MM&M THERAPEUTIC FOCUS

Oncology

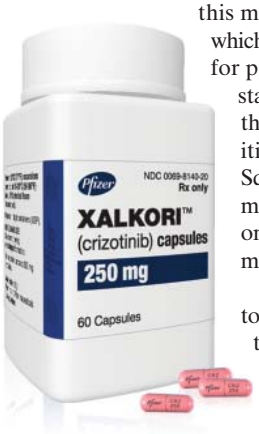
Targeted therapies have opened doors to tumor control, especially when paired with appropriate diagnostics and their use in ever-evolving combinations. As drugmakers aim for smaller and more focused patient groups, setting realistic expectations on pricing and revenue potential remains challenging, finds **Noah Pines**

Cancer stands alone among therapeutic categories as far as the number of high-tech personalized medicines available. The specific mutations that spawn a variety of cancers are the bulls eye for these treatments, as opposed to normal healthy cells.

As Tim Anderson, the Sanford Bernstein analyst, tells *MM&M*, "With a few exceptions, achieving a deep molecular understanding and coming up with targeted therapeutics is unique to oncology."

A decade ago, Genentech's Herceptin (trastuzumab), Novartis' Gleevec (imatinib) and Roche/Genentech's Avastin (bevacizumab) demonstrated that companies could succeed through targeted therapeutics. Today, these medicines, and Avastin in particular (despite its recent failure in breast cancer), are among the world's top-selling blockbusters. Indeed, cancer medicines are a major counterbalance to the impending $50 billion-dollar patent cliff facing the industry during the next three years.

More recent additions to the arsenal of targeted medicines for cancer include Roche/Genentech's Zelboraf (vemurafenib), which was approved in August for malignant melanoma involving the V600E BRAF mutation (approximately 60% of melanomas have this mutation); Pfizer's Xalkori (crizotinib), which received accelerated approval in August for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase-positive (ALK-positive); and Bristol-Myers Squibb's Yervoy (ipilimumab), which won marketing clearance in March after demonstrating increased survival in late-stage melanoma patients.



But there are perils in big pharma's shift toward precision medicine. Xalkori shows that focusing on one subgroup with a greater response rate doesn't necessarily lower economic potential; it could still achieve blockbuster returns, Anderson says. Approximately 4% of the 220,000 Americans diagnosed with lung cancer annually possess the ALK fusion gene, and 45,000 newly diagnosed NSCLC patients are ALK-positive worldwide.

At $9,600/patient per month, Xalkori could cost $80,000 for an average patient. It's been approved with a $250 molecular test from Abbott.

"Just a reminder that this is 3-5% of lung cancer patients in the US," says Garry Nicholson, president and GM of Pfizer's oncology business unit, "and we're going to be treating people more effectively and avoiding treatments that don't work."

Nevertheless, pricing is becoming a real issue, and companies can meet resistance from payers. Cost pressure is mounting because the incidence of cancer is increasing, targeted therapies are expensive and in some tumors, treatment is shifting from acute to more chronic care settings, notes IMS Health. (See sidebar, p. 44, to read how some manufacturers are finding common ground with payers and other strategies for launching an oncologic).

Companies are clearly getting more efficient at linking disease knowledge with clinical outcomes. "The challenge that remains from a commercial perspective is translating this science to the community and patient level with appropriate diagnostics and setting realistic expectations on pricing and revenue potential from a much smaller and more focused patient population," says Dave Querry, EVP/managing director of The Navicor Group, an ad agency focused on the oncology market.

Dendreon's Provenge (sipuleucel-T) highlights the headwinds these drugs can face. A therapeutic cancer vaccine for prostate cancer that teaches the immune system to identify and disable tumor cells, Provenge has run into reimbursement issues due to its $93,000 price tag and, more recently, potential off-label usage of Johnson & Johnson's Zytiga (abiraterone acetate), which was approved in April for metastatic prostate carcinoma. In combination with prednisone, Zytiga works by inhibiting actions of androgens and is indicated in

TOP 50 CHEMOTHERAPY & TARGETED CANCER PRODUCTS, 2010

Category leaders, ranked by 2010 US sales, and their media spend

Rank	Product	Manufacturer	US sales dollars (millions)	% change vs. prior 12 mos.	US total media spend dollars (thousands)*	% change vs. prior 12 mos.	US DTC media spend dollars (thousands)	US journal spend dollars (thousands)
1	Avastin	Genentech/Roche	$3,091.6	2.5%	$2,677.0	-33.9%	$1.0	$2,676.0
2	Rituxan	Genentech/Roche	$2,762.3	4.7%	$2,268.0	-15.9%	$45.0	$2,223.0
3	Herceptin	Genentech/Roche	$1,537.6	6.8%	$869.0	-26.2%	$0.0	$869.0
4	Gleevec	Novartis	$1,332.5	21.1%	$493.0	-28.4%	$16.0	$478.0
5	Taxotere	Sanofi	$1,197.9	-3.2%	$0.0	NA	$0.0	$0.0
6	Alimta	Eli Lilly	$991.7	17.0%	$941.0	-16.4%	$14.0	$928.0
7	Gemzar	Eli Lilly	$723.1	-8.2%	$267.0	-37.1%	$27.0	$240.0
8	Erbitux	BMS/ImClone	$708.8	-2.9%	$1,118.0	43.1%	$0.0	$1,118.0
9	Oxaliplatin	*Generic*	$688.0	94.7%	$0.0	NA	$0.0	$0.0
10	Femara	Novartis	$682.4	16.5%	$1,135.0	51.7%	$712.0	$423.0
11	Velcade	Millennium/Takeda	$580.4	21.3%	$184.0	118.0%	$1.0	$184.0
12	Xeloda	Genentech/Roche	$545.6	13.2%	$368.0	7.2%	$3.0	$365.0
13	Arimidex	AstraZeneca	$540.0	-39.1%	$0.0	-100.0%	$0.0	$0.0
14	Tarceva	Genentech/Roche	$519.4	5.9%	$723.0	30.9%	$73.0	$651.0
15	Treanda	Cephalon	$393.4	73.9%	$502.0	-48.2%	$36.0	$465.0
16	Temodar	Merck	$389.2	4.5%	$78.0	-72.7%	$0.0	$78.0
17	Abraxane	Celgene	$345.3	6.3%	$0.0	-100.0%	$0.0	$0.0
18	Revlimid	Celgene	$323.6	70.1%	$0.0	NA	$0.0	$0.0
19	Vidaza	Celgene	$292.2	18.0%	$0.0	-100.0%	$0.0	$0.0
20	Sutent	Pfizer	$259.3	-3.7%	$1,909.0	27.0%	$0.0	$1,909.0
21	Eloxatin	Sanofi	$252.2	-74.6%	$0.0	NA	$0.0	$0.0
22	Doxil	Johnson & Johnson	$242.0	8.4%	$214.0	-17.0%	$6.0	$209.0
23	Lupron Depot-3 mo.	Abbott	$205.9	0.6%	$0.0	NA	$0.0	$0.0
24	Dacogen	Eisai	$195.1	13.5%	$288.0	-20.7%	$0.0	$288.0
25	Sprycel	Bristol-Myers Squibb	$182.9	38.2%	$413.0	200.0%	$0.0	$413.0
26	Lupron Depot-4 mo.	Abbott	$162.7	-6.8%	$0.0	NA	$0.0	$0.0
27	Hycamtin	GlaxoSmithKline	$158.1	-6.6%	$0.0	NA	$0.0	$0.0
28	Aromasin	Pfizer	$156.3	-2.2%	$0.0	-100.0%	$0.0	$0.0
29	Faslodex	AstraZeneca	$152.2	29.6%	$1.0	10.2%	$1.0	$0.0
30	Tasigna	Novartis	$148.9	115.1%	$1,507.0	82.9%	$15.0	$1,492.0
31	Vectibix	Amgen	$123.0	23.0%	$622.0	-33.9%	$0.0	$622.0
32	Tykerb	GlaxoSmithKline	$110.2	24.9%	$141.0	-19.9%	$0.0	$141.0
33	Afinitor	Novartis	$103.8	110.9%	$2,154.0	12.7%	$21.0	$2,133.0
34	Jevtana	Sanofi	$103.7	NA	$0.0	NA	$0.0	$0.0
35	Ixempra	Bristol-Myers Squibb	$102.1	1.8%	$375.0	-15.7%	$0.0	$375.0
36	Lupron Depot	Abbott	$101.5	-5.0%	$40.0	NA	$0.0	$40.0
37	Megace ES	Par Pharmaceuticals	$90.9	-3.8%	$0.0	NA	$0.0	$0.0
38	Eligard	Sanofi	$84.1	1.7%	$0.0	NA	$0.0	$0.0
39	Fluorouracil	*Generic*	$83.9	6.8%	$0.0	NA	$0.0	$0.0
40	Torisel	Pfizer	$79.2	-9.5%	$783.0	-5.5%	$9.0	$774.0
41	Lupron Depot-Ped.	Abbott	$77.4	-2.5%	$62.0	NA	$62.0	$0.0
42	Cyclophosphamide	*Generic*	$68.3	30.1%	$0.0	NA	$0.0	$0.0
43	Gemcitabine HCl	*Generic*	$57.1	NA	$0.0	NA	$0.0	$0.0
44	Votrient	GlaxoSmithKline	$57.1	NA	$262.0	NA	$0.0	$262.0
45	Melphalan HCl	*Generic*	$55.1	227.7%	$0.0	-100.0%	$0.0	$0.0
46	Zoladex	AstraZeneca	$52.9	-15.1%	$0.0	-100.0%	$0.0	$0.0
47	Arzerra	GlaxoSmithKline	$52.2	NA	$562.0	NA	$0.0	$562.0
48	Methotrexate Sodium	*Generic*	$50.8	5.0%	$0.0	NA	$0.0	$0.0
49	Campath	Genzyme	$48.6	-1.2%	$0.0	NA	$0.0	$0.0
50	Paclitaxel	*Generic*	$48.1	-17.8%	$0.0	NA	$0.0	$0.0

*DTC/journal spend
Sources: Sales, IMS Health; media spend, SDI

patients who have previously received docetaxel. GlaxoSmithKline also has a cancer vaccine in late-stage development.

Despite these pitfalls, almost every large manufacturer has players in the game or programs in development. According to a report from PhRMA, nearly 900 medicines are in development for cancer, more than double the number in the pipeline six years ago.

There are several reasons for this, says Anderson: "It's unmet need, the fact that they are biologics, and the fact that you don't need 2,000 reps."

Most companies spend very little on DTC advertising for the top oncology products (see SDI's media spend figures in the table, p. 43), and across the board, journal buys for the cancer therapeutics and chemo categories combined were less than $20 million last year.

At a policy level, "There is more of a tolerance for risk in cancer. Also, FDA leadership has made the path to approval more predictable, which industry is more comfortable with," says Wayne Pines, a former FDA associate commissioner who is now president of regulatory services and healthcare at APCO Worldwide.

A pipeline report from Bernstein Research shows oncology remains the most prolific in terms of the number of compounds in late-stage development (18 out of 57 compounds covered).

These include bosutinib, which Pfizer plans to file this year for Philadelphia chromosome positive chronic myeloid leukemia; Pfizer's axitinib, already submitted to FDA for metastatic kidney cancer; Roche/Genentech's pertuzumab, which the firm hopes to file this year for HER2+ metastatic breast cancer; and Sanofi's iniparib, which recently failed to meet its primary endpoint in a trial involving triple-negative breast cancer patients.

Cancer is still the second leading cause of death by disease in the US, and remains a lucrative investment thesis.

Going forward, longer average lifespans here in the US will create even more demand for new cancer therapies, and emerging markets also represent an important horizon of untapped potential. ■

MM&M's bi-monthly Therapeutic Focus series will conclude for the year with December's Pipeline Report.

The four drivers of highly successful oncology launches

It's becoming increasingly difficult to achieve commercial success in oncology. IMS Health has uncovered four key launch drivers, based on its analysis of 16 of the most influential product introductions across 10 countries.

1 Pursue optimal indication sequencing Upon entering Phase II, companies should build a sequencing strategy. This involves determining how broad a therapeutic footprint to pursue; whether to go for market niche or a more comprehensive approach; the sequence of indications that will work best over the lifecycle; how the product can be differentiated and what clinical endpoints to require; and financial commitment.

Next, determine tumor indications to advance to Phase III. While large patient populations were historically the first area for investment, today companies must consider the payers' view of unmet need. This changes the "attractiveness" of a number of tumor types.

2 Make segmentation trade-offs Given how restrictive the market is for some tumor types, companies should develop a patient profile that makes the right trade-offs between the benefits/drawbacks of targeting large patient populations vs. sub-segments. One viable strategy is to limit a market to a sub-group of patients for whom the product produces a greater response rate and, hopefully, a higher overall survival rate.

Using biomarkers to segment the patient pool means sacrificing a larger patient population for the sake of a stronger value proposition. This translates into market access and potentially premium pricing, as well as further indication approvals and acceptance among physicians.

3 Gain payer acceptance Companies need a realistic understanding of what payers in different countries are prepared to pay for and a flexible approach to meeting their criteria. Finding common ground between payers and pharma has meant sacrifice through risk-sharing agreements. Manufacturers are now making concessions if certain performance levels are not met, thereby limiting payers' financial exposure.

In the US, commercial payer reviews have become more cumbersome and physicians are troubled with highly bureaucratic processes, such as prior authorizations for the use of oncologics. The US payer landscape is slowly following in the footsteps of Europe, with an increased emphasis on comparative effectiveness and cost-shifting to patients. For pharma, this means more head-to-head trials, an increasing focus on biomarkers and demonstrating overall cost-effectiveness.

4 Build a strong oncology franchise A "halo" emanates from companies with an established and well-regarded oncology franchise.

Companies can establish a leading franchise by being mindful that thought leaders are customers, and engaging them in clinical trial design and expanded access programs is critical, and payer influence over prescribing decisions in oncology has not overshadowed the physicians.

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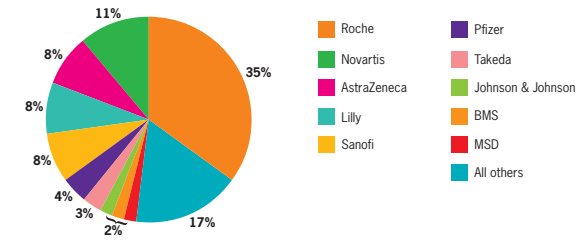
Oncology franchises by share of sales

Global sales =$47.2 Billion



Source: IMS MIDAS MAT September 2010; limited to ethical, non-generic

Top oncology launches

Manufacturer	Product (year of launch)
Roche	Avastin (2004), Tarceva (2004), Herceptin (1998), Mabthera (1997)
Novartis	Afinitor (2009),Tasigna (2007), Glivec (2001),
AstraZeneca	Iressa (2002), Arimidex (1995), Casodex (1995), Zoladex (1987)

Source: IMS Health