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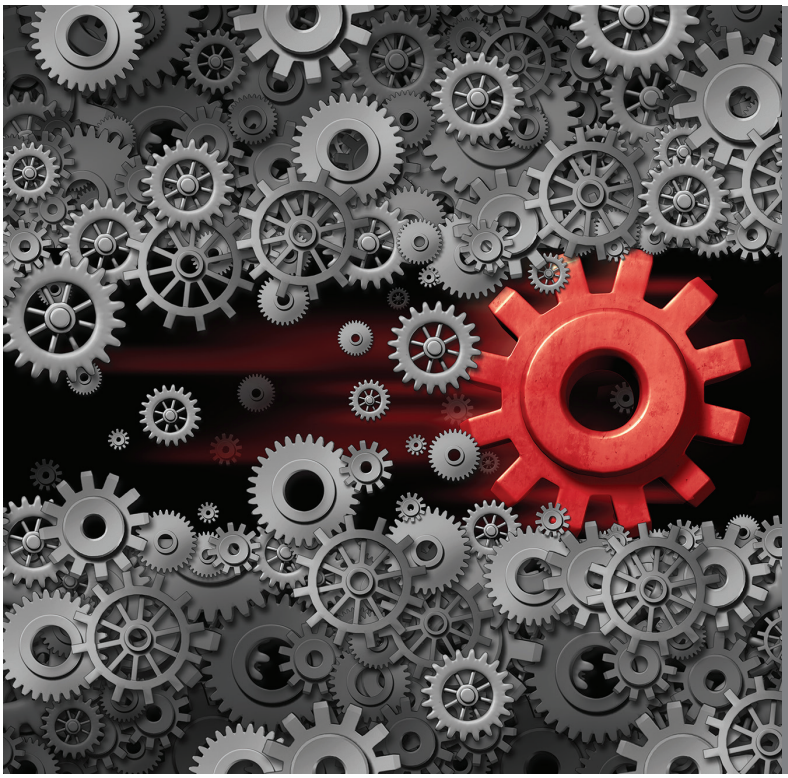
Success in Oncology

Oncology Disruption Demands Strategic Transformation



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The rapidly accelerating complexity of oncology drug development demands a new way of doing business. To succeed in this new landscape, biopharma companies must transform their portfolios and partnerships, and shift toward more dynamic business and operating models and decision-making processes.

BY TROY NORRIS, KEYURI SHAH AND KRISTIN POTHIER

Developing the first or best molecule in a class is no longer enough to sustain a differentiated market position in oncology. Pharmas must create patient-centric strategies, often combining medicines produced by different companies.

Creative partnerships with a network of collaborators are essential in this new marketplace, particularly given the advent of immuno-oncology and targeted therapies, both of which are exponentially increasing competitive intensity and the number of possible therapeutic combinations.

So what? Facing market disruption, oncology-focused pharma companies must rethink their approach to leadership. Strategic transformation of portfolios, partnership networks and organizational dynamics will be critical. Organizations that don't transform rapidly risk obsolescence.

With multiple modalities of care for cancer patients, oncology treatment decision-making has always been complex, but accelerating innovation is driving exponential growth in treatment complexity. Genomic advances continue to enable development of new targeted therapies and immunotherapy agents have demonstrated promising outcome improvements across multiple tumor types. These new treatments are being overlaid upon the more traditional chemotherapies and hormone therapies, producing a wide variety of possible treatment pathways.

The pace of new drug development continues to accelerate: there are more than 650 cancer treatment candidates in late-stage clinical development (Phases II and III). Based on historical success rates, these could potentially lead to the launch of nearly 100 new treatments across roughly 30 clinical indications over the next five to seven years. This accelerating pace has shortened the window for breakthrough drugs to capture value before facing therapeutic substitution, diminishing financial returns for pharma companies. In response, these companies are aggressively broadening the number of molecules, mechanisms and tumor indications for development, creating even more complexity. (*See Exhibit 1.*)

In particular, large pharma companies are placing their bets on the new class of promising immunotherapies. Although there are only a handful of drugs currently marketed in this segment, more than 200 immunotherapies are under study, including cell therapies and cancer vaccines. (*See Exhibit 2.*) Primary checkpoint inhibitors are the most advanced mechanistic category, with five drugs approved or in registration, and another eight drugs in Phase II or Phase III. Together, these checkpoint inhibitors are expected to become the backbone of combination therapy going forward.

The plethora of new molecules with complementary treatment mechanisms is driving further complexity through proliferation of possible combination regimens. Liz Barrett, global president and general manager, oncology, at **Pfizer Inc.**, emphasized at the *UBS Global Healthcare Conference* that "PD-1 will always be a backbone of immuno-oncology,", adding that "the winning formulation for patients will ultimately be in the combinations of multiple immuno-oncology medicines and also in combination with targeted therapies." Consequently, more than 750 clinical studies, according to Informa's *Trialtrove*, are ongoing – testing the eight PD-1/PD-L1 inhibitor drugs in Phase III or later in combination with other therapies. (*See Exhibit 3.*) More than a quarter of these experimental regimens are testing combinations of three or more drugs. Many of these trials are exploratory, with small sample sizes, which will make interpretation of results challenging.

The sheer number of potential treatment combinations that these trials are expected to create across tumor types and stages promises to make treatment decision-making even more challenging for care providers. Adding to the challenge, some combination trials have seen mixed results, with little or no improvement to progression-free survival rates or even an increase in fatalities. This proliferation of treatment combinations, coupled with the unpredictability of combination trial outcomes, makes it ever more difficult for a drug to separate from the pack, while making it ever more imperative to establish a role in standard-of-care regimens.

Value Shift Toward Treatment Decisions

With so many similar compounds and combinations competing for a role in the standard-of-care treatment path, patient selection and optimization of the overall treatment regimen are paramount for success. The experiences of **Merck & Co. Inc.**'s *Keytruda* (pembrolizumab) and **Bristol-Myers Squibb Co.**'s *Opdivo* (nivolumab) are prime examples of the impact of patient selection on clinical outcomes and product positioning across tumor types and treatment lines.

Effective competitive differentiation therefore depends critically on designing the optimal clinical program for a molecule – targeting the right patients, with the appropriate treatment regimens, and using the best diagnostics. In addition to very strong clinical and molecular science, deciding upon the appropriate patients and regimens requires access to complex data, which are controlled by providers and payers. Treatment decisions at the clinic can no longer rely on package inserts, nor even standard clinical guidelines. Robust predictive treatment algorithms are needed to make clinical decisions using advanced data mining capabilities, analytics tools and statistical methods.

Driving toward optimal outcomes, major cancer centers and industry consortiums are combining their clinical expertise and access to patient data to develop advanced clinical decision support systems. *(Also see "Free And Open: The Next Wave In Clinical Trial Data?" - In Vivo, May 2017.)*

Transforming Portfolios, Partnerships And Organizations

Differentiating within this shifting paradigm toward personalized combination therapy requires pharma companies to rethink their approach to market leadership. Traditional approaches to product development and operational management will no longer ensure success. This strategic transformation of oncology manufacturers requires coordination on

Exhibit 1

The New Cancer Drug Development Path

Disruptive forces are reshaping the traditional development path for cancer therapies, creating complex webs of optionality and decision-making earlier in development

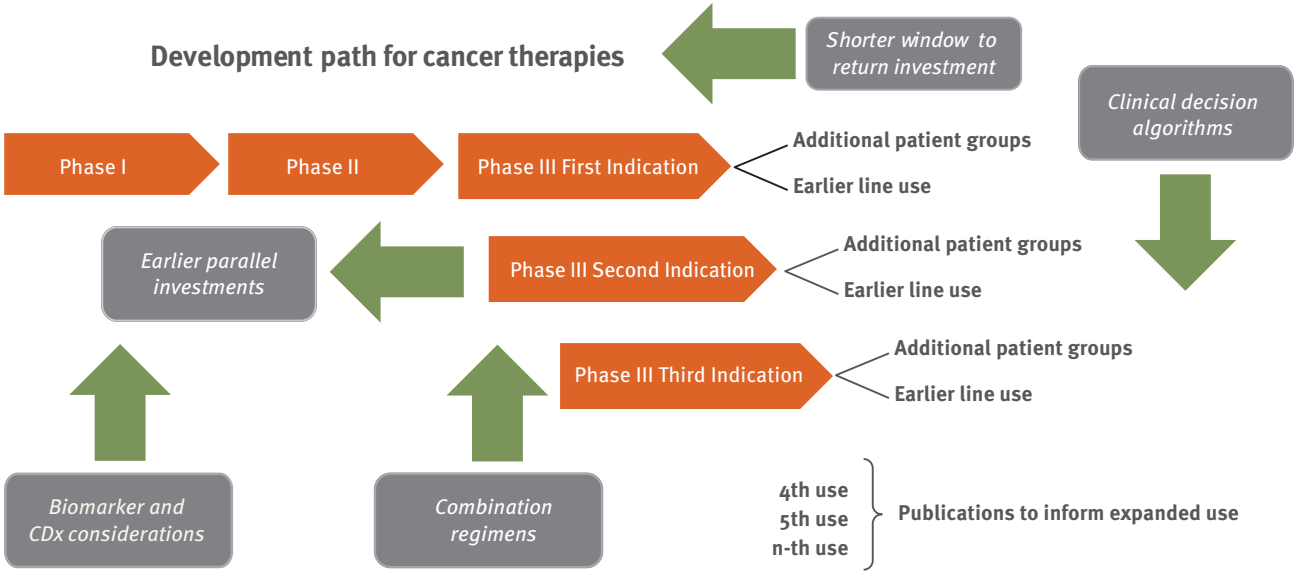

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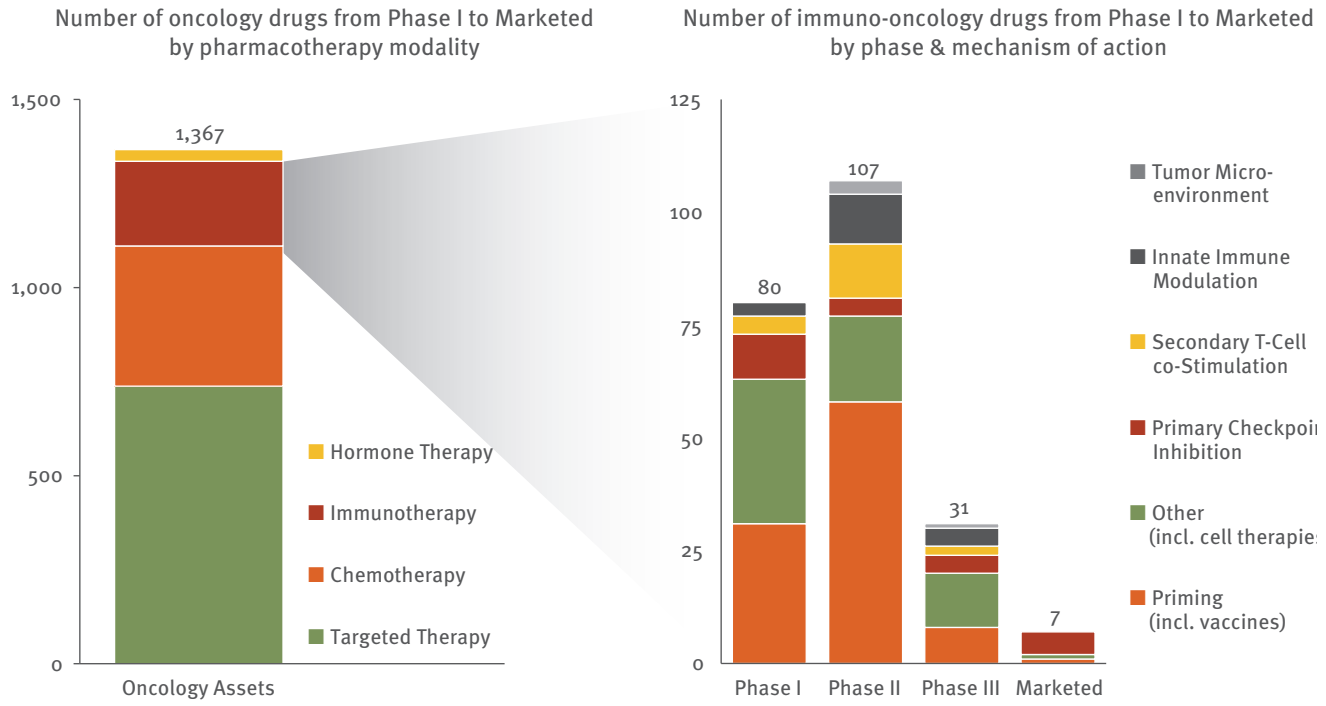
Exhibit 2
I-O Therapies In Development



Notes: Numbers are for unique brands, not for unique indications by brand; (*) counted by lead indication only. Drugs currently filed for NDAs/BLAs are grouped into Phase III. Data through March 30, 2017.

three dimensions: 1) refocused portfolio management, 2) innovative partnership networks and 3) dynamic organizational decision processes. (*See Exhibit 4.*)

A Shift In Investment Focus

Accelerating complexity and personalization of care requires increased investment across the care continuum to establish leadership. As having the first or best molecule in a class becomes a more short-lived differentiator, market leaders need a portfolio of complementary mechanisms with a central role in combination regimens across tumor types. Consequently, innovators must balance the need to pursue complementary mechanisms and combination regimens against the greater intensity of investment required to develop and position each molecule. Discussing their oncology strategy on an earnings call, Vasant Narasimhan, global head of drug development and chief medical officer of **Novartis AG**, pointed out: "We continue to evaluate a range of different options, whether it's in IO-IO combination or in combination with our targeted therapies ... the key is going to be for us to prioritize amongst all of these opportunities."

Portfolio decision-making has traditionally aimed to identify the highest-value individual assets and to diversify risk through investment across multiple unrelated mechanisms. Going forward, portfolio strategy needs to optimize the collective value of a franchise within and across tumor types – evaluating different asset combinations to optimize the risk-reward balance and maximize overall portfolio value under a range of scenarios. Minimizing asset overlap and facilitating co-positioning of compounds may require delaying or deprioritizing otherwise attractive clinical candidates, or focusing specific molecules on a narrower set of indications and patient populations.

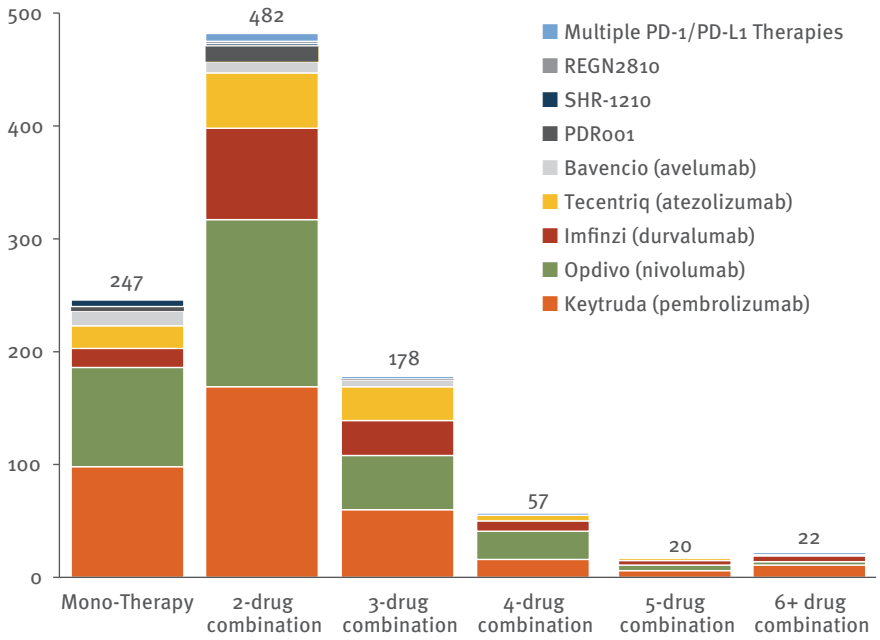
Companies also need to decide whether to co-develop combinations of candidates in their own pipeline or to partner, to access either promising clinical candidates or compounds already established as standard of care. Portfolio decision-makers must make complex trade-offs among achieving the best clinical profile in the broadest population, enabling creative outcomes-based premium pricing strategies and capturing a fair share of the economic value realized. (*See Exhibit 5.*)

The move toward expensive combination regimens will exacerbate reimbursement challenges. Payers are likely to demand lower pricing for new therapies when used as part of a combination rather than monotherapy. Companies with multiple effective and complementary therapies, especially including backbone immune checkpoint inhibitors, will be well-positioned to pursue premium pricing through aggressive outcomes-based contracting for their combination regimens. Without this portfolio scope and scale, partnering to create the most effective combination therapies will be critical to capture value.

To support portfolio decision-making with this complex set of potential partners, development paths and clinical outcomes scenarios, more sophisticated scenario modeling and simulation tools are needed. Data analytics companies are developing tools, such as **InveniAI Corp.**'s *PharmGPS*, that can assess competitive gaming and potential partnering scenarios, as well as the commercial value across indications considering complementarity and cannibalization. These tools aim to determine the optimal development paths for individual

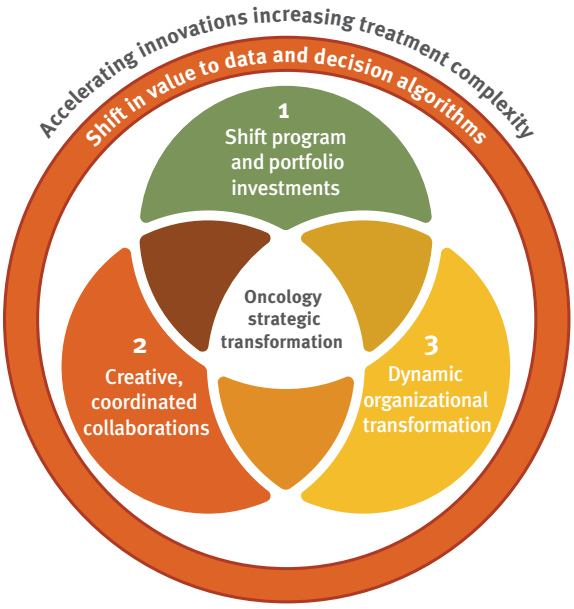
Exhibit 3
PD-1/PD-L1 Trials

Number of PD-1/PD-L1 clinical trials[1] by number of drugs in combination therapy



Notes: (1) Only includes PD-1/PD-L1 inhibitors in Phase III, registered or marketed. Data through May 22, 2017

Exhibit 4
Oncology Strategic Transformation



oncology treatment candidates that will collectively maximize overall portfolio value across indications, patient populations and treatment regimens.

To help providers and patients grapple with the flood of new clinical findings, pharma companies are creating digital solutions to support their portfolio strategies. For example, **Boehringer Ingelheim GMBH** is developing an online portal to connect key opinion leaders and provide online resources for health care professionals, journalists and patients. And companies such as **AstraZeneca PLC** and **Eli Lilly & Co.** have developed mobile applications to provide easy access to educational resources. These digital educational channels can create crucial dialogue with clinicians that enhances a company's portfolio position.

Creative, Coordinated And Purposeful Collaboration

To succeed in this new environment, biopharma companies need to create a vibrant network of partnerships. (*See Exhibit 6.*) Oncology innovators and marketers can no longer drive growth solely through traditional compound licensing and acquisitions. Partnerships with other companies will increasingly be needed to access compounds for combination regimens, co-develop diagnostics to identify the right patient populations and use real-world data to maximize therapeutic value and patient outcomes.

For each partnership category, companies must clearly define the objectives and role in achieving the target market position amid the emerging collaboration network. These partnerships will need to be carefully coordinated to assure alignment to support the portfolio as a whole, specific brands and potentially new revenue streams.

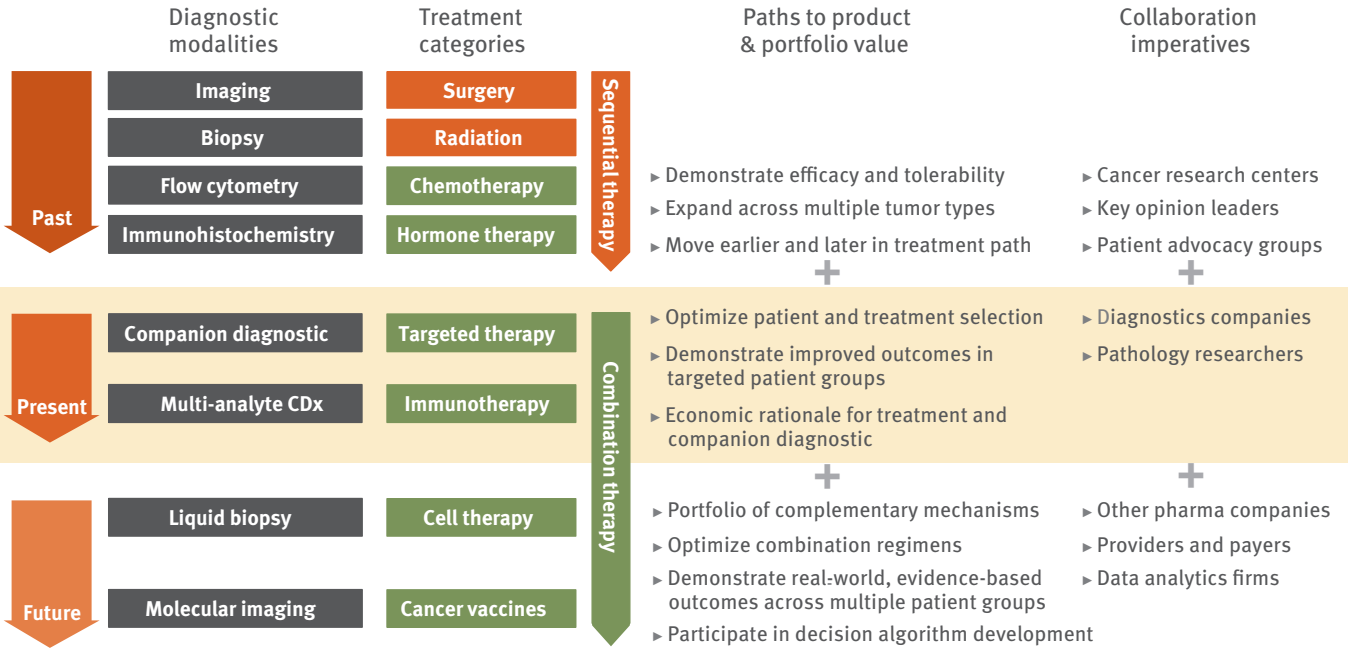
Companion Diagnostics

For immuno-oncology and targeted therapies alike, pharma companies will need to continue to partner with diagnostic companies to identify subsets of high responders. Testing technologies continue to advance quickly, enabling more rapid and robust treatment response prediction.

For example, researchers at companies such as **PerkinElmer Inc.**, **NanoString Technologies Inc.** and **Genoptix Inc.** are developing more quantitative multiplexed immunohistochemistry (IHC) protein expression assays. Continued advances in nucleic acid testing methods are enabling routine analysis of comprehensive gene panels and overall tumor mutation burden. And new modalities that enable less invasive, more rapid treatment response and recurrence monitoring are emerging, such as liquid biopsy and advanced imaging techniques.

Exhibit 5
Complex Path To Value Creation

As the available diagnostic and therapeutic options expand, pharma product, portfolio and partnering decisions have become highly complex



Assuring access to these new technologies, and anticipating future diagnostic pathways, will continue to be critical for successfully positioning products in the treatment path to drive rapid uptake into clinical practice.

"Coopetition" Among Pharmas

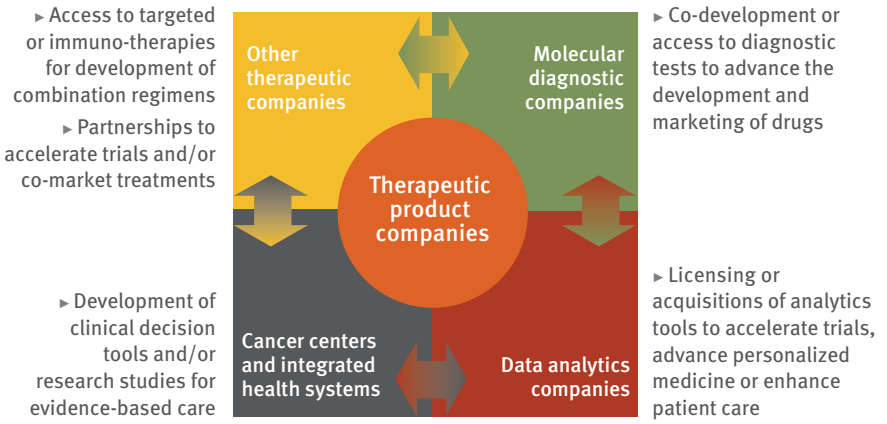
Companies with novel targeted and immuno-oncology therapies increasingly need to consider which other molecule and mechanism combinations will be optimal for which tumor types. The many companies with multiple compounds on the market and under development can no longer rely solely on compounds in their own portfolio, and instead must choose to partner with others with the aim to develop the best and broadest standard-of-care regimen.

Cooperation among pharma companies, forced by the clinical science to work together to secure a position in treatment pathways by creating best-in-class combination regimens, has risen dramatically. Within immuno-oncology, the growth in combination drug partnerships has outpaced growth in single drug agreements (e.g., traditional in- and out-licensing). According to an April 2017 report, "Immuno-Oncology Deal Trends, 2012–16," from Informa Pharma Intelligence's *Datamonitor Healthcare*, combination deals recently outnumbered single asset deals by two-fold. (*See Exhibit 7.*)

More than half of these immuno-oncology combination agreements involve PD-1 and PD-L1 inhibitors, with 137 of these deals occurring over the past five years. For example, Merck has partnered with Pfizer and AstraZeneca to combine selected immuno-oncology and targeted

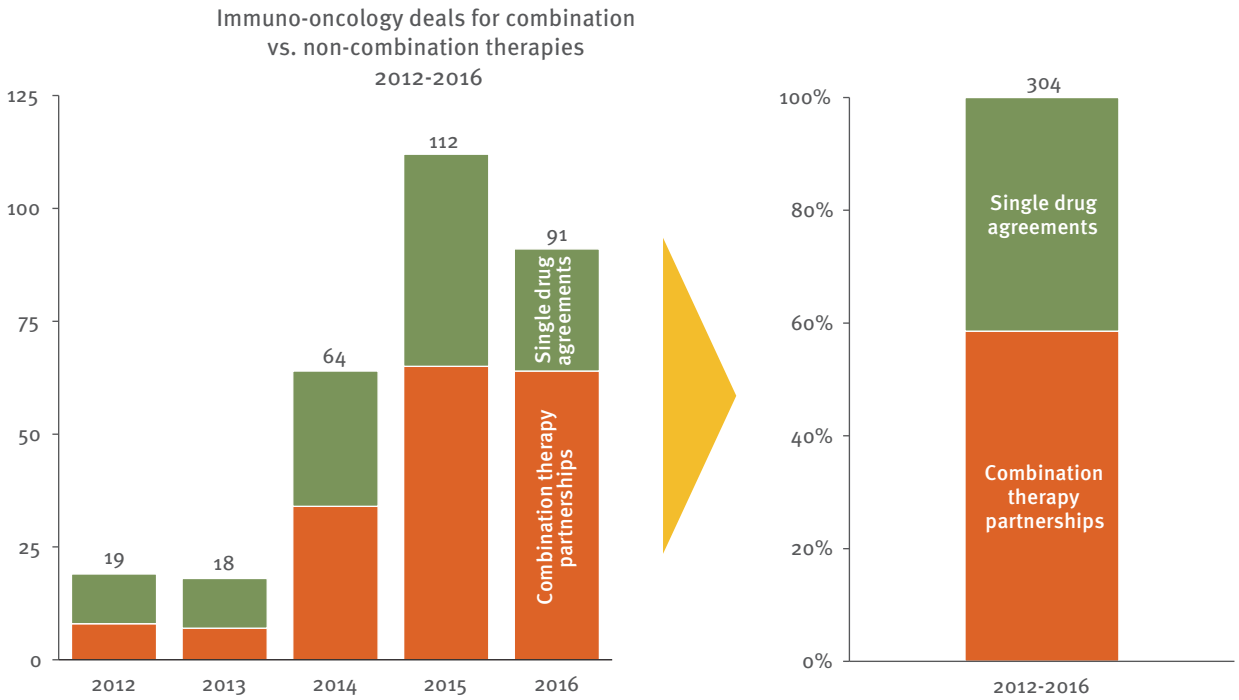
Exhibit 6
Creating A Collaborative Network

Therapeutic companies must actively establish themselves as hubs within a value network of cross-sector collaborative partnerships



Companies are forging relationships without pharma that are shifting the value equation

Exhibit 7
I-O Combination Deals



SOURCES: Datamonitor Healthcare | Pharma Intelligence, 2017; Parthenon-EY analysis

medicines. BMS has entered into a wide range of co-development partnerships for Opdivo across tumor types. With a full portfolio of immuno-oncology and targeted medicines for solid tumors, AstraZeneca chose to license its checkpoint inhibitor and other immuno-oncology candidates to **Celgene Corp.** to develop for hematological malignancies.

Data Analytics

Increasingly, complex treatment choices and new diagnostic methods are catalyzing efforts to harness "big data" to guide translational programs, patient selection, health economics and outcomes research, market access and treatment algorithms.

These data analytics collaborations are expected to lead to improved therapies and more effective positioning and use of these drugs, while helping secure a place in future treatment algorithms and potentially enabling new revenue models derived from the clinical value of the analytics solutions. (*See sidebar, "Pharma's Big Data Deals."*)

Health Care Providers

As the oncology landscape becomes more competitive and complex, capturing full value for innovative products will require real-world evidence of a therapy's ability to improve outcomes in specific patient populations. Pharma companies are thus partnering with cancer centers and health systems to access and analyze real-world data. For example, AstraZeneca has begun an initiative to collect and analyze real-world data to combine patient experience insights with molecular and clinical data from electronic health records.

As data technologies advance, some medical products companies are thinking even more holistically about the use of real-world data. For example, **Partners HealthCare System Inc.**and **GE Healthcare** recently announced a clinical data science collaboration to leverage clinical data sets and artificial intelligence to improve the entire continuum of cancer care, from reducing unnecessary biopsies to optimizing treatment. In its press release, Keith Dreyer, chief data science officer, Departments of Radiology and MGH and BWH, Partners Healthcare, emphasized the criticality of partnerships between hospitals and the industry for the advancement of clinical data science: "We're evolving the health care system to be able to take advantage of the benefits of deep learning, bringing together hospitals, data sets and clinical and technical minds unlike ever before."

Leveraging real-world evidence to identify novel approaches to patient care can also identify new treatment populations and reduce clinical program risk. For example, Celgene has recently partnered with **Dana-Farber Cancer Institute** and the **University of Arkansas** to compile a large data set of genomic and clinical information, to identify distinct molecular disease segments within multiple myeloma to be leveraged for future treatment development.

Dynamic Organizational Models And Decision Processes

The rapid pace of market and technology disruption coupled with the increasing complexity of decision-making is stressing the organizations of large multinational oncology businesses. The standard matrixed model of molecule-centric global R&D and brand teams with geographically focused sales and marketing organizations, typically coordinated centrally, needs to shift toward more agile, dynamic, delegated decision processes.

To support the responsive coordination needed to succeed in oncology,

companies such as AstraZeneca, **Bayer AG** and Novartis have separated their oncology business units from their broader pharma businesses. In Bayer's annual news conference in 2017, Dieter Weinand, head of Bayer's pharmaceutical division, defended his company's decision to reorganize, reiterating the need for agility in oncology: "The unit will enable us to get to market first and fast with our oncology products. It is very important to be first to market, otherwise the standard of therapy is changed and your studies were against the old standard of therapy." More nimble resource allocation and clinical progression decisions are expected to speed development and repositioning of pipeline agents in the quickly evolving cancer market.

Development and partnering decisions, especially regarding combination regimens and companion diagnostics, will require substantial clinical and commercial involvement, coordinated globally across brands and tumor types. To make more responsive decisions for their programs, brands and deals, functional teams across R&D, commercial and business development need greater coordination with predefined decision criteria and real-time competitive intelligence.

To manage increasingly complex collaboration networks, organizations need to revisit how they are structured and resourced to effectively identify, evaluate, transact and manage these alliances. For example, effective coordination of data partnerships often requires centers of technology expertise with governance aligned to the organizational matrix to activate data across a wide range of clinical development, market access and commercial applications.

> *"To make more responsive decisions for their programs, brands and deals, functional teams across R&D, commercial and business development need greater coordination with predefined decision criteria and real-time competitive intelligence."*

The need for rapid decision-making based on accurate and timely information will require dynamic, anticipatory decision processes that incorporate and integrate diverse inputs from across the organization to drive rapid, adaptive, coordinated decision-making and implementation. Companies will need to deploy more sophisticated decision tools to manage complexity and uncertainty while supporting less centralized decision-making processes. Those that successfully design and align a more dynamic organizational model will have a critical source of competitive advantage in oncology.

Implications For Oncology Innovators And Marketers

As the future oncology landscape becomes increasingly competitive, complex and data-driven, businesses that move confidently to adapt to and capitalize on this rapid disruption will have a strong competitive advantage and are more likely to achieve a profitable and growing market position. Transformation will require a shift in portfolio focus and scope, partnering creatively and purposefully with a wide range of stakeholders, and a more dynamic organizational model that enables rapid evaluation of strategic options and real-time decision-making. Innovators and established players alike must proactively adapt to secure a sustainable position in the future oncology ecosystem.

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PHARMA'S BIG DATA DEALS

Several biopharmas, such as **Celgene Corp.** and **Pfizer Inc.**, have partnered with **IBM Watson Health** to speed the identification of new targets and patient selection strategies for immunotherapies.

Novartis AG has also partnered with IBM Watson Health to develop a cognitive solution that uses real-world data to predict response to breast cancer treatments, which follows on Novartis' collaboration with **COTA Inc.** to apply its evidence-based analytics platform to improve outcomes and costs for breast cancer patients.

Celgene has invested in **NantHealth LLC** to support the creation of evidence-based personalized health tools across diagnoses, treatment decision support, monitoring and patient care.

And oncology developers are partnering with data analytics firms, such as **GNS Healthcare**, to discover new biological pathways, identify target populations and predict patient outcomes, or **MediData Solutions Inc.**, to develop improved targeted therapies and evaluate new oncology indications.

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Inside Bayer Oncology: An Interview With Robert LaCaze

Bayer AG may more often make headlines for its deal-making in consumer health and agriculture, but the massive German conglomerate sees oncology drugs as a key engine of future success within its high-growth pharmaceuticals business.

A Q&A with Robert LaCaze, EVP of Bayer's new Oncology Strategic Business Unit.

BY CHRIS MORRISON

Robert LaCaze joined Bayer AG in October 2015 from Bristol-Myers Squibb Co., where he was head of product and portfolio strategy, to help lay the foundation of Bayer's oncology strategic business unit that went into effect in February 2017. LaCaze was tapped as the unit's first leader, combining Bayer's strategic oncology operations, regulatory affairs, clinical development, marketing, medical affairs, pricing and access functions in a single organization to accelerate development and commercialization of new cancer therapies.

Bayer is not a top-10 oncology company, and LaCaze avoids too specifically pinning down the firm's aspirations in biopharma's biggest market. Instead, he points to the vastness and the heterogeneity of opportunities within the oncology space, suggesting that even a second-tier cancer company can achieve significant growth if it plays to its own strengths and knows how to stay focused.

Over the past several years, Bayer has indeed pulled together a small handful of platforms for future growth in the oncology area, building up its antibody-drug-conjugate technology and acquiring the radiopharmaceuticals specialist Algeta ASA for $2.6 billion in December 2013. These assets complement Bayer's strength in small-molecule targeted cancer therapies, such as its marketed multi-kinase inhibitor Stivarga (regorafenib) or the promising PI3k inhibitor copanlisib, which is under priority review at FDA to treat certain lymphomas. The company has yet to make a big splash in the increasingly important immuno-oncology space, but LaCaze is confident that by eschewing first-generation immuno-oncology assets such as anti-PD-1 therapies, Bayer can position itself for the next wave of IO growth. To that end the company has allied with the Israeli biotech Compugen Ltd.[See Deal] for that business' next-generation checkpoint inhibitors.

The moves Bayer has made outside oncology – outside its pharmaceutical business entirely – dwarf deals like the Algeta acquisition and greatly diminish the potential for any expensive moves in the oncology area. In October 2014, Bayer paid Merck & Co. Inc. $14.2 billion to acquire a portfolio of consumer health assets. And the company is currently in the midst of a $66 billion acquisition of agriculture giant Monsanto Co., as well as reducing its stake in the materials science company Covestro AG, which spun out of Bayer in 2015. But regardless of the massive deal-making elsewhere in the conglomerate, LaCaze notes the ongoing success of Bayer's pharmaceuticals business and the central role oncology plays within that group.

In Vivo interviewed LaCaze at the BIO International Convention in San Diego in late June. In a wide-ranging discussion, LaCaze talked about the importance of being focused within oncology, Bayer's oncology platforms, and why oncology is increasingly a key priority at the massive conglomerate.

In Vivo: Why is the strategic business unit the right structure for oncology within Bayer's pharmaceuticals group? How does the SBU operate?

Robert LaCaze: The business unit itself is in place to make rapid decisions and also be able to get medicines to patients as quickly and prudently as possible. Rapid decisions still need the right rigor – we want to make sure as we move forward that we understand the science and our customer base and bring important medicines that are highly differentiated to the marketplace.

And this isn't an approach that would necessarily work in other areas of our pharmaceutical business. In oncology there's an established regulatory approval process where you can move from Phase II into regulatory approval, or Phase I directly into Phase III. You can't typically do that in cardiovascular disease. If you look at cardiovascular disease trials, there can be ten to twenty thousand patients, so it's very different. In oncology there's this massive amount of innovation, and so much competition, to compete you need to move quickly and decisively.

Once we agreed to the strategic approaches we wanted to take, then the question became how do we best implement those strategies we've agreed to as a company, the approaches we want to take, and where we want to be. It quickly became obvious that a very focused organization in oncology was going to be a good approach, especially as you think about who we're competing against.

We're in the oncology market with several large pharma companies, but we're also competing with smaller oncology-focused biotechs with different structures. We kind of have a hybrid between those two different types of approaches, one that fits the needs that we have. Importantly, we wanted to make sure we were appropriately focused. When you look at the therapeutic area, it's the largest growth therapeutic area, it's the fastest growing area, but it's very segmented. Nobody really owns a big piece of all the different platforms and technologies. And it's an area that's rapidly changing. We know that half of the breakthrough designations from the Food and Drug Administration are given in oncology. And that 35% to 40% of all the Phase Is in development across industry are in oncology. So you really need to focus in the areas where you choose to compete if you want to be successful in this space.

What are the areas in oncology where Bayer is choosing to focus? How do you make those decisions, based on your current portfolio and the lure of exciting areas like immuno-oncology?

We think about it in terms of where we want to play to win, in terms of our resources and investments. Which platforms do we want to focus on, and which tumor types do we want to focus on. As we think about the platforms for example, strategically as a company we have a good pipeline. It's one of the things that attracted me to Bayer in the first place. But in terms of the focus, as opposed to being too diluted across too many different platforms, we decided to focus on four different key areas.

The first oncology area where we're really good as a company is our targeted small-molecule approach. Cell cycling, cell signaling and tying in the pharmacodiagnostics early on, a priori, before we move to first-in-humans. We're trying to figure out the biomarker approach with these small molecules as we move forward, and focus on developing first-in-class treatments.

Our second area of focus is our antibody-drug-conjugate platform and our ADC technology. We have a compound in clinical development and many preclinical-stage compounds in the ADC space. (*Also see "Cancer's Next-Gen Smart Bomb: Who Will Be First To Weaponize?" - In Vivo, May 2017.*)

The third area is around our targeted alpha therapies. And obviously we have Xofigo [radium-223 dichloride, approved for treating patients with castration-resistant prostate cancer who have bone metastases] in the market currently but we have a whole platform with our acquisition of Algeta, our thorium platform (thorium degrades into radium, which is what our Xofigo is). But you can also actually take thorium and conjugate it with a linker, and target it like an ADC. That platform is highly differentiated for us as a company. If the platform continues to prove successful – the science is still early, we're in Phase I with one of our compounds and have several more moving into Phase I over the next few quarters – but if successful, it offers many opportunities.

As a company we want to be focused on the second-generation, second wave of immuno-oncology. That first wave of checkpoint inhibitors, specifically antibodies against PD-1 and CTLA4, are very important compounds. But we don't want to be the seventh or eighth company out with a PD-1 inhibitor. And also when we look at the science, we know that about seven out of 10 patients won't respond to a PD-1 inhibitor, with the possible exception of melanoma patients. But even within 12 months, unfortunately about 80% to 90% of those patients will need additional treatment options due to progression. The first-wave immuno-oncology drugs do benefit patients and there's a subset of patients who will receive a long-term benefit. But it's still a huge unmet medical need and we need a second-generation approach to immuno-oncology. The question we're asking is how do you turn what we call a "cold" tumor into a "hot" tumor, susceptible to an attack from the immune system.

There are several ways to do that. It could be an immuno-oncology approach, it might be a targeted therapy approach, it might be a radiopharmaceutical approach. The tumor is "cold" because T cells aren't infiltrating the tumor; and using something to damage the tumor, an "IO-IO" approach or otherwise, is necessary. We're not disclosing the targets we're going after just yet, but we have some unique approaches and we're looking at both biologics and small-molecule strategies. It's still early.

When you look at our pipeline, we have gone from a one-drug company 10 years ago, Nexavar, with two indications,

to today, three drugs on the market with seven indications. And hopefully by 2019 or 2020 we'll have additional drugs on the market, in additional indications. So we really are growing as an oncology company. (*See Exhibit 1.*)

Bayer has highlighted Xofigo as an example of the kind of innovation the company will pursue in oncology, and it's a cornerstone of one of the four platforms you just highlighted. It's not an ordinary drug, so how's it performing?

Obviously, as you come into the market with a drug like Xofigo, there's a lot to learn. You have to establish the distribution and the connectivity between the oncologists and the urologists and the radiation oncologists, and so it takes a bit longer to get it going. Country by country these distribution systems and relationships vary greatly. It's complex and that's why every account is different. And that's part of the pleasure of working in that area but also part of the challenge.

But Xofigo is doing very well in the marketplace. [In the second quarter of this year total revenue for the drug reached $105 million, a 30% increase over the prior year.] We are well ahead of where we thought we'd be in Japan, where the drug was only launched in May 2016. We're having tremendous growth in the US, in parts of Europe, and it's one of those things that when people understand it, where and how to utilize it with patients, it's going to grow. The drug is given over six cycles, and you want patients to get as close to those six cycles as possible. If they use the drug too late, patients may not receive enough of the drug to have the overall survival benefit. You want to use it earlier in the lines of therapy, and then patients can receive the five or six cycles. And patients do a lot better when they get more of the drug, partially because of the drug, partially because they're earlier in the cycle of the disease, so you can have that positive impact for the patient.

We actually have completed a trial with Xofigo with abiraterone [Johnson & Johnson's Zytiga] in earlier stages of prostate cancer with bone metastases. We're waiting for the results, it's a results-driven trial. The enrollment has completed and we have announced that we should have the data sometime next year.

Bayer is a diversified company, and other parts of the business must consume a lot of resources and attention – particularly as the company is working to close the $66 billion Monsanto acquisition. How does oncology, which is relatively small, maintain an adequate share of voice?

Those other businesses are important, but they're individual business units. The new Bayer, the way we're set up, our head of crop sciences, head of consumer, head of pharma are all part of the board of management. Within the pharmaceuticals business, our key growth is coming from cardiovascular therapies and from oncology, and there continues to be tremendous opportunity in oncology. Remember, that the oncology market itself is the fastest growing market, and it's also the largest market.

Oncology is also a very diverse market, so we can focus on those areas where we are strong as a company. Again, immuno-oncology is an important area, but there re-

Exhibit 1
Bayer's Oncology Pipeline

DRUG NAME	DISEASE	STATUS
entinostat	Cancer, breast	Phase III
Darolutamide (licensed from Orion)	Cancer, prostate	Phase III
roniciclib	Cancer, lung, small cell	Phase II
Refametinib (licensed from AstraZeneca)	Cancer, colorectal	Phase II
anetumab ravtansine	Cancer, solid, unspecified	Phase II
rogaratinib	Cancer, bladder	Phase I
Pasotuxizumab (licensed from Amgen)	Cancer, prostate	Phase I
lupartumab amadotin	Cancer, squamous cell	Phase I
epratuzumab-thorium-227	Cancer, lymphoma, non-Hodgkin's	Phase I
BAY-1895344	Cancer, solid, unspecified	Phase I
BAY-1436032	Cancer, solid, unspecified	Phase I
BAY-1251152	Cancer, solid, unspecified	Phase I
BAY-1217389	Cancer, solid, unspecified	Phase I
BAY-1179470	Cancer, solid, unspecified	Phase I
BAY-1161909	Cancer, breast	Phase I
BAY-1143572	Cancer, unspecified	Phase I
BAY-1125976	Cancer, breast	Phase I
BAY-1082439	Cancer, solid, unspecified	Phase I

SOURCE: Pharmaprojects | Pharma Intelligence 2017

> *We have a broad global footprint now as a company. In addition to the US and Europe, we consider markets like China and Japan to be focused markets for us as a company.*

mains a huge unmet medical need. And we feel that we have a differentiated approach with our ADC, alpha-therapy, and small-molecule platforms, in addition to what we are developing in immuno-oncology.

Our funding hasn't gone down in oncology. It continues to be increased. And R&D for pharma is a major growth driver for us as a company, probably the largest part of our overall growth. And so it's not hard to deduce that if you want to be in pharma, it is important to leverage your oncology expertise. And to do that, we need to be focused on our areas of differentiation. We created the oncology strategic business unit to drive this process.

How are you equipping the oncology strategic business unit to compete in the emerging value-based care paradigm?

Part of the reason for establishing the oncology strategic business unit is that we wanted to make sure we could move fast but with rigor. We have a head of oncology development that has both late-stage and early-stage clinical operations and regulatory affairs reporting in to that person. But it was important not to just have the clinical component of it, we needed to emphasize market access. The head of market access and pricing for oncology sits in the business unit as well, reporting directly to the head of the business unit. The head of medical affairs for oncology is in the business unit and a lot of the real-world evidence medicine is done through our medical affairs organization. Now you have both market access and medical affairs as the main drivers of establishing our therapies' value, setting the endpoints for, and shaping, the trials we need to conduct to demonstrate value.

Everything we're doing right now, even early on, we're incorporating the real-world evidence approaches. We want to make sure we're collecting the right data in our clinical trials so we know how these drugs are utilized in real life. That's an imperfect science, and it's difficult. But you have to implement it. We're spending quite a bit of investment on collecting that type of data across our major brands and our new brands that are coming.

How does the oncology unit fit alongside some of the priority business functions you'll need to grow the portfolio, for example business development?

Business development is outside the oncology business unit, but we have people in BD dedicated to oncology. We have early- and late-stage oncology business development, and somebody within the business unit at the senior leadership team that works with early- and late-stage BD to make sure the strategies are tight and the partnerships we're evaluating stay aligned with our core oncology strategies. Because we have many good drug candidates in our pipeline the opportunities have to add value. But we do partner a lot, as no one company has all the answers.

Take our deal with Orion Corp. for example, around the androgen receptor inhibitor darolutamide. [Bayer paid €50 million up front to license worldwide rights to the then-Phase II compound in 2014.] That compound is in Phase III development and one of the important differentiators is that it doesn't cross the blood-brain barrier and so may have a more competitive adverse event profile. The Algeta acquisition also brought us a differentiated strategic platform. And we also have an immuno-oncology partnership with Compugen and partnerships with the Broad Institute and the German Cancer Research Center where we're looking at early preclinical assets that may be future candidates for clinical development.

I'm also in constant contact with the Bayer LifeScience Center, our innovation unit that has made key investments in our CRISPR joint venture Casebia Therapeutics and our stem cells joint venture BlueRock Therapeutics. [See Deal][See Deal]Oncology isn't part of those deals as of right now – they're focused on cardiology and hematology, as well as ophthalmology. But we're looking for oncology opportunities as well. The idea behind the Bayer LifeScience Center and those ventures is to be able to run with innovation as quickly as possible.

And what about the broader commercial organization – how can the oncology strategic business unit better leverage Bayer's global footprint in places like Asia?

We have a broad global footprint now as a company. In addition to the US and Europe, we consider markets like China and Japan to be focused markets for us as a company. And they're very important markets for us in oncology. Our HCC [hepatocellular carcinoma] franchise is quite healthy in those markets, for example. If you look at the launch of Xofigo in Japan, we're doing very well there. And when you think about Stivarga [approved globally in multiple indications including metastatic colorectal cancer and gastrointestinal stromal tumors], we just received FDA approval for Stivarga in second-line HCC, but when we filed HCC with Stivarga we did it on a global scale, in all countries where we operate.

We're trying to speed up those approvals and have strategies where we can do clinical trials that are truly global in scope. Sometimes it would make sense to focus in the US where the FDA may grant a priority review in a high unmet medical need, like we've done with our refractory follicular lymphoma drug copanlisib. We'll know later this year if FDA approves it.

This type of regulatory opportunity is not available in all countries, but we're following it up with two large Phase III trials for the global filings.

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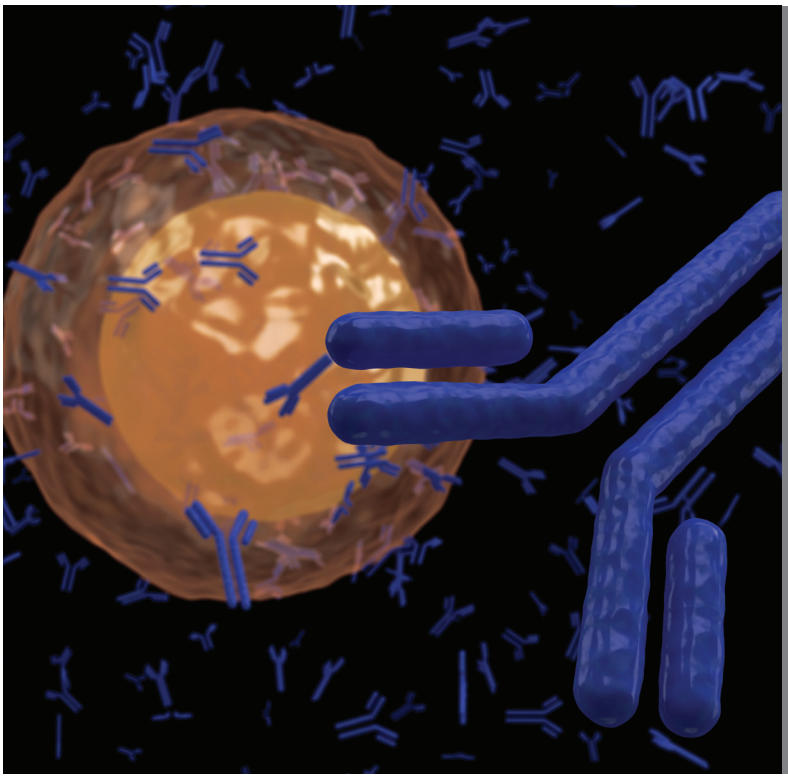
Cancer's Next-Gen Smart Bomb: Who Will Be First To Weaponize?



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With 70 clinical trials now underway on a next generation of more precisely targeted antibody drug conjugates, we profile Ambrx and Sutro Biopharma, two smaller biotechs with promising technologies and powerful partners that augment their strong science with disease awareness, deep commercial networks and global geographic reach.

BY WILLIAM LOONEY

Research is intensifying around the complex technology of antibody drug conjugates as a weapon against cancer.

To date, ADCs have had only scattershot success in delivering cytotoxic "warheads" that bind to tumor cells and kill them, without the harsh patient side effects that impair standard chemotherapy.

Big pharma is active in the space, but some of the most significant work is being done by smaller biotechs such as Ambrx and Sutro.

So what? Advances in ADCs, if realized in clinical trials, will provide patients with one of the first tangible benefits of precision medicine. ADCs may also answer the question that has dogged cancer treatment for decades: how to destroy a tumor without killing the patient in the process.

While innovations in drug discovery occupy center stage in the battle against cancer, it is the obscure mechanics of drug delivery that may have the edge in attacking – selectively, with laser-like precision – the mutant cell growth that leads to lethal tumors. New platform technologies linked to improved understanding of the genetic origins of most cancers are driving the creation of engineered protein antibodies that can be weaponized with toxins to single out cancer cells and kill them. The precise targeting of cancerous cells carries significant benefit to patients, minimizing the dangerous side effects of scorched earth chemotherapies, controlling the collateral damage to healthy tissue and raising the overall tolerability of a more potent treatment regimen.

The concept of using antibodies to fight cancer cell proliferation has been around for more than a decade, with two products currently in commercial use: **Seattle Genetics Inc.**'s *Adcentris* (brentuximab vedotin), approved by the FDA in 2011 for treatment of Hodgkin's lymphoma; and the **Roche** drug *Kadcyla* (trastuzumab emtansine), FDA approved in 2013 for metastatic breast cancer. The basic thrust is the assembly of an antibody-based conjugate (ADC) drug consisting of an engineered cell antibody to seek out and bind to a tumor antigen cell, then release a cytotoxin "warhead" that kills it.

Interest in this field is strong mainly because the concept – and the emerging science behind it – promises to upend the scattershot response of conventional drug therapy against the relentless proliferation of mutant cells that cause cancer. According to Informa Pharma Intelligence's *Medtrack*, three of the top 10 partnering deals in 2016 focused on the antibody space: a $3 billion deal between **Merus NV** and **Incyte Corp.** for a bispecific antibody platform for cancer; **Celgene Corp.**'s $2.5 billion deal with **Jounce Therapeutics Inc.** to access JTX-2011, an mAb investigational compound for cancer; and

Novartis AG's acquisition from **Xencor Inc.** of another antibody platform, again, for cancer, at $2.6 billion.

More important, some 70 ADC compounds are presently in clinical trials, according to Pharma Intelligence's *Trialtrove*, mostly in the early test phases and involving six of the big pharma top 10, including Roche, the early leader in the field. (*See Exhibit 1*).

Pint-Size Potential

However, some of the most significant work on ADCs is underway in the smaller biotech segment. While Roche and Seattle Genetics are seeking to build on their first-to-market breakthroughs, two small California-based biotechs – privately held **Sutro Biopharma Inc.**, founded in 2004, and **Ambrx Inc.**, established in 2003 and now owned by a consortium of leading Chinese pharma players – are pursuing a variant path to enhance the effectiveness of ADC therapy in the individual patient.

Their approach centers on creating a stable, chemically homogenous and site-specific antibody warhead that dramatically increases the success rate in delivering that cytotoxic "payload" to the tumor cell target, precisely and at the fullest concentration that can be safely tolerated by the patient. It's a thesis that, if realized in human trials, will refine and extend the clinical impact on tumor regression, in comparison with the current standard of care.

Although the technology differs, both companies appear evenly matched in pipeline potential. Ambrx's lead ADC, ARX788, targeting the HER2 gene mutation in breast cancer, is now in Phase I trials in Australia and New Zealand. It also has an approved IND from the FDA for a similar trial in the US, to start later this year, as well as a novel off-licensing deal with Chinese partner **Zhejiang Medicine Co. Ltd.** (ZMC) through which the latter will coordinate a Chinese Phase I trial on ARX788, simultaneously with the one in the US. *(Also see "Ambrx breaks deal mold with Zhejiang ADC alliance" - Scrip, June 18, 2013.)*

"We will initiate the Phase I US trial in September or October, involving a cohort of 50 patients for a duration of approximately one year," Yong Hei, MD, chief medical officer for Ambrx, told *In Vivo*. "Depending on the results, we should be ready to commence to a Phase II trial by the end of 2018." Hei also noted that the two trials in Australia and New Zealand on ARX788 are progressing well. "We're optimistic that data from the trials will be available by mid-year 2018, perhaps along with some preliminary feedback on the US trial."

Sutro has no candidate in trials as yet, but it expects to obtain INDs from the FDA for two ADC products within the next 12 to 18 months. First is STRO-001, an ADC that targets the protein CD74 associated with B-cell malignancies that cause non-Hodgkin's lymphoma and multiple myeloma. The second, STRO-002, targets the overexpression of the folate receptor alpha protein found in ovarian cancer and other solid tumors. Last month, at the annual meeting of the American Association for Cancer Research, Sutro announced results of an animal study on STRO-001 demonstrating potent antitumor activity against multiple myeloma, diffuse large B-cell lymphoma and mantle cell lymphoma models while reducing the potential for toxic secondary effects on adjacent healthy cells – a nearly ideal outcome for an ADC, albeit in mice.

In anticipation of future market commercialization, Sutro in March 2016 recruited two industry veterans to progress the company's late-stage efforts on ADCs: former Johnson & Johnson oncologist Arturo Molina, MD, as chief medical officer; and Mark Lupher, PhD, in a new position as VP for translational pharmacology and preclinical development. In addition, Joseph Lobacki, former chief commercial officer of Medivation as well as lead manager for Genzyme's global hematology business, was elected to Sutro's board of directors last month.

Beyond these new leadership hires, Sutro has an exclusive claim to operating the world's only cell-free cGMP

Exhibit 1
ADC Compounds In Clinical Trials

	PHASE							
SPONSOR	(N/A)	I	I/II	II	II/III	III	IV	ALL
Roche		2	4	8		1	2	17
AbbVie	1	2	4	2	1	2		12
Ambrx		1						1
Pfizer			3	2		3	1	9
Seattle Genetics		3	5			1		9
Bayer		4						4
Celldex Therapeutics			1	3				4
ImmunoGen			1	1		1		3
Astellas Pharma		2						2
Genmab			2					2
Amgen						1		1
Biotest			1					1
Bristol-Myers Squibb			1					1
Immunomedics			1					1
Merck & Co.		1						1
Puma Biotechnology			1					1
Sanofi				1				1
Totals	1	15	24	17	1	9	3	70

SOURCE: Trialtrove | Pharma Intelligence 2017

manufacturing facility that eliminates reliance on complex, hard to replicate cultures of living cells in building an ADC arsenal. The patented process relies on transcripted material drawn from *Escherichia coli* bacteria to accelerate the speed and efficiency of a cell-free extract and protein base used to build an ADC; the time cycle for this process can be as short as 12 hours.

Big Pharma Connections

In addition, both companies can call on strong partnering links that carry differentiating advantages in geographic market reach. Sutro's long-standing ties to Celgene, which began in 2012 and expanded into a formal strategic collaboration agreement in October 2014, gives it access to one of the industry's strongest oncology sales and marketing networks.The two companies are currently advancing seven out of a total of 15 research and preclinical programs on multi-specific antibodies and ADCs. Sutro is responsible for early-stage research and preclinical development activities as well as the manufacturing of preclinical product candidates, whereas Celgene is responsible for global commercialization and, in that regard, holds or can acquire worldwide rights to market all products that stem directly from the collaboration.

The 2014 agreement burnishes the biotech's *bona fides* by including an option for Celgene to acquire Sutro – that right expires in September but is subject to renewal through March 2019 if Celgene decides by September to request it. If Celgene opts not to acquire the company by the end of this period, US commercial rights for an unspecified number of the collaboration's projects will revert to Sutro. It's no surprise that this is when the evidence will be in hand as to the clinical potential of the STRO-001 and -002 ADC candidates.

Likewise, Ambrx, with its new owners, is poised to achieve a "world class standard" for ADC products in China, across a range of therapies. These owners, which include the **Shanghai Fosun Pharmaceutical Group Co. Ltd.** and **WuXi PharmaTech Inc.**, carry marquee status in navigating China's complex, politicized regulatory environment.With additional field-based support from ZMC, Ambrx's Chinese partner on ARX788, these ties give company management better insights on how to build an ADC franchise not only in the world's second largest drug market, but in other emerging middle-income countries as well. Supply chain logistics and manufacturing expertise are just a few of the capabilities these Chinese partners bring to the table. *(Also see "Ambrx Looks Across Pacific For A Secure Future" - Scrip, May 26, 2015.)*

"China lags in medicines innovation and knows that currently the world has only two ADC anti-cancer products available, at a time when the technology behind this novel precision medicine platform is rapidly improving," Ambrx CMO Hei said. "The Chinese regulatory authorities have been constructive in approving trials on ADC products – Roche already has a China trial underway on Kadcyla, its first-generation ADC product. Our partnership with ZMC on ARX788 complements these efforts, where we can see ARX788 being positioned in China not as a third-in-line treatment, but as potentially first-in-line."

Technology Boost For Target Delivery

Kadcyla and Adcentris have had some success therapeutically with patients. Nevertheless, creating an ADC with a payload for accurate delivery to the tumor is complex, time-consuming and cumbersome against the infinite variations in tumor cell patterns – there is a "hit or miss" aspect to these first-generation technologies. Reports indicate that under current therapy, only about 1% of a systemic cytotoxic dose actually penetrates the tumor cell – obviously, that's a number that bears improving.

And there is the need to develop living cell cultures to construct the ADC, which can take weeks or months, as well as to keep the constituent parts of the antibody stable in the bloodstream, ready to link seamlessly once they bind to the protein target on the surface of the tumor cell and insert the cytotoxin. This requires enormous precision in customizing an antibody capable of linking to the site, recognizing the tumor antigen, binding to it and ensuring the cytotoxin has sufficient potency to penetrate tumor cell defenses.

Drug design has thus centered on loading the antibody warhead with the molecular equivalent of multiple shots on target, using an assortment of different ADC molecules to maximize tumor kill potential. Unfortunately, that conventional approach has led to persistent drug efficacy issues like breakdown or partial impairment of the cytotoxin prior to reaching the tumor cell. This leaves the cancerous mutation unscathed along with dangerous side effects in patients when the cytotoxin is expressed not at the tumor site, but in the bloodstream or in otherwise healthy tissue. And the amount of cytotoxin delivered may be subpar, enabling tumor cells to develop resistance. The point is when the dose does not find its target, the desired therapeutic result – cancer regression at lower patient exposure to toxicities – is not achieved.

Do The Biotechs Have The Edge?

The good news is the science behind ADC is progressing. Rival biotechs Sutro and Ambrx contend their "third generation" technologies promise to boost the reliability of target delivery, providing a better patient experience and a superior clinical outcome. Here's how they do it.

Sutro's innovative step is twofold. First, it has introduced an artificial cell generation production technology that can be used interchangeably with different DNA strands to speed the assembly of ADCs, at lower cost, rather than replicating living cells on a one-time basis. Second, by enhancing the accuracy and stability of an ADC in delivering its cytotoxin payload directly to the tumor cell target, it improves the prospect for a safer and more clinically efficacious outcome for patients.

In a recent interview with *In Vivo*, Sutro CEO William Newell said, "For years, we've advocated that homogenous ADCs based on site-specific conjugation will improve efficacy and reduce toxicity to cancer patients. Many pharmaceutical companies have now come to adopt this view and they use different technologies to attempt to achieve it. What we've proven preclinically is that this is necessary but not sufficient to maximize the therapeutic index – the ratio between efficacy and toxicity – for an ADC. To do that, you

have to select the optimal site (or sites) for attachment of a preferred linker and the cytotoxin. We believe Sutro's *Xpress CF+* platform technology is uniquely suited to do this, as we can access any site in an antibody as a place for the payload attachment – and we can do it all in only a few weeks, much faster than the norm with conventional discovery approaches. We can thus determine, by direct observation of a patient's tumor profile, which site or sites are optimal. No one else in the industry can do that." (*See online-only sidebar, "Q&A With Sutro's Bill Newell.*)

Ambrx is pursuing the same end as Sutro, but with a structurally different approach focused on a process that replaces the amino acid in the cell protein with a non-natural variant of the amino acid. This facilitates the site-specific conjugation of a more concentrated toxin to attach to the tumor cell and kill it. "The Ambrx approach is radically homogenous," said Chief Medical Officer Hei. "We have devised a technology hook that produces the necessary chemical reaction with the toxin without diversion into non-cancerous cell groups, translating into a better efficacy and safety profile for the patient."

Hei also noted that the first-generation technology used by Roche and Seattle Genetics relies on a mixture of cytotoxins – as many as six – that tend to dilute the potency of the overall dose. "To us, homogenous is a synonym for concentrated; our model requires no more than two cytotoxins per warhead. And, in contrast to Sutro, our antibody is a natural antibody, generated from living cells. We think this promotes greater efficacy and tolerability for use in the human population."

A Look Forward

There are two subtexts to these confident assessments of the therapeutic potential of next-generation ADCs. The first is that advancing targeted drug delivery while fighting the endless adaptability of a cancerous cell remains a daunting – some might say quixotic – task. Given the overall poor tumor penetration rates from the two ADCs in current use, any improvement must progress from a modest starting point. Literally, there is no place to go but up. How far and how fast pose contrasting implications for the future health of cancer patients, ranging from life-threatening side effects to full tumor regression.

▶READ MORE ONLINE

Q&A With Sutro's Bill Newell

Sutro Biopharma's most visible advocate is CEO Bill Newell, 58, who has led the company since January 2009 – almost an eternity in the unpredictable culture of the start-up enterprise. This has helped ensure Sutro is well financed and prominently positioned for the external partnerships that will build a market for the company's complex proprietary technology and boost the accuracy and potency of drug delivery in destroying cancerous tumor cells, with minimum impact on patient well-being. In our online-only interview, Newell discusses the progress of Sutro's commercialization programs on ADCs as well as lessons on leading a small biotech in a crowded competitive field of big pharma players.

http://bit.ly/2qP2Wmb

The second is that the ADC space is competitive and crowded, with nearly 20 different platforms to deliver that lethal warhead in various stages of testing. All told, more than 40 pharma and biotech companies are engaged in next-generation ADC development, along with a variety of public and academic institutions, including the **Scripps Research Institute**, the **National Cancer Institute**, the **University of Georgia**, the **University of California, Davis** and **University College London**. "ADCs have clearly attracted the attention of Wall Street," Les Fundleyder, portfolio manager for E Squared Capital Management, told *In Vivo*. "We are seeing an increase in transactions, which does suggest some third-party validation of the potential of the clinical class presently under development."

As is the case in cancer treatment generally, scrutiny among payers on pricing is growing, so it is to be expected that new ADC regimens now in development will face market access issues based on comparisons against the current state of practice. A clear, clinically measurable advantage must be demonstrated around important oncology indicators like progression-free survival, backed up by evidence. In this regard, the therapeutic index – balancing efficacy with tolerability – will be determinative in establishing an appropriate P&R rate.

There are opportunities from the new science as well. These include the application of ADCs to other conditions beyond cancer, terrain that has been only lightly explored by big pharma to date. There is also promise in replacing or combining the toxic chemotherapy drugs as ADC "weapons of choice" with the checkpoint inhibitor immunotherapies that, in active clinical use, have brought virtual cures to some cancer patients. This would deliver a superior dose to combat the cancer while minimizing adverse effects on the patient. Likewise, new weapons in the ADC arsenal will discourage the onset of tumor resistance, the Achilles' heel in all cancer drug therapies.

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