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Market RECISTs Vincerx's 'amazing' phase I cancer data

By Randy Osborne, Staff Writer

Stable disease in about half the patients tested wasn't enough for Wall Street, and shares of Vincerx Pharma Inc. (NASDAQ:VINC) nosedived by $3.72, or 78%, to close April 9 at $1.06 on the disclosure of preliminary phase I data with small-molecule drug conjugate (SMDC) VIP-236 in metastatic solid tumors.

Palo Alto, Calif.-based Vincerx offered the findings during the American Association for Cancer Research (AACR) annual meeting in San Diego. Designed to target alpha-v beta-3 integrins in tumor tissue and to release the payload 7-ethyl camptothecin 1, VIP-236 yielded encouraging signs, said Vincerx, including tumor reduction and an improved safety profile in heavily pretreated patients. The pharmacokinetic (PK) data show very little free payload in circulation, consistent with other research so far.

Vivek Subbiah, chief of early phase drug development, Sarah Cannon Research Institute

"You clearly have a drug in your hands," said Vivek Subbiah, chief of early phase drug development at the Sarah Cannon Research Institute, who spoke during Vincerx's presentation. Next, the company needs to try various doses against specific indications. Examining the waterfall plot of the study, he called the enrolled subjects "typical of an all-comers solid tumor phase I study," with colorectal cancer (CRC) and sarcomas, the latter standing as "one of the toughest cancers that don't respond to anything."

On the matter of CRC, he pointed out that the several drugs approved for the condition recently were green-lighted on the basis of progression-free survival rather than overall response rate. VIP-236, with its option for repeated dosing, could improve the setup for CRC patients. "We have so many [antibody-drug conjugates (ADCs)] with the same payloads going after the same targets," he said. "We need a breath of fresh air" such as VIP-236 could provide.

Leerink analyst Jonathan Chang observed in a report that "the AACR poster [on VIP-236] marked the first clinical data disclosure from the trial" and may have landed "below investor expectations leading up to the event," with 53.8% of 13 patients achieving stable disease. "Though lacking RECIST [Response Evaluation Criteria in Solid Tumors] responses, [members of] management said that they believe they are approaching the range of efficacious doses and that they expect a deepening of responses with time." Chang maintained his "outperform" rating.

Raquel Izumi, chief operations officer, Vincerx

Raquel Izumi, chief operations officer, pointed out that "we had no DLTs [dose-limiting toxicities]. That means that we have room to go up. We're headed in the right direction, we're just not done escalating yet." Patients, she told *BioWorld*, are "begging to be escalated to the next cohort because they're tolerating the drug so well. Think about that for a minute."

Regarding the market reaction, she said the scenario is "damned if you do, damned if you don't," and the company is unveiling what was promised: early results, which can't show the kind of detail that Vincerx backers probably want. "They punish you for something that's, in my opinion, very unrealistic," she said – possibly a sign of the times. "We have vetted our data with the people who actually treat patients," Izumi said. "Every single one of them is saying this is looking absolutely amazing."

The main objectives of the dose-escalation effort are to assess safety and tolerability while establishing an optimal dose and schedule, so discovering dose-dependent clinical activity – albeit early – provides hope, the company said. Study VNC-236-101 is an open-label, multicenter bid with monotherapy VIP-236 for patients who have exhausted all standard therapy options. Fifteen patients have been dosed to date on the once-every-three-weeks (Q3W) schedule. Sequential dose-escalation cohorts with the Q3W schedule were 0.2 mg/kg (n=2), 0.4 mg/kg (n=5), 0.6 mg/kg (n=5) and 0.8 mg/kg (n=3). Results of the Q3W regimen show that the patient population is typical of a phase I study with heavily pretreated patients and a wide range of tumor types. The schedule is well-tolerated with no DLTs in any patients, and no patients have discontinued VIP-236 due to an adverse event. No severe or life-threatening diarrhea has turned up (unlike with other camptothecin agents), validating

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the purposeful design of VIP-236's optimized payload, the company said.

'We're tracking well'

Vincerx did the first efficacy assessment at the end of the second cycle (that is, after only two doses on the Q3W schedule). Seven patients have achieved objective stable disease, including tumor reduction. Four patients remain on study with the longest treated patient on study for 168 days. Dose escalation continues on the Q3W schedule, and the company said more phase I data should be available this summer. "I would hope that we would at least get to our maximum tolerated dose so we can understand where that is, and then we'll be able to give guidance in terms of where we're going to go in our expansion cohorts," Izumi said.

Ahmed Hamdy, CEO, Vincerx

CEO Ahmed Hamdy shied away from cross-trial comparisons but mentioned as an example of early research's uphill path, Trodelvy (sacituzumab govitecan, Gilead Sciences Inc.), a Trop-2-directed antibody and topoisomerase inhibitor conjugate used for the treatment of breast cancer and urothelial cancer. The drug won its first U.S. FDA nod in April 2020. In a phase I dose-escalation trial with the compound, 16 of 21 patients gained stable disease as their best response. Eventually two achieved partial responses, but they had to undergo treatment for two to eight months. "It takes time for deepening the responses," he said. "We're tracking well."

Vincerx is the first to come up with an SMDC in oncology. Investors are "missing that part of it," Izumi said. "Everybody else is spending their time developing a bunch of me-too ADCs. Same linkers, same payloads, same targeting antibodies – that's not going to move the dial." FDA officials already made their position known, she said. "They're not interested in the fifth, sixth, seventh" versions of the same ADC.

Also offered at the AACR meeting was an update on VIP-943, the firm's next-generation ADC that binds to CD123, a validated target in myeloid malignancies. Once inside the cell, it is only cleaved by an intracellular protein called legumain, allowing specific release and activation of the kinesin spindle protein inhibitor payload within the cancer cell. Study VNC-943-101 with the compound is an open-label, multicenter, phase I dose-escalation trial with monotherapy VIP-943 for the treatment of patients with CD123-positive acute myeloid leukemia, B-cell acute lymphocytic leukemia or myelodysplastic syndromes (MDS) who have run out of treatment options. The study's main objective is to determine a safe dose and schedule for VIP-943 for further work.

Given once per week, VIP-943 was dosed in three patients in cohort 1 (0.2 mg/kg) and four patients in cohort 2 (0.4 mg/kg). Despite the initial low doses, all seven sequentially enrolled patients completed the 28-day DLT evaluation period. Five out of seven received a second-cycle dose and two of these patients started cycle three. One patient with MDS is still on study on cycle three. No DLTs occurred in cohorts 1 and 2. Four patients have been enrolled in cohort 3 (0.7 mg/kg) and are undergoing DLT assessment. As with the other drug, VIP-943 PK data show very little free payload circulating, similar to previous research. As the study moves through further dose escalation, Vincerx will roll out more phase I data at or near the time of the 2024 European Hematology Association annual meeting in June 2024.