FDA Updates Gleevec Label for GIST Patients

By Charlie Schmidt

At the American Society of Clinical Oncology’s (ASCO) annual meeting last June, researchers presented data showing that 3 years of adjuvant treatment with imatinib (Gleevec, Novartis) provided better survival benefits than treatment for 1 year among patients with gastrointestinal stromal tumors (GISTs) positive for the kit gene. On February 1, after a priority review, the U.S. Food and Drug Administration has updated Gleevec’s label to that effect.

“We already knew that longer treatment extends relapse-free survival in these patients, but the new data show it also extends life,” said Michael Heinrich, M.D., a GIST specialist and professor at the Oregon Health and Science University in Portland. “So this is a game changer for standard of care.” The unpublished data come from a multicenter, phase III clinical trial run jointly by Scandinavian and German research teams.

According to Heinrich, the FDA’s decision applies solely to patients who meet inclusion criteria for the European trial: a high risk of recurrence as identified with risk tables that consider tumor size, location, and mitotic cell count (in general, larger tumors and higher mitotic counts predict worse outcomes). Roughly 20%–30% of all nonmetastatic GIST patients fall into that category. For patients with low recurrence risk after surgery, 1 year’s treatment is adequate, Heinrich said, whereas those with metastatic disease can take the drug indefinitely.

Second Chance at Life

The label change furthers a long winning streak for imatinib in GIST patients. Before Japanese researchers linked GIST to mutations of the kit gene in 1998, the cancers were misidentified as leiomyosarcomas, which don’t respond to chemotherapy; survival rates generally didn’t exceed 10% by 30 months after diagnosis, according to Heinrich. Scientists now know that roughly 95% of GIST cases involve kit mutations. Connecting GIST to the kit gene was pivotal because imatinib—developed initially against bcr-abl mutations in chronic myelogenous leukemia—also hits kit as an unintended target. Today, 65%–70% of imatinib-treated GIST patients are alive at 30 months, Heinrich said.

The first GIST patient treated with imatinib was a Finnish woman with metastatic disease. She had family connections to Novartis executives, who gave her the drug. Known only as “patient zero,” she achieved a miraculous response, according to Norman Scherzer, executive director of the Life Raft Group, a GIST advocacy group, in Wayne, N.J.

So in 2000, Heinrich, together with Jonathan Fletcher, M.D., and George DeMatteo, M.D., both from the Dana–Farber Cancer Institute in Boston, followed up with a phase II study of imatinib in 147 patients with metastatic disease. Among them was Scherzer’s wife, Anita, who still takes imatinib. Like patient zero, most of these individuals achieved dramatic responses, prompting the FDA to grant accelerated approval for imatinib in the metastatic setting in 2002. A much larger phase III trial, headed by DeMatteo, which compared imatinib at doses of either 400 or 800 mg per day in patients with unresectable or metastatic disease, later confirmed the phase II results. Published in the Journal of Clinical Oncology in February 2008, the results didn’t show substantial differences between the two doses. The FDA gave final approval for imatinib in metastatic patients the same year.

Accelerated approval for imatinib in the adjuvant setting also came in 2008, based on results from a phase III trial comparing 400 mg per day for 1 year with placebo in postsurgical patients with no evidence of disease. Headed by Ronald DeMatteo, M.D., of the Memorial Sloan–Kettering Cancer Center in New York, that study found a statistically significant benefit from treatment: Recurrence-free survival was 98% at 19.7 months, compared with 83% among control subjects.

Questions Over Treatment Duration

According to Heinrich, decisions to treat for 1 year in this earlier trial and then 3 years in the current European study were arbitrary. “In general, adjuvant treatments tend to produce better outcomes with longer durations,” he said. According to the abstract from the European study, 36 months of imatinib dropped the risk of recurrence by 54% at 42 months, and of death by 55% at 48 months, compared with 1 year of treatment. “We’ve got a 5-year trial ongoing now, but it’s just in phase II,” DeMatteo said. “We realize that 3 years is better than 1, and so 5 years is probably going to be better than 3.” Added Scherzer, “For metastatic illness, it’s a no-brainer—imatinib suppresses the disease, and it comes back if you stop taking it. For adjuvant therapy, the situation is more complicated. GIST experts say there’s no reason to stop. So what do you do when the 3 years is up?” Those who look to imatinib’s label won’t get a clear answer: It now states that 36 months is better than 12 but that the optimal duration of therapy is unknown.