgkin lymphoma
Nivolumab	Bristol-Myers Squibb Co	Anti-PD-1 antibody	BTD	Head and neck cancer, second line
Polio vaccine	Duke University	Oncolytic virus	BTD	Glioblastoma
CPX-351	Celator Pharmaceuticals	Chemotherapy combination	BTD	AML with myelodysplasia-related changes
Ruxolitinib	Incyte Corp	JAK1/JAK2 inhibitor	BTD	Acute graft-versus-host disease
Nivolumab	Bristol-Myers Squibb Co	Anti-PD-1 antibody	BTD	Urothelial cancer, second line
Ibrutinib	AbbVie Inc	Bruton's kinase inhibitor	BTD	Chronic graft-versus-host disease
Loxo-101	Loxo Oncology Inc	Targets tropomyosin receptor kinase (TRK)	BTD	Solid tumours expressing TRK
Daratumumab	Johnson & Johnson/Genmab A/S	Anti-CD38 antibody	BTD	Multiple myeloma, second line
Pracinostat	MEI Pharma Inc	HDAC inhibitor	BTD	AML in patients over the age of 75 years
Ribociclib	Novartis	Cyclin dependent kinase 4/6 inhibitor	BTD	HR and HER2 breast cancer
SL-401	Stemline Therapeutics Inc	Targets interleukin-3 receptor	BTD	Blastic plasmacytoid dendritic cell neoplasm
Pembrolizumab	Merck & Co Inc	Anti-PD-1 antibody	BTD	NSCLC, first line, with high PD-L1 expression
Alectinib	Roche Group	Anaplastic lymphoma kinase (ALK) inhibitor	BTD	NSCLC, first line, with ALK expression
NiCord	Gamida Cell	Umbilical cord blood-derived stem cells	BTD	Bone marrow transplantation
Brentuximab vedotin	Seattle Genetics Inc	Anti-CD30 antibody conjugate	BTD	Cutaneous T cell lymphoma expressing CD30
Pembrolizumab	Merck & Co Inc	Anti-PD-1 antibody	BTD	Microsatellite instability-high cancer
JCAR017	Juno Therapeutics Inc	CAR T cells	BTD	Relapsed /refractory non-Hodgkin lymphoma
KTE-C19	Kite Pharma Inc	Chimeric antigen receptor T cell therapy	PRIME	Diffuse large B-cell lymphoma
CTL019	Novartis	Chimeric antigen receptor T cell therapy	PRIME	Relapsed/refractory paediatric ALL
DNX-2401	DNAtrix Therapeutics Inc	Oncolytic virus	PRIME	Glioblastoma
NY-ESO TCR	Adaptimmune Therapeutics Plc	T cell receptor therapy	PRIME	Synovial sarcoma
JCAR015	Juno Therapeutics Inc	Chimeric antigen receptor T cell therapy	PRIME	Relapsed/refractory ALL in adults
EBV-CTL	Atara Biotherapeutics Inc	Targets Epstein-Barr virus infected cells	PRIME	Post-transplant lymphomas
JCAR017	Juno Therapeutics Inc	CAR T cells	PRIME	Relapsed /refractory non-Hodgkin lymphoma

Note: BTD=breakthrough therapy designation; PRIME=priority medicines; ALL=acute lymphoblastic leukaemia; CLL=chronic lymphocytic leukaemia; NSCLC=non-small-cell lung cancer

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Table 3 Worldwide new drug applications at end 2016				
Compound	**Type**	**Sponsor**	**Regulator**	**Indication**
Vosaroxin	ND	Sunesis Pharmaceuticals Inc	EU	Acute myeloid leukaemia, second line
Anamorelin	ND	Helsinn Healthcare SA	EU	Non-small cell lung cancer with cachexia
Tivozanib	ND	Eusa Pharma/Aveo Pharmaceuticals	EU	Kidney cancer, first line
Xilonix	ND	XBiotech Inc	EU	Colorectal cancer with cachexia
Luthathera	ND	Advanced Accelerator Applications SA	EU	Neuroendocrine tumours
Inotuzumab oxogamicin	ND	Pfizer Inc	US, EU	Acute myeloid leukaemia, second line
Neratinib	ND	Puma Biotechnology Inc	US, EU	Adjuvant treatment for breast cancer
Binimetinib	ND	Array BioPharma Inc	US, EU	Melanoma, second line, with NRAS expression
Etirinotecan pegol	ND	Nektar Therapeutics/Daiichi Sankyo	EU	Breast cancer, third line + brain metastases
Brigantinib	ND	Ariad Pharmaceuticals Inc	US	Non-small cell lung cancer, second line, ALK+
Pacritinib	ND	CTI BioPharma Corp	EU	Myelofibrosis
Midostaurin	ND	Novartis	US, EU	Acute myeloid leukaemia, first line, FLT3+
Plitidepsin	ND	PharmaMar SA	EU	Multiple myeloma, fourth line
Ribociclib	ND	Novartis	US, EU	Breast cancer, hormone receptor positive, first line
Niraparib	ND	Tesaro Inc	US, EU	Ovarian cancer, second line, maintenance
Avelumab	ND	Merck KGaA/Pfizer Inc	US, EU	Merkel cell carcinoma
NGR-hTNF	ND	Molmed SpA	EU	Mesothelioma second line
Durvalumab	ND	AstraZeneca Plc	US	Urothelial cancer second line

By comparison, there were 25 regulatory failures in the EU over the same five years, of which 13 were filings only made to the European Medicines Agency, and not to the FDA. Total EU approvals amounted to 117, giving a failure rate of 17.6%. There is no immediate explanation for why the two agencies had such different outcomes. Having said this, companies may have improved the quality of the dossiers presented to the FDA. And the US agency may have relaxed some of its requirements, especially through the use of its accelerated approval procedures.

Going into 2017, there were 18 new oncology drugs and 12 new indications in the pre-registration global pipeline. Table 3 lists the new drugs, which include several kinase inhibitors, two new antibody checkpoint inhibitors, an antibody drug conjugate, one poly ADP-ribose polymerase (PARP) inhibitor and a nuclear medicine targeting carcinoid tumours. In addition to these developers, Kite Pharma Inc plans to start a rolling submission to the FDA of its lead chimeric antigen receptor (CAR) T cell therapy for patients with non-Hodgkin lymphoma before the end of the year.

Conclusion

The decline in new drug approvals in 2016 appears to be a one-off event. Based on the number of new drugs currently under regulatory review and in late-stage trials, regulatory approvals should increase in 2017 and beyond, laying the foundation for the launch of more new compounds in the coming years. The therapeutic revolution represented by the new immuno-oncology drugs will fuel this expansion, as will the launch of the first CAR T cell therapies.

At the end of 2016, the oncology drug pipeline was extremely rich and included 18 compounds in pre-registration and 118 drugs in Phase 3 or Phase 2 pivotal studies. On the basis of our recent estimates, which show an 83.3% approval rate for drugs in pre-registration, and a 38.7% approval rate for Phase 3, we expect the oncology pipeline to produce 61 approved drugs, probably in the next five years. Over the longer term, this figure could be as high as 86 additional new drug approvals, taking into account the 279 candidate compounds that are currently in Phase 2 and the 659 in Phase 1.

References:

1. Brennan, Z. "FDA's Jenkins on decline in new drug approvals in 2016: not due to standards shift," 4 November 2016, www.raps.org.

2. Pagliara, B, "Global oncology has many first-in-class compounds," *MedNous* November 2016.

All statistics in this article come from the On-kòs Pharma Consulting database.

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