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FLIPPING THE SWITCH ON KINASES

Deciphera advancing oncology pipeline with $75M series B round

By Jennifer Boggs, Managing Editor

After making the jump from drug discovery to drug development and quietly ramping up a clinical-stage oncology pipeline, Deciphera Pharmaceuticals LLC found a new backer in New Leaf Venture Partners, which led a $75 million series B round aimed at getting its lead switch control kinase inhibitor candidates through proof of concept and moving others into human testing.

"It's a pretty rich pipeline for a small company," said President and CEO Michael Taylor, who joined the firm in April 2014. Prior to his appointment, Deciphera, led by founder Dan Flynn, who now serves as chief scientific officer, had produced five clinical candidates, including one that emerged from a 2008 research collaboration with Eli Lilly and Co. on B-Raf kinase inhibitors.

That deal, which was big news for the young company at the time – and remains ongoing, having provided Deciphera with more than $30 million in nondilutive funding so far – includes potential milestone payments of up to $130 million per program. But similar deals are unlikely to be forthcoming. (See *BioWorld Today*, Oct. 6, 2008.)

While those early stage, research deals can be lucrative for firms starting out – and Taylor completed a number of those at his previous company, Ensemble Therapeutics Inc. – "to really build out a company it makes sense to discover and develop interesting candidates" to the point where it's more appropriate to seek a partner, "when it's proven they have a target profile that merits further development," he said.

That's what Deciphera plans to do. "We have a number of programs in or about to start phase I clinical trials, so the [series B] round is really designed to provide the resources to get those programs through key inflection points over the coming years," Taylor told *BioWorld Today*, later clarifying that to "say the next nine to 15 months."

The most advanced compound, altiratinib, is "well along in a dose-escalation phase I and will be starting a phase I expansion around the first of the year," Taylor said. The study is testing the drug in patients with solid tumors, and the expansion phase will involve patients with actionable MET genomic alterations.

Altiratinib, designed as a spectrum-selective inhibitor of MET, TIE2, VEGFR2 and TRK kinases, emerged from the firm's switch control kinase program. Kinases are involved in signaling cascades and "are generally highly controlled within cells, so they only switch on as needed," Taylor explained. Oncogenic mutations in kinases lead to a malfunction of that activation loop, or "on" switch, causing those switches to turn on when they shouldn't or to stay frozen in the on position, leading to uncontrolled cell growth.

Researchers found ways years ago to block those switches. Leukemia drug Gleevec (imatinib, Novartis AG), for example, works by selectively blocking Bcr-Abl, a tyrosine kinase found on cancer cells that is stuck in the "on" position, causing it to continue adding phosphates. Deciphera's candidates are designed to improve on that kind of selective activity.

Its founder, Flynn, spent more than a decade working out how to improve the binding of type II kinase inhibitors "in such a way as to make it impossible for that off switch to move from off to on," Taylor said. The result is a compound capable of binding to the region of the molecule that receives that on switch – the switch pocket – and "really lock it into place so the kinase cannot be switched on."

Going one better, Deciphera's compounds can also "sneak into kinases when they are on and turn them off," he added. "So we can inhibit not only wild-type, but virtually all types of mutant forms."

Altiratinib, for instance, demonstrated an ability to inhibit both wild-type and mutant forms of MET, including some mutant forms of MET not easily blocked by other MET inhibitors, according to data published in this month's issue of *Molecular Cancer Therapeutics*. MET mutations are well known as driver mutations in certain cancer types; they also are associated with resistance mechanisms, suggesting altiratinib could prove more durable than existing drugs.

Taylor said altiratinib has potential in multiple indications – "lung cancer and colorectal cancer are two important ones," he said – but the drug will rely on a precision medicine approach to select patients whose cancers carry those specific mutations. Whether that will require

Deciphera to develop a companion diagnostic, however, will depend on how the whole notion of precision medicine advances within the health care system.

"We are doing extensive biomarker work alongside drugs in clinical trials," Taylor acknowledged. But the precision medicine field is moving fast. "We're coming to the point where almost all patients will be screened for genetic abnormalities. We think it's quite likely over the next few years these patients will be identified at the hospital when they're diagnosed," preventing the need for companies to develop their own companion diagnostics.

That said, "We have built it into our plans," Taylor added, just in case.

PIPELINE POTENTIAL

Behind altiratinib, Deciphera has DCC-2618, a pan-KIT inhibitor that has been shown in preclinical studies to block exon 17 KIT mutations that are refractory to existing therapies. The company is set to start a phase I dose-escalation study, "so by the middle of 2016 we should have readouts on that compound," Taylor said.

DCC-2618 previously received FDA orphan designation for gastrointestinal stromal tumors.

With rebastinib, formerly DCC-2036, a kinase inhibitor designed to block TIE2, VEGFR1 and Bcr-Abl, Deciphera is planning combination trials with checkpoint inhibitors. Those studies are expected to start at the end of this year or early next year.

Earlier in development is DCC-3014, described as an "ultra-selective" inhibitor of FMS kinase, another compound that might work in combination with immuno-oncology drugs. For the combination programs, Taylor said, Deciphera might look at partnering earlier. "Those are going to be complicated development programs so partnering with a major pharma at an appropriate point would make sense."

Meanwhile, the Lilly-partnered compound, LY300912 (DP-4978) is proceeding in phase I development, being testing in several cancer types, including melanoma, colorectal cancer and mutant Ras-driven cancers.

To date, work at Deciphera has been funded by the Lilly agreement and by a series of investments totaling $85 million from a single, wealthy investor in the Midwest. Deciphera was founded in 2003 and retains a research facility in Lawrence, Kan., though it's also expanded with an office in Waltham, Mass. Altogether, the firm boasts roughly 20 employees; that number is expected to increase.

"We've transitioned from a research-heavy [firm] to a more development focus," Taylor said. "So we expect to grow pretty rapidly."

Deciphera is adding to its board, with New Leaf's Liam Ratcliffe taking a seat. Taylor described Ratcliffe as a "very experienced" drug developer who "knows kinase inhibitors."

The series B funding should carry the firm at least through 2016.