Oncology

As genetically targeted immunotherapies blaze a trail through mid- and late-stage clinical trials, the days of traditional chemotherapy in taming tumors may be numbered. **Noah Pines** on the race to market cancer drugs that harness the PD-1 pathway, other standouts in the oncology pipeline, plus what's already making waves in the market

The data are still early, but the investigational PD-1s appear to be the Next Big Thing in oncology. By training the body's immune system to repel cancer cells, they've smashed through previous durable response-rate ceilings—one reason why agents that harness this pathway stood out from other gene-based therapies presented at June's American Society of Clinical Oncology (ASCO) meeting.

The compounds, which have shown efficacy even against the most stubborn tumors, have analysts talking about a sea change in therapy. "If they pan out, [PD-1s] could fundamentally change how solid tumors are treated," said *in*Thought analyst Dr. Marc Engelsgjard. "That is a big deal. It is not one discrete event, more of a momentum story for that class of therapeutics."

The hoopla over PD-1s highlights the revolution in oncology. At press time, eight of the 14 new drugs approved by the FDA this year were cancer medicines. The latest was July's approval of Boehringer Ingelheim's Gilotrif (afatinib) for people with non-small cell lung cancer (NSCLC) whose tumors express specific types of gene mutations, as detected by a Qiagen diagnostic test.

Along with other cancer drugs, those paired with companion tests that can detect a mutation—so-called targeted treatments—lifted the overall oncology market by 7.3% last year to $25.6 billion, according to figures from IMS Health.

Drug makers are increasingly personalizing their NSCLC cancer treatments. BI's Gilotrif targets the EGFR mutation, much like Roche's Tarceva, approved for use in the same subset two months prior. Pfizer's Xalkori hits the ALK mutation. And there are dozens more targeted NSCLC agents in development, says Sharon Karlsberg, an associate principal at ZS Associates, the implication being that "pathology and molecular testing of NSCLC tissue will become an essential part of any patient's overall treatment plan."

But targeted therapies have a big drawback: cancer cells can often build up resistance. Roche/Genentech's Zelboraf, for instance, targets the roughly 50% of melanoma patients whose tumors carry the BRAF gene mutation. In virtually all of these patients, the tumor starts to progress again in about five months.

Immunotherapies work differently. They retrain the body's immune system to kill cancer cells, potentially offering a durable effect and sustained response (possibly long-term survival). They have potential across multiple tumor types. Goldman Sachs, according to a July research note, estimates the market for PD-1/PD-L1 agents could reach $10-$15 billion, and that's just for NSCLC, renal and melanoma.

Those are the three tumors for which Bristol-Myers Squibb antibody nivolumab produced durable tumor response in heavily pretreated patients, an unprecedented feat. It's backed by a broad clinical development program. Phase I results were so promising that nivolumab is leapfrogging to Phase III across the three cancers.

With Yervoy, the first checkpoint immunotherapy approved for melanoma in 2011, and now possibly nivolumab, BMS "could have the first immunotherapy portfolio," says Dr. Sam Falsetti, medical director, Cambridge BioMarketing.

Merck has stolen some of BMS' thunder with its PD-1, lambrolizumab, which showed a potentially better overall response rate (ORR) in advanced melanoma and got FDA's "breakthrough therapy

TOP 50 CHEMOTHERAPY AND TARGETED CANCER PRODUCTS, 2012

Category leaders, ranked by 2012 US sales, and their journal spend

Rank	Product	Manufacturer	US sales dollars (millions)	% change vs. prior 12 mos.	2012 US journal spend dollars (thousands)	% change vs. prior 12 mos.	2011 US journal spend dollars (thousands)	% change vs. prior 12 mos.
1	**Rituxan**	Genentech/Roche	$3,197.2	8.0%	$0.0	N/A	$0.0	-100.0%
2	**Avastin**	Genentech/Roche	$2,660.9	0.0%	$1,523.0	-37.9%	$2,451.0	-29.1%
3	**Herceptin**	Genentech/Roche	$1,854.3	12	$0.0	-100.0%	$1,344.0	-20.0%
4	**Gleevec**	Novartis	$1,816.7	13.0%	$0.0	-100.0%	$498.0	-36.6%
5	**Alimta**	Eli Lilly	$1,160.2	11.0%	$92.0	-92.3%	$1,182.0	-20.2%
6	**Eloxatin**	Sanofi	$1,149.9	-5.0%	$0.0	N/A	$0.0	N/A
7	**Xeloda**	Genentech/Roche	$724.3	8.0%	$22.0	-96.0%	$538.0	-23.0%
8	**Velcade**	Takeda	$714.6	4.0%	$1,564.0	>100.0%	$589.0	39.4%
9	**Erbitux**	BMS/Imclone	$690.4	-2.0%	$749.0	-70.3%	$2,522.0	37.2%
10	**Xgeva**	Amgen	$663.4	85.0%	$2,346.0	-2.4%	$2,404.0	>100.0%
11	**Tarceva**	Genentech/Roche	$626.2	6.0%	$419.0	-66.1%	$1,236.0	-16.2%
12	**Treanda**	Cephalon/Teva	$605.9	21.0%	$1,365.0	-1.8%	$1,389.0	15.7%
13	**Revlimid**	Celgene	$555.9	25.0%	$0.0	N/A	$0.0	-100.0%
14	**Yervoy**	Bristol-Myers Squibb	$532.7	52.0%	$823.0	-39.7%	$1,365.0	N/A
15	**Zytiga**	Johnson & Johnson	$498.6	>100.0%	$5,211.0	>100.0%	$1,339.0	N/A
16	**Docetaxel**	Generic	$472.7	-14.0%	$0.0	-100.0%	$72.0	N/A
17	**Afinitor**	Novartis	$422.8	>100.0%	$1,307.0	9.2%	$1,197.0	-60.7%
18	**Temodar**	Merck	$419.3	3.0%	$112.0	-83.2%	$667.0	>100.0%
19	**Sprycel**	Bristol-Myers Squibb	$411.0	37.0%	$568.0	-51.4%	$1,168.0	81.1%
20	**Tasigna**	Novartis	$400.0	40.0%	$1,218.0	-22.5%	$1,571.0	-28.1%
21	**Vidaza**	Celgene	$362.0	11.0%	$0.0	N/A	$0.0	N/A
22	**Abraxane**	Celgene	$361.0	4.0%	$618.0	21.2%	$510.0	N/A
23	**Sutent**	Pfizer	$337.0	8.0%	$299.0	-65.6%	$869.0	-69.4%
24	**Faslodex**	AstraZeneca	$310.1	14.0%	$0.0	N/A	$0.0	N/A
25	**Dacogen**	Eisai	$253.9	10.0%	$79.0	-81.0%	$416.0	-8.6%
26	**Cyclophosphamide**	Generic	$235.7	82.0%	$0.0	N/A	$0.0	N/A
27	**Lupron Depot-3 mo.**	AbbVie	$210.8	-3.0%	$0.0	N/A	$0.0	N/A
28	**Votrient**	GlaxoSmithKline	$174.1	57.0%	$1,552.0	54.7%	$1,003.0	>100.0%
29	**Halaven**	Eisai	$148.7	23.0%	$711.0	-32.3%	$1,051.0	>100.0%
30	**Jevtana**	Sanofi	$146.8	-24.0%	$12.0	-92.9%	$176.0	>100.0%
31	**Zelboraf**	Genentech/Roche	$130.2	>100.0%	$1,380.0	58.1%	$873.0	N/A
32	**Vectibix**	Amgen	$129.9	0.0%	$0.0	-100.0%	$641.0	-24.5%
33	**Tykerb**	GlaxoSmithKline	$127.7	7.0%	$468.0	N/A	$0.0	-100.0%
34	**Lupron Depot-4 mo.**	AbbVie	$106.9	-27.0%	$0.0	N/A	N/A	N/A
35	**Fluorouracil**	Generic	$100.0	10.0%	$0.0	N/A	$0.0	N/A
36	**Lupron Depot**	AbbVie	$98.8	-4.0%	$0.0	N/A	$0.0	N/A
37	**Gemcitabine HCl**	Generic	$85.9	-77.0%	$0.0	-100.0%	$124.0	N/A
38	**Megace ES**	Par Pharmaceuticals	$85.5	-7.0%	$0.0	N/A	$0.0	N/A
39	**Clolar**	Genzyme/Sanofi	$83.0	9.0%	$0.0	N/A	$0.0	N/A
40	**Lupron Depot-6 mo.**	AbbVie	$83.0	>100.0%	$0.0	N/A	$0.0	N/A
41	**Oxaliplatin**	Generic	$81.1	-74.0%	$25.0	N/A	$0.0	N/A
42	**LipoDox**	Sun Pharma	$77.9	N/A	$0.0	N/A	$0.0	N/A
43	**Melphalan HCl**	Generic	$76.2	5.0%	$0.0	N/A	$0.0	N/A
44	**Exemestane**	Generic	$76.0	49.0%	$0.0	N/A	$0.0	N/A
45	**Eligard**	Sanofi	$75.4	-8.0%	$0.0	N/A	$0.0	N/A
46	**Ixempra**	Bristol-Myers Squibb	$71.6	-14.0%	$413.0	7.8%	$383.0	-23.2%
47	**Torisel**	Pfizer	$70.4	-3.0%	$58.0	-93.5%	$894.0	-32.9%
48	**Arzerra**	GlaxoSmithKline	$69.2	19.0%	$1,008.0	30.0%	$775.0	7.9%
49	**Methotrexate Sod**	Generic	$68.2	21.0%	$0.0	N/A	$0.0	N/A
50	**Xalkori**	Pfizer	$67.7	>100.0%	$1,059.0	31.8%	$803.0	N/A

Sources: Sales, IMS Health; journals, Kantar Media

CLINICAL CORNER

As drug makers better understand the biology of cancer, the number of drugs the industry is putting forth to hunt tumors has proliferated. Yet, the amount of patients available for clinical trials hasn't kept pace.

Novel agents sport unique mechanisms of action, each designed to strike relevant targets—growth factors, growth receptor, components in signal transduction pathway, or a cell in the tumor lifecycle.

The abundance of clinical studies in these areas means increasing "competition" for a limited scope of subjects, says Alexander Zukiwski, MD, chief medical officer, Arno Therapeutics. R&D in these areas has generated "a larger number of clinical studies going after a limited patient population which is willing to participate," he says.

Denis Miller, MD

The patient-shortage challenge is shared by clinical research organizations—again, contrasted with R&D advancements. New trials are evaluating Bristol-Myers Squibb's Yervoy and anti-PD1 or PD ligand monoclonals, but there is a shortage of available patients. "In the US, for example, only 5%-10% of potentially eligible adult cancer patients are enrolled in clinical trials," says Denis Miller, MD, global therapeutic area leader, oncology-hematology within the CRO Parexel International, "largely because they are not informed about an open trial designed for them."

Many still harbor a mistrust or fear of "experimental" therapy, says Miller, citing additional reasons such as the amount of time and money needed by clinicians to attract their patients to a new clinical trial, fund the research projects at a level that will be attractive to clinical investigators and remain compliant with federal regulations.

Harish Dave, MD, MBA, VP of medical and scientific services at Quintiles, adds an important oncology drug-development challenge: tissue sampling. Researchers collect tissue to determine, for instance, whether the patient has a target mutation. "[Tissue samples] allow for identification of the patient subset that is most appropriate for a therapy," explains Dave. So the initial sample is relevant, but in instances where patients have metastatic disease and have failed multiple therapies, "it is important to look at the tumor that has spread and determine what mutations/features it has," adds Dave.

This can result in a patient-profiling hang-up: when patients' gene expression profiles and mutations change during treatment and disease recurrence or metastasis. Targeted therapy directed against that gene mutation expressed in the original tumor may no longer be effective.

CROs call this instability of gene expression. And it can be seen in programs involving companion diagnostics, or biomarker programs, which need to be developed in parallel with targeted compounds. These diagnostics are what permit personalized cancer therapy.

"For example," says Miller, "the HER2 status may change from positive to negative in 10%-15% of patients with breast cancer. Thus, an agent directed against overexpression of HER2 may no longer be active."

designation," which could pump the accelerator on its road to market.

"Merck seemed to be trailing by a year, but they may have the potential to close that gap," observes Engelsgjard. "They started a very large Phase II study last November…that could be a registration trial. If that is the case, then it might be a dead [heat] in terms of regulatory foot race." Not to be upstaged, oncology stalwart Genentech presented Phase I data from its investigational immunotherapy. Called MPDL3280A (also known or RG7446), a medicine which works slightly differently mechanistically. It's designed to make cancer cells more vulnerable to the body's immune system by interfering with the protein PD-L1.

It's thought that any immune-related adverse events can be managed by clinicians. And while studies initially have centered on later lines of treatment, immuno-oncology agents could be used in first-line settings, similar to the way chemotherapy has been used, notes Goldman Sachs, which forecasts the BMS and Merck PD-1s reaching $3.2 billion and $1 billion in sales, respectively, by 2018. (It doesn't include a forecast for Roche's PD-L1 agent.)

Versatility could add to their potential. "From the physician's viewpoint, the fact that these agents might be easy to combine with other targeted therapies to potentiate clinical efficacy is very lucrative," says Neesha Suvarna, a consultant with Kantar Health.

This year brought more momentum on the targeted-therapy front, including the February approval of Genentech's Kadcyla (T-DM1 or ado-trastuzumab emtansine), the first antibody-drug conjugate sanctioned by FDA for treating HER2-positive metastatic breast cancer.

And the agency is slated to decide this year whether the drug maker's breast cancer drug Perjeta can be used in the neoadjuvant (pre-surgey) setting for HER2-positive, early stage breast cancer—a first. GlaxoSmithKline's Tykerb is also being studied in this setting.

Also of interest is Genentech's anti-CD20 antibody conjugate GA101 (obinutuzumab), the so-called heir to Genentech's best-selling Rituxan. GA101 is designed to work with the body's own immune system to attack B cells that can cause common blood cancers.

The company recently submitted data to the FDA for newly diagnosed chronic lymphocytic leukemia (CLL), and the medicine was granted a priority review and breakthrough designation by the FDA. GA101 is also being studied in non-Hodgkin's lymphoma (NHL).

GA101 could help to extend Genentech's $7-billion Rituxan franchise, which soon will be subject to biosimilar competition. "This is a commercially important program for Genentech and Roche," opines *in*Thought's Engelsgjard.

When asked to identify an in-line oncology "product of the year" for 2013, Engelsgjard points to Xtandi (enzalutamide), Astellas' prostate cancer drug that was developed with Medivation and approved in the US last September and in the EU in June. Xtandi has had a decent launch in the US with $57 million in Q4 2012 and $75 million in Q1 2013, a trajectory that mirrors J&J's Zytiga.

It's being studied in a Phase III study called PREVAIL which evaluates its role in chemotherapy-naïve prostate cancer patients and, if labeled such, puts it into more direct competition with Zytiga.

Among other strides being made: in hematology, Gilead reported results for idelalisib (GS-1101), its first-in-class agent for CLL. "In the hematology sections, idelalisib and other B-Cell receptor pathway drugs were mentioned in multiple [ASCO] presentations for CLL, iNHL and MCL," reports Abelson Taylor SVP Jay Carter. In a Phase II study of idelalisib + rituximab, the overall response rate was 97%, consisting of 19% complete responses and 78% partial responses. ■