IN brief

MEK inhibitor nears approval

The first MEK inhibitor trametinib (GSK 1120212) could be close to reaching the market. On December 4, a US Food and Drug Administration advisory committee discussed materials on the mitogen-activated, extracellular signal-regulated kinase 1 (MEK1) and MEK2 inhibitors submitted by its maker, London-based GlaxoSmithKline. The committee discussed the drug's effectiveness for treating unresectable or metastatic BRAF-V600-mutation-positive melanoma, including safety monitoring in light of ophthalmologic and cardiac toxicities observed in adults receiving the drug. "There's hope that MEK inhibitors will become the standard of care in patients with BRAF mutant tumors," says David Solit, an associate professor of Medicine, Cell and Developmental Biology at Memorial Sloan-Kettering Cancer Center in New York. Kevin Koch, president and CEO of Array BioPharma in Boulder, Colorado, sees further possibilities. "The pathway MEK resides in is upregulated in a large number of tumor types," he says, adding that the drugs are similar to VEGF inhibitors and "much more potent in combination." Array has partnerships around the MEK inhibitor MEK162 with Novartis of Basel and with AstraZeneca of London over selumetinib (AZD 6244). MEK162 is expected to be in phase 3 melanoma studies by 2013, selumetinib could also go into phase 3, but in KRAS-mutated non-small cell lung cancer. Roche of Basel is also starting a phase 3 trial in melanoma combining the company's BRAF inhibitor (Zelboraf/vemurafenib) with Genentech's GADC-0973, a MEK inhibitor. For now, "trametinib is the only MEK inhibitor with major clinical data behind it," says Solit. Those data include results from a phase 3 trial of combined BRAF and MEK inhibition in almost 250 patients with BRAF-V600-mutation-positive melanoma. The study reported a marked increase (9.4 months versus 5.8 months) in progression-free survival among patients on the combination therapy (*NEJM* 367, 1694–1703, 2012). Hervé Hoppenot, president of Novartis Oncology, says success will be determined by "what we see in clinical trials and the ability to pursue MEK162 in the right combinations to target multiple pathways." So far, MEK inhibitors have shown a surprising range of effectiveness, given that they are allosteric inhibitors. "You'd expect them to be extremely specific, but results may start to iron out as more companies go into bigger trials," says Keiran Smalley, an assistant professor at the Moffitt Cancer Center in Tampa, Florida. *Malorye Allison*

lyst at Barclays Capital, a New York investment bank, puts peak Xeljanz sales at \$2.5 billion by decade's end.

But Xeljanz could do much better. "If the safety holds up, it's a big market and sales could be very large," says Scala. In its only head-to-head phase 3 trial against a TNF inhibitor, Xeljanz produced better ACR50 and ACR70 responses overall than Abbott's Humira (adalimumab), the world's top-selling drug, although the trial was not designed or powered to definitively compare the two treatments (*New Engl. J. Med.* 367, 508–519, 2012). Scala puts Xeljanz about three years ahead of the next JAK inhibitor in line, baricitinib from Incyte of Wilmington, Delaware, and Eli Lilly of Indianapolis, which just entered phase 3.

Xeljanz treatment was generally well tolerated in clinical trials. Side effects include infections like tuberculosis (12 cases out of 5,460 patients treated) and herpes zoster (239 cases, only a few serious), as well as drops in white and red blood counts. Levels of both low-density lipoprotein and high-density lipoprotein and/or cholesterol rose. There were 65 malignancies, including 16 lung cancers, 11 breast cancers and 6 lymphomas.

Similar side effects are seen with biologic rheumatoid arthritis treatments, but herpes zoster (shingles) stands out for Xeljanz. The FDA recommends vaccination with the herpes zoster vaccine before starting rheumatoid arthritis therapy with it or with other immunomodulatory drugs. Given the number of herpes zoster infections in the Xeljanz trials, "I'm going to be much more aggressive about vaccinating my patients prior to starting any biologic," says Massarotti. The drug label recommends monitoring blood counts, liver enzymes and lipids during treatment. (Laboratory monitoring is already routine with rheumatoid arthritis methotrexate therapy.)

It may take years to sort out Xeljanz's long-term side-effect profile. For example, progressive multifocal leukoencephalopathy, a severe demyelinating disease, did not emerge as a risk for Biogen Idec's Tysabri (natalizumab) in multiple sclerosis treatment until the drug was in wide use. "We'll have to keep our eyes open," says Crofford, who is worried that rheumatologists might double down on the Xeljanz dose off-label to increase efficacy. (The FDA only approved the 5 mg twice-a-day dose, not 10 mg, as Pfizer also requested.) "If it's too immunosuppressive...at high doses, you'd get into more infectious and potentially malignant complications," she says. Part of her concern is that JAK inhibitors block signaling from multiple cytokines. "But that also may be a reason that [Xeljanz] will be effective in some patients

who are resistant or refractory to other available drugs," Crofford adds.

Pfizer priced Xeljanz unexpectedly high, which will fuel some third-party payer resistance, predict analysts. At \$2,055 a month wholesale, it's discounted about 7% from anti-TNF biologics. "The company could have, and maybe should have, been a bit more aggressive on price," says Scala. "Maybe doctors would have been more willing to try it earlier."

The price came as a surprise to Crofford. "The manufacturing costs [for small molecules] are a fraction of a biologic," she says. "I was shocked. And disappointed."

Xeljanz arrives in the context of a rheumatology field already coping with the very high cost of biologics. "They're all outrageously priced—completely outrageous," says the Mayo Clinic's Matteson. Crofford is worried about the encroachment in rheumatoid arthritis of "tier four pricing," a cost-shifting strategy where insurers charge patients a percentage cost of the drug, not a fixed co-pay. "Costs just have to come down," she says.

As a first-in-class drug, Xeljanz represents a high level of scientific innovation. But its development involved more government research than is typical. Early in Pfizer's JAK3 inhibitor program, the company entered into a cooperative research and development agreement (CRADA) with the NIH. Beginning in 1996, the company worked with the laboratory of John O'Shea, an NIH immunologist who cloned human JAK3 in 1994, to define the structure and function of JAK3 and its interaction with cytokine receptors. (Drug discovery and preclinical and clinical development took place exclusively at Pfizer.)

According to government documents obtained by *Nature Biotechnology* through the US Freedom of Information Act, Pfizer had discussed a CRADA with the NIH two years earlier, in 1994. But the company declined to proceed at that point because of an NIH policy stating that there should be "a reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public." Only after NIH policy changed to remove such "reasonable pricing" clauses did Pfizer proceed with the CRADA.

In a statement, Pfizer said that "the price of Xeljanz is based on the value it will provide patients and healthcare providers, the scientific innovation it represents and our investment in the comprehensive, multistudy, global clinical development program." The company also mentioned its co-pay support program and other assistance available for qualifying patients.

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a blog from Bioentrepreneur