Global oncology has many first-in-class compounds

Over the past four years, the outlook for cancer treatment has fundamentally changed as drugs that target molecular pathways, or modulate the immune system, have shown for the first time that they can halt the progression of disease, or even reverse it. Some of the newest agents are still in clinical development, while others have already made it to the market and are becoming a standard of care.

In this article, we supply statistics on the late-stage pharma pipeline in order to give a picture of what medicines will be coming up for a regulatory review in the near future. Based on the richness of the pipeline, we are likely to see more new drugs with unique modes of action coming to the market over the next five years, than we have in the past.

However 2016 will be an exception. In the first 10 months of this year, five new drugs have been turned back by a regulator in either the US or the European Union, while only four have been approved. Meanwhile, 18 new drugs failed to meet their endpoints in Phase 3 studies or were abandoned by their developers for safety, efficacy or strategic reasons.

The net result is that as of 31 October there were 106 new drugs in either Phase 3 development or in Phase 2 registration studies. A total of 18 were in pre-registration. This pipeline is full of some very innovative treatments.

The regulatory approvals up to this date include Venclexta (venetoclax), a small molecule drug that targets the B cell lymphoma 2 protein (BCL-2), for patients with chronic lymphocytic leukaemia who have a 17p chromosomal deletion. Venclexta is the first Food and Drug Administration approved treatment targeting BCL-2. The FDA also approved Tecentriq (atezolizumab), a PD-L1 inhibitor for bladder cancer, and Lartruvo (olaratumab), a platelet-derived growth factor receptor inhibitor, for soft tissue sarcoma. Finally, the European Commission approved Zalmoxis, a somatic cell therapy to help restore a patient's immune system after a haematopoietic stem cell transplant.

The regulatory failures include the issuance by the FDA of complete response letters to Telesta Therapeutics Inc for urocidin in bladder cancer and to Clovis Oncology Inc for rociletinib in non-small cell lung cancer. Elsewhere, CTI Biopharma Corp withdrew its new drug application from the FDA for pacritinib in myelofibrosis (the drug is still under regulatory review in the EU), and AstraZeneca Plc withdrew its application from the European Medicines Agency for cediranib in ovarian cancer. In September, the FDA's Oncologic Drugs Advisory Committee voted 14-0 against the approval of Spectrum Pharmaceuticals Inc's apaziquone for bladder cancer.

We have previously reported in *MedNous* that the success rate of new oncology drugs reaching pre-registration was 83.3%.[1] The success rate for drugs reaching Phase 3 is much lower at 38.7%. These percentages are based on statistics from 2004 to 2014. Assuming that these success rates remain unchanged, we would expect that 56 new oncology drugs would be approved in the near future. This would be very similar to the number of approvals recorded over the past five years.

What are the characteristics of the late-stage pipeline? Our statistics show five distinct categories. Of the 124 drugs in development, a total of 35, or 28.2%, are signal transduction kinase inhibitors. A second category encompasses the monoclonal antibodies and antibody-drug conjugates. A total of 23, or 18.5% of the late-stage pipeline, consists of these drugs. Three of these are immuno-oncology drugs.

Chemotherapy is still an important category. Fourteen cytotoxic agents, or 11.3% of the late-stage pipeline, is made up of these drugs. A fourth category consists of vaccines and immunotherapies of which there are 18 compounds or 14.5% of the total. Many of these vaccine products have been in clinical development for 10 to 12 years. Finally, we have a miscellaneous category for drugs that have a mechanism of action which is not shared by the other four groups. There are 34 drugs, or 27.4% of the total, represented by this group.

Nearly half, or 47%, of the late-stage compounds can be considered first-in-class, which means that they are not matched by any other drug on the market in terms of their mechanism of action. The first-in-class medicines include three chimeric antigen receptor (CAR) T cell therapies targeting the CD19 antigen on haematologic malignancies. An example is the Novartis CAR T therapy CTL019 which has been developed with the University of Pennsylvania for paediatric leukaemia. This is expected to be submitted for regulatory review early in 2017. A prospective CAR T therapy from Kite Pharma Inc is also being prepared for regulatory submissions early in 2017 for non-Hodgkin lymphoma.

The first-in-class compounds include 13 therapeutic cancer vaccines and immunotherapies. Ten of these are vaccines that induce antibodies to target cancer-associated antigens, while three use different methods to modulate the immune system. Thus far, only one therapeutic cancer vaccine has made it to the market. This is Dendreon Corp's Provenge (sipuleucel-T) for prostate cancer. However, Provenge is no longer available in Europe following Dendreon's bankruptcy and a decision by the vaccine's new owner to withdraw the marketing authorisation.

Among the 124 drugs in late-stage development or pre-registration, only 42 are owned or co-owned by Big Pharma. This is remarkable when one considers that the large pharma companies owned 80% of the new oncology drugs as recently as five years ago. The Big Pharma companies that are most active are AstraZeneca Plc, with six late-stage compounds; Pfizer Inc with five and Daiichi Sankyo Co Ltd with five. Ten of the candidate drugs have been developed by small pharmaceutical companies and 65 by biotech companies.

Reference:

1. Pagliara, B, "A window onto oncology drug success rates," *MedNous*, March 2015.

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Table 1 First-in-class vaccines and immunotherapies in late-stage development

Compound	Mechanism of Action	Developer	Indication
Racotumumab	Therapeutic vaccine	Recombio	Non-small cell lung cancer
POL-103A	Therapeutic vaccine	Polynoma LLC	Melanoma
AGS-003	Personalised therapeutic vaccine	Argos Therapeutics Inc	Metastatic renal cell carcinoma
DCVax-L	Personalised therapeutic vaccine	Northwest Biotherapeutics Inc	Glioblastoma multiforme
EGF vaccine	Therapeutic vaccine	Biovest International Inc	Non-small cell lung cancer
FANG vaccine	Personalised therapeutic vaccine	Gradalis Inc	Ovarian cancer
S-588410	Cancer peptide vaccine	Shionogi & Company Ltd	Oeosophageal cancer
ICT-107	Patient-specific dendritic cell vaccine	Immunocellular Therapeutics Ltd	Glioblastoma multiforme
OSE-2101	DNA therapeutic vaccine	OSE Pharma SA	Non-small cell lung cancer
ADXS11	Vaccine encoding human papillomavirus type 16 E7	Advaxis Inc	Cervical cancer
Z-100	Immunomodulator extracted from mycobacterium tuberculosis	Zeria Pharmaceutical Co. Ltd	Cervical cancer
Instiladrin	Adenovirally mediated interferon alfa	FKD Therapies Oy	Bladder cancer
Multikine	Leukocyte interleukin injection	Cel-Sci Corporation	Head and neck cancer

Table 2 Selected first-in-class anticancer drugs in late-stage development

Compound	Mechanism of Action	Company	Indication
Inotuzumab ozogamicin	Anti-CD22 antibody conjugated to calicheamicin	Pfizer Inc	Acute lymphoblastic leukaemia
Midostaurin	Multi-targeted kinase inhibitor	Novartis AG	FLT3-mutated acute myeloid leukaemia
Lutathera	Lu-177 somatostatin analogue	Advanced Accelerator Applications SA	Neuroendocrine cancers
Idasanutlin	Small molecule antagonist of MDM2	Roche Group	Acute myeloid leukaemia
GS-5745	Anti-MMP9 monoclonal antibody	Gilead Sciences Inc	Gastric cancer
AG-221	IDH2 mutant inhibitor	Agios Pharmaceuticals with Celgene Corp	IDH2 mutant acute myeloid leukaemia
Imetelstat	Oligonucleotide inhibitor of telomerase	Geron Corp/Johnson & Johnson	Myelodysplastic syndrome
MOR208	Monoclonal antibody targeting CD19	Morphosys AG	Non-Hodgkin's lymphoma
Epacadostat	Inhibitor of indoleamine 2,3-dioxygenase	Incyte Corp	Melanoma
Rovalpituzumab tesirine	Antibody-drug conjugate targeting DLL3	AbbVie Inc	Small cell lung cancer
IMMU-132	Antibody-drug conjugate targeting TROP-2	Immunomedics Inc	Breast cancer
CDX-011	Antibody-drug conjugate targeting GPNB	Celldex Therapeutics Inc	Breast cancer
Bay94-9343	Antibody-drug conjugate targeting mesothelin	Immunogen Inc with Bayer AG	Mesothelioma
SGN-CD33A	Antibody-drug conjugate targeting CD33	Seattle Genetics Inc	Acute myeloid leukaemia
Napabucasin (BBI-608)	STAT3 inhibitor	Sumitomo Dainippon Pharma Co Ltd	Gastric cancer and colorectal cancer