IN brief

Avastin loses breast cancer indication

US Food and Drug Administration (FDA) Commissioner Margaret Hamburg handed down in November the final decision to revoke approval of Genentech's Avastin (bevacizumab) in metastatic breast cancer. Avastin, which binds to vascular endothelial growth factor, received accelerated approval in 2008 obligating the S. San Francisco-based company to confirm promising data in post-marketing studies, but two confirmatory trials failed to support the 5.5-month improvement of progression-free survival seen in the pivotal study. Citing a poor benefit-to-risk profile, FDA's Center for Drug Evaluation and Research (CDER) proposed withdrawing approval due to serious hypertension and kidney toxicity side effects, but the Roche unit challenged the move—the first time a drugmaker has ever done so—requesting a two-day hearing last summer. Following the hearing, the FDA's Oncologic Drugs Advisory Committee supported CDER's recommendation, as did Hamburg, but Genentech has not given up. It is launching a new phase 3 trial of Avastin with paclitaxel, evaluating a potential biomarker to help identify metastatic breast cancer patients who benefit the most. Hamburg says she will reconsider her decision if Genentech is able to identify super-responders. "FDA will work with Genentech on the design of trials to explore whether such a subset of patients exists," says FDA spokesperson Karen Riley, "and if so, develop ways to identify such patients for whom Avastin treatment is safe and effective. But while these studies are going on, the breast cancer indication should not remain on the drug's labeling." Avastin is approved for colon, lung, kidney and brain cancers.

Karen Carey

Pivotal FDA/Exelixis dispute

The US Food & Drug Administration (FDA) stunned Exelixis when it failed to agree on a special protocol assessment (SPA) of a pivotal trial of the company's small molecule, cabozantinib, in metastatic castration-resistant prostate cancer. The S. San Francisco-based biotech requested an SPA because it intends to use pain response to gauge the efficacy of cabozantinib, a dual inhibitor of the mesenchymal epithelial transition and vascular endothelial growth factor signaling pathways. This novel end point gave FDA pause. The trial will proceed, but Exelixis not having the SPA imprimatur discomfited analysts and Exelixis' stock price has been cut almost in half since the FDA decision. Along with the added regulatory uncertainty, analysts were also concerned by a shorter time to confirmation of the pain response end point than previously announced and a lower starting dose. That said, Lazard Capital Markets biotech analyst Ryan Martins believes cabozantinib will be active and differentiated from its competitors. Founded to pursue drug discovery using genomics and one of biotech's notable initial public offerings in 2000, Exelixis has 11 outlicensed or partnered clinical-stage compounds. But internally, it has narrowed its focus to developing cabozantinib.

Mark Ratner

Safety profiles come to fore as more drugs approach MS market

Two long-awaited multiple sclerosis (MS) drugs, Sanofi's (Genzyme) alemtuzumab (Lemtrada) and Biogen Idec's BG-12 (dimethyl fumarate) are due to enter the approval process in the coming months, following the publication of promising phase 3 trial data last year (Table 1). Each has fast-track designation and could, with a priority review, reach patients in the US before the year is out. Approval for another Sanofi drug, teriflunomide (Aubagio), could come even earlier (Box 1). But some highlight Cambridge, Massachusetts-based Biogen Idec's oral small molecule BG-12 as the pipeline drug with the greatest potential to reconcile the twin goals of efficacy and safety. "I don't think everything out there is a game changer—but one possible exception is BG-12," says Lawrence Steinman, of Stanford University School of Medicine, California, adding "it's a game changer that's not a cure."

In addition to these front-runners, several other molecules acting by means of alternative mechanisms have completed, or are undergoing, late-stage trials, including Petach Tikva, Israel-based Teva's oral immunomodulator laquinimod (originally licensed from Active Biotech of Lund, Sweden) and Deerfield, Illinois-based Abbott/Biogen Idec's interleukin-2 receptor-binding humanized monoclonal antibody (mAb) daclizumab (originally licensed

from Redwood City, California-based Facet Biotech/PDL Biopharma). For all the progress in drug development, this push has not, however, been matched by a greater understanding of why some patients respond to certain therapies and some do not. Clinicians are still a long way from being able to stratify patients to achieve the best outcomes.

MS drugs are currently sold on the basis of sales and marketing efforts, says Steinman. "In 20 to 25 years, we'll be doing this intelligently," Steinman says. The wide range of different drug classes under consideration for MS—and the surprising results seen in some clinical trials—point to the continued uncertainties surrounding the pathophysiological mechanism of the disease and its precise trigger(s).

MS manifests itself as an autoimmune attack on the insulating myelin sheath that coats nerve fibers. The focus of most drug development strategies is on dampening down or wiping out excessive activation of the immune system (efforts to focus on immunotolerance or on neuroprotection are at an earlier stage). Achieving an acceptable trade-off between safety and efficacy is a major theme. At one end of the spectrum is Biogen Idec's Tysabri (natalizumab), an $\alpha 4 \beta 1$ -integrin inhibitor that reduces the migration of T cells into the central nervous system, offers strong efficacy, but has the risk

George Scangos, CEO of Biogen, is eager to strengthen the biotech's multiple sclerosis franchise. Now Biogen's oral molecule BG-12 is being touted as a potential game changer.

REUTERS/Mike Segar