Jounce checkpoint lures Celgene

In July, the immunotherapy biotech Jounce Therapeutics, of Cambridge, Massachusetts, hit pay dirt in signing its first partnership. In a deal potentially worth over $2 billion, Celgene of Summit, New Jersey, and Jounce will co-develop and co-commercialize Jounce's lead compound JTX-2011, a monoclonal antibody targeting the inducible T cell co-stimulator (ICOS), which is a member of the immune checkpoint family of proteins and provides an agonistic stimulus for T cell activation. Jounce, founded in 2013 by a stellar group of cancer immuno-oncologists, joins a long list of immunotherapy companies in which Celgene has invested (*Nat. Biotechnol.* **33**, 892–893, 2015). Other investments include one in Juno Therapeutics of Seattle, which is developing CAR-T cell based immunotherapies, and a collaboration with London-based AstraZeneca, which has a checkpoint inhibitor (durvalumab) in clinical trials. Under the terms of the deal, Jounce will get $225 million up front, with a $36 million investment in the company. In return, Celgene will get 40% share of the US profits from JTX-2011, which is still in clinical development, 75% for those from an unnamed successor, and 50% of up to three other programs.

"It will provide fair and objective information without stigmatizing foods that are completely safe." Senator Joe Donnelly (D-IN) comments on a new Senate bill proposing one of three options for GMO food labeling rather than a blanket labeling law like the one that went into effect in Vermont in July. (*Science*, 8 July 2016)

"It's a massive ass-covering move as far as I can tell." Russ Poldrack, a Stanford University professor and director of the Stanford Center for Reproducible Neuroscience, refers to a proposal, backed by 280 researchers, published in the *New England Journal of Medicine* that would allow clinical researchers to wait as long as 5 years to publish clinical trial results. (STAT, 4 August 2016)

"I wish we had started earlier on building a scientific board and working toward peer-reviewed data." Elizabeth Holmes, CEO of embattled Theranos, says in a presentation to the American Association of Clinical Chemistry in Philadelphia in August. (*GEN News Highlights*, 2 August 2016)

Box 1 Victoza safety profile heralds "new era"

In June, at the American Diabetes Association's annual meeting, results from a trial of Novo Nordisk's GLP-1 agonist Victoza (liraglutide), showed that the drug significantly reduced the risk of cardiovascular death, heart attack or non-fatal stroke by 13% in high-risk patients "I think this really changes the conversation," said John Buse, who heads the division of endocrinology at University of North Carolina School of Medicine. Buse led the study of Victoza, dubbed LEADER.

The controversy over heart safety risks associated with diabetes drugs erupted in 2007 with an article in the *New England Journal of Medicine* (**356**, 2457–2471, 2007) of a meta-analysis of 42 trials comparing Avandia (rosiglitazone) with placebo. The publication reported an apparent link between the drug made by Brentford, UK–based GlaxoSmithKline and a 43% increase in myocardial infarction and a 64% increase in cardiovascular mortality. The finding led to thousands of lawsuits and threw open a discussion over the wisdom of choosing diabetes agents based only on lowering blood glucose benefits.

The following year, the FDA published a draft guidance asking developers to show that their drugs don't raise cardiovascular risk. Although most diabetes agents have cleared this hurdle, two drugs have grabbed the spotlight by not only showing a benign risk profile, but by showing a cardiovascular benefit.

Jardiance (empagliflozin), developed by Ingelheim, Germany–based Boehringer Ingelheim and Indianapolis-based Eli Lilly, showed in a clinical trial of high-risk patients with type 2 diabetes that Jardiance cut the risk of non-fatal heart attack or non-fatal stroke by 14% when added to the standard of care, and a 38% reduction in the risk of cardiovascular death (*N. Engl. J. Med.* **373**, 2117–2128, 2015). Avandia was cleared by the FDA in 2013 after an independent analysis called RECORD showed that the drug doesn't carry a higher risk of death, heart attack or stroke.

It may still be too early to decide to use one agent over another based on these results, according to Clifford Rosen, a senior scientist at Maine Medical Center in Portland, Maine. "This is a new era for diabetes," says Michael Nauck, head of clinical diabetes research of Ruhr University in Bochum, Germany. "For years we tried to prove diabetes drugs didn't raise CV [cardiovascular] risk, and now we have two drugs that are beneficial for patients." Nauck was a member of the LEADER steering committee.

Jardiance and Victoza may soon have company. Novo Nordisk in April announced that its experimental once-weekly GLP-1 receptor agonist semaglutide reduced cardiovascular risk. Details of the study, SUSTAIN 6, will be released at a later date. Novo Nordisk expects to file semaglutide for regulatory review in the US and EU in the fourth quarter of 2016. *EVS*

dine), a combination of three drugs, and Foster City, California–based Gilead's Stribild a combination of four agents (cobicistat/elvitegravir/emtricitabine/tenofovir). Other examples include Brentford, UK–based GlaxoSmithKline's Advair (fluticasone propionate/salmeterol xinafoate), a combination of a long-acting beta agonist and an inhaled corticosteroid, and Novartis' Exforge (amlodipine besylate/valsartan) and Co-Diovan (hydrochlorothiazide/valsartan), drugs that add a second agent to the Basel, Switzerland–based company's best-selling drug to treat hypertension, Diovan (valsartan). In 2015, the FDA approved Eli Lilly's Glyxambi a fixed-dose combination drug for type 2 diabetes, that pairs two different drug classes by combining Jardiance (empagliflozin), a sodium-dependent glucose transporter-2 inhibitor (SGLT-2 inhibitor), with Tradjenta (linagliptin), a long-acting dipeptidyl peptidase IV (DPP-4) inhibitor, in a single pill.

IDegLira and iGlarLixi are the first fixed-dose combinations to contain long-acting insulin in the formulations. These once-a day shots delivered by a pen injector device both include GLP-1 receptor agonists, compounds that mimic the peptide hormone GLP-1 and its effect in stimulating insulin production and suppressing glucagon secretion from the pancreas. Because GLP-1 is released in response to the presence of carbohydrates in the gut, the risk of hypoglycemia is low, and another advantage is the weight loss associated with GLP-1 receptor agonist use. Both Novo Nordisk and Sanofi hope to capitalize on one benefit of fixed-dose combinations: fewer side effects. This reduction is likely because the individual components work by two different pathways but on a single therapeutic target, and the doubling in efficacy allows doctors to prescribe lower doses. "That is the biggest single advantage of fixed-dose combinations," says Tony Ellery, former