

1. From the Editors, with Dr. Zoe Cournia, Editor

Message from the Editor:

I am pleased to welcome you to this year's newsletter as the new Editor of the quarterly CICR newsletter. The Editorial Board would like to recognize and thank our **immediate Past Editor, Dr. George Sheppard** for his service to the CICR Newsletter. His continuous efforts for improvements, his inspiration, and leadership have reformed the CICR newsletter; he has set a high standard upon which we hope to continue to build in the coming year.

This year I have selected cutting edge areas of Chemistry in Cancer Research to highlight in our newsletter: immunotherapies in cancer, precision medicine, metabolic and epigenetic signaling in cancer, and nanomedicine advances. Each newsletter will include selected research highlights and a related profile of an early-career researcher, along with global news, upcoming conferences, grant opportunities and, of course, we will continue to update you on CICR news and activities. In this newsletter we also review the 2017 FDA approvals, as they reached a 20-year high since 1996.

Our topic this quarter is Immunotherapies in Cancer. In my debut as Editor for this year, I have taken the lead in assembling an overview of the topic.

IMMUNOTHERAPIES IN CANCER

Harnessing the immune system to recognize and destroy tumor cells has recently brought revolutionary advances in immuno-oncology that are transforming cancer treatment. In 2016, the FDA approved immunotherapies for the treatment of bladder cancer, head and neck cancer, Hodgkin's lymphoma, and lung cancer. In 2017, the FDA approved the first two treatments that use a patient's own genetically engineered cells to combat specific kinds of hematopoietic malignancies. Four types of immunotherapies now exist for cancer treatment:

- **Immune Checkpoint Inhibitors**

An immune response in the human body requires that a number of immunological checkpoints be passed. These checkpoints protect unwanted and harmful self-directed immune responses. The function of immune checkpoints relies upon the crosstalk between two cells one expressing a ligand (for example PDL-1, programmed death ligand-1) and the other the cognate receptor (for example PD-1, programmed death-1). This interaction drives the receptor-expressing cells to undergo cell death. Monoclonal antibodies against either the ligand or the receptor block this interaction and thus protect immune cells from dying. Because these cells attack the tumor, protecting them from cell death enhances the immune response leading to cancer cell eradication.

Checkpoint inhibitors include:

- PD-1 or PD-L1 inhibitors: These target checkpoints (PD-1 or its ligand PD-L1) that are found on T cells in the immune system. PD-1 inhibitors treat melanoma, non-small-cell lung cancer, kidney cancer, bladder cancer, head and neck cancers, and Hodgkin's lymphoma.
- CTLA-4 inhibitors: These turn off a checkpoint called CTLA-4, which is also found on T cells.

Recent approvals in the market include biologics that target immune-checkpoint pathways, such as ipilimumab (Yervoy®), pembrolizumab (Keytruda®) and nivolumab (Opdivo®). The 2017 approval list included two more PD-L1 inhibitors. Also, in May, FDA approved Merck's cancer immunotherapy Keytruda for use in

patients harboring a specific genetic profile (defect in DNA mismatch repair leading to microsatellite instability). Keytruda had already been on the market for three years for a variety of cancer types. Last year, the agency gave the drug its first “tissue agnostic” approval, meaning that a genetic biomarker, rather than the location of the cancer—lung or colon, for example—guides use of the treatment.

Although checkpoint inhibition can be highly efficacious for some patients, this immunotherapy approach is non-specific and can also unleash autoimmune T cell responses against healthy host tissue, leading to significant autoimmune toxicities. You can learn more about advances in immunotherapy from the [AACR blogpost collection](#).

- **Adoptive T Cell Transfer**

Using this approach, T cells are harvested from a patient's blood or tumor, then stimulated to grow and expand in an *in vitro* culture system. After sufficient *in vitro* expansion, these cells are reinfused into the host with the goal of recognizing, targeting, and destroying tumor cells. There are several types of adoptive cell transfer (ACT); however only the Chimeric antigen receptors (CARs) T-cell therapy has gained FDA approval in 2017. CAR-T are engineered receptors which graft the specificity of a monoclonal antibody onto a T-cell, with transfer of their coding sequence facilitated by retroviral vectors. The two CAR T-cell immunotherapies that have been FDA-approved are Kymriah from Novartis and Kite Pharma's Yescarta.

Despite the excitement, many challenges remain for CAR-T therapies. The treatments are approved for only a small subset of cancers. Kymriah treats people up to 25 years old who have acute lymphoblastic leukemia of B-cell origin who are resistant to treatment or have relapsed twice, limiting potential patients to a few hundred per year. Yescarta treats large B-cell lymphoma in adults after two other treatments have failed. Toxicity may appear from CAR-T therapies from body-wide immune reactions after injection of the drug. Finally, due to the personalized nature of CAR-T manufacturing, pricing remains a key issue, with Kymriah's one-time cost being \$475,000 and Yescarta's \$373,000.

- **Monoclonal Antibodies**

Researchers can design antibodies that specifically target a certain antigen, such as one found on cancer cells; copies of that antibody made in the lab are known as monoclonal antibodies (mAbs). Monoclonal antibodies are used for immunotherapies in cancer after identifying the right cancer antigen to attack.

Over the past couple of decades, the US Food and Drug Administration (FDA) has approved more than a dozen mAbs to treat certain cancers. Examples include **alemtuzumab (Campath®)**, which is used to treat some patients with chronic lymphocytic leukemia (CLL). Alemtuzumab binds to the CD52 antigen, which is found on cells called *lymphocytes* (which include the leukemia cells). Once attached, the antibody attracts immune cells to destroy these cells. **trastuzumab (Herceptin®)** is an antibody against the HER2 protein. **Britumomab tiuxetan (Zevalin®)** is an example of a radiolabeled mAb. This is an antibody against the CD20 antigen, which is found on lymphocytes called B cells. The antibody delivers radioactivity directly to cancerous B cells and can be used to treat some types of non-Hodgkin lymphoma.

- **Cancer Vaccines**

Vaccines treat cancer by spurring a patient's immune system to attack tumor cells. On April 29, 2010, the Food and Drug Administration (FDA) approved sipuleucel-T (PROVENGE®, Dendreon Corporation), an autologous cellular immunotherapy for the treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant (hormone refractory) prostate cancer. Sipuleucel-T is composed of autologous mononuclear cells incubated with a fusion protein consisting of a common prostate cancer antigen (prostatic acid phosphatase) linked to an adjuvant (granulocyte-macrophage colony-stimulating factor). It is postulated that when the vaccine is infused into the patient, the activated antigen-presenting cells displaying the fusion protein will induce an immune response against the tumor antigen.

One of the pioneers in the development of immunotherapies in cancer is David Spiegel, Professor at Yale University with appointments in the departments of Chemistry and Pharmacology. The Spiegel Research Group has created two new therapeutic concepts centered on bi-functional small molecules, which harness the immune system to fight cancer and infectious diseases — antibody-recruiting molecules (ARMs) and synthetic antibody mimics (SyAMs). These are small molecules that can recruit either antibodies (ARMs) or immune cells (SyAMs) directly to cancer cells, thus inducing immune-mediated destruction. (link to Spiegel's bio)

Immunology and immunotherapy will be well represented at the AACR Annual Meeting 2018; for more information visit a [curated selection of immunotherapy sessions](#) at the Annual Meeting.

2. 2018 AACR Annual Meeting, April 14-18 2018, Chicago, IL

The 2018 AACR Annual Meeting is less than two months away. A list of CICR-sponsored sessions can be viewed on the [CICR at the Annual Meeting page](#). Among the highlights are the "From Chemistry to the Clinic" educational sessions on Saturday, April 14 and the "New Drugs on the Horizon" session on Sunday, April 15. Note that the CICR Town Hall Meeting and Reception will immediately follow this session, in the same room. We encourage you to stay, enjoy refreshments, network and learn more about CICR before heading out for dinner. The program will include updates on current and planned CICR initiatives and a Q&A session with the CICR leadership. The Editor and Newsletter Editorial Board members will also be present, and we would be happy to hear your input on how to make this newsletter valuable for all CICR members.

A message from the CICR Chairperson Dr. Melissa Vasbinder:

"On behalf of our CICR Working Group, I would like to invite you all to attend the following chemistry sessions during the upcoming [AACR Annual Meeting 2018](#) in Chicago, Illinois, April 14-18, 2018. We also invite you to attend our CICR Town Hall meeting for an opportunity to hear more about our CICR Working Group and meet and network with colleagues during the Annual Meeting. The CICR Steering Committee and I look forward to seeing you this April! Don't miss the following sessions:

Saturday, April 14, 2018

From Chemistry to the Clinic (3-part session)

Chemical Probes for Identifying and Validating Drug Targets

Chair: Angela Koehler (Koch Institute of MIT)

Lead Optimization in Cancer Drug Discovery

Co-chairs: Philip Jones (Institute for Applied Cancer Science UT MD Anderson Cancer Center) and John Wang (Eisai, Inc.)

Approaches to Drug Design for Neuro-Oncology
Chair: Tim Heffron (Genentech)

Sunday April 15, 2018

New Drugs on the Horizon (2-part session)

Program to be announced

Co-chairs Part 1: Julian Blagg (Institute of Cancer Research, London, UK) and Andrew Phillips (C4 Therapeutics)

Co-chairs Part 2: Melissa Vasbinder (Ribon Therapeutics) and Alan Olivero (Genentech)

CICR Town Hall Meeting and Reception

Immediately following the New Drugs on the Horizon session

Sunday, April 15, 5.30 p.m. – 7:00 p.m.

Refreshments will be served.

Tuesday, April 17, 2018, 3-3:45 p.m.

12th Annual AACR Award for Outstanding Achievement in Chemistry in Cancer Research

Generously supported by Piramal Pharma Solutions

Recipient and Lecture Topic to be announced

3. Selected Research Highlights

Review Article

“Small-Molecule Targets in Immuno-Oncology”

Dashyant Dhanak, James P. Edwards, Ancho Nguyen and Peter J. Tummino

Cell Chem Biol. **2017** 24(9) 1148-1160

<http://dx.doi.org/10.1016/j.chembiol.2017.08.019>

A review focused on intracellular pathways where small molecule therapeutic agents may have the potential to be synergistic with extracellular biological therapeutic-mediated immune checkpoint blockade.

Research Articles

“IL4 Receptor-Targeted Proapoptotic Peptide Blocks Tumor Growth and Metastasis by Enhancing Antitumor Immunity”

SMP Vadevoo, et al. *Mol Cancer Therap*, **2017**, 16(12):2803-2816

<http://dx.doi.org/10.1158/1535-7163.MCT-17-0339>

Read “IL4 Receptor-Targeted Proapoptotic Peptide Blocks Tumor Growth and Metastasis by Enhancing Antitumor Immunity” in *Molecular Cancer Therapeutics*. Upregulation of IL4 receptor (IL4R) is observed in diverse tumors and tumor-associated macrophages (TAM). In this study by Vadevoo and colleagues, an IL4R-targeted proapoptotic peptide, IL4RPep-1-K, was designed by adding the proapoptotic peptide (KLAKLAK)2 to the end of IL4RPep-1 to kill IL4R-expressing cells selectively. Systemic administration of IL4RPep-1-K inhibited tumor growth and metastasis in 4T1 breast tumor-bearing mice. Interestingly, IL4RPep-1-K treatment increased the number of activated cytotoxic CD8+ T cells while reducing the numbers of immunosuppressive regulatory T cells and M2-polarized TAMs. These results suggest that IL4R-targeted proapoptotic peptide has potential for treating diverse IL4R-expressing cancers. Read more from *Molecular Cancer Therapeutics*.

“The target landscape of clinical kinase drugs”

Susan Klaeger, et al. *Science*, **2017**, 358, eaan4368

<http://dx.doi.org/10.1126/science.aan4368>

Kinase inhibitors represent an important class of clinical anticancer agents, and played a special role in oncology by helping launch the current targeted therapy paradigm. While it is known that many kinase inhibitors target more than one protein, the extent of this “polypharmacology” is understood for only a handful of drugs. In this study, Klaeger *et al.*, apply an established chemical proteomic approach to investigate the target repertoire of >200 clinical and pre-clinical kinase inhibitors. The breadth of this study is remarkable, in that it comprehensively defines and equalizes our knowledge of the selectivity of an entire class of targeted small molecule therapies in a complex proteome. Applying this chemoproteomics approach, the authors establish a publically available data resource and show how it may be mined to find new therapeutic indications for kinase inhibitors, for example repurposing to treat FLT3-ITD-positive acute myeloid leukemia. In addition to these direct applications, this study provides a methodological roadmap that will be useful for understanding the mechanism and activity of emerging targeted therapy approaches that utilize small molecule drugs.

“Discovery of a Novel and Selective Indoleamine 2,3-Dioxygenase (IDO-1) Inhibitor 3-(5-Fluoro-1H-indol-3-yl)pyrrolidine-2,5-dione (EOS200271/ PF-06840003) and Its Characterization as a Potential Clinical Candidate”

Stefano Crosignani et al. *J Med Chem*, **2017**, 60, 9617-9629.

<http://dx.doi.org/10.1021/acs.jmedchem.7b00974>

IDO-1 continues to attract significant attention as an immunotherapeutic target in oncology, with INCB24360 leading the way in clinical development. Clinical candidate EOS200271/PF-06840003 appears to differentiate from many other IDO-1 inhibitors in its binding mode, in that it doesn't bind to the heme iron atom. Indoleamine 2,3-dioxygenase (IDO-1) is involved in the oxidative cleavage of tryptophan to *N*-formyl kynurenine. IDO-1 limits T cell function and has become an important molecular target in oncology immunotherapy. Crosignani et al., describe the discovery and development of EOS200271/PF-06840003, an inhibitor of IDO-1. An X-ray crystal structure shows that, unlike other IDO-1 inhibitors, EOS200271/PF-06840003 does not bind to the heme iron of IDO-1; rather, all four heteroatoms are hydrogen-bonded to residues in the IDO-1 binding pocket. Enzymatic activity lies with the *R*-isomer, but rapid racemization in cell culture and plasma annulled the benefits of administration of a single enantiomer. EOS200271/PF-06840003 shows good activity in a human whole blood assay that measures kynurenine formation. Additionally, EOS200271/PF-06840003 shows good exposure after oral dosing and the half-life in humans is projected to be 19 hours.

“Allosteric Inhibitors of SHP2 with Therapeutic Potential for Cancer Treatment”

Jingjing Xie, et al. *J Med Chem* **2017** 60(24) 10205-10219

<http://dx.doi.org/10.1021/acs.jmedchem.7b01520>

Phosphatase **SHP2** has long been seen as an attractive target in tumor cell proliferation, and has more recently gained added interest due to its role in the regulation of T-cell activation. The identification of drug-like orthosteric inhibitors of phosphatases is challenging due to the nature of the substrate binding site. However, an increasing number of reports of allosteric inhibitors has appeared recently. This paper reports the identification of 1-(4-(6-bromonaphthalen-2-yl)thiazol-2-yl)-4-

ethylpiperidin-4-amine, a novel allosteric inhibitor that locks SHP2 in a closed conformation.

Dual Allosteric Inhibition of SHP2 Phosphatase

M Fodor et al, *ACS Chem Biol.* **2018** Jan 5 [Epub ahead of print]

<http://dx.doi.org/10.1021/acschembio.7b00980>

This paper builds on the previous (2016) report of SHP099, an allosteric inhibitor that stabilizes an auto-inhibited conformation of SHP2, with the disclosure of SHP244, which binds to a distinct allosteric site, resulting in weak inhibition. Most interestingly, concurrent occupation of both allosteric sites is shown both to be possible and to result in enhanced pharmacological pathway inhibition.

Small Molecule Inhibitors of PD-1/PD-L1

K Guzik et al *J. Med. Chem.*, **2017**, 60 (13), 5857–5867

<http://dx.doi.org/10.1021/acs.jmedchem.7b00293>

One of the most exciting recent themes in cancer research is the clinical validation of inhibition of checkpoint proteins such as the programmed death protein 1 (PD-1) / programmed cell death ligand 1 (PD-L1). Clinical utility, including dramatic anti-tumor effects and lasting remissions for some patients, has been established with antibody-based therapies in several cancer types. However, small molecule equivalents to these antibody therapies have yet to achieve significant success. In an article in the *Journal of Medicinal Chemistry* from mid-2017, new small molecule inhibitors of this immune checkpoint pathway, based on prior patent reports from Bristol-Meyers Squibb, were reported. The researchers present both X-ray characterization of the binding mode of these inhibitors, showing that they bind to defined hydrophobic channel formed by a PD-L1 homodimer and further show, by NMR, that the molecules induce oligomerization of the proteins in solution. These molecules may represent an important first step toward the discovery of small molecule immune checkpoint blockage.

Cyclin D-CDK4 kinase destabilizes PD-L1 via cullin 3-SPOP to control cancer immune surveillance

J Zhang et al *Nature*, **2018**, 553(7686), 91-95

<http://dx.doi.org/10.1038/nature25015>

The article uncovers a new molecular mechanism regulating PD-L1 protein stability by a cell cycle kinase, revealing a potential new treatment combination for enhancing the efficacy of checkpoint inhibitors in patients. Not all patients respond to PD/PD-L1 checkpoint inhibitors, and there has been a focus on determining the mechanistic factors responsible for this effect. Recent studies have found that response to these inhibitors correlates with PD-L1 expression levels in tumor cells. This article discloses that PD-L1 protein levels are regulated by cyclin D-CDK4 and the cullin 3-SPOP E3 ligase via proteasome-mediated degradation. Inhibition of CDK4/6 *in vivo* increases PD-L1 protein levels by impeding cyclin D-CDK4-mediated phosphorylation of speckle-type POZ protein (SPOP), promoting SPOP degradation by the anaphase promoting complex activator FZR1. PD-L1 is recognized at the C-tail by SPOP, such that deletion of its last eight amino-acids prevents binding and renders it resistant to degradation. Loss-of-function mutations in SPOP compromise ubiquitination-mediated PD-L1 degradation, leading to increased PD-L1 levels and reduced numbers of CD3⁺ tumor infiltrating lymphocytes in mouse tumors. Combining a CDK4/6 inhibitor with an anti-PD-1 immunotherapy enhanced tumor regression and markedly improved overall survival rates in mouse tumor models. These results suggest the possibility of enhancing the clinical efficacy of PD/PD-L1 checkpoint inhibitors by using them in combination with CDK4/6 inhibitors.

Inhibition of USP10 induces degradation of oncogenic FLT3

EL Weisberg et al. *Nat Chem Biol.*, **2017**, 13(12), 1207-1215.

<http://dx.doi.org/10.1038/nchembio.2486>

The authors present a new strategy for reducing the activity of FLT3, an important therapeutic target in acute myeloid leukemia (AML). The reduction of FLT3 protein levels may be achieved by proteasome-mediated degradation, promoted by inhibitors of the deubiquitinating enzymes (DUBs) responsible for cleaving ubiquitin from FLT3. Since the relevant DUBs for FLT3 were unknown, the authors screened a focused library of reported DUB inhibitors and carried out a cellular phenotypic screen to identify compounds that could induce the degradation of oncogenic FLT3. In particular, 29 reported small molecule DUB inhibitors were screened in a phenotypic assay for their ability to selectively kill Ba/F3 cells expressing mutant FLT3-ITD oncoprotein. Two chemical hits had antiproliferative activity which correlated with reduction of FLT3 protein levels and increased FLT3 ubiquitination. Screening the inhibitors across a panel of recombinant USBs allowed identification of USP10 as the critical DUB required to stabilize FLT3. Inhibition of USP10 stabilizes mutant FLT3-ITD more than wild-type FLT3 and the knockdown of USP10 resulted in robust degradation of FLT3-ITD as well as growth inhibition of FLT3-ITD positive cells. The targeting of USP10 showed efficacy in preclinical models of mutant-FLT3 AML, including cell lines, primary patient specimens and mouse models of oncogenic-FLT3-driven leukemia.

4. Profile of an Early-career Researcher: Professor David A. Spiegel

David Spiegel, MD, PhD is a Professor at Yale University with appointments in the departments of Chemistry and Pharmacology. He graduated Magna Cum Laude, with Highest Honors in Chemistry, from Harvard University in 1995, having worked in the laboratory of Professor Yoshito Kishi. He then went on to pursue a combined MD/PhD degree at Yale University, where he worked in the laboratory of Professor John L. Wood, focusing on synthetic organic chemistry, and graduating in 2005. After a brief postdoctoral stint at the Broad Institute of Harvard and MIT under Professor Stuart L. Schreiber, Professor Spiegel started his independent academic career at Yale University in 2007.

The central focus of the Spiegel Research Group is the development of novel, small molecule-based strategies for manipulating and regulating human immunity and biological processes. The strategies they develop allow them to study the molecular mechanisms that underlie human diseases and design novel therapeutic approaches to address a number of pathologic conditions. Studies performed in the Spiegel Laboratory have significantly contributed to both fundamental and applied areas of research.

The Spiegel Research Group has already created two new therapeutic concepts centered on bi-functional small molecules, which harness the immune system to fight cancer and infectious diseases — antibody-recruiting molecules (ARMs) and synthetic antibody mimics (SyAMs). These are small molecules that can recruit either antibodies (ARMs) or immune cells (SyAMs) directly to cancer cells, thus inducing immune-mediated destruction. They are currently working to bring ARM- and SyAM-based drugs to market and hope to expand their scope and utility toward the development of next-generation, customizable immunotherapeutics.

Moving forward, the Spiegel Research Group will be focusing on several areas with great clinical relevance: expanding on customized responses against cancer and infectious diseases, reversing damage associated with aging, and developing low-cost screening strategies for targeted immunotherapies.

Professor Spiegel has co-authored over 40 peer-reviewed publications and has over a dozen patents. He is the Chief Scientific Advisor and co-founder of Kleo Pharmaceuticals. He has also served as a consultant for International Flavors and Fragrances, Novartis Institute for Biomedical Research, Bristol-Myers Squibb, and Pharmaseq.

Professor Spiegel has been recognized for his achievements with various awards and honors, including the NIH Director's New Innovator Award, the Department of Defense Era of Hope Scholar Award, the Ellison Medical Foundation New Scholar Award in Aging Research, the Novartis Early Career Award in Organic Chemistry, the Bill and Melinda Gates Foundation Grand Challenges Explorations Award, the Alfred P. Sloan Foundation Fellowship, and others.

5. Report on FDA Drug Approvals 2017

FDA approved 56 new molecular entities and biologic therapies in 2017, hitting a 20-year high since 1996. Cancer and rare-disease drugs dominated the list of new medicines.

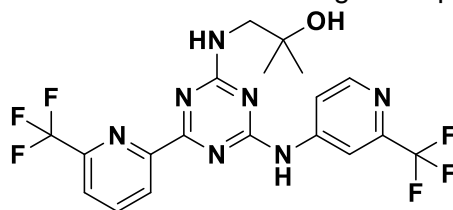
Interesting facts:

- 33% of the products the FDA approved belong to new classes of compounds.
- Cancer treatments represented 25% of all new small molecules approved in 2017.
- The approval list included two more CDK4/6 inhibitors, two more PD-L1 inhibitors, and more compounds that block the proteins PARP, BTK, and ALK.
- Of the 12 oncology products approved, nine had breakthrough therapy designation.
- New cancer treatment prices range between \$10,000 – 25,000/month.
- Conventional, small molecule drugs represented 2/3 of the approvals in 2017.

Small molecule and biologics approvals in cancer

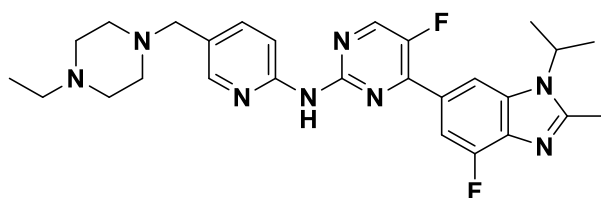
FDA Approval of Enasidenib (Idhifa)

The isocitrate dehydrogenase 2 (IDH2) inhibitor enasidenib (Agiros/Celgene) was approved on August 1, 2017 to treat relapsed or refractory acute myeloid leukemia (AML). IDH2 enzymes catalyze the conversion of isocitrate to alpha-ketoglutarate (alphaKG) in the mitochondria. Mutations in *IDH2* occur in about 12% of patients with AML. Mutated forms of *IDH2* reduce alphaKG to produce the oncometabolite 2-hydroxyglutarate (2-HG), which inhibits alphaKG dependent enzymes leading to DNA and histone hypermethylation. The approval occurred with a companion diagnostic to check specific mutations in the *IDH2* gene in patients with AML.



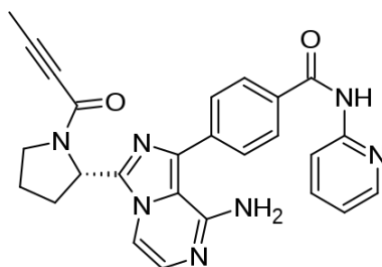
FDA Approval of Abemaciclib (Verzenio)

The selective CDK4/6 inhibitor abemaciclib (Eli Lilly) was approved on September 28, 2017 for adults with HR+/HER2- advanced or metastatic breast cancer that has advanced after endocrine therapy. This is the third approval of a CDK4/6 inhibitor, following palbociclib (Pfizer, 2015) and ribociclib (Novartis, 2017). The approval is based on the MONARCH 1 & 2 clinical studies, which showed efficacy in combination with fulvestrant (endocrine therapy), or on its own depending on the treatment the patient had already received. See related [blogpost](#).



FDA Approval of Acalabrutinib (Calquence)

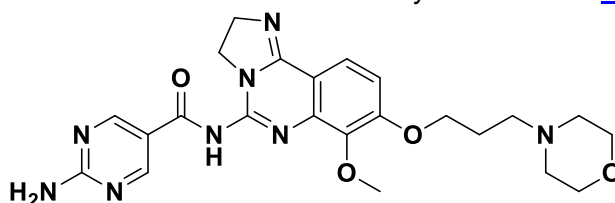
The Bruton's tyrosine kinase (BTK) inhibitor acalabrutinib (Acerta Pharma/Astra Zeneca) was approved on October 31, 2017 for the treatment of adults with mantle cell lymphoma (MCL) who have received at least one prior therapy. This is the second approval of a BTK inhibitor following ibrutinib (Pharmacyclics/Johnson & Johnson, 2013). Acalabrutinib is an irreversible inhibitor containing an acyl alkyne electrophilic warhead. This second generation molecule is more potent and selective than ibrutinib, with reduced targeting of off-target kinases, such as EGFR, TEC, and ITK, and improved pharmacologic features. See related [blogpost](#).



FDA Approval of Copanlisib (Aliqopa)

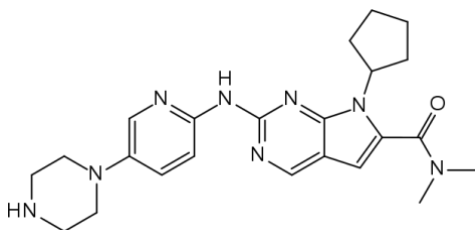
The class I phosphoinositide 3-kinase (PI3K) inhibitor copanlisib (Bayer) was approved on September 14, 2017 for the treatment of adults with relapsed follicular lymphoma that has returned after two or more treatments. Follicular lymphoma is a slow-growing type of non-Hodgkin lymphoma, a cancer of the lymph system and a hematologic malignancy. Copanlisib is known to target the alpha and delta isoforms

of PI3K with sub-nanomolar IC₅₀ values, although it also inhibits beta and gamma isoforms and mTOR with somewhat weaker activity. See related [blogpost](#).



FDA Approval of Ribociclib (Kisqali)

The CDK4/6 inhibitor was approved on March 2017 for the treatment of HR-positive/HER2-negative advanced or metastatic breast cancer. Ribociclib, developed jointly by Novartis and Astex Pharmaceuticals, works by blocking the function of two proteins called cyclin-dependent kinase 4 (CDK4) and CDK6. These proteins play a role in driving cell multiplication, which is key for tumor growth. The approval of ribociclib in combination with letrozole was based on results from the phase III MONALEESA-2 clinical trial. The progression-free survival rate was 63.0 percent among those randomly assigned ribociclib and letrozole and 42.2 percent among those randomly assigned placebo and letrozole. See related [blogpost](#).

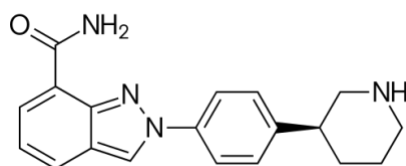


FDA Approval of Avelumab (Bavencio)

On March 23 2017, the U.S. Food and Drug Administration announced the first-ever approval of a treatment for patients with a rare, aggressive form of skin cancer called Merkel cell carcinoma. Avelumab (Merck KGaA/Pfizer) was also approved for treating bladder cancer and non-small-cell lung carcinoma (NSCLC). Avelumab is an immunotherapeutic targeting the PD-L1/PD-1 pathway. Immune checkpoint inhibitors work by releasing brakes on cancer-fighting immune cells called T cells. Avelumab targets the protein PD-L1, which normally engages a T-cell brake called PD-1. Once the PD-1 brake is released by avelumab, the T cells can destroy cancer cells. See related [blogpost](#) and another [blogpost](#).

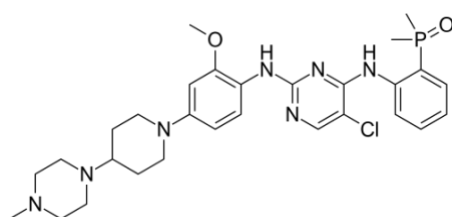
FDA Approval of Niraparib (Zejula)

Niraparib (Tesaro) was approved on 27 March 2017, is a PARP inhibitor for recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer that are responding to platinum-based chemotherapy. Niraparib is the third in a class of molecularly targeted therapeutics called poly ADP-ribose polymerase (PARP) inhibitors to be approved by the FDA. However, it is the first to be approved for use in treating both BRCA mutation-positive and -negative cancers. The first and second therapeutics in the class, olaparib (Lynparza) and rucaparib (Rubraca), are both approved for use only in treating women who have ovarian cancer associated with BRCA gene mutations. See related [blogpost](#).



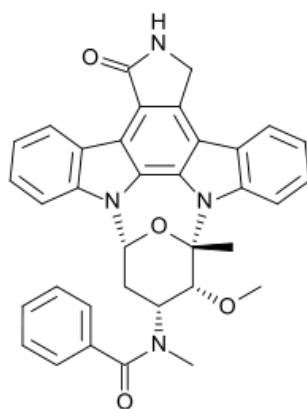
FDA Approval of Brigatinib (Alunbrig)

Brigatinib (Takeda) was approved on April 28, 2017 for patients who have metastatic NSCLC driven by mutations in the ALK gene and whose disease is not responding to treatment with crizotinib (Xalkori). Crizotinib was the first ALK inhibitor to be approved by the FDA, in August 2011, and it is now the standard of care for patients with metastatic ALK-positive NSCLC. However, most patients whose NSCLC responds to crizotinib have disease progression within a year of starting treatment because the tumors develop resistance to the anticancer therapeutic. See related [blogpost](#).



FDA Approval of Midostaurin (Rydapt)

Midostaurin (Novartis) was approved on 28 April 2017 as the first molecularly targeted therapeutic for acute myeloid leukemia (AML), midostaurin (Rydapt). About 25% of AML cases are characterized by the presence of mutations in the FLT3 gene. Patients with this form of AML have particularly poor outcomes. The FLT3 mutations lead to constitutive FLT3 activation, which promotes survival and proliferation of the leukemia cells. Midostaurin is a semi-synthetic derivative of staurosporine, an alkaloid from the bacterium *Streptomyces staurosporeus*, which targets several related molecules called tyrosine kinase receptors, including FLT3 and KIT. The FDA also approved a companion diagnostic test to identify those AML patients eligible to receive it: adults newly diagnosed with AML harboring a mutation in the FLT3 gene. See related [blogpost](#).



FDA Approval of Tisagenlecleucel (Kymriah)

30 August 2017 marked a milestone for the cancer therapies as the FDA announced the first approval of a type of immunotherapy known as CAR T-cell therapy. Kymriah (Novartis) was approved for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse. Tisagenlecleucel is a cell-based therapy that targets CD19-positive cells. Each patient receives a customized dose of tisagenlecleucel that is created using immune cells called T cells harvested from his or her blood. Once the T cells have been harvested, they are genetically modified to have a new gene that encodes a protein called a chimeric antigen receptor (CAR). After the T cells are modified, they are expanded in number and then infused back into the patient. The CAR directs the infused modified T cells to CD19-positive B cell ALL cells and triggers them to attack once they get there. See related [blogpost](#).

FDA Approval of axicabtagene ciloleucel (Yescarta)

Yescarta (Kite Pharma) was the second immunotherapy known as chimeric antigen receptor (CAR) T-cell therapy to be approved on 18 October 2017 by the FDA. The CAR T-cell therapy, which is called axicabtagene ciloleucel, was approved for treating adults with certain types of non-Hodgkin lymphoma whose disease has progressed despite them having tried at least two other kinds of treatment. Specifically, it was approved for treating diffuse large B-cell lymphoma (DLBCL), primary mediastinal large B-cell lymphoma, high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma. Axicabtagene ciloleucel targets CD19-positive cells. Each patient's axicabtagene ciloleucel treatment is customized using immune cells called T cells harvested from his or her blood. Once the T cells have been harvested, they are genetically modified to have a new gene that encodes a protein called a CAR, which is why this type of treatment is often referred to as cell-based gene therapy. After the T cells are modified, they are expanded in number and then infused back into the patient. The external facing portion of the CAR in axicabtagene ciloleucel recognizes and attaches to CD19 on the surface of the non-Hodgkin lymphoma B cells, which causes the internal facing portion of the CAR to trigger a signaling network that results in the CAR T cells attacking the cancer cells. See related [blogpost](#).

6. Spotlight on World News

FDA makes history, approving first-ever gene therapy

The FDA approved the first-ever gene therapy for a rare form of blindness caused by a genetic condition. Luxturna is given to treat Leber's congenital amaurosis, in which affected patients have a mutated RPE65 gene. The enzyme RPE65 is vital for normal vision and a faulty gene can lead to impaired vision or even complete blindness. Luxturna is a single injection that works by delivering 150 billion viral vector particles containing a correct copy of the RPE65 gene to retinal cells, restoring the patient's ability to make the missing enzyme. The safety and efficacy of Luxturna were established in a clinical development program with a total of 41 patients between the ages of 4 and 44 years. All participants had confirmed biallelic RPE65 mutations.

[Source: Pharmforum.org](http://Pharmforum.org)

CRISPR gene editing will go into a first clinical trial by Vertex and CRISPR Therapeutics

Vertex Pharmaceuticals and CRISPR Therapeutics will begin the first human studies of a CRISPR therapy in the U.S. and Europe next year. They are using the gene-editing technology to treat people with sickle cell anemia and another rare blood disorder called beta-thalassemia. CRISPR Therapeutics CEO declared that extensive computer prediction, followed by cell and animal testing, has led them to a guide RNA in the CRISPR therapy that has no detectable off-target activity—a potential side effect in which CRISPR accidentally cuts the DNA in the wrong location. Off-target activity is one of the biggest safety concerns for gene editing in humans.

[Source: C&E News](#)

Two personalized immune-cell therapies came to the market, and more are likely on the way

Both new drugs are CAR T-cell immunotherapies, created by injecting an individual's T cells with DNA that encodes a chimeric antigen receptor (CAR). The CAR proteins jut from the immune cells' surfaces and direct them to seek and destroy tumor cells. Some 83% of people treated with the first approved CAR-T drug, Kymriah (Novartis) achieved complete remission—no cancer detected—within three months. More than 50% of people treated with the second drug, Kite Pharma's Yescarta, are in complete remission.

[Source: C&E News](#)

Gilead Sciences Completes Acquisition of Kite Pharma

Kite is a biopharmaceutical company engaged in the development of innovative cancer immunotherapies with a goal of providing rapid, long-term, durable response and eliminating the burden of chronic care. The company is focused on chimeric antigen receptor (CAR) and T cell receptor (TCR) engineered cell therapies designed to empower the immune system's ability to recognize and kill tumors. The acquisition was completed for \$11.9 billion.

[Source: Gilead](#)

Boehringer Ingelheim partners with Research institute for immune-oncology therapy development

Boehringer Ingelheim and Sarah Cannon Research Institute announced an expansion of their partnership to bring innovative treatments to cancer patients by developing novel immuno-oncology therapies. The new effort combines Boehringer Ingelheim's oncology research and Sarah Cannon's expertise in clinical trial design and recruitment to evaluate BI 891065, alone and in combination with PD-1-directed cancer therapy. This collaboration [expansion] evaluates BI 891065, a novel and potent SMAC mimetic, alone and as a potential combination partner with PD-1-directed cancer therapy. SMAC mimetics are a new class of targeted small molecules that trigger tumor cell death and immune system activation, which may enhance the activity of immunotherapies in the treatment of cancer. Through this collaboration, Boehringer Ingelheim's BI 891065 will be studied in a Phase 1 clinical trial (NCT03166631), both alone and in combination with BI 754091 (anti-PD-1) in patients with advanced metastatic solid tumors.

[Source: DDN News](#)

CRISPR-Cas9 approach identifies new drug targets to aid cancer immunotherapy

Researchers at Dana-Farber/Boston Children's Cancer and Blood Disorders Center (Boston, MA, USA) have recently developed a novel *in vivo* genetic screening approach, utilizing CRISPR-Cas9 genome editing technology in transplantable

tumors in murine models treated with immunotherapy to discover previously undescribed immunotherapy targets. The team revealed promising new drug targets that could potentially enhance the effectiveness of PD-1 checkpoint inhibitors, which are employed in cancer immunotherapy. The findings of the paper indicated that deletion of the Ptpn2 gene in tumor cells made them more susceptible to PD-1 checkpoint inhibitors.

[Source: MedChemNet](#)

ITUS and Moffitt Cancer Center partner for new CAR-T therapy

ITUS Corporation and Moffitt Cancer Center have inked a cooperative research and development agreement with the goal of moving a chimeric antigen receptor T-cell (CAR-T) technology into human clinical testing. The initial focus will be ovarian cancer, but it's thought that the technology could also have applications in prostate and pancreatic cancer, as well as others.

[Source: Drug Discovery News](#)

7. Grant opportunities

Funding Body	Grant Type	Deadline
AACR	AACR-Johnson & Johnson Lung Cancer Innovation Science Grants	3/2/2018
Alliance For Cancer Gene Therapy	2018 Investigator Award	5/15/2018
American Cancer Society	Clinician Scientist Career Development Grant	4/2/2018
American Cancer Society	Institutional Research Grant	4/2/2018
American Cancer Society	Mentored Research Scholar Grant	4/2/2018
American Cancer Society	Postdoctoral Fellowship	4/2/2018
American Cancer Society	Research Scholar Grants	4/2/2018
American Cancer Society	Mission Boost Grant	4/2/2018

8. Upcoming Conferences

Frontiers in Medicinal Chemistry

March 11-14, 2018. Jena, Germany

[Web Site](#)

CHI Thirteenth Annual Fragment-Based Drug Discovery

April 2-6, San Diego, California, USA

[Web Site](#)

AACR Annual Meeting 2018

April 14-18, Chicago, IL, USA

[Web Site](#)

36th ACS National Medicinal Chemistry Symposium

April 29-May 2, Nashville, Tennessee, USA

[Web Site](#)

[Accelerating Anticancer Agent Development and Validation Workshop](#)

May 2 - 4, 2018, Bethesda, Maryland

Kinase 2018: towards new frontiers - 8th RSC / SCI symposium on kinase inhibitor design

May 14 - 15 2018, Cambridge, United Kingdom

[Web Site](#)

101st Canadian Chemistry Conference and Exhibition

May 27-31, 2018. Edmonton, Alberta Canada

[Web Site](#)

5th NovAliX Conference on Biophysics in Drug Discovery

June 13-15, Boston, Massachusetts, USA

[Web Site](#)

Gordon Research Conference in Heterocyclic Compounds 2018

June 17-22, 2018. Newport, RI

[Web Site](#)

54th International Conference on Medicinal Chemistry (RICT 2018)

July 4-6, 2018. Strasbourg, France

[Web Site](#)

Gordon Research Conference in Organic Reactions & Processes 2018

July 15-20, 2018. Easton, MA

[Web Site](#)

Gordon Research Conference in Computational Chemistry 2018

July 22-27, 2018. Mount Snow, VT

[Web Site](#)

Gordon Research Conference in Natural Products & Bioactive Compounds 2018

July 29 – August 3, 2018. Andover, NH

[Web Site](#)

256th ACS National Meeting & Exposition

August 19-23, 2018. Boston, Massachusetts

[Web Site](#)

XXV EFMC International Symposium on Medicinal Chemistry (EFMC-ISMC 2018)

September 2-6, 2018. Ljubljana, Slovenia

[Web Site](#)

Fragment-Based Lead Discovery 2018

October 7-10, San Diego, California, USA

[Web Site](#)