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Immuno-oncology dominates big pharma's deal agenda

With the first wave of cancer immunotherapies continuing to show their potential to revolutionize treatment paradigms, major pharmaceutical companies are leaving no stone unturned in the search for winning combination therapies that harness immuno-oncology drugs.

Chris Morrison

It is not uncommon for the deal deluge that routinely kicks off the biopharma calendar each January to feature alliances and acquisitions that total billions of dollars in up-front and milestone payments. However, it is unusual for those deals to be so conspicuously concentrated in a single therapeutic space. Immuno-oncology, with only slight exaggeration, utterly dominates biopharma's current deal agenda: in announcements timed to coincide with the start of the annual JP Morgan Healthcare Conference on January 11, large pharma companies, including Novartis, Sanofi, Merck & Co., AstraZeneca, Roche, Bristol-Myers Squibb (BMS), Celgene, Amgen and Pfizer, unveiled immuno-oncology alliances, acquisitions and investments potentially worth billions of dollars in total.

Immuno-oncology therapies work by taking the brakes off the immune system or otherwise boosting its ability to detect and destroy tumor cells. First-generation therapies, such as the checkpoint inhibitors from BMS and Merck & Co. that target cytotoxic T lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein 1 (PD1) receptors, have quickly redefined standards of care for people with diseases such as non-small cell lung cancer (NSCLC) and melanoma, for which the drugs have shown early and considerable promise.

The common driver of most immuno-oncology deals in recent months has been an attempt by those in pharma to assemble the multiple components of next-generation combination therapies to augment or supplant the checkpoint-inhibitor 'backbone' therapy. For nearly every major biopharmaceutical company seeking a share in the future immuno-oncology marketplace, "figuring out what combinations will be important and locking up the complementary assets sooner rather than later is key," said Andrew Forman of Ernst & Young's global life sciences transaction-advisory services division. "Immuno-oncology is a big part of the most crowded and competitive therapeutic battlefield, and companies are doing whatever they can to assemble these strategic weapons," he said.

A banner day for immuno-oncology deals

The spate of deals announced on just a single day—January 11—helps to illustrate the breadth of pharma's interest in, and the value of, biotech companies' early-stage immuno-oncology research programs. Sanofi made a particularly big splash by announcing a pair of deals to add to its stable of oncology partnerships (among which is a broad, multi-therapeutic area alliance with Regeneron that includes the investigational PD1-specific mAb REGN2810). Sanofi is launching a new partnership with Innate Pharma focused on anticancer bispecific antibodies. Innate Pharma could receive up to €400 million in milestones, and eventually royalties, for its contributions to the development of bispecific antibodies that engage natural killer cells to target tumors. Sanofi also said that it is modifying an existing relationship with Warp Drive Bio to include a research collaboration and an exclusive license for the biotech company's early-stage candidates, which target oncogenes such as *RAS*. The extended and reshaped deal (first signed in 2012) is worth as much as $750 million in cumulative payments across four programs.

Novartis and Surface Oncology, a startup founded by Atlas Venture in 2014, also teamed up on January 11. Novartis gains access to Surface's four preclinical programs targeting regulatory T cells, inhibitory cytokines and immunosuppressive metabolites in the tumor microenvironment, and Surface is eligible to receive $170 million in 'near-term' up-front, equity and milestone payments. On the same day, Roche announced that it would pay up to $420 million to acquire Tensha Therapeutics ($115 million up front), whose lead candidate, the small-molecule inhibitor of bromodomain and extra terminal domain (BET) TEN-010, is in phase 1.

And not to be left out of the immuno-oncology deal parade, AstraZeneca reported that it would team up with messenger RNA-drug pioneer Moderna Therapeutics to codevelop and cocommercialize mRNA therapies in immuno-oncology, building on an earlier collaboration from 2013 in the cardiovascular and metabolic disease area. Meanwhile, Celgene, Amgen and a host of smaller biopharma companies joined forces with academic medical centers and insurers to form the National Immunotherapy Coalition, which will test combinations of at least 60 investigational and approved therapies by 2020 in trials involving roughly 20,000 people and many tumor types.

Identifying the right combinations

BMS's Yervoy (or ipilimumab, a CTLA4-specific monoclonal antibody (mAb)) and Opdivo (the PD1-specific mAb nivolumab), along with Merck's Keytruda (the PD1-specific mAb pembrolizumab), have quickly reached blockbuster status and markedly raised the efficacy bar in a handful of oncology indications for which they have so far been approved. Monotherapy with one of these checkpoint inhibitors has resulted in dramatic responses in some individuals; not every person responds, however, and the responses often are not durable.

The challenge for researchers developing combination regimens is to increase response rates and the durability of response without substantially increasing side effects, and companies are faced with a smorgasbord of potential combination options as the science around them continues to evolve. "Pharma companies are still being thoughtful about where they want to make their immuno-oncology investments, but it's much broader than in a lot of other therapeutic areas," said Ben Bonifant, a partner at Triangle Insights

> **"Nobody knows exactly what the killer combination will be"**

Group, a strategy-consulting firm. Every tumor type and position in a therapeutic sequence is being investigated. "The strategy is to fill in the entire matrix," he said.

Whether a combination includes multiple immuno-oncology therapies or agents with chemotherapy or other targeted oncology functions, the key "is to be very disciplined and focused on rational combinations," with decisions being guided by clear biological hypotheses and/or strong preclinical data, said Chris Boshoff, vice president of early development, translational and immuno-oncology at Pfizer.

Pfizer's immuno-oncology program is anchored by avelumab, a clinical-stage mAb that is specific for PDL1 (the ligand of PD1), which it is developing with Merck KGaA (Pfizer paid $850 million up front for the privilege in 2014, and it may pay an additional $2 billion in future milestones). Pfizer also has two mAbs that spur an immune response by targeting OX40 and 4-1BB, which stimulate $CD4^+$ and $CD8^+$ T lymphocytes, respectively, "and there's very nice preclinical data to show combining a checkpoint inhibitor with one or both of these will work better than the checkpoint inhibitor itself," said Boshoff. Pfizer is evaluating (or plans to evaluate) those combinations in a variety of tumor types, such as NSCLC, head-and-neck cancer and melanoma. The company is also working with pharma peers to test its internal candidates with a variety of marketed or experimental therapies elsewhere: the 4-1BB-specific mAb, for example, is in clinical trials in combination with Merck's Keytruda, Roche's Rituxan (rituximab), and mogamulizumab, a CCR4-specific mAb from Kyowa Hakko Kirin.

Pfizer and Merck KGaA are also pairing avelumab with Pfizer's on-market targeted cancer drugs in areas such as ALK-positive NSCLC (for which Pfizer markets Xalkori (crizotinib) and is developing a next-generation compound called lorlatinib) and renal cancer (for which Pfizer markets Inlyta (axitinib)). In both instances, said Boshoff, preclinical models suggest that a combination approach will lead to improved efficacy.

Even older chemotherapies may be combined rationally with new immuno-oncology agents. When cytotoxic chemotherapies kill cancer cells, "they elicit an immune response, and T cells can get into the tumor," said Boshoff. Combining a checkpoint inhibitor with an older chemotherapy such as doxorubicin (Janssen's Doxil) "could be additive, maybe synergistic," he said. Pfizer is running a registration trial of avelumab in combination with Doxil in refractory ovarian cancer.

It is not surprising, given their place at the epicenter of the immuno-oncology earthquake that those companies with marketed or clinical-stage PD1 or PDL1 assets find such agents to be in great partnering demand. Beyond Pfizer, Merck & Co. and BMS, AstraZeneca's PDL1-specific mAb durvalumab and Roche's PDL1-specific mAb atezolizumab form the foundations of broad immuno-oncology programs and deals, such as AstraZeneca's strategic alliances with Eli Lilly. This deal will see durvalumab tested in combination with several of Lilly's immuno-oncology candidates, as well as with Celgene, AstraZeneca's partner for durvalumab in hematology indications.

Table 1: Selected immuno-oncology partnerships involving big pharma in the past two years

Companies involved	Total potential deal value (excluding royalties)	Date	Summary
Pfizer, Merck KGaA	$2.85 billion	November 2014	Pfizer licenses PDL1-specific mAb avelumab from Merck KGaA to jointly develop and market. Merck could receive almost $2 billion in regulatory and milestone payments.
Bristol-Myers Squibb, Flexus Biosciences, Inc.	$1.25 billion	February 2015	Bristol-Myers Squibb acquires Flexus Biosciences and its lead preclinical IDO1 inhibitor F001287, as well as additional IDO/TDO programs.
AstraZeneca, Celgene Corporation	$450 million (up front)	April 2015	Celgene and AstraZeneca partner for the development of durvalumab (MEDI4736), AstraZeneca's PDL1-specific mAb, for the treatment of a range of blood cancers.
AstraZeneca, Eli Lilly	Undisclosed	October 2015	AstraZeneca and Lilly extend existing collaboration to explore further immuno-oncology combinations for the treatment of solid tumors. Eli Lilly's candidates (a TGFβ kinase inhibitor, a CXCR4 peptide antagonist and a CSF1R-specific mAb) will be tested in combination with AstraZeneca's durvalumab.
Bristol-Myers Squibb, Five Prime Therapeutics	$1.74 billion	October 2015	Bristol-Myers Squibb and Five Prime to codevelop Five Prime's CSF1R-specific mAb program.
Amgen, Merck & Co.	Undisclosed	December 2015	Amgen and Merck initiate immuno-oncology collaboration to support trials investigating Amgen's CD19 bispecific T cell engager Blincyto in combination with Merck's PD1-specific mAb Keytruda for non-Hodgkin lymphoma.
Sanofi, Innate Pharma	€400 million	January 2016	Sanofi and Innate Pharma to collaborate in immuno-oncology to develop bispecific natural killer cell engagers that activate the receptor NKp46.
Janssen Biotech, Inc., Scholar Rock	Undisclosed	January 2016	Janssen exercises option on Scholar Rock immuno-oncology program initiated in 2014, which is developing antibodies to inhibit the growth factor TGFβ1.
Baxalta, Symphogen	$1.6 billion	January 2016	Baxalta to collaborate with Symphogen to develop immune-checkpoint inhibitors against six targets.
Merck, IOmet Pharma	Undisclosed	January 2016	IOmet Pharma and its dual-acting IDO/TDO inhibitors are acquired by Merck to become a wholly owned subsidiary.
AstraZeneca, Moderna Therapeutics	Undisclosed	January 2016	AstraZeneca collaborates with Moderna Therapeutics to codevelop and cocommercialize two mRNA therapeutic programs for oncology.
Merck KGaA, Pfizer and Syndax Pharmaceuticals Inc.	Undisclosed	January 2016	Merck KGaA and Pfizer collaborate with Syndax to evaluate the combination of the PDL1-specific avelumab (developed by Merck and Pfizer) with the HDAC inhibitor entinostat (developed by Syndax) for the treatment of ovarian cancer.
Novartis, Surface Oncology	$170 million (up front and near-term milestones)	January 2016	Novartis signs a licensing agreement with Surface Oncology to gain access to four of its preclinical programs to be investigated as both mono- and combination therapies. These programs target regulatory T cells, inhibitory cytokines and immunosuppressive metabolites.

Rapid turnover

Novartis CEO Joseph Jiminez noted during his presentation at the JP Morgan meeting that although the company has been "criticized" for falling behind in the checkpoint-inhibitor competition, those drugs may not always represent the core of every immuno-oncology combination. Novartis has ten immuno-oncology therapies in development, he said, seven of which are in the clinic. Indeed, the unrelenting pace of immuno-oncology advances may some day overtake work on PD1 and/or PDL1.

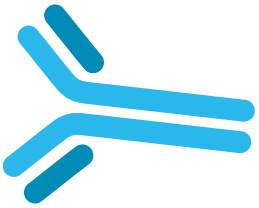
Meanwhile, those first-generation immunotherapies have considerably shortened the shelf life of other, once-promising oncology drug candidates, and they have caused others to take unexpectedly circuitous routes to market. In early January, GSK and Five Prime Therapeutics announced that they would stop enrolling people with squamous NSCLC in an ongoing early-stage trial of their FG-ligand trap FP-1039 because of rapidly changing treatment paradigms for the disease, thanks to approved immuno-oncology agents (the partners will continue to study the drug in mesothelioma). Those same approved drugs—namely, Keytruda and Opdivo—have altered the paths to market for other PD1 and PDL1 therapies. For example, AstraZeneca had hoped to receive accelerated approval for durvalumab in third-line NSCLC, but those hopes were dashed by the approvals of Keytruda and Opdivo in second-line NSCLC.

Opdivo and Keytruda are expected to post solid results of first-line NSCLC clinical trials in 2016. Even so, "the real future of front-line [NSCLC treatment] is, what are you going to combine PD1s with?" said Evercore ISI analyst Mark Schoenbaum in a video released to clients on January 8, noting that each of the existing and future players is making its own bet: Merck with an IDO inhibitor, Bristol-Myers with Yervoy, AstraZeneca with its own CTLA4-specific mAb tremelimumab, Roche with Avastin (the VEGF-specific blockbuster bevacizumab), and so on. "This is the real debate," he said, and the winner could be any company with its own PD1 or PDL1 drug.

Given the sales projections for PD1 drugs that have yet to reach the market—consensus estimates tabulated by Evaluate Pharma suggest that analysts expect sales of Roche's atezolizumab to reach $2.6 billion by 2020, for example—that scenario is likely to play out across multiple tumor types. Analysts at JP Morgan argued in a December note that although it is still too early to predict which particular pairings of immuno-oncology compounds will emerge, combinations "will eventually reset the competitive landscape in select tumors or niche segments of the market." In short, today's leaders may be tomorrow's also-rans.

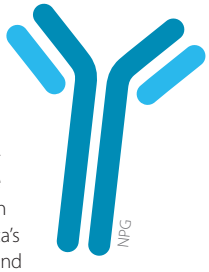
That is not to say that the current immuno-oncology leaders are letting up. On January 11—there's that date again—Merck & Co. acquired IOmet for an undisclosed amount to add the biotech's IDO, TDO and dual-acting IDO/TDO inhibitors to its portfolio. Keytruda has been evaluated in 200 clinical studies across 30 tumor types, and it has been tested in 80 combinations, in what Merck CEO Kenneth Frazier described in his presentation at the JP Morgan meeting as "the broadest clinical program of any PD1/PDL1 asset." Calling Keytruda a "pipeline within a product," Frazier said that the therapy "will be a foundational treatment across many tumor types."

BMS has also been active; Opdivo has been tested across 25 tumor types in 50 trials, and the Opdivo–Yervoy combination is the only all-immuno-oncology combination approved to date (for now, the combination is approved in the US to treat unresectable or metastatic melanoma, regardless of BRAF mutational status). Its deal with Five Prime in October 2015 for the biotech firm's phase 1 CSF1R-specific mAb FPA008 is worth up to $1.74 billion, including a $350-million up-front payment, and it acquired its own IDO and TDO inhibitors in February 2015 through the acquisition of Flexus Bioscience for $800 million up front and up to $450 million in milestones—an impressive haul for what are still, nearly a year later, preclinical candidates. More recently, on January 8, Dual Therapeutics announced that it would collaborate with BMS to develop small-molecule inhibitors of oncology growth and survival pathways in a deal worth up to $255 million, plus royalties.



Every tool in the box

Alongside conventional M&A, strategic alliances and option deals, no-strings-attached clinical trial partnerships have driven combination-therapy trials in immuno-oncology. These deals—and there are dozens of them—are typically limited to two companies agreeing to test their assets together in the clinic, without downstream commitment. "Clinical trial partnerships can take weeks to get in place, rather than months" as is common for traditional alliances, said Chris Sheldon, AstraZeneca's director of search and evaluation in immuno-oncology, and they enable companies to rapidly test clinical hypotheses. Preclinical data can be predictive, but rarely perfectly so, he said: "Nobody knows exactly what the killer combination will be—hence why we're adopting a common-sense approach to combination therapy." AstraZeneca is spreading its bets, following the science and leveraging internal expertise. When "everyone is calling themselves an immuno-oncology company and labeling their assets as immuno-oncology assets," having an extensive internal network to critically assess the data is key, said Sheldon.



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And not every clinical trial partnership is designed to foster assets' total promiscuity. For example, in a deal with Pfizer and Merck KGaA that was announced in early January, Syndax Pharmaceuticals plans to test its drug entinostat, a small-molecule histone deacetylase (HDAC) inhibitor, with avelumab in individuals with heavily pretreated recurrent ovarian cancer. That deal is exclusive, to a point: in ovarian cancer, Syndax will combine entinostat only with avelumab, but it can (and has) combined the HDAC inhibitor with other immuno-oncology assets such as Merck & Co's Keytruda in different indications (that particular combination is being tested in NSCLC and melanoma under a deal made in March 2015).

Large companies are, unsurprisingly, also getting to know potential partners and early-stage science through corporate venture investments. Pfizer said in early January, for example, that as part of a broader push to expand investment in early-stage research, it will back BioAlta and NextCure, two immuno-oncology–focused biotechs. Pfizer's investment in NextCure was part of that biotech's $67-million Series A financing that also attracted Lilly Asia Ventures, alongside other conventional venture capitalists.

Future platforms

Alongside small-molecule and mAb therapies in immuno-oncology, various flavors of clinic-based cell therapy for hematological malignancies may also have a role in future combinations. RNA-based therapies, such as those emerging from Moderna's mRNA platform, could also be combined with more conventional modalities. And new biologics that home in on more than one target can be paired with existing therapies or tested on their own. The US Food and Drug Administration approved the first marketed bispecific antibody, Amgen's Blincyto (blinatumomab), in late 2014, and Amgen and Merck are now testing it in combination with Keytruda in a variety of hematologic cancers.

Outside of its avelumab alliance with Pfizer, Merck KGaA is developing bifunctional fusion proteins. One compound, which is in early-stage clinical trials, combines a PD1-specific antibody with a TGFβ trap, said the company's R&D chief Luciano Rossetti. "We have a major effort in bispecifics and fusion proteins," he said, noting that the program went from lead molecule to 'first in humans' in only 11 months. Future combination strategies may be increasingly oriented around building multiple mechanisms into a single molecule, he said.

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