Biologics Clinical Trials, Research, and FDA Actions

MICHAEL D. DALZELL

Hopes raised, hopes dashed — the last half of 2012 has seen plenty of both. Enthusiasm over a bumper crop of U.S. Food and Drug Administration approvals has been tempered by a long list of phase 3 trial disappointments.

Oncology agents led the way, starting with two drugs being studied for the treatment of non-small cell lung cancer. The addition of Eli Lilly's **pemetrexed (Alimta)** to a regimen of **bevacizumab (Avastin)** and chemotherapy produced improvements in progression-free survival (PFS) but not overall survival (OS). ArQule and Daiichi Sankyo stopped a phase 3 study of **tivantinib** after concluding that improvements in OS would not be reached. For ArQule, the silver lining was the FDA's grant of a special protocol assessment, allowing the start up of a phase 3 trial of tivantinib in patients with liver cancer.

Amgen ended a large phase 3 trial of **ganitumab** after a data monitoring committee determined that the addition of ganitumab to **gemcitabine (Gemzar)** would not result in significant OS improvements in patients with pancreatic cancer versus gemcitabine alone. A phase 2 trial of ganitumab in locally advanced pancreatic cancer was also stopped.

Two separate studies of agents to treat kidney cancer also caused consternation. **Temsirolimus (Torisel),** currently on the market for advanced renal cell carcinoma, was no better at extending PFS when combined with bevacizumab than a combination of bevacizumab and **interferon alfa-2a.** And Aveo is reevaluating data from a head-to-head trial of its **tivozanib** versus **sorafenib (Nexavar)** after the FDA expressed concern about OS data that Aveo planned to include in a new drug application later this year.

Not all news from oncology was disappointing. Immunogen released a deeper dive into OS data for **trastuzumab emtansine,** or **T-DM1 (Kadcyla),** showing a 5.8-month OS benefit in previously treated HER2-positive metastatic breast cancer patients versus **lapatinib (Tykerb)** plus **capecitabine (Xeloda).** And Celgene's multiple myeloma oral drug, **pomalidomide** — a derivative of thalidomide — improved PFS in patients who were refractory to **lenalidomide (Revlimid)** and **bortezomib (Velcade).**

Alzheimer's data quandary

Is half a loaf better than nothing? That seems to be the message from researchers who conducted two large studies of **solanezumab,** Eli Lilly's experimental Alzheimer's agent.

Solanezumab missed its primary endpoint in two pivotal trials, but in a subsequent analysis, researchers found a biomarker they say opens a new avenue for Alzheimer's research. Reduced levels of beta-amyloid in the blood, they contend, can be a surrogate for lower levels of the protein in the brain. Moreover, they believe this finding explains how a subpopulation in one of the studies met a secondary endpoint, reduction in cognitive decline.

As Lilly mulls whether to pursue FDA approval on secondary data, observers raise questions: Will the FDA require another phase 3 trial to validate the biomarker theory? Or will the agency be willing to accept substandard data to help Alzheimer's patients cope as best as they can with a disease for which no effective therapies exist? The questions loom larger in the wake of Janssen and Pfizer's announcement on Aug. 6 that they had pulled the plug on development of an IV formulation of another hyped Alzheimer's treatment in late-stage development, **bapineuzumab**.

MS drugs take spotlight

Biogen Idec steamed toward approval of its oral MS agent, **BG-12,** with publication of two pivotal studies in the *New England Journal of Medicine.* In both the DEFINE and CONFIRM studies, the primary endpoint (reductions in relapse rates) was reached with ease. Safety profiles were favorable in both studies as well, bolstering the perception among patient advocates that BG-12 may have come as close as anything to bridging the efficacy/safety tradeoff that defines MS therapies. In DEFINE, BG-12 was compared to placebo; in CONFIRM, glatiramer acetate (Copaxone) was a comparator drug.

On BG-12's heels, Sanofi and Genzyme published positive data from two pivotal trials of **alemtuzumab (Lemtrada)** in the *Lancet.* In both, alemtuzumab was significantly more effective at reducing

FDA BIOLOGIC AND SPECIALTY DRUG APPROVALS, AUG. 1–OCT. 31, 2012				
Date (type)	**Manufacturer**	**Drug (trade name); administration**	**Indication**	**Notes**
New marketing approvals				
Aug. 3 (BLA)	Sanofi/ Regeneron	ziv-aflibercept **(Zaltrap)**; IV infusion	In combination with FOLFIRI, for mCRC resistant to oxaliplatin chemo regimen	Angiogenesis inhibitor is a reformulation of aflibercept **(Eylea)**, approved for wet AMD
Aug. 9 (NDA)	Talon Therapeutics	vincristine sulfate LIPOSOME injection **(Marqibo)**; IV infusion	Relapsing Ph-negative acute lymphoblastic leukemia in adults	Patient population in U.S. is less than 500
Aug. 27 (NDA)	Gilead	elvitegravir, cobicistat, emtricitabine, tenofovir **(Stribild)**; oral	HIV in treatment-naive adults	Single-pill, daily regimen; known as "Quad" during clinical trials
Aug. 31 (NDA)	Medivation/ Astellas	enzalutamide **(Xtandi)**; oral	mCRPC in men previously treated with docetaxel	OS gain 4.8 mo. vs placebo; yearly $90,000 cost similar to **Provenge**
Sept. 4 (NDA)	Pfizer	bosutinib **(Bosulif)**; oral	Ph-positive CML resistant or intolerant to prior therapy	For use in patients with chronic, accelerated, or blast phase
Sept. 12 (NDA)	Sanofi/ Genzyme	teriflunomide **(Aubagio)**; oral	Relapsing multiple sclerosis	36% drop in relapse vs placebo, but failed head-to-head vs **Rebif**
Sept. 27 (NDA)	Onyx/Bayer	regorafenib **(Stivarga)**; oral	mCRC after treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy	Approved under accelerated review; Bayer also filed supplemental NDA Aug. 30 for gastrointestinal cancer indication
Oct. 26 (NDA)	Teva	omacetaxine mepesuccinate **(Synribo)**; SC injection	CML with resistance and/or intolerance to two or more tyrosine kinase inhibitors	For use in patients with chronic or accelerated phase
New indication				
Sept. 28 (sBLA)	Abbott	adalimumab **(Humira)**; SC injection	Ulcerative colitis (UC)	UC becomes seventh indication for the TNF-α blocker

SELECTED FDA-RELATED ACTIVITIES, AUG. 1–OCT. 31, 2012				
Manufacturer	**Drug (trade name)**	**Type of drug**	**Proposed use**	**Notes**
Halozyme/ Baxter	**HyQ**	Immune globulin 10% and recombinant human hyaluronidase (rHuPH20)	Primary immunodeficiency disease	Aug. 1 CRL asked for additional preclinical data; FDA concerned about effect of non-neutralizing antibodies on reproduction
Janssen	abiraterone **(Zytiga)**	androgen deprivation therapy	mCRPC in men who have not yet undergone chemo	Now approved in post-chemo setting; FDA Aug. 28 gave priority review to extended indication

AMD=age-related macular degeneration, BLA=biologics license application, CML=chronic myelogenous leukemia, CRL=complete response letter, EGFR=epidermal growth factor receptor, IV=intravenous, mCRC=metastatic colorectal cancer, mCRPC=metastatic castration-resistant prostate cancer, NDA=new drug application, OS=overall survival, SC=subcutaneous, VEGF=vascular endothelial growth factor.

Sources: FDA, FierceBiotech; manufacturers' news releases, product labeling, and SEC filings; weblogs; and wire reports

annualized relapse rates than the active comparator, interferon beta-1a (Rebif).

Both drugs, along with the approval of teriflunomide (see table) and others in development (see article on page 24) usher in a new phase of MS treatment.

Did you hear?

Sloan Kettering officials wrote in the *New York Times* that the cancer center won't give patients **ziv-aflibercept (Zaltrap)** because of its $11,000 a month price. ... Teva and Samsung have given up trying to reproduce **rituximab,** ending those biosimilar programs.

All clinical trials described in Drug Track are phase 3, randomized, controlled studies unless otherwise specified.