# Oncology

Personalized medicines that use companion diagnostics to identify a patient sub-population are the theme of this year's crop of cancer drug approvals. But they're no panacea for a healthcare system with limited resources. **Noah Pines** offers some cautionary tales, as he reviews the newest launches and previews what's next.

In cancer medicine, precision-guided technology is the name of the game. Take Roche's Genentech unit. The company has launched three anti-cancer medicines in the past 10 months, and two were approved in conjunction with a companion biomarker diagnostic.

Perjeta (pertuzumab), launching this year, was designed to complement Roche's antibody Herceptin for patients with advanced HER2-positive breast cancer. Zelboraf (vemurafenib) won approval in 2011 for melanoma patients with a mutation in the BRAF gene.

"It's required that every Roche/Genentech medicine in development have a corresponding biomarker program," Alexander Hardy, VP, sales and marketing for the company's HER2 franchise, tells *MM&M*. (Genentech's Erivedge, which got the nod for advanced basal cell carcinoma (BCC) in January, has no biomarker because it's designed to inhibit an abnormal signaling pathway present in 90% of BCC cases, he says.) "Since we developed Herceptin, the first personalized medicine for cancer, we have continued to better understand the underlying biology of a tumor and tailor our medicines to target that tumor's unique behavior," he adds.

Genentech's success has come amidst a rise in filings for cancer drugs overall. Last year 10 of the 30 new drugs were for treating cancer, many of them tailored treatments like Pfizer's lung cancer med Xalkori (crizotinib) and immunotherapies like Dendreon's Provenge. Spending on targeted agents rose $1.3 billion last year, more than the $1.1 billion in 2010, IMS Health says. The research firm expects drugmakers to file 20 applications for oncology meds this year.


The explosion in personalized medicines has led to an increase in companion diagnostics. Biomarkers and diagnostics, in turn, have improved study design and probability of success of clinical trials.

"The regulatory approval strategies have fundamentally changed," says Steve Gavel, of IMS Health's strategic marketing group. "Companies are now looking at small subsets that are expressing a specific biomarker, and targeting them with small trials."

These drugs often get an FDA okay more rapidly. It doesn't mean every cancer drug that demonstrates a statistically significant benefit is a shoo-in, but the strategy enabled Onyx to score an accelerated FDA approval for Kyprolis (carfilzomib) in July, with approval for multiple myeloma supported by only a single-arm study.

So too for another cancer drug to get the nod in 2010, Sanofi's Jevtana for prostate cancer. "We were able to file that in three to four months after Phase III results, and we had approval in 60 days—well ahead of the PDUFA date," says Paul Hawthorne, head of Sanofi's US oncology business unit. For colorectal cancer drug Zaltrap (ziv-aflibercept), approved in August, Sanofi and partner Regeneron got priority FDA review. Biomarker studies are under way.

Speedier approvals, fewer wasted therapies, and better care. Seems like a win-win. Yet, as the industry realizes the promise of personalized medicine, it's noticing some difficulties. For instance, Zelboraf, the Roche/Genentech drug, targets the roughly 50% of melanoma patients whose tumors carry a specific mutation on the BRAF gene, giving it a genetically pre-defined patient population.

"What we are now seeing is that virtually all [patients] develop resistance to this drug, and now the field has moved on," as drugmakers try to find a way to prevent the development of resistance, says Dr. Marc Engelsgjerd, senior analyst with *in*Thought Research.

GlaxoSmithKline is advancing a MEK inhibitor (trametinib) that, when used with a BRAF inhibitor like Zelboraf, could delay progression. GSK also has a BRAF inhibitor in its pipeline, dabrafenib,

# TOP 50 CHEMOTHERAPY & TARGETED CANCER PRODUCTS, 2011

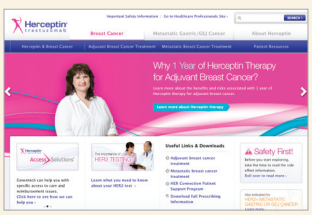
Category leaders, ranked by 2011 US sales, and their media spend

| 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 | **Rituxan** | Genentech/Roche | $3,004.9 | 8.9% | $53.0 | -97.7% | $0.0 | $53.0 |
| 2 | **Avastin** | Genentech/Roche | $2,662.1 | -13.9% | $1,081.0 | -51.7% | $0.0 | $1,081.0 |
| 3 | **Herceptin** | Genentech/Roche | $1,655.8 | 7.8% | $628.0 | -16.7% | $0.0 | $628.0 |
| 4 | **Gleevec** | Novartis | $1,512.8 | 13.6% | $219.0 | -52.1% | $0.0 | $219.0 |
| 5 | **Eloxatin** | Sanofi | $1,205.1 | 378.9% | $0.0 | N/A | $0.0 | $0.0 |
| 6 | **Alimta** | Eli Lilly | $1,042.6 | 5.2% | $541.0 | -38.6% | $0.0 | $541.0 |
| 7 | **Erbitux** | BMS/ImClone | $703.9 | -0.7% | $1,012.0 | -10.5% | $0.0 | $1,012.0 |
| 8 | **Velcade** | Millennium/Takeda | $693.0 | 19.4% | $31.0 | -92.5% | $0.0 | $31.0 |
| 9 | **Xeloda** | Genentech/Roche | $647.4 | 18.8% | $431.0 | -19.60% | $0.0 | $431.0 |
| 10 | **Tarceva** | Genentech/Roche | $564.1 | 8.6% | $581.0 | -28.2% | $0.0 | $581.0 |
| 11 | **Docetaxel** | *Generic* | $551.9 | N/A | $50.0 | N/A | $0.0 | $50.0 |
| 12 | **Treanda** | Cephalon/Teva | $501.6 | 27.6% | $500.0 | -15.0% | $0.0 | $500.0 |
| 13 | **Revlimid** | Celgene | $444.8 | 37.4% | $0.0 | N/A | $0.0 | $0.0 |
| 14 | **Temodar** | Merck | $392.4 | 0.9% | $712.0 | 513.8% | $0.0 | $712.0 |
| 15 | **Gemcitabine HCl** | *Generic* | $367.3 | 542.9% | $59.0 | N/A | $0.0 | $59.00 |
| 16 | **Taxotere** | Sanofi | $363.1 | -69.6% | $0.0 | N/A | $0.0 | $0.00 |
| 17 | **Yervoy** | Bristol-Myers Squibb | $350.1 | N/A | $475.0 | N/A | $0.0 | $475.0 |
| 18 | **Abraxane** | Celgene | $347.6 | 0.7% | $194.0 | 1,193.3% | $0.0 | $194.0 |
| 19 | **Vidaza** | Celgene | $325.7 | 11.5% | $0.0 | -100.0% | $0.0 | $0.0 |
| 20 | **Femara** | Novartis | $313.7 | -54.0% | $0.0 | -100.0% | $0.0 | $0.0 |
| 21 | **Oxaliplatin** | *Generic* | $311.6 | -54.7% | $0.0 | N/A | $0.0 | $0.0 |
| 22 | **Sutent** | Pfizer | $296.8 | 14.5% | $426.0 | -69.0% | $0.0 | $426.0 |
| 23 | **Sprycel** | Bristol-Myers Squibb | $285.4 | 56.1% | $669.0 | 30.7% | $0.0 | $669.0 |
| 24 | **Tasigna** | Novartis | $278.0 | 86.5% | $645.0 | -59.1% | $0.0 | $645.0 |
| 25 | **Faslodex** | AstraZeneca | $271.8 | 78.5% | $0.0 | N/A | $0.0 | $0.0 |
| 26 | **Dacogen** | Eisai | $230.7 | 18.3% | $287.0 | 6.7% | $0.0 | $287.0 |
| 27 | **Lupron Depot-3 mo.** | Abbott | $212.7 | 3.4% | $0.0 | N/A | $0.0 | $0.0 |
| 28 | **Jevtana** | Sanofi | $192.8 | 86.3% | $0.0 | N/A | $0.0 | $0.0 |
| 29 | **Afinitor** | Novartis | $171.6 | 65.2% | $707.0 | -67.0% | $0.0 | $707.0 |
| 30 | **Zytiga** | Johnson & Johnson | $169.5 | N/A | $452.0 | N/A | $0.0 | $452.0 |
| 31 | **Doxil** | Johnson & Johnson | $150.0 | -38.0% | $157.0 | 55.4% | $0.0 | $157.0 |
| 32 | **Lupron Depot-4 mo.** | Abbott | $144.8 | -10.9% | $0.0 | N/A | $0.0 | $0.0 |
| 33 | **Vectibix** | Amgen | $130.0 | 5.8% | $314.0 | -30.7% | $0.0 | $314.0 |
| 34 | **Cyclophosphamide** | *Generic* | $129.2 | 89.3% | $0.0 | N/A | $0.0 | $0.0 |
| 35 | **Halaven** | Eisai | $120.8 | 4,778.0% | $599.0 | 2,118.5% | $0.0 | $599.0 |
| 36 | **Tykerb** | GlaxoSmithKline | $114.4 | 4.1% | $0.0 | -100.0% | $0.0 | $0.0 |
| 37 | **Votrient** | GlaxoSmithKline | $105.3 | 84.8% | $438.0 | 29.2% | $0.0 | $438.0 |
| 38 | **Lupron Depot** | Abbott | $100.4 | -1.1% | $142.0 | 343.80% | $0.0 | $142.0 |
| 39 | **Megace ES** | Par Pharmaceuticals | $91.7 | 0.9% | $0.0 | N/A | $0.0 | $0.0 |
| 40 | **Fluorouracil** | *Generic* | $90.7 | 8.0% | $0.0 | N/A | $0.0 | $0.0 |
| 41 | **Ixempra** | Bristol-Myers Squibb | $83.3 | -18.4% | $345.0 | -18.2% | $0.0 | $345.0 |
| 42 | **Eligard** | Sanofi | $81.6 | -3.0% | $0.0 | N/A | $0.0 | $0.0 |
| 43 | **Clolar** | Genzyme/Sanofi | $76.3 | 70.6% | $0.0 | N/A | $0.0 | $0.0 |
| 44 | **Lupron Depot-Ped.** | Abbott | $74.5 | -3.6% | $0.0 | N/A | $0.0 | $0.0 |
| 45 | **Melphalan HCl** | *Generic* | $72.8 | 32.1% | $0.0 | N/A | $0.0 | $0.0 |
| 46 | **Torisel** | Pfizer | $72.4 | -8.6% | $283.0 | -50.9% | $0.0 | $283.0 |
| 47 | **Aromasin** | Pfizer | $68.6 | -56.1% | $0.0 | N/A | $0.0 | $0.0 |
| 48 | **Arzerra** | GlaxoSmithKline | $58.0 | 11.4% | $554.0 | 35.5% | $0.0 | $554.0 |
| 49 | **Letrozole** | *Generic* | $54.9 | N/A | $0.0 | N/A | $0.0 | $0.0 |
| 50 | **Methotrexate Sodium** | *Generic* | $54.1 | 6.5% | $0.0 | N/A | $0.0 | $0.0 |

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

## Oncology currents

**BONE** In July Onyx Pharmaceuticals won FDA approval, despite concerns about toxicity, to market Kyprolis (carfilzomib), an IV drug for patients with relapsed/refractory multiple myeloma. Its edge over incumbents Velcade (Takeda/Millennium) and Revlimid (Celgene): improved tolerability. On deck is Celgene's follow-on to Revlimid, the next-generation immuno-modulating drug (IMiD) pomalidomide. Not likely to reach market for several months, the oral drug may ultimately win over more patients and outperform Kyprolis on efficacy, notes *in*Thought Research.




**BREAST** Genentech may have the year's most exciting oncology launch in Perjeta (pertuzumab), a monoclonal antibody approved to complement Herceptin in treating HER-2 positive breast cancer. Also impressive is Genentech's antibody-drug conjugate T-DM1, comprised of Herceptin and the chemotherapy DM1. It compares well to Xeloda (Genentech) and Tykerb (GSK); an NDA is expected this year. Genentech had one recent setback: Last November the FDA yanked Avastin's breast cancer indication, citing negative data and side effects.


**COLON** In August Sanofi got FDA approval for the first new colorectal cancer (CRC) therapy in five years: Zaltrap (ziv-aflibercept). Indicated for second-line therapy of metastatic CRC in conjunction with standard of care, it can be used regardless of a patient's K-ras mutation status (BMS/Lilly's Erbitux works best in those whose tumor lacks the mutation). Phase III results were mixed.

**LUNG** Pfizer's Xalkori, approved last year for non-small cell lung cancer (NSCLC), is not expected to drive major sales. Analysts think Bristol-Myers Squibb's anti-PD1 agent BMS-936558 could. Like BMS melanoma drug Yervoy, it's an immunomodulatory antibody, only better tolerated and with activity across three tumors including NSCLC. The caveat: Phase I results need to be confirmed by larger Phase III studies, now under way. "But in NSCLC, you were seeing response rates between 15-30% in heavily refractory patients," says Dr. Marc Engelsgjerd of *in*-Thought Research. "That lets you know the anti-PD1 approach is viable."

**PROSTATE** Medivation and Astellas are awaiting approval for enzalutamide (née MDV3100) in metastatic castration-resistant prostate cancer patients. It does not require dosing with steroids, a big advantage over Johnson & Johnson's Zytiga. Part of a new class of drugs generating a lot of buzz, both could move into the pre-chemo setting and take on Dendreon's Provenge. "We are executing on what professionals…have been talking about for 10 years," says Paul Hagopian, an SVP with Giant Creative Strategy, AOR for enzalutamide.

**SKIN** Approval of Genentech's Zelboraf, preceded by BMS skin cancer drug Yervoy last year, brought needed innovation to the melanoma field. Zelboraf targets a genetic mutation in the BRAF gene, present in half of cases. But "virtually all develop resistance to this drug," says Engelsgjerd. GSK is developing a MEK inhibitor (trametinib) that, used with a BRAF inhibitor, could delay progression. The drugmaker also has a BRAF inhibitor under its roof, dabrafenib, and is running Phase III trials of both. "GSK seems particularly well-positioned to capitalize," says Engelsgjerd.

and is testing both in Phase III trials. So while Roche/Genentech was first with Zelboraf, GSK threatens. "The promise of targeted therapies is real, but…combination therapy holds even more promise," says Engelsgjerd.

This trend leads to a resource-related question. "How many molecular therapies can you layer on before we all go bankrupt?" asks Engelsgjerd. He calls Perjeta the most important oncology drug launch so far in 2012. The duo kept advanced tumors from growing for a median of six months longer than Herceptin alone. But "Perjeta is $6,000 a month; then Herceptin is $4,500 a month."

Further up the pipeline, Roche/Genentech is developing another combination therapy, T-DM1, which packages Herceptin (trastuzumab) with a chemotherapy, DM1. The goal is for Herceptin to bind to a tumor site, where the chemo is locally released. Initial data in breast cancer look promising, but will the elegant technology buy pricing leeway? "Products that are getting launched are not replacing therapies, but are getting added on top," says Debbie Warner, who leads the cancer impact team at Kantar Health. She expects payors to continue addressing the cost issue.

Scott Raidel, VP and medical strategy director for GSW Worldwide, advises such clients as Lilly Oncology to help payors understand why a drug is appropriate. "You actually can build brand loyalty in the payor and government space by helping them understand the issues."

With ObamaCare set to add millions more people into the system, will access become a bigger problem? "I am not sure that expanding coverage is going to change too much," says Sanford Bernstein analyst Tim Anderson. "In high-priced specialty therapies, if someone needs the drug, they are going to get it." Genentech employs 350 staff to help patients navigate the access and reimbursement shoals. Still, pharma's biggest customers—CMS and, increasingly, accountable care organizations (ACOs)—are becoming value shoppers.

"The other issue is cost-shifting," adds Warner, "there will be fewer uninsured patients, but undoubtedly more under-insured patients as a result of healthcare reform." Thus, "Pharma companies," says Warner, "need to be thinking [about] what to teach the physician to tell the patient, because the patient is paying more out of pocket."

Educating patients about biomarkers is becoming more common for companies in pre-launch marketing. One is Boehringer Ingelheim, which has a broad oncology pipeline but no cancer drugs on the market yet. "We want to take that personalized medicine approach further," says BI's Kevin Lokay, VP and oncology business unit head, "and really focus on those patients who will most likely benefit."

As oncology clinics close and treatment shifts into medical centers, the value message is being directed at institutions. "Pharmaceutical companies will need to understand how they can help customers satisfy their quality improvement [QI] goals—and brand managers need to think about how their brand fits into this QI dynamic," says Dave Dierk, president of Pinnacle Health Communications.

"Academic cancer centers are making cost and quality improvement programs a priority," agrees David Guy, who previously headed oncology marketing at both Sanofi and Genentech and is now a consultant. "Accessing and influencing the institutional decision makers implementing these programs requires a collaborative key account management approach that includes developing unbranded, patient centric, quality improvement programs." ■

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