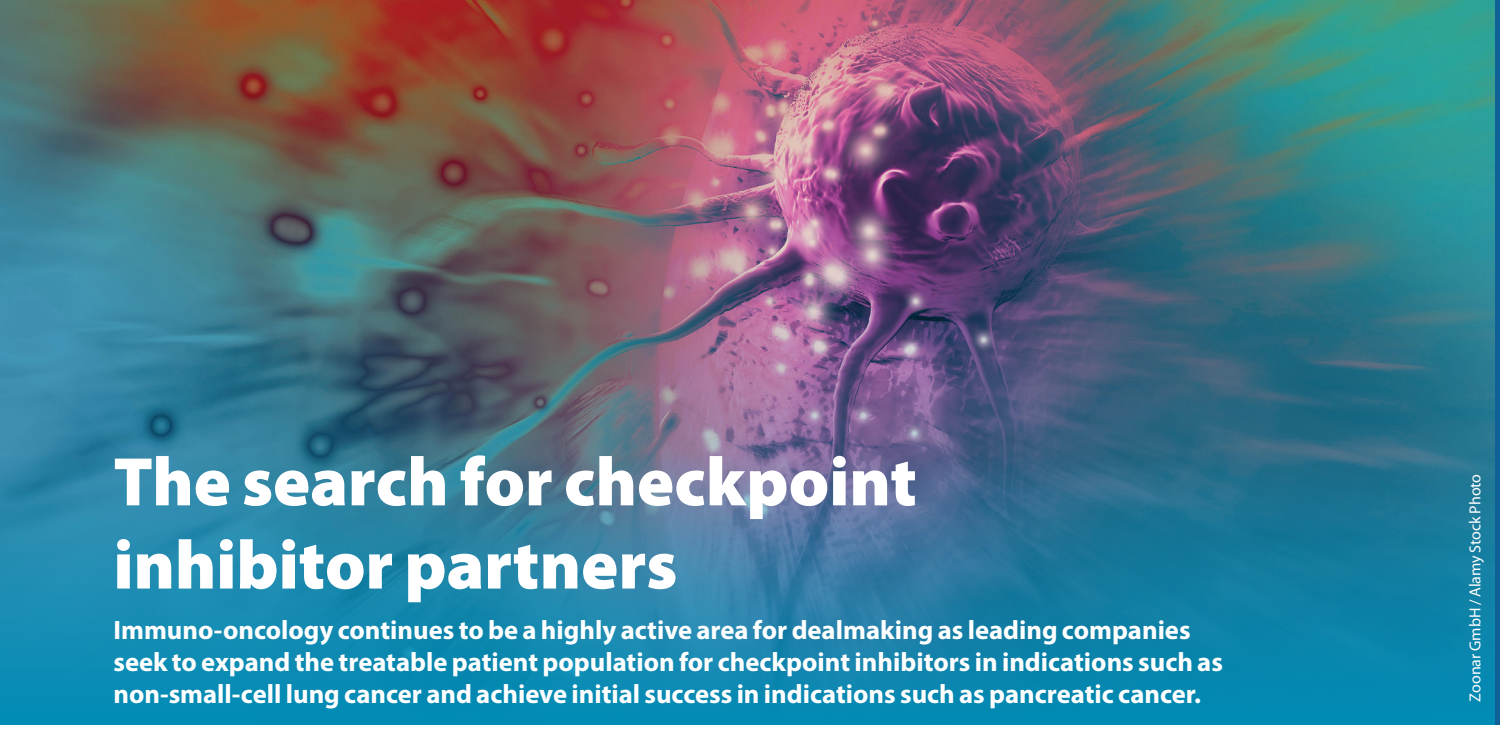

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# The search for checkpoint inhibitor partners

**Immuno-oncology continues to be a highly active area for dealmaking as leading companies seek to expand the treatable patient population for checkpoint inhibitors in indications such as non-small-cell lung cancer and achieve initial success in indications such as pancreatic cancer.**

Nick Taylor

Cancer care has changed dramatically since the 2011 approval of the immune checkpoint inhibitor Yervoy (ipilimuab) for melanoma marked the start of the immuno-oncology era. Yet, significant unmet medical needs remain. In indications such as melanoma and non-small-cell lung cancer (NSCLC), programmed cell death 1/programmed cell death 1 ligand 1 (PD-1/PD-L1) checkpoint inhibitors are having a major impact on a subset of patients, but they need to be enhanced to overcome primary and acquired resistance. In other indications such as pancreatic cancer, new drugs to partner with checkpoint inhibitors may be needed for the immuno-oncology concept to work at all.

These needs have driven investment into research and development and extensive dealmaking, with immuno-oncology licensing deal size increasing in value by 51% from 2017 to 2018, while deal volume increased by 8% **(Fig. 1).** Yet, with once-promising approaches such as indoleamine 2,3-dioxygenase inhibition falling away, the search for pathways that enhance checkpoint blockade in these indications is taking longer than hoped.

"The expectation that other pathways would be found quickly to augment the PD-1, PD-L1 and CTLA-4 [cytotoxic T lymphocyte protein 4] pathways hasn't really been realized. And so there's increasing interest in what's next," said Kevin Horgan, executive VP and CMO at Seres Therapeutics.

## Expanding the impact

Some of the biggest deals in the past year involve drugs that could improve on the efficacy achieved by checkpoint inhibitors in melanoma and NSCLC, for which the companies with the leading PD-1 checkpoint inhibitors—Merck & Co. with Keytruda (pembrolizumab) and Bristol-Myers Squibb (BMS) with Opdivo (nivolumab)—are jostling for dominance.

Leading the top ten list of deals by total value in 2018 **(Table 1)** is Merck's partnership with Eisai on its approved multikinase inhibitor Lenvima (lenvatinib), with a $300 million upfront payment and more than $5 billion in potential milestones. A range of indications will be pursued for the drug as a monotherapy and in combination with Keytruda, including NSCLC, melanoma, hepatocellular carcinoma, endometrial cancer, head and neck cancer and bladder cancer.

And Keytruda's rival was the focus of another huge partnership, when BMS paid a record-breaking $1 billion upfront to partner with Nektar Therapeutics on its bempegaldesleukin, a PEGylated drug that targets a pathway involving the cytokine interleukin-2 (IL-2) to boost immune responses.

"If there are no immune cells in the tumor, you can give any checkpoint you want; it's going to be very, very difficult to have any sort of biological effects," said Jonathan Zalevsky, CSO at Nektar. Targeting IL-2 signalling is expected to help bring T cells into tumors and thereby improve responses to checkpoint inhibitors for tumors such as NSCLC and melanoma.

Nektar provided early evidence to validate that idea late in 2017 when it posted data from a phase 1/2 trial that tested the drug in combination with Opdivo, which linked the combination to response rates in melanoma and PD-L1-negative NSCLC of 63% and 75%, respectively. Three months later, BMS struck what Hilliard Lyons analyst Kurt Kemper called "an interesting and admittedly expensive deal for an asset with very strong but also very early data." The jury is still out on whether the early responses will translate into long-term effects that justify the huge outlay.

Other deals in the top ten list **(Table 1)** typically involve earlier-stage assets in development for multiple indications such as melanoma and NSCLC. The second most valuable deal, Genentech's 2018 deal with Affimed, falls into that category. The Roche subsidiary committed $96 million upfront and almost $5 billion in potential milestones to partner with Affimed on natural killer (NK) and T cell engager-based immunotherapies against multiple cancers. Merck has also signalled interest in the potential of targeting NK cells,

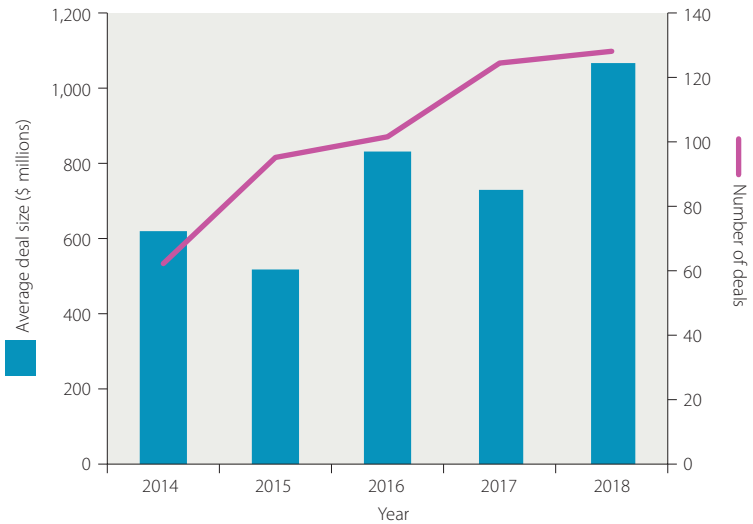


**Fig. 1 | Trends in immuno-oncology drug licensing.** 2018 was the biggest year yet for immuno-oncology (IO) drug licensing in terms of deal size and volume. IO licensing deal size increased in value by 51% from 2017 to 2018, while volume increased by 8%. Only licensing deals for drugs or drug platforms applicable to IO therapeutics were included. Data from Cortellis Deals Intelligence from Clarivate Analytics.

**Table 1 | Immuno-oncology drug licensing deals in 2018 valued at more than $1 billion**

| Buy side | Sell side | Upfront payment ($ millions) | Milestone and other payments ($ millions) | Total projected at signing ($ millions) | Technology | Drug asset | Drugs' highest status at deal start | Date |
|---|---|---|---|---|---|---|---|---|
| Merck & Co. | Eisai | 300 | 5,455 | 5,755 | Small molecule | Lenvatinib mesylate | Launched | March |
| Roche (Genentech) | Affimed | 96 | 4,950 | 5,046 | Cell therapy | NK cell engager | Discovery | August |
| Bristol-Myers Squibb | Nektar Therapeutics | 1,000 | 2,630 | 3,630 | Recombinant protein | NKTR-214 | Phase 3 | February |
| Gilead (Kite Pharma) | Sangamo Therapeutics | 150 | 3,010 | 3,160 | CAR T cell therapy | T cell and NK cell therapies | Preclinical | February |
| Allogene | Cellectis | – | 2,800 | 2,800 | CAR T cell therapy | ALLO-647, ALLO-715 and ALLO-819 | Preclinical | April |
| Gilead | Agenus | 120 | 1,752 | 1,873 | Multivalent antibody | AGEN-1223, AGEN-1423 and AGEN2373 | Preclinical | December |
| Gilead | Tango Therapeutics | 50 | 1,700 | 1,750 | Target identification platform | Target discovery platform | Discovery | October |
| Merck & Co. | Sutro | 60 | 1,620 | 1,680 | Recombinant protein | Cytokine derivatives | Discovery | July |
| Cilag | arGEN-X | 300 | 1,300 | 1,600 | Antibody | Cusatuzmab | Phase 2 | December |
| Boehringer Ingelheim | OSE Immunotherapeutics | 18 | 1,370 | 1,389 | Antibody | BI-754091 and BI-765063 | Phase 1 | April |
| Roche | SQZ Biotech | – | 1,375 | 1,375 | Cell therapy | Antigen-loaded APCs | Preclinical | October |
| Oncologie | Mologen | 4 | 1,335 | 1,339 | Cell therapy | Lefitolimod | Phase 3 | February |
| ONO Pharmaceutical | Fate Therapeutics | 10 | 1,240 | 1,250 | CAR T cell therapy | CAR T cell therapy | Discovery | September |
| Seattle Genetics | Pieris | 30 | 1,200 | 1,230 | Fusion protein | Bispecific mAb/ anticalin costimulator | Discovery | February |
| LG Chem | Cue Biopharma | 5 | 1,080 | 1,085 | Fusion protein | CUE-101 and CUE-102 | Preclinical | November |

Only licensing deals for drugs or drug platforms applicable to immuno-oncology (IO) therapeutics were included. 10 out of 15 of 2018's biggest licensing deals in IO were for discovery and preclinical-stage programs, and 11 out of 15 were for next-generation biologics. The highest upfront payments are for late-stage transactions. APC, antigen-presenting cell; CAR, chimeric antigen receptor; mAb, monoclonal antibody; NK, natural killer. Data from Cortellis Deals Intelligence from Clarivate Analytics.

with a $695 million tie-up with Dragonfly Therapeutics announced in October 2018 to license Dragonfly's candidate NK cell engager immunotherapies in selected solid tumors.

Cell therapies are also a strong focus in the remaining deals in the top ten list, and have driven some of the biggest acquisitions in the immuno-oncology space in recent years (**Table 2**), such as Celgene's purchase of one of the chimeric antigen receptor T cell pioneers Juno Therapeutics for $9 billion in early 2018. While cell therapies are not the focus of this article as their approvals thus far have been in blood cancers, there is continuing interest in expanding their applicability to solid tumors.

## Penetrating new areas

As well as expanding the treatment-responsive patient population in solid tumor indications such as melanoma and NSCLC, companies are also seeking to bring immuno-oncology approaches to indications in which checkpoint inhibitors have not been as successful thus far, either by developing new checkpoint inhibitor combinations or pioneering alternative immunomodulatory strategies.

Pancreatic cancer, a notoriously hard-to-treat disease, is one such indication. Eli Lilly made its play for the indication in May 2018 when it paid $1.6 billion to buy Armo BioSciences (**Table 2**). The deal gave

**Table 2 | Immuno-oncology M&As in 2018 valued at more than $1 billion**

| Buy side | Sell side | Upfront payment ($ millions) | Milestones and other payments ($ millions) | Total projected at signing ($ millions) | Date |
|---|---|---|---|---|---|
| Celgene | Juno Therapeutics | 9,000 | – | 9,000 | January |
| GlaxoSmithKline | Tesaro | 5,100 | – | 5,100 | December |
| Sanofi | Ablynx | 4,593 | – | 4,593 | January |
| Eli Lilly | Armo BioSciences | 1,600 | – | 1,600 | May |
| Janssen | BeneVir Biopharm | 149 | 900 | 1,040 | February |

Only merger and acquisition (M&A) deals for companies with an applicable immuno-oncology therapeutic program with a value greater than $1 billion were included. Data from Cortellis Deals Intelligence from Clarivate Analytics.

**Box 1 | Data and methodology**

All immuno-oncology transactions with a deal start date between 1 January 2014 and 31 December 2018 were extracted from Cortellis Deals Intelligence, from Clarivate Analytics. "Deal Transaction" type for Acquisitions (100% or Majority Stake), Mergers, Reverse Mergers and all "License" subtypes were selected for analysis.

The resulting datasets were filtered to exclude nontherapeutic-focused deals using the "Deal Asset Type" categorization. Deals for which the primary focus was any of the following were excluded: Assays, Bioinformatics, Biomarkers, Diagnostic Methods, Drug Formulation, Generics, Genomics Technologies, Imaging, Instruments, Lab Reagents, Manufacturing, Medical and other devices, Radiolabelling, Service agreements and Software.

Also excluded were transactions that did not have at least one commercial partner.

The final datasets were comprised as follows.

- Merger and acquisition (44)
- Licensing (576)

Financial details are only available for 222 of these 620 deals.

Lilly ownership of pegilodecakin, a PEGylated form of the anti-inflammatory cytokine IL-10 that was once in development at Merck. Armo's breakthrough was to recognize that pegilodecakin, which Merck tested in autoimmune conditions such as psoriasis, could be repurposed as an oncology drug. Pegilodecakin began a pivotal trial in metastatic pancreatic cancer in 2016.

Also in May 2018, Merck expanded its collaboration with Moderna Therapeutics to cover mRNA KRAS cancer vaccine mRNA-5671, making a $125 million investment and committing to covering clinical development costs in the process. KRAS is mutated in around 95% of patients with the most common form of pancreatic cancer and is thought to drive the growth and maintenance of the disease. Merck has since initiated a phase 1 clinical trial of mRNA-5671, also known as V941, in combination with Keytruda in patients with KRAS-mutated pancreatic neoplasms and other solid tumors.

Months before striking the mRNA-5671 deal, Merck entered into an agreement with AstraZeneca to gain the chance to test its PARP inhibitor Lynparza (olaparib) in combination with Keytruda. AstraZeneca posted encouraging data on Lynparza in BRCA-mutated pancreatic cancer in June 2019, but Merck is yet to start combination trials in the indication.

Another PARP inhibitor, Zejula (neraparib), was the focus of the second largest merger and acquisition (M&A) deal in 2018, GlaxoSmithKline's $5.1 billion purchase of Tesaro **(Table 2)**. Zejula, thus far approved for ovarian cancer, is being investigated for other cancers such as breast cancer and prostate cancer as a monotherapy and in combination with Tesaro's PD-1 investigational checkpoint inhibitor dostarlimab.

## Advancing the field

The history of immuno-oncology shows how hard it is to predict which of the bets placed by drug developers will pay off. Schering-Plough and Merck each initially deemed the PD-1 inhibitor pembrolizumab to be a low priority when they acquired it through successive M&As in the late 2000s: Schering-Plough with Organon in 2007 and then Merck with Schering-Plough in 2009. Today, the product pembrolizumab became—Keytruda—is predicted to be the biggest-selling drug globally by 2024. The star products of the later waves of immuno-oncology drugs could be languishing in relative obscurity, or today's most closely watched assets may fail to deliver on their promise. What is more certain is that the immune system will continue to play a central role in the treatment of cancer, setting the stage for ongoing dealmaking and drugs that bring the power of immuno-oncology to more patients.

*Nick Taylor writes about the biopharmaceutical industry.*

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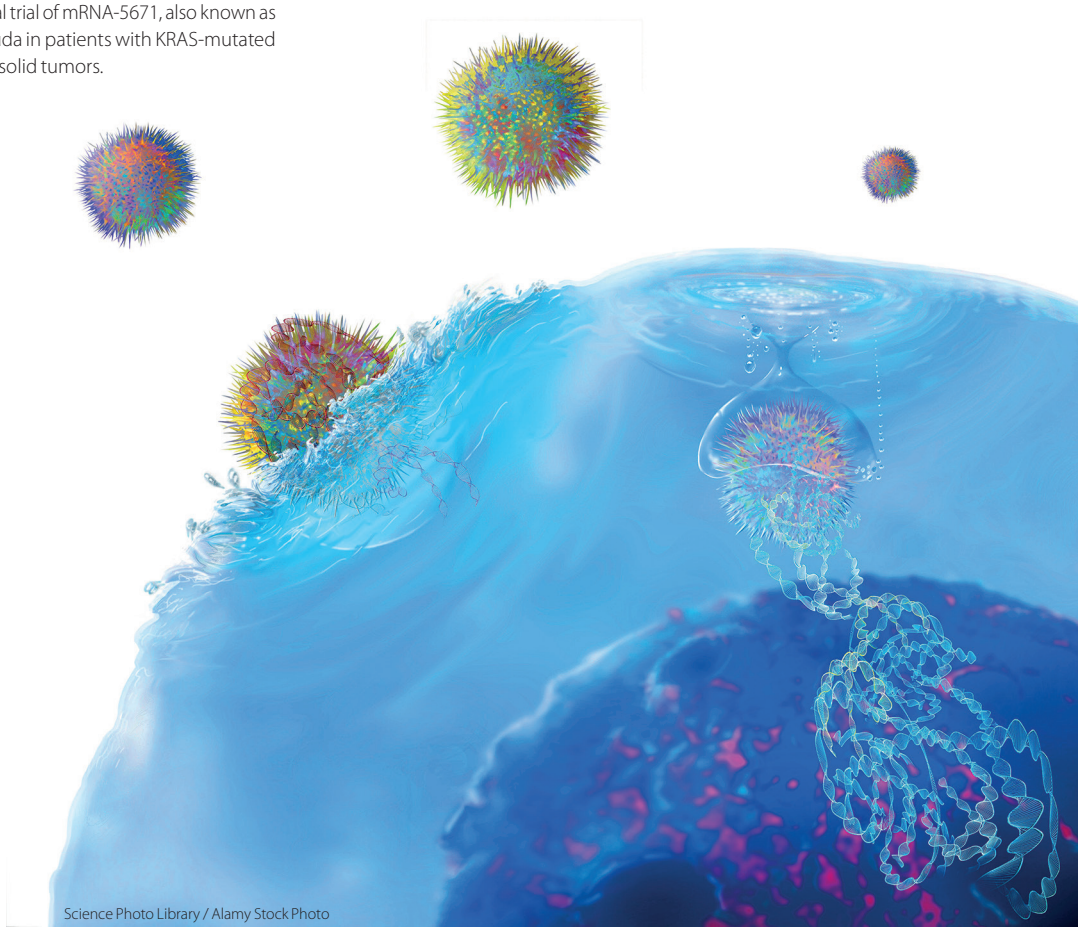

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