Go-ahead for first anti-IL-23 mAb to treat psoriasis

On July 13, the US Food and Drug Administration (FDA) approved Tremfya (guselkumab) to treat moderate to severe plaque psoriasis. Tremfya, developed by Johnson & Johnson's subsidiary Janssen, of Beers, Belgium, is the first and only human monoclonal antibody (mAb) that selectively blocks interleukin 23 (IL-23), a pro-inflammatory cytokine involved in the pathogenesis of plaque psoriasis (*Nat. Biotechnol.* **34**,1218–1219, 2016). The FDA expedited its review because Janssen used a Priority Review Voucher it won in 2012 for the approval of Sirturo (bedaquiline), a treatment for multi-drug-resistant tuberculosis. Tremfya will launch at an annual wholesale acquisition cost of $58,100, says spokesperson Brian Kenney. Tremfya's approval also marks the first antibody produced using MorphoSys' HuCAL (Human Combinatorial Antibody Library) technology platform, for which Planegg, Germany's MorphoSys will receive an undisclosed milestone payment. Tremfya targets and shuts off IL-23, a cytokine at the top of the inflammatory cascade that, in turn, will block disease-causing T-helper-17 cells that produce IL-17, known to play a pivotal role in the disease. But IL-23 is a heterodimer with two subunits, p19 and p40. Tremfya is the first agent to block only the p19 subunit, whereas other approved biologics work by inhibiting both components, including Janssen's Stelara (ustekinumab). Stelara targets the p40 component that is shared between the IL-23 and IL-12 pathways. A selective anti-p19 therapy was deemed a bonus and, indeed, in phase 3 data, Tremfya outscored the placebo on complete and near-complete skin clearance at week 16. With Tremfya, 70% of patients scored a significant improvement in skin clearance (PASI 90), including less itch, pain and stinging, compared with 50% skin clearance with Humira (adalimumab); an anti-TNF inhibitor from North Chicago, Illinois–based AbbVie (*Nat. Biotechnol.* **34**, 1218–1219, 2016). In addition, Stelara non-responder patients showed significant improvements in plaque clearance when treated with Tremfya. The dosing regimen at one injection every 8 weeks is less frequent than with other biologics. Tremfya is in phase 3 development for treating psoriatic arthritis. Janssen is also conducting a phase 3 trial comparing Tremfya with IL-17-blocker Cosentyx (secukinumab) from Novartis of Basel, Switzerland.

> **"I'm talking about editing vs. vandalism. Ripping pages out of a book is what most of the editing enzymes like CRISPR do, while we should be reserving the term 'editing' for the sign of finesse that an editor would have where they say, you're missing a comma here, let's change this word."** George Church discusses the state of editing technologies. (*Mendelspod*, 13 July 2017)

Table 1 Selected clinical stage drugs targeting the adenosine checkpoint in cancer tested in combination with anti-PD1 agents

Collaborating companies	Agent	Target	Combination agent	Stage
Corvus Pharma/Genentech	CPI-444 (V81444)	A2AR	Tecentriq	Phase 1
Novartis/ Palobiofarma SL (Pamplona, Spain)	PBF-509	A2AR	PDR001	Phase 1
Medimmune (Gaithersburg, Maryland)/AstraZeneca	MEDI9447	CD73	Imfinzi (durvalumab)	Phase 1
Merck	MK-3814 (preladenant) (SCH 420814)	A2AR	Keytruda	Phase 1
AstraZeneca/ Heptares (of the Sosei Group, London)	AZD4635 (HTL-1071)	A2AR	Imfinzi	Phase 1
Bristol-Myers Squibb	BMS-986179	CD73	Opdivo (nivolumab)	Phase 1

A2AR, A2A receptor.

This checkpoint is different from PD-1, says Leone, in that it has less-specific effects. "It's a very ancient and maybe underlying pathway that may be… a master controller," he says. "That doesn't mean that it's incredibly robust, downregulating everything, but I think it is having some control over multiple pathways, so [it's] a very feasible…platform to combine with other checkpoint blockade [agents]…you can probably get a lot of synergism."

Disabling the adenosine cloud should restore the T-cell immune response. One way is to block the A2A receptor, preventing downstream immunosuppressive signals that temporarily inactivate T cells. This may work even when PD-1 checkpoint blockade doesn't, because T cells can respond to PD-1 inhibitors by expressing more A2A surface receptors. Adenosine binds these receptors and shuts down the T cells. As a result, adenosine receptor blockade could potentially overcome resistance to anti-PD-1 therapy (*Cancer Immunol. Res.* **3**, 506–517, 2015).

Adenosine receptors first came to pharma's attention as a potential target for neuroactive drugs. Vernalis and licensee Biogen Idec developed CPI-444 for Parkinson's disease, to enhance treatment with the drug L-dopa. Other companies did the same with their A2A receptor blockers. Most trials in Parkinson's patients showed safety but disappointing efficacy, ending clinical development until companies seized the opportunity to treat cancer. Miller, who'd co-founded and later sold both IDEC Pharmaceuticals and Pharmacyclics, was looking for an opportunity with new partners. "We said…A2A is an important immune checkpoint, there's human experience with blocking that receptor that says it can be done safely, that's a great target for us," Miller says. With adenosine inhibition in cancer as their goal, the partners founded Corvus in late 2014 and licensed CPI-444 from Vernalis in Winnersh, UK, in 2015.

Corvus presented interim phase 1 data at the annual meeting of the American Association for Cancer Research (AACR) in April—the first report of an adenosine-targeted drug in cancer (AACR abstract CT119; http://investor.corvuspharma.com/phoenix.zhtml?c=254276&p=irol-newsArticle&ID=2259735). CPI-444 was tested alone and combined with the Genentech's PD-L1 inhibitor Tecentriq (atezolizumab). In 96 patients, more than half of whom had failed prior anti-PD-1 therapy, the overall disease control rate (objective responses plus stable disease) was 38%. There were three partial responses, two in patients who'd failed anti-PD-1 therapy, including a monotherapy response to CPI-444. Investigators presented data on kidney and lung cancer patients at the June annual meeting of the American Society of Clinical Oncology (ASCO), with 4 of 49 patients responding, including 3 of 23 on combination therapy. There were few serious side effects. The overall disease control rate was 75%.

The markets did not like Corvus' AACR presentation, and the biotech lost half its stock value in a single day. But experts point out that Corvus was mostly testing CPI-444 in a tough population, who had failed or were refractory to PD-1 blockade. "You can see it as [a] glass half full or [a] glass half empty," says Linden, who puts himself in the half-full camp, because the drug was active in PD-1 failures. Eight patients saw tumor shrinkage from the single agent CPI-444. "That certainly suggests there's something real there," says Naiyer Rizvi, an oncologist at Columbia University Medical Center in New York, who adds that the much-publicized indoleamine 2,3-dioxygenase (IDO) inhibitors, for instance, have not shown any single-agent activity.

And IDO inhibitors and other effec-