Epizyme Taps Roche to Develop Cobas 4800 CDx for Epizyme/Eisai Lymphoma Drug Candidate

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Epizyme this week announced a collaboration with Eisai and Roche to develop an in vitro, PCR-based companion diagnostic test to help treat genetically defined lymphomas.

The agreement is Epizyme's first companion diagnostic partnership, and will focus on identifying lymphoma patients with mutations in the EZH2 gene in order to potentially select patients for therapy with an experimental EZH2 inhibitor that Epizyme is currently developing with partner Eisai.

For its part, Roche will develop the companion diagnostic test on its Cobas 4800, the platform on which Roche has developed all of its companion diagnostic tests to date, for both internally and externally developed therapeutics, a Roche spokesperson told PCR Insider.

According to Epizyme officials, when considering development partners for its first companion test, the company chose to work with Roche primarily because of its extensive CDx development experience.

"We looked at a set of diagnostic companies, and wanted people who had not only experience developing diagnostic tests, but whose platforms were broadly used," Jason Rhodes, executive vice president and chief business officer of Epizyme, told PCR Insider this week.

"Not only is Roche a very experienced diagnostic company, but they have very relevant and recent experience developing companion diagnostics for personalized therapeutics in the oncology space," Rhodes added. "When you look across that set of selection criteria, they were obviously a very good fit across all of them."
Roche has successfully marketed Cobas 4800-based tests to detect mutations in KRAS codons 12, 13, and 61 to identify colorectal cancer patients not likely to respond to anti-EGFR monoclonal antibody treatments; the BRAF V600 mutation in FFPE melanoma tissue to help select patients for treatment with vemurafenib (Zelboraf), developed by Plexxikon (now part of Daiichi Sankyo) and Roche; and mutations of EGFR exons 18, 19, 20, and 21 to help select non-small cell lung cancer patients for treatment with EGFR inhibitors.

Of these, only the BRAF test has been approved by the US Food and Drug Administration. The Roche spokesperson also noted that the company has several undisclosed companion diagnostic programs in "early-stage development." Roche also offers infectious disease tests on the Cobas 4800, such as its assay for human papillomavirus and its combined assay for diagnosing chlamydia and gonorrhea.

The Cobas 4800 is a fully automated system that combines the Cobas x 480 instrument for fully automated sample prep and the Cobas z 480 analyzer for real-time PCR. The combined system can set up 94 samples in less than 20 minutes and process up to 384 samples a day.

Epizyme noted that the pedigree of the Cobas 4800 was also an important factor in its decision to partner with Roche.

"We are really focused on the therapeutic, and we partner with companies like Roche on a program-by-program basis based on their expertise with the technology," said Robert Copeland, executive vice president and chief scientific officer at Epizyme. "We're not heavily invested in technology development. What specific PCR platform might have particular advantages — we're certainly versed in that enough to make good decisions on partners. But it's not really in our wheelhouse. We're really focused on making the small molecular medicines for therapeutics, and partnering with the right diagnostic companies for the companion diagnostic test."

Rhodes added that Epizyme "doesn't want to take on any new technologies or commercialization risks on the diagnostics side — we want to work with an experienced party that has a broad presence in the space … and the technology that we need to develop the drug and for regulatory purposes … and achieve that goal in a very clear way."

Epizyme, based in Cambridge, Mass., develops personalized therapeutics for patients with genetically defined cancers, and in particular is pursuing that strategy in the histone methyltransferase class of enzyme targets.

The first of Epizyme's lead programs, currently in clinical development, focuses on a histone H3 methyltransferase called DOT1L, translocations of which are associated with a subtype of leukemia called MML-rearranged leukemia.

Its second program, targeting EZH2, is in pre-clinical development. In a study published in September in Nature Chemical Biology, Epizyme researchers demonstrated that lymphomas with a point mutation in EZH2 require H3K27 methylation activity to proliferate, suggesting that EZH2 is a driving oncogene in these cancers and thus a potential therapeutic target.
"Our entire strategy is predicated on going into those genetically defined patients as early as possible in clinical development," Rhodes said. "In the case of EZH2, and non-Hodgkins lymphoma patients generally, we very quickly will go into an expansion cohort that only has genetically defined patients. Once we demonstrate efficacy we'll very quickly move into registration studies. So it's very much the kind of clinical development strategy that Xalkori and Zelboraf, two personalized therapeutics approved in 2011, went through."

In 2011 Epizyme entered into a worldwide partnership with Eisai to develop therapeutics targeting EZH2. As part of that deal, Epizyme received $6 million in upfront and initial milestone payments, and may earn more than $200 million in additional research, development, and sales milestones, and up to double-digit royalties.

Additionally, Eisai is funding 100 percent of R&D through human proof of concept, at which point Epizyme has the right to opt into a profit share and co-commercialization arrangement for the US.

Meantime, "there is a research plan for the CDx that really sits parallel to the clinical development plan for the therapeutic, so the activities are very coordinated," Rhodes said. "The actual specific development work around the diagnostic kit will be done by Roche, but it's done in coordination with us … because obviously bits and pieces need to go hand in hand."

Following that, "there will be a joint commercialization effort … which we haven't described in more detail," Rhodes added. "But obviously the commercialization needs to be coordinated because it's a test that will be used to identify patients who will be treated with our EZH2 therapeutic."

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