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TAKE IT ON CHIN, TRABECTEDIN?

Cytrx as Lazarus: Buoyed by aldox findings, set to file NDA late next year

By Randy Osborne, Staff Writer

In July, aldoxorubicin "seemed dead and buried," Cytrx Corp.'s chief medical officer, Daniel Levitt, acknowledged to *BioWorld Today*, but sifting updated data from the phase III trial in soft-tissue sarcoma (STS) turned up enough promise that the company plans to file an NDA late next year.

Los Angeles-based Cytrx tested aldoxorubicin against investigator's choice in patients with relapsed or refractory disease, narrowly missing statistical significance in the entire study population but making the grade in progression-free survival (PFS) among the North American segment enrolled: 312 patients out of the total 433 subjects that signed up.

Specifically, the experiment met its goal in PFS in 246 patients with leiomyosarcoma and liposarcoma (p=0.007), the two most common forms of STS, which accounted for 57 percent of patients in the trial. The hazard ratio was 0.62 (95 percent CI 0.44-0.88), representing a 38 percent reduction in the risk of tumor progression for patients receiving aldoxorubicin when compared to the treatment chosen by investigators.

Levitt said PFS in North American patients was especially satisfying (p=0.028; HR=0.71, 95 percent CI 0.53-0.97), and for the whole study group, aldoxorubicin performed better than treatments doctors selected, though it only came near and did not reach statistical significance (p=0.12; HR=0.81, 95 percent CI 0.64-1.06). "Looking at the individual drugs, if we had chosen simply one of them [as a comparator], it's likely that we would have had a significant difference for the entire population," he said, but the FDA was "very supportive" of the investigator's-choice route. "It was one of the reasons we had such an easy time getting a special protocol assessment," he said.

In the entire study population, aldoxorubicin achieved a statistically significant improvement with regard to disease control rate (DCR, defined as objective response rate [ORR] plus stable disease for at least four months): 29.4 percent vs. 20.5 percent for the patients treated with investigator's choice (p=0.030). In North American patients, those treated with aldoxorubicin showed a DCR of 32.9 percent, compared to 19.2 percent for patients treated with investigator's choice (p=0.007), an overall improvement of 71 percent. ORR in North American patients also favored aldoxorubicin, 8.7 percent vs. 3.3 percent (p=0.058). Cytrx noted that no objective responses were observed in patients treated with Votrient (pazopanib, Novartis AG), approved by the FDA for STS in 2012. Patients continue to be followed for overall survival (OS), a secondary endpoint, and Cytrx expects the OS data to be available in 2017.

The company took some lumps over the summer upon disclosing then-available data, showing a miss on the primary endpoint of PFS, which the firm said might have been due to a two-month clinical hold placed on the trial in late 2014. "The clinical hold probably slowed us down in terms of completing enrollment, but by this time, I can't say it had a significant negative effect on the study itself," Levitt said. Jefferies analyst Chris Howerton said at the time that, "despite the potential for another analysis and other indications, we see no path forward" for aldoxorubicin. The PFS bar is too high when compared to Votrient, he said, and "doubling" the ORR/DCR would not "be meaningful in this population, as the reported ORR of Votrient was 4 percent." Based upon the results in July and those detailed earlier at the American Society of Clinical Oncology meeting, there was not "sufficient evidence to support the continued development" of the compound, he wrote in a report. (See *BioWorld Today*, July 12, 2016.)

NON-SPECIFIED ENDPOINTS APLENTY

"We were very pleased that the data from the North American group came out very positive overall, and for the whole group, the data for leiomyosarcoma and liposarcoma patients also looked extremely positive," Levitt said. "That was not something, just based upon the initial analysis, that we really expected, although we did pre-specify these analyses for the tumor histopathologies and for geographic areas." The company also hired independent consultants "to check on the contract research organization [CRO], and they confirmed that the CRO's programming and analysis matched theirs," he said, adding that he was "not really disappointed in this sort of complicated study," which was

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"probably the most stringent clinical study design in sarcoma that's ever been undertaken. We allowed any of the standard treatments that were being used at the time we started the study to be used by the study sites in the control arm," a practice that has not been standard.

"Looking at the individual drugs, if we had chosen simply one of them [as a comparator], it's very likely that we would have had a significant difference for the entire population," he said. "Other studies in this indication actually did that," rather than let the doctor decide which therapy was best, an approach that raises ethical problems.

Aldoxorubicin combines doxorubicin with a novel single-molecule linker that binds directly and specifically to circulating albumin. Since tumors concentrate albumin, delivery of the linker molecule with the attached doxorubicin is greater to the cancer site and – in the acidic environment of the tumor, but not the neutral environment of healthy tissues – doxorubicin is released as much greater possible doses with less toxicity.

Although Levitt conceded it's "hard to compare one study to the other," he said the phase III results as sorted further suggest that aldoxorubicin performed in a manner "comparable" to Yondelis (trabectedin), from Madrid-based Pharmamar SA and partnered with Johnson & Johnson, of New Brunswick, N.J. Yondelis is indicated for the treatment of patients with unresectable or metastatic liposarcoma or leiomyosarcoma who received a prior anthracycline-containing regimen.

Patients treated with Yondelis must be medicated first with dexamethasone and get the Yondelis infusion over a 24-hour period.

"With aldoxorubicin, they receive a 30-minute infusion and maybe stay around [the clinic] for another 30 minutes, and then can go home," he said. "The side effect profile with aldoxorubicin is what you would expect with doxorubicin. We saw no significant cardiac events, unlike Yondelis, which has a cardiomyopathy issue in about 6 percent of patients."

More parsing of the data will look at differences in patient populations in the aldoxorubicin study, and will include "at least 30 different non-specified endpoints for more color on what may have contributed to the outcome," he said. Cytrx officials "met with about a dozen of the investigators in this study, and they were all very positive about aldoxorubicin," he added. "It certainly is an active drug."

Shares of Cytrx (NASDAQ:CYTR) traded high in the premarket activity Tuesday but ended at 57 cents, up 1 cent. //

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