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UCLA Spinout Trethera Trials Novel DNA Metabolism Combination

Executive Summary

Emerging Company Profile: University spinout, Trethera – which recently signed a licensing deal to develop Nanotherapeutics Inc.'s ribonucleotide reductase inhibitor Triapine – believes it is the first company to target cancer nucleotide metabolism through a combination approach.

Trethera, a small biotech based in Santa Monica, California, is using a dual-targeting therapy approach that it believes no other company is testing currently to treat hematological and solid cancers.

The company highlights that, unlike many cancer drugs in development based on targeted inhibitors as single treatments, it is adopting a fundamentally different approach by combining small molecule, metabolic therapies.

Trethera's technology enables the simultaneous inhibition of different biosynthetic pathways that cancer cells utilize to overcome single agent therapies. The company is focused on the interface between the several metabolic pathways that control the production of nucleic acids and the signal transduction pathways that allow cells to adapt to replication stress and DNA damage repair.

By using a dual-targeting approach at the very beginning of treatment, the risks of drug resistance and/or poor response rates are minimized, Trethera says.

"In the history of oncology and the treatment of solid tumors, there is surgery, hormonal therapy, chemotherapy and new immunotherapies – but there are still tumors that are not treated as they should be," Johanna Holldack, president and CEO of Trethera told *Scrip*. "There is one aspect that hasn't been addressed yet, in a way to open new treatment doors, and that is nucleotide metabolism."

The company, which has been launched on angel financing from "friends and family" investors, is a spinout from the University of California Los Angeles (UCLA). It is developing a novel deoxycytidine Kinase (dCK) inhibitor, TRE-515, which has been chemically engineered to improve bioavailability and has demonstrated anti-tumor activity in preclinical studies.

Trethera will develop TRE-515 in leukemia as the first indication. An investigational new drug application for TRE-515 is expected to be filed in the first half of this year. The company will launch a Phase I dose escalation study for the product as a single agent therapy in the summer of this year, with proof-of-concept data expected by the end of 2018.

Trethera then plans to initiate preclinical studies for its dCK inhibitor in combination with other drugs. In January 2017, the small biotech signed an exclusive worldwide licensing agreement with Nanotherapeutics Inc. for the global development, manufacturing and marketing of Triapine, and all formulations, for hematological malignancies. Triapine is a clinical-stage, small molecule inhibitor of ribonucleotide reductase (RNR), a key enzyme in the *de novo* pathway of nucleotide biosynthesis. Trethera plans to use this product in combination with TRE-515, initially targeting acute leukemia.

Johanna Holldack, Trethera CEO

Trethera Holldack said, "We are trying to inhibit two convergent pathways, so we are doing a combination trial with two small molecules."

The combination clinical trial program will be an "all-comers" study for leukemia patients, Holldack noted. "This differentiates us from other developers. We are able to open up the study to all leukemia patients because we are targeting nucleotide metabolism, not a specific cell surface antigen," she said.

The company will study its combination therapy in acute lymphocytic leukemia, acute myeloid leukemia and chronic myeloid leukemia patients to begin with, but if patients with a particular leukemia indication respond better in early trials the company may pursue one group only when it gets to Phase IIb. However, Holldack said this is something Trethera will only be able to address as it progresses its combination research and trials.

Challenges & Opportunities

"Our approach is completely novel, so from an FDA or regulatory perspective the questions are always around safety in early, innovative studies," Holldack noted when asked about potential development challenges ahead for TRE-515. She highlighted that Trethera has developed a "huge toxicology profile" for its novel agent and has not, to date, seen any concerning effects. "The safety profile of both drugs for the doses we will use in the clinic are surprisingly good," Holldack said. "Safety is always a key question when you try something new." Holldack added that the company has already tested TRE-515 in non-human primates, in which it saw positive results and a good amount of target engagement.

Trethera's CEO noted that there is currently no direct competition in the pipeline for its DNA repair combination therapy. But she said this position is "a blessing and a curse because we have to convince everybody that it is a promising treatment approach." There is a lot of competition within leukemia drug development, but Trethera believes one of the benefits of its compounds later down the line will be affordability. "These are small

molecules, therefore the costs for manufacturing will be reasonable. Some other treatments are very costly, so this is an advantage for our therapy," she said.

Financing

Holldack said a challenge for the company in 2017 will be the transition from drug discovery into clinical development. The company plans to initiate a series A financing within the first half of 2017, with a target of $25m. The funding will be used to get Trethera's lead combination therapy into Phase IIa trials. This will be a change for the business, which currently only has six employees and is a virtual setup that contracts out much of its work.

Holldack said the company is looking for partners, specifically those with other compounds to test in combination with its dCK drug pipeline, or partners for future clinical development of its lead compound.

Trethera became operational in 2015 after hiring its first employees and raising $10m from angel investors, the funding was initially a debt financing but was converted into a preferred seed round in February 2016.

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