IN brief

Amylin's $7 billion GLP-1 deal

In June, Bristol-Myers Squibb (BMS), of New York, agreed to purchase San Diego-based Amylin Pharmaceuticals. In an acquisition twist, BMS negotiated a deal to sell half of Amylin to AstraZeneca, of London, expanding their diabetes partnership. The total value of the purchase is ~$7 billion including Amylin's net debt and a contractual payment obligation to Amylin's former partner Eli Lilly, of Indianapolis. "I thought it was a good deal with a creative structure," says Mark Schoenebaum, an analyst with New York–based ISI Group. The purchase includes three marketed drugs, Symlin (pramlintide acetate), Byetta (exenatide) and Bydureon, the recently approved, once-weekly version of Byetta (*Nat. Biotechnol.* **30**, 201, 2012). But most of the acquisition's value is tied up in a once-monthly version of exenatide, an analog of the insulin-boosting, glucagon-like peptide 1 (GLP-1) still in development. "The value is 90% Bydureon and Bydureon life-cycle extensions," Schoenebaum says. Other assets in Amylin's pipeline are metreleptin, a recombinant form of human leptin, currently under review at the US Food and Drug Administration, to treat diabetes and/or hypertriglyceridemia in patients with rare forms of inherited or acquired lipodystrophy. Amylin is also developing AC165198, a hybrid fusion of two different peptide hormones, to treat diabetes. *Brian Orelli*

Agilent buys Her2 test firm

In the biggest deal in its history, scientific testing equipment maker Agilent Technologies acquired diagnostics firm Dako for $2.2 billion. The all-cash deal signals Santa Clara, California–based Agilent's intention to strengthen its presence in the life sciences industry. Dako, headquartered in Glostrup, Denmark, is a leading supplier of cancer diagnostic antibodies and kits to pathology laboratories. The Danish firm markets HercepTest, a HER2 companion diagnostic kit for Roche's breast cancer drug Herceptin (trastuzumab), and in June received US Food and Drug Administration approval for HER2 FISH pharmDX, as companion diagnostic for the recently approved Perjeta (pertuzumab) (*Nat. Biotechnol.* **30,** 570, 2012). Agilent also has a large portfolio of molecular diagnostics technologies. "Agilent's acquisition of Dako highlights the continued convergence of research tools companies and diagnostic companies," says analyst Peter Lawson, of New York's Mizuho Securities. Other notable tools-diagnostics acquisitions over the last five years have been Qiagen acquiring Digene, Danaher acquiring Beckman Coulter, Roche acquiring Ventana Medical and Thermo acquiring Phadia. "We expect this trend to continue," says Lawson. Agilent also gains access to Dako's vast experience dealing with regulators, and taking a product through to approval. The deal is a merger of complementary strengths, doubling Agilent's reagents business and accelerating its penetration into the life science and diagnostic markets. *Susan Aldridge*

are not the best way to measure benefit from immunotherapy," Topalian says. In addition to those patients who had objective response rates, others—including an additional 27% of the RCC patients—had stable disease for at least six months.

The study also yielded preliminary evidence of an association between response to therapy and the PDL-1 status of patients' tumors. Although tumor biopsies were only taken from 42 of 236 evaluable patients, 36% of those with PDL-1–positive cancers also achieved an objective response and, strikingly, no responses were detected in patients with PDL-1–negative cancers. "This molecular marker may be more predictive of one cancer than another," Topalian says.

Another BMS mAb drug, BMS-936559, also a fully human IgG4 mAb, targets the PD-1 pathway by binding PDL-1 and blocking its interaction with PD-1. It is currently being tested in a phase 1 multiple ascending dose trial, code named CA210-001, which is recruiting 286 patients with advanced cancer. Initial data suggest that it may not be as active as BMS-936558—it induced response rates ranging from 6% to 17% in different types of cancer—although the two studies are not directly comparable (*N. Engl. J. Med.* **366**, 2455–2465, 2012). "BMS-963559 is in an earlier stage of development, and results from CA210-001, which is ongoing, will inform decisions about its future development," says BMS spokeswoman Sarah Koenig.

So far, data for only one other PD-1 blocker, CT-011, have been reported. In an open-label phase 2 trial in 72 patients with diffuse large B-cell lymphoma (DLBCL), 70% attained progression-free survival at 18 months. They had previously received a combination of the anti-CD20 antibody Rituxan (rituximab) from Basel-based Roche and Biogen Idec, of Weston, Massachusetts, with chemotherapy, followed by autologous stem cell transplantation. The trial protocol involved the administration of radiation to a single metastatic site, to release tumor antigen, as well as an immunostimulatory CpG oligonucleotide to activate natural killer and T-cell responses. "It looked better than historical controls—especially in the Rituxan era," says Leo Gordon, of Northwestern University Feinberg School of Medicine, in Chicago. "When you relapse after Rituxan things are definitely worse." The molecule, a humanized IgG1 antibody directed at PD-1, may act by a dual mechanism, involving both immune activation and direct targeting of PDL-1. "Within 24 hours you saw this sort of rush of memory T cells that were markedly increased compared to the day before," Gordon says. "If it worked by inhibiting [only] apoptosis, it wouldn't have worked so quickly."

Amplimmune, of Gaithersburg, Maryland, is targeting PD-1 with a fusion protein, AMP-224, comprising an Fc antibody domain and PDL-2. London-based GlaxoSmithKline inlicensed the then-preclinical molecule two years ago in a deal worth up to $508 million in upfront and milestone payments. According to Amplimmune CSO Sol Langermann, it is designed to restore immune function in the tumor microenvironment, which is otherwise suppressed by the cytokine milieu associated with infiltrating T lymphocytes. "The PD-1 levels are extremely high," he says. "You go from activation to what we call exhaustion." AMP-224 appears to work either by depleting the population of cells expressing PD-1 or by lowering the level at which the receptor is expressed. "Our molecule specifically eliminates the cells expressing very high levels of PD-1, but not those expressing intermediate or low levels of PD-1," he says. That selectivity is simply a function of the fusion protein having less affinity for its target than the various antibody molecules have for theirs. It could, he says, translate to a better safety profile for AMP-224, although at this point that's a conjectural claim. The drug is administered after a pre-treatment regimen with a chemotherapeutic agent that first depletes rapidly proliferating T-regulatory cells to boost the subsequent immune activation effect associated with PD-1 signal inhibition. "The regimen itself is proprietary and unique," says Amplimmune CEO Michael Richman.

Targeting immune checkpoint inhibitors carries a general risk that autoimmune reactions will develop. In the phase 3 registration trial of Yervoy in melanoma, 15% of patients taking the drug as a single agent developed severe, life-threatening or fatal immune-related conditions, including enterocolitis, hepatitis, dermatitis, neuropathy and endocrinopathy. In the BMS-936558 study, three deaths due to pulmonary toxicity occurred, and the drug caused severe, life-threatening or disabling adverse events in 14% of patients. "It goes without saying that in any phase 1 trial you're on a learning curve," says Topalian. "We rapidly learned to recognize the pulmonary toxicity cases early and to treat them aggressively." Given the prospects for the patients taking these therapies up to now, the risk-benefit ratio is still favorable to PD-1 blockers. But optimizing their use will require far more clinical data than has been generated to date. "We still have to realize that over half of the patients treated on this trial did not benefit," Topalian says of the BMS-936558 study.

Cormac Sheridan *Dublin*