IN brief

Eylea approval transforms Regeneron

Following the anticipated November Food & Drug Administration approval of Eylea (aflibercept), the biotech firm Regeneron Pharmaceuticals is entering the highly competitive, \$3 billion-plus worldwide market for drugs to treat wet age-related macular degeneration (wet AMD). The US regulator had extended the review period for the drug, an injectable fusion protein designed to bind to vascular endothelial growth factor-A (VEGF-A) and placental growth factor, from August to give the agency time to digest additional manufacturing information it had requested. Although that move delayed the commercial launch, it did little to dampen excitement around the molecule, which in phase 3 trials helped maintain visual acuity as effectively as the standard of care, Roche unit Genentech's VEGF-A-binding monoclonal antibody (mAb) fragment Lucentis (ranibizumab). Genentech, in S. San Francisco, California, has drawn fire over Lucentis's hefty \$2,000 per dose price tag, especially in light of data showing that Genentech's own cancer drug Avastin (bevacizumab), the full-length version of the mAb that is being used off-label to treat wet AMD at much lower cost, is equally effective (*Nat. Biotechnol.* **29**, 560, 2011). Priced at a 7.5% discount to Lucentis per dose, Eylea creates "a compelling cost-saving argument for the system by virtue of the potential for fewer injections and more importantly fewer monitoring visits," says RBC Capital Markets analyst Jason Kantor, in San Francisco, saving patients roughly \$2,500 annually. Regeneron is collaborating with Berlin-based Bayer HealthCare on global development of Eylea in wet AMD. The Tarrytown, New York, biotech is also pursuing indications for it in central retinal vein occlusion and diabetic macular edema, and is developing an infusion-based form of the drug for cancer therapy. Bayer submitted an application for marketing authorization of the drug in Europe for wet AMD in June 2011. Regeneron's launch of Eylea effectively changes the company from one dependent on partnering and licensing into a commercial organization. Leerink Swann analyst Joshua Schimmer, in Boston, calls it one of the transformational events in the biotech industry in 2011.

Mark Ratner

Regeneron's Tarrytown R&D headquarters

219-patient European study run by Novartis (Box 1). The FDA gave the go-ahead to use Jakafi as a treatment for intermediate or high-risk myelofibrosis in advance of the designated Prescription Drug User Fee Act date of December 3.

JAK inhibitors provide a nuanced approach: although they do not completely abrogate tumor mitogenic signaling, they do offer the opportunity to block multiple cytokines and growth factors, unlike other cytostatic drugs that target just one signaling pathway. In the case of JAK2, the kinase also migrates to the nucleus, where it phosphorylates Tyr41 on histone 3, leading to the overexpression of oncogenes. Each JAK associates with different cytokine or growth factor receptors. JAK2 signaling, for example, is associated with cytokine receptors activated by growth hormone, thrombopoietin, erythropoietin and interleukin 3, among others. Although the exact cause of myelofibrosis is unclear, the disease is known to be associated with disruptions to intracellular JAK signaling and high circulating levels of cytokines.

Patients have a range of mutations, of which JAK2^{V617F} is the most common, occurring in 50% of patients with primary myelofibrosis and in erythrocythemia, and in >90% of patients with polycythemia vera. Although the presence of this mutation can be a diagnostic aid, its contribution to overall pathology is not understood.

Myelofibrosis involves excessive generation of blood cells, leading on to the fibrosis and subsequent failure of the bone marrow. This prompts the spleen and the liver to take over production of blood cells, causing enlargement of the spleen, and related, debilitating, symptoms including anemia, extreme fatigue, pruritus (itching), early satiety and bone pain. In the two phase 3 trials of Jakafi, there were significant reductions in spleen size—the primary end point—and

also improvements in six other symptoms.

"This is a really dismal disease [in which] there's never been a phase 3 study, suddenly people are interested, things are happening and things are moving on at a dramatic pace," says Claire Harrison, consultant hematologist at Guy's and St. Thomas' Hospital, London, who was chief investigator for the Comfort 2 trial. Of the Jakafi approval, she adds that it is "a massive step forward for patients for several reasons. There is clinical benefit from reduced splenomegaly and dramatic control of some very nasty constitutional symptoms."

Jakafi has fallen short of initial expectations, however. Although treatment relieves symptoms, there was no difference in progression of the disease between Jakafi-treated and control patients in the phase 3 studies. Unlike Gleevec (imatinib), Novartis's treatment for another myeloproliferative disease, chronic myeloid leukemia, Jakafi is not a cure, Harrison notes. It is encouraging, though, that Harrison is beginning to see slight signs of a disease-modifying effect in patients who remained on the drug after the end of the Comfort 2 trial, and have now been taking Jakafi for over two years, as demonstrated by an increase in hemoglobin levels over baseline. This may be due to an effect on inflammatory cytokines, and may mean there is less fibrosis, Harrison says, noting even bone marrow transplants take time to influence fibrosis.

Two studies presented at the American Society of Hematology meeting in San Diego in December revealed conflicting data on the survival benefit of Jakafi. One study matching patients in the phase 1/2 study treated at the MD Anderson Cancer Center, with historical controls, found a significant effect on overall survival. On the other hand, a long-term outcome study in 51 patients treated at the Mayo Clinic who took part in the phase

Table 1 Selected JAK inhibitors in efficacy trials for myeloproliferative neoplasms^a

Company	Compound and description	Indication	Phase
Incyte/Novartis	Jakafi is a potent small-molecule inhibitor of JAK1 and JAK2 and a moderate inhibitor of TYK2	Myelofibrosis	Approved
		Myeloproliferative disorders	Approved
		Polycythemia vera	Phase 3
		Essential thrombocythemia	Phase 2
Sanofi	SAR302503 (TG101308) is an ATP competitive small-molecule inhibitor of JAK1 and JAK2	Myelofibrosis	Phase 3
S*Bio	Pacritinib is a small-molecule inhibitor with potent selectivity for JAK2 and JAK2 ^{V617F}	Hematologic cancer	Phase 2
YM Biosciences	CYT387 is a small-molecule inhibitor of JAK1 and JAK2	Various hematological disorders	Phase 1/2

^aTwo JAK inhibitors have already failed in efficacy trials: Cephalon's lestaurtinib and Exelixis' XL019. Source: Biomedtracker