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Emerging Company Profile

ACTing selectively

By Michael Flanagan
Senior Writer

Tyrosine kinase inhibitors that target VEGF receptor have revolutionized the treatment of renal cell carcinoma (RCC). However, off-target effects have resulted in little success of the first-generation drugs in other solid tumors aside from two relatively uncommon cancers: hepatocellular carcinoma (HCC) and gastrointestinal stromal tumors (GIST).

ACT Biotech Inc. believes the selectivity of its telatinib will allow it to be combined with full-dose chemotherapy in a variety of solid tumor types. ACT has encouraging response data from a Phase II trial of telatinib as part of front-line therapy for gastric cancer, and hopes to find a partner and begin Phase III testing this year.

The three marketed anti-VEGF receptor TKIs are **Pfizer Inc.**'s Sutent sunitinib; Nexavar sorafenib from **Onyx Pharmaceuticals Inc.** and **Bayer AG**; and **GlaxoSmithKline plc**'s Votrient pazopanib.

All three are approved for RCC, while Nexavar also is marketed for HCC and Sutent for GIST. Each of the labels contains instructions on interrupting or adjusting dosing based on side effects.

In every case, the drugs are indicated for use as monotherapy.

ACT Biotech Inc.

San Francisco, Calif.

Technology: Oral small molecule kinase inhibitors

Disease focus: Cancer

Clinical status: Phase II

Founded: 2008 by Ali Fattaey and Wolf Busse

University collaborators: None

Corporate partners: None

Number of employees: 6

Funds raised: \$18 million

Investors: NGN Capital

CEO: Wolf Busse

Patents: Four, covering composition of matter and use of various tyrosine kinase inhibitors to treat proliferative diseases

RCC and HCC are both hypervascular cancers, while the majority of GIST tumors express mutations in stem cell factor (SCF) receptor tyrosine kinase (c-Kit; KIT; CD117), one of the many kinases blocked by Sutent.

Ali Fattaey, ACT's president and COO, noted Nexavar and Sutent have been tried in Phase III trials in breast, colorectal, lung,

pancreatic and prostate cancers, among others.

He said promiscuous binding profiles are primarily to blame for the lack of success in these settings, where the drugs also have not proven sufficiently effective as single agents.

Side effects associated with poor selectivity are exacerbated when the TKIs are added to chemotherapies, which have plenty of problems themselves, Fattaey noted. As a consequence, one or both drugs must be given at a lower dose or in regimens that include drug holidays, resulting in suboptimal efficacy.

The compound is a highly selective inhibitor of all three VEGF receptors, platelet derived growth factor receptor (PDGFR) and c-Kit. Fattaey believes this selectivity will allow telatinib to be used with chemotherapy at full doses.

ACT licensed exclusive rights to telatinib from Bayer in 2008.

The compound already had completed multiple Phase I trials in solid tumors and in combination with several chemotherapies. What caught Fattaey's eye was telatinib's "exceptionally clean safety profile that surpassed all of our expectations for an anti-angiogenic agent."

According to Fattaey, telatinib's dose-

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ACT Biotech Inc.,
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limiting toxicity was not reached in Phase I testing. The observed toxicities, he said, “are hypertension, which is a class effect of anti-angiogenic agents, and a small amount of short-lived fatigue, both of which are manageable.”

Fattaey said ACT has little interest in developing telatinib for RCC, which he said is no longer an underserved market.

“We settled on metastatic stomach cancer because it rivals pancreatic cancer in terms of deadliness, with patients only having 6-7 months of survival,” and because telatinib already had human safety data when combined with capecitabine plus irinotecan — the current standard of care in this setting.

In January, ACT reported interim data from an open-label Phase II trial showing 900 mg oral telatinib given twice daily plus SOC produced one complete response and 21 partial responses in 32 patients. ACT will report final Phase II data this year.

In the meantime, Fattaey is focusing on finding a partner for telatinib. In March, the company submitted an SPA to FDA for a Phase III trial that will enroll 700 patients. Overall survival is the primary endpoint. Fattaey expects the trial will start this year and take three years.

Telatinib also has shown activity in Phase I testing for colorectal cancer.

There are at least three VEGF receptor TKIs in Phase III testing, including Pfizer’s axitinib, tivozanib from **Aveo Pharmaceuticals Inc.** and Recentin cediranib from **AstraZeneca plc** (see *BioCentury*,

March 15 & Dec. 13, 2010 & Feb. 21, 2011).

According to Fattaey, “nobody has any data showing they can combine the full dose [TKI] with full doses of chemotherapy like we’ve shown with telatinib in stomach cancer.”

Fattaey hopes to raise \$40-\$50 million in a series B round this year to fund the Phase III trial, though he also hopes to announce a partnership around the same time to defray costs. This would also allow ACT to put more resources towards the rest of its pipeline.

ACT’s next most advanced program, ACTBI003, is an oral kinase inhibitor of phosphoinositide 3-kinase (PI3K) and fibroblast growth factor (FGF) pathways. The compound, which also came from Bayer, will enter Phase I testing for solid tumors this year.

In conjunction with the 2008 deal with Bayer, ACT raised \$12 million in a series A round from NGN Capital (see *BioCentury*, May 12, 2008). The company raised \$3.5 million in venture debt in 2010 and \$2.7 million in a 2011 convertible note deal, both with NGN.

COMPANIES AND INSTITUTIONS MENTIONED

ACT Biotech Inc., San Francisco, Calif.

AstraZeneca plc (LSE:AZN; NYSE:AZN), London, U.K.

Aveo Pharmaceuticals Inc. (NASDAQ:AVEO), Cambridge, Mass.

Bayer AG (Xetra:BAY), Leverkusen, Germany

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Onyx Pharmaceuticals Inc. (NASDAQ:ONXX), Emeryville, Calif.

Pfizer Inc. (NYSE:PFE) New York, N.Y.