Oncology

Today's cancer therapies have an unlikely champion in their corner: the immune system. Scientists are training the natural disease defender to KO cancer for good—and pharma companies are drooling over the flashy premium prices and commercial success of marketed immunotherapies, which have ignited vigorous pipeline work. **Rebecca Mayer Knutsen** surveys the $32-billion US cancer segment

Immunotherapies are dangling on the edge of a treatment paradigm shift, potentially slipping into the first-line option spot where cytotoxic chemotherapies have been comfortably seated for some time. The promise of immunotherapies, ranging from monoclonal antibodies (mAbs) to interferons and checkpoint inhibitors, has to do with target specificity to reduce toxicity.

"Immuno-oncology drugs offer a potential cure," says Savade Solanki, PhD, head of oncology insight at Ipsos Healthcare. "Oncologists are starting to use that terminology for the very first time."

Our immune systems, designed to rid the body of toxins, rely on multiple checkpoints to prevent overactivation on healthy cells. Tumor cells, however, know how to manipulate the checkpoints to escape the immune system's detection. Checkpoints studied as cancer therapy targets include CTLA-4 and PD-1.

Merck's Keytruda, with Bristol-Myers Squibb's Opdivo, numbers among the PD-1 inhibitor group

"Immunotherapies unleash the immune system to identify tumors and activate cells to seek and destroy," explains Christopher Clark, co-portfolio manager at RS Investments.

Still in its infancy in many respects, immunotherapy got its start with the approval of Dendreon's Provenge in 2010 to treat asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer. Fast-forward five years and the industry finds that it is still wrestling with questions of price, manufacturing and commercialization.

"The essence of immunotherapy is personalized care. The patient is at the start and conclusion of the manufacturing process," says Gil Bashe, managing partner health, Finn Partners. "The journey has many steps—and there are ample opportunities to stumble."

Effective diagnostic tests set the course for the use of drugs targeting specific tumor types. The field is mobilizing around biomarker-directed treatments to ensure that the right patients receive the right drug at the right time.

Of course, I/O drugs don't have a lock on targeting therapy. In the CDK 4/6 inhibitor area, Ibrance launched for the treatment of metastatic HER2-negative HR-positive breast cancer. Analysts are split on whether Novartis's LEE001 and Eli Lilly's abemaciclib, both in late-stage development, will be able to play catch up. And AstraZeneca's Iressa is returning to the US market, after a five-year hiatus, on the heels of the FDA's approval for use in NSCLC, with a companion diagnostic.

Pharma giants, who stockpile resources and innovation know-how, continue to dominate the oncology market, which reached $32 billion in US sales in the 12 months ending May 31, up 17.7% over the year-ago period, according to IMS Health. While Roche's Genentech has basked in category domination for several years, competition might be just around the corner.

TOP 25 ONCOLOGY PRODUCTS

Category leaders, ranked by US sales and media spend

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 mos.	TRx	Vs. prior 12 mos.	US DTC media $ (000s)	Vs. prior 12 mos.	US journal media $ (000s)	Vs. prior 12 mos.
1	**Rituxan**	Genentech	$3,586.4	7.7%	9,487	11.3%	$2.1	N/A	$2.0	N/A
2	**Avastin**	Genentech	$3,012.6	9.4%	13,768	30.0%	$0.0	N/A	$1,359.0	-26.3%
3	**Gleevec**	Novartis	$2,502.7	17.5%	244,091	-2.7%	$0.0	N/A	$0.0	N/A
4	**Herceptin**	Genentech	$2,357.9	18.1%	4,507	8.9%	$0.0	N/A	$0.0	N/A
5	**Alimta**	Eli Lilly	$1,227.0	2.3%	1,894	-13.4%	$0.0	N/A	$1,458.0	118.9%
6	**Zytiga**	Janssen	$1,077.8	16.4%	118,225	3.0%	$0.0	-100.0%	$2,168.0	-55.0%
7	**Afinitor**	Novartis	$869.3	16.9%	71,483	3.4%	$0.0	N/A	$2,330.0	-9.5%
8	**Sprycel**	Bristol-Myers Squibb	$832.5	30.1%	72,390	20.7%	$0.0	N/A	$558.0	38.0%
9	**Yervoy**	Bristol-Myers Squibb	$740.8	24.6%	208	-27.3%	$0.0	N/A	$656.0	178.8%
10	**Perjeta**	Genentech	$716.4	94.3%	1,356	43.0%	$0.0	N/A	$882.0	-48.8%
11	**Treanda**	Cephalon	$708.5	2.8%	1,031	0.1%	$0.0	N/A	$1,452.0	72.5%
12	**Velcade**	Takeda	$673.6	6.4%	3,003	10.0%	$0.0	N/A	$303.0	-27.1%
13	**Abraxane**	Celgene	$671.5	11.8%	1,034	-17.6%	$9.0	N/A	$1,340.0	12.4%
14	**Imbruvica**	Pharmacyclics	$666.4	416.6%	61,829	421.5%	$13.0	N/A	$1,420.0	927.1%
15	**Tasigna**	Novartis	$663.1	19.9%	65,596	10.4%	$0.0	N/A	$0.0	N/A
16	**Erbitux**	ImClone	$661.9	-0.3%	730	-1.2%	$0.0	N/A	$665.0	-39.3%
17	**Xtandi**	Astellas	$598.3	533.1%	70,697	1,014.0%	$40.0	N/A	$2,761.0	-10.6%
18	**Tarceva**	Genentech	$586.3	-3.6%	77,782	-20.2%	$0.0	N/A	$0.0	-100.0%
19	**Cyclophosphamide**	Generic	$502.0	12.4%	74,018	-4.6%	$0.0	N/A	$24.0	N/A
20	**Capecitabine**	Generic	$474.1	514.9%	225,306	653.1%	$0.0	N/A	$0.0	N/A
21	**Kyprolis**	Onyx	$441.5	37.0%	183	33.6%	$0.0	N/A	$788.0	42.1%
22	**Votrient**	GlaxoSmithKline	$426.3	32.2%	35,732	25.4%	$0.0	N/A	$2,303.0	-21.9%
23	**Sutent**	Pfizer	$368.6	5.3%	34,474	-12.9%	$0.0	N/A	$0.0	N/A
24	**Faslodex**	MedImmune	$351.6	6.0%	3,096	-12.2%	$0.0	N/A	$0.0	0.0%
25	**Methotrexate Sodium**	Generic	$323.9	80.0%	6,741,503	1.1%	$0.0	N/A	$0.0	0.0%

Sources: Sales, IMS Health; DTC media spend, Nielsen; journal media spend, Kantar Media
Sales and TRx data run from June 2014–May 2015; DTC and journal data run from January 2014–December 2014

Smaller players innovate ...

Much of the push-the-envelope innovation is coming from smaller players, who are quickly clambering up the cancer therapy ladder. Some therapies in development may be given the green light by a more-forward-thinking FDA to skip a few rungs.

Kite Pharma and bluebird bio are teaming up to produce second-generation T-Cell Receptor (TCR) technology that uses bluebird's genetic engineering platform to fight cancer targets related to a specific strain of human papillomavirus. Kite developed the closely related Chimeric Antigen Receptor Technology (CAR-T) therapies. It plans to advance its lead product candidate to a multicenter clinical trial in refractory diffuse large B cell lymphoma, with additional clinical filings anticipated in multiple B-cell malignancies.

Juno Therapeutics' CAR-T and TCR technologies attracted a $1-billion investment from Celgene in June. CAR T-cell therapy might hold the keys to hematological malignancies including acute lymphoblastic leukemia and non-Hodgkin lymphoma, with early studies showing a long durable response. (See Clinical Corner, p. 44.)

Today's oncology players move at a swift pace, thereby investing uncharacteristically in the promise of early pipeline entrants. "With so many players on the field, innovation is moving quickly from the big anti-PD1 breakthrough just five years ago," Solanki observes.

... as do the big guys

Competition for non-small cell lung cancer (NSCLC) is at an all-time high, with a surplus of developed and marketed products. Comprising the PD-1/PD-L1 inhibitor class are Bristol-Myers Squibb's Opdivo and Merck's Keytruda as well as investigational drugs like Roche's atezolizumab.

MedImmune is focused on developing novel immunotherapy combinations to target a variety of immune escape mechanisms employed by NSCLC tumors. "This approach has the best potential to benefit the largest proportion of patients, especially those with PD-L1 negative tumors, which are less likely to benefit from monotherapies," says Mohammed Dar, MD, MedImmune's VP of clinical development in oncology.

About 70% of NSCLC patients are PD-L1 negative, according to Dar. Based on Phase-I data, MedImmune's MEDI4736 is in late-stage development for NSCLC and SCCHN, both as monotherapy and in combination with tremelimumab.

The first anti-PD-1 to gain FDA approval for melanoma, Keytruda, is being evaluated in combination with other therapies, including Syndax Pharmaceuticals' entinostat for NSCLC or melanoma.

Bristol-Myers Squibb raced to achieve first-to-market status in second-line NSCLC—but industry analysts' tongues are wagging over the first-line setting. It is playing some serious defense with its recently announced intention to focus solely on cancer research and is planning a slew of trials, including Opdivo and Yervoy, its CTLA-4 I/O drug, in the first-line NSCLC setting later this year.

Others rely on different strategies. Roche, for one, has shown the effectiveness of PD-L1 inhibition in combination with chemotherapy, while others are actively seeking partnerships to bridge gaps in innovation and resources. "Companies want to get on the bandwagon in the PD-1 space," Solanki notes. "They may not have their own drugs but they could get there through collaborations."

David Hewitt, MD, VP, medical and scientific affairs, inVentiv Health, adds: "Immunotherapies are hot because they work and they work well. They have had a profound effect on extending the

CLINICAL CORNER

Surgery, chemotherapy and radiation therapy are making room for a dizzying number of new cancer therapy solutions that rely on technology, genetics and precision medicine. Excitement is growing over Adoptive Cell Transfer (ACT) technology, a highly personalized cancer therapy that transfers immune-derived cells into a patient.

T-cells, a white blood cell variation that travels through our bodies in pursuit of cellular abnormalities and infections, are key to ACT's success. Collected from the patient's blood and then genetically engineered, T-cells are tasked with producing unique cell-surface receptors known as Chimeric Antigen Receptors (CARs). These cells are multiplied by the billions in-vitro before being infused into the patient with an order to search and destroy.

Sravanthi Addapally

"These cells hold the potential to identify tumor-specific antigens and lead to destruction of abnormal cancer cells," explains Technavio senior analyst Sravanthi Addapally (photo, left). "The CAR T-cell therapy approach has opened a whole new avenue for treating cancer patients."

Frenzied activity in this sector has launched a few US-based companies into the spotlight. Juno, Kite, bluebird bio and Cellectis are either in the lab or working on partnerships with the mega players. On a larger scale, Amgen, AstraZeneca, Celgene and Pfizer have the determination to play, and win, in the sector.

Novartis's CTL019, a second-generation CAR-T, is being evaluated for treatment of multiple cancers including ALL, NHL and DLBCL. Cellectis's UCART19 is being studied to treat B-cell lymphomas NHL, CLL and SLL. Juno Therapeutics' JCAR015 is being evaluated to treat refractive ALL patients.

The industry cannot count academic clinical discovery teams out of the mix, says Gil Bashe, managing partner health, Finn Partners. "Academic researchers from University of Texas MD Anderson Cancer Center, Baylor University and Ohio State University have the insight and talent to validate the next wave of discovery targets."

R&D activity related to CAR T-cell therapy involves various types of cancers, including the hematological cancers, brain tumors and multiple other solid tumors. Although this technique has yet to hit late-stage trials, the treatments involving this technique have demonstrated highly impressive outcomes, according to Addapally.

MedImmune is collaborating with Juno to test the concept of CAR T-cells in combination with MEDI4736 in patients with lymphoma to see if the activity of CAR T-cells can be enhanced with checkpoint inhibition.

The industry is waiting to see if this approach can also be expanded to solid tumors. "But the data here are less mature," cautions Mohammed Dar, MD, MedImmune's VP of clinical development in oncology. "Given the dynamic nature of this research area, there are likely to be newer approaches to the development of CAR T-cells."

lives of some really sick people, including those with metastatic melanoma and NSCLC."

Don't forget diagnostics

All cancer types have unique genetic and enzymatic profiles that contribute to the development of targeted therapies and companion diagnostics. "Some companies develop diagnostic kits along with the drugs," says Edward Buthusiem, managing director, Berkeley Research Group. "They design the assay that can measure the expression and then match it to the tumor type."

Roche has a leg up on the competition with its in-house diagnostics technology, but other key players including Amgen, Genzyme and Genentech are creating a stir. The cancer diagnostics pathway is more advanced than other therapeutic categories, but the area contends with significant scientific, economic and regulatory obstacles.

Another area of interest is antiangiogenic therapy, designed to inhibit the growth of blood vessels rather than tumor cells. "It downregulates cancer cells' ability to manipulate the microenvironment, particularly the blood flow that helps cancer growth," Hewitt says.

Compared with market mainstays of recent years, cancer biologics flaunt improved life expectancy, efficacy and safety profiles. "Commercial emergence of immunotherapies elevated standard-of-care levels and has partially addressed the existing unmet needs to a notable level," notes Sravanthi Addapally, senior analyst, Technavio.

At what price?

Opdivo, the PD-1 inhibitor, improved the life expectancy in lung-cancer patients by an average of 3.2 months, according to Addapally. Extended survival, however, comes with a variety of drawbacks. At the center of the debate is the seemingly unjustified cost of the breakthrough cancer solutions.

The Cancer Drug Coverage Parity Act of 2013 proclaims that oral drugs have to be in parity with injectable drugs. "Critics say the bill doesn't do anything to pressure manufacturers to lower the costs," Buthusiem explains. "The costs are shifted to a new bucket, but they aren't lowered."

The price of a drug needs to reflect the pharma company's investment, Buthusiem adds. "Development of a one-shot disease cure costs no less than the medication a patient might take for the duration of a lifetime."

Pharma companies are beginning to be more sensitive to cost issues and are starting to provide support programs for patients. "Traditionally, we focus our marketing on the professional side, but now we're educating consumers and giving them a voice in the treatment path," says Sarah Bast, a VP at Publicis Health Media. "Patients need to know everything about the treatment they are facing, including the pricing."

Finn Partners' Bashe is confident that improving the predictability of the cancer drug development process will allay payer concerns and advance treatment. "Immunotherapies extend, even save, lives, but the lingering question is in what patients," he says.

According to Clark, the industry will be caught blindsided by the pace of innovation. He predicts that the payer infrastructure will lag due to the volume once a therapy hits the market.

For his part, Solanki believes that the industry is "moving away from the chemotherapy era. Immuno-oncology will become the backbone of cancer treatment. There may be treatments layered on top, but the first layer will be immuno-oncology." ■