Oncology

Immunotherapy is an emerging powerhouse in cancer treatment. Early gains being made in multiple tumor types provide a glimpse of the effectiveness of several agents and regimens. While longer follow-up is needed, the results have analysts talking about a big shift in the war on cancer. **Joe Dysart** reports

While results are preliminary, continued head-turning advances in cancer treatment using immunotherapy have many drug makers in oncology wondering: have we turned the corner on the war on cancer? Research released earlier this summer indicates that immunotherapy—once perceived as an interesting treatment for a handful of cancer tumors—may be effective against a much wider range of cancers. Moreover, the research is being greeted by an eager FDA, which a few years back created a fast-track approval program—known as Breakthrough Therapy designation—to bring drugs that treat life-threatening diseases to market much more quickly.

Janssen's Imbruvica (lymphoma) and Novartis's Zykadia (NSCLC), for example, received Breakthrough Therapy designation early enough in their clinical development to reach the market much more quickly than normal, according to Alan Gray, senior director, oncology strategy group, Kantar Health.

Essentially a class of drugs that use the body's immune system to fight cancer tumors, much of the research in immunotherapy has centered on a subset of formulations in that class—checkpoint inhibitors. These inhibitors can interrupt cancer's ability to "switch-off" immune system cells that ordinarily fight off an invader like cancer. And they could emerge as the backbone of cancer management to fight 60% of all cancers in the developed world within the next decade, according to a report released by Citigroup last summer, "Immunotherapy: The Beginning of the End for Cancer."

Stephanie Hawthorne, PhD, senior director, Kantar Health, sees similar prospects: "We will likely see these immunotherapies expand beyond the few tumors in which they will initially launch, and eventually penetrate nearly all solid tumors and even some hematologic indications," she tells *MM&M*. "In general, in the metastatic setting, I can see these drugs being used in 50% to 60% of patients at some time during the course of their disease."

Adds Marc Engelsgjerd, MD, senior principal, *in*Thought Research: "Immunotherapeutics hold out the promise of sustained, profound responses in an expanding set of solid tumors."

Hawthorne says the key Big Pharma players in immunotherapy right now are Merck, Bristol-Myers Squibb, AstraZeneca and Roche. "The compounds by these four companies are the most advanced and have the most data published to evaluate their potential—and the data for all four look very promising.

"Merck's [PD-1] pembrolizumab is expected to be first to market—in Yervoy-treated melanoma, an FDA decision is expected Q4 2014—but the others are not far behind and all are being explored in a number of oncology indications," she adds.

All told, as much as $1.3 billon

TOP 25 CHEMOTHERAPY AND TARGETED CANCER PRODUCTS, 2013

Category leaders, ranked by US sales, and their media spend

Rank	Product	Manufacturer	US sales dollars (millions)	% change vs. prior 12 months	2013 US journal spend dollars (thousands)	% change vs. prior 12 months	2012 US journal spend dollars (thousands)	% change vs. prior 12 months
1	**Rituxan**	Genentech/Roche	$3,299.8	5.1%	$0.0	0.0%	$0.0	N/A
2	**Avastin**	Genentech/Roche	$2,697.4	2.8%	$1,844.0	21.1%	$1,523.0	-37.9%
3	**Herceptin**	Genentech/Roche	$1,945.7	5.3%	$0.0	0.0%	$0.0	-100.0%
4	**Gleevec**	Novartis	$1,900.3	9.6%	$0.0	0.0%	$0.0	-100.0%
5	**Alimta**	Eli Lilly	$1,197.1	5.4%	$666.0	>100.0%	$92.0	-92.3%
6	**Xgeva**	Amgen	$788.6	19.2%	$1,441.0	-32.9%	$2,346.0	-2.4%
7	**Zytiga**	Johnson & Johnson	$775.9	64.9%	$4,818.0	-1.8%	$5,221.0	>100.0%
8	**Xeloda**	Genentech/Roche	$754.7	7.0%	$88.0	>100.0%	$22.0	-96.0%
9	**Afinitor**	Novartis	$720.7	69.8%	$2,573.0	96.9%	$1,307.0	9.2%
10	**Treanda**	Cephalon/Teva	$681.4	14.9%	$841.0	-38.3%	$1,365.0	-1.8%
11	**Erbitux**	BMS/Imclone	$651.6	-3.4%	$1,096.0	46.4%	$749.0	-70.3%
12	**Tarceva**	Genentech/Roche	$641.6	5.4%	$110.0	-73.8%	$419.0	-66.1%
13	**Velcade**	Takeda	$625.6	-12.5%	$415.0	-73.5%	$1,564.0	>100.0%
14	**Sprycel**	Bristol-Myers Squibb	$560.1	42.2%	$404.0	-28.8%	$568.0	-51.4%
15	**Yervoy**	Bristol-Myers Squibb	$558.5	6.3%	$235.0	-71.4%	$823.0	-39.7%
16	**Revlimid**	Celgene	$545.2	-1.9%	$1,155.0	>100.0%	$0.0	0.0%
17	**Abraxane**	Celgene	$523.2	45.2%	$1,174.0	>100.0%	$618.0	21.2%
18	**Tasigna**	Novartis	$497.7	24.0%	$0.0	-100.0%	$1,218.0	-22.5%
19	**Cyclophosphamide**	Generic	$385.0	64.7%	$0.0	N/A	$0.0	N/A
20	**Temodar**	Merck	$338.7	-17.6%	$0.0	-100.0%	$112.0	-83.2%
21	**Sutent**	Pfizer	$336.2	5.5%	$181.0	-39.4%	$299.0	-65.6%
22	**Faslodex**	AstraZeneca	$327.4	5.7%	$844.0	>100.0%	$0.0	0.0%
23	**Vidaza**	Celgene	$313.7	-13.3%	$0.0	0.0%	$0.0	N/A
24	**Kyprolis**	Onyx/Amgen	$307.7	>100.0%	$554.0	>100.0%	$250.0	N/A
25	**Docetaxel**	Generic	$289.4	-38.8%	$0.0	0.0%	$0.0	-100.0%

Sources: Sales, IMS Health; journals, Kantar Media

in research could be spent on immunotherapy research during the next nine years, according to the Citigroup report. But the pay-off could be substantial: The immunotherapy market could reach $35 billion a year within the next nine years, according to Citigroup.

Earlier this summer, the annual meeting of the American Society of Clinical Oncology (ASCO 2014) was awash with encouraging research from scores of researchers working in immunotherapy.

But perhaps most startling were results from a small, federally funded Phase-II study, in which two patients experienced complete cancer remission after an immunotherapy treatment known as adoptive T-cell therapy (see sidebar). The study, according to Dr. David Hafler, principal investigator at the Hafler Lab at Yale University, was nothing short of a "breakthrough."

Meanwhile, the Big Four in immunotherapy also released research promising major advances in cancer treatment. Merck presented study results revealing that 69% of patients treated with its drug MK-3475 (pembrolizumab) were still alive—a year after tests began.

The results were considered especially impressive, given that more than half of the 411 patients in the study were in the most advanced stages of melanoma, and 77% had been treated with other drugs—including Bristol-Myers Squibb's Yervoy.

Yervoy is viewed as an industry standard, and the therapy to beat.

"The overall survival data for pembrolizumab is outstanding," says Kantar Health's Hawthorne. "Until three years ago, the one-year survival rate for metastatic melanoma was 30-40%. Yervoy improved those outcomes to approximately 50%, and to now see pembrolizumab increase survival further to 69%—74% in Yervoy-naïve patients—is very exciting. Essentially these new agents have doubled survival in just a short three years. What will be even more influential is to see the longer-term follow-up."

MK-3475 is another immunotherapy drug that has been awarded a Breakthrough Therapy designation by the FDA. By the close of 2014, Merck plans to have more than 24 clinical trials up-and-running focused on MK-3745—which will target 30 tumor types, according to Ian McConnell, a Merck press spokesperson.

Perhaps even more encouraging was research data released at ASCO by BMS, which studied a treatment regimen using two immunotherapy drugs to combat melanoma. With that study, the company reported a one-year survival rate of 94% and a two-year survival rate of 88% when two of its immunotherapy drugs—nivolumab and Yervoy—were used together to fight advanced melanoma.

Says Kantar Health's Hawthorne: "The gains being made in survival of melanoma are very significant. One-year OS data is our earliest glimpse at the effectiveness of these agents and regimens, but we also need longer follow-up to see how the curves taper or plateau. Historical five-year survival rate for metastatic melanoma is less than 15%. Could the single agent or combinations of immunotherapeutics raise that to 30%? 50%? Higher? Will we eventually start talking about 'cure' in patients with metastatic disease?"

In an interview with *MM&M*, *in*Thought's Engelsgjerd echoes her assessment: "These results are potentially transformational with

CLINICAL CORNER

Perhaps one of the most startling new cancer studies making waves this summer is one from the National Cancer Institute, in which cervical cancer in two women went into complete remission with one treatment.

Both women have been cancer-free for more than a year.

The immunotherapy treatment, known as adoptive, T-cell therapy, works by growing T-cells—human cells that attack cancers—outside the body, and infusing them back into the body to fight cancer anew.

While considered a small and preliminary Phase-II study that will need years of follow-ups, the research was nevertheless called a "breakthrough" by Dr. David Hafler, a leading researcher in the study of cancer and principal investigator at Yale University's Hafler Lab.

Christian Hinrichs

All told, nine women with metastatic cervical cancer were treated with the T-cell therapy. Six of the women showed no response to the treatment, while two experienced complete remission. Another woman saw a 39% reduction in tumor size.

The two women who responded to the treatment with complete remission were suffering from widespread metastases—and had not responded to other therapies, according to Christian Hinrichs, MD, assistant clinical investigator at the National Cancer Institute and lead author on the study submitted this summer at ASCO 2014.

"I've been surprised by the variation between patients in the quantity and quality of the tumor-infiltrating T-cell reactivity against HPV," Hinrichs tells *MM&M*."This is something that we hope to address by using T-cell receptor genetically engineered T-cells in some of our future clinical trials," he says.

The treatment comes with a trade-off, however. Side effects included low blood counts, infections and metabolic disorders, Hinrichs says.

One of the reasons Hinrichs' study has triggered such hope is that ordinarily, the survival rate for women afflicted with metastatic cervical cancer—caused by the human papilloma virus (HPV)—is grim.

Currently, afflicted women survive only an additional 13-17 months with conventional therapy, which relies on chemotherapy or a combination of chemotherapy and bevacizumab.

Hinrichs' research was inspired, in part, by T-cell therapy treatments that had shown promise in combating melanoma, leukemia and sarcoma.

The National Cancer Institute plans to test T-cell therapy against other cancers. "We are studying, as a part of the protocol presented at ASCO, a cohort of patients with non-cervical HPV+ cancers including oropharyngeal, anal, vulvar, vaginal, and penile malignancies," Hinrichs says. "Our group, in research led by Dr. Steven Rosenberg, also recently described in *Science* a technique for identifying T-cells targeting abnormal tumor proteins that might be applied to wide-ranging cancers.

Meanwhile, Dr. James Yang, another researcher at the Institute, is studying how T-cell therapy might be used to combat non-small cell lung cancers with tumor-infiltrating lymphocytes, Hinrichs says.

unprecedented one-and two-year survival rates north of 80%—and a significant proportion of patients experiencing a complete response. The combination of these two immune checkpoint inhibitors seems to work better, potentially much better, than either one used alone. The strategy comes with a price, however, as over 60% of patients experienced grade three or four adverse events and nearly a quarter had to discontinue therapy due to toxicity."

Simultaneously, BMS released Phase-III study findings of the use of Yervoy (ipilimumab) alone in the treatment of advanced melanoma. In that research, 46.5% of patients treated with Yervoy after a melanoma surgery were disease-free after three years—as compared to 34.8% of patients on placebo. "These findings are significant not only because ipilimumab is the first immune-checkpoint inhibitor to demonstrate an improvement in recurrence-free survival in this earlier treatment setting, but also because this benefit was observed across all patient sub-groups," stated Alexander Eggermont, director general, Gustave Roussy Cancer Campus Grand Paris, Villejuif, who presented the study findings at ASCO 2014.

Opdivo (formerly nivolumab) is one of Bristol-Myers's key immunotherapy drugs, and the drugmaker is testing it in 35 trials featuring 7,000+ patients—one of the largest drug development programs ever conducted in oncology, according to Fouad Namouni, a BMS vice president. Overall, Bristol-Myers's numerous gains in immunotherapy have secured its role as the company to beat among the major pharma players in the sector, according to Vamil Divan, a senior research analyst at Credit Suisse. At press time, BMS said it planed to file Opdivo in the melanoma setting by this fall.

AstraZeneca also reported encouraging study findings, including results from a Phase-I study of its MEDI4736. Thirty-nine percent of patients with advanced solid tumors in that study achieved disease control when treated with MEDI4736, and another 19% achieved a partial response. All told, 27 patients participated in the study. The company is also trying to achieve better results by combining MEDI4736 with other drugs such as dabrafenib, trametinib, carboplatin/paclitaxel, paclitaxel and bevacizumab.

Even so, Tim Anderson, global pharmaceuticals analyst with Sanford C. Berstein, sees AstraZeneca's prospects in immunotherapy as mixed. "Over the years, AZN has often struggled to get R&D right, but its pipeline has been improving," Anderson writes in an investor note. "Immuno-oncology is the therapeutic area that is getting the most investor attention now, but AZN will be a late entrant into the category and it is unclear how the company will compete effectively if there is no differentiation with its approach—perhaps novel combinations will position it better versus peer companies."

Yet another set of encouraging study results were released by Roche, which reported that 43% of all bladder cancer patients treated with its drug MPDL3280A saw their tumors shrink. That drug has also been granted Breakthrough Therapy designation by the FDA.

"There has been little recent innovation in the pharmacotherapy of advanced bladder cancer and so these results are quite encouraging," says *in*Thought's Engelsgjerd. "They expand the solid tumor repertoire in which inhibition of the PD-1 axis has shown impressive activity. The response rate of 43% in PD-L1-positive tumors is impressive but will require confirmation in larger studies."

Stated Sandra Horning, MD, head of global product development at Roche, "We are evaluating MPDL3280A in a broad range of tumors, and have begun pivotal studies that include a companion diagnostic test in lung and bladder cancers." ■