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Confirmatory Trial Plan For Acrotech's Folotyn, Beleodaq Needs Rethinking, FDA Panel Says

by Sue Sutter

Seven-year timeline for Phase III trial in first-line peripheral T-cell lymphoma is too long, advisory committee members say, also questioning study feasibility; some panelists favor Richard Pazdur's push for a second, concurrent trial in the relapsed/refractory setting that could read out sooner.

Acrotech Biopharma LLC's current seven-year timeline for confirming clinical benefit of the lymphoma drugs Folotyn (pralatrexate) and Beleodaq (belinostat) under accelerated approval is excessive, and the company should consider additional studies to better clarify the drugs' efficacy and safety in a shorter period of time, a US Food and Drug Administration advisory committee said.

Specifically, many panelists seemed to favor an idea put forth by Oncology Center of Excellence Director Richard Pazdur for a shorter, smaller study in a refractory population of peripheral T-cell lymphoma patients conducted concurrently with the recently initiated confirmatory trial in the first-line setting.

The 16 November meeting of the Oncologic Drugs Advisory Committee served as an unpleasant time in the spotlight for Acrotech, which acquired pralatrexate and belinostat in 2019 but was on the hook for explaining why clinical benefit still has yet to be confirmed more than 14 and nine years after their respective accelerated approvals for treatment of patients with relapsed/refractory PTCL.

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> *"I think the consensus of the advisory committee is that we have significant concerns about the very prolonged delay and getting these confirmatory studies underway." – Oregon Health and Science University's Andy Chen*

Pazdur described the drugs' development as "suboptimal … and I'm being kind." Panelists used terms such as "sloppy" and suggested the seven-year duration of the new confirmatory trial may be part of a business strategy to run out the patents on the drugs.

Several panelists said one or both of the drugs should be withdrawn from the market because of their prolonged status under accelerated approval without confirming clinical benefit, and that doing so would make it easier to conduct randomized trials.

ODAC members' recommendations to withdraw approval were particularly notable because the FDA was not calling for such an action due to the high unmet need in PTCL, a rare disease, and the limited therapeutic options available to patients with relapsed/refractory disease. (Also see "*Accelerated Approval: Acrotech's Confirmatory Trial For Folotyn, Beleodaq More Than A Decade Behind Schedule*" - Pink Sheet, 14 Nov, 2023.)

"I think the consensus of the advisory committee is that we have significant concerns about the very prolonged delay and getting these confirmatory studies underway," said the panel's acting chairman, Andy Chen, associate professor at Oregen Health and Science University, summarizing the panel's discussion.

"We also have concerns about the dosing and whether or not these are the appropriate studies to be doing, or should there be an additional study in a subset of T-cell lymphoma or in the relapsed/refractory setting."

"We would like the FDA and sponsor to strategize about other possible ways to have a shorter study readout than waiting another seven years from now, which would be essentially 20 years from the initial approval of pralatrexate," Chen sad.

Confirmatory Trial Timeline Unacceptable

The FDA did not pose any voting questions to the panel, but rather asked the group to discuss whether Acrotech's current plans to verify clinical benefit for the two drugs is reasonable considering the proposed timelines, and whether insights from this experience may facilitate

completion of confirmatory trials for future accelerated approval products.

> *"It feels like we're trying to rationalize this plan, which extends this time out to potentially 2030. … The current plan to verify clinical benefit is not reasonable given the proposed timelines and the risks to which we are subjecting patients and potentially causing harm." – Patients for Affordable Drugs' David Mitchell*

Acrotech only recently initiated its confirmatory trial for both drugs, a randomized, Phase III trial in newly diagnosed, untreated PTCL patients.

Part 1 of the study will involve selection of an optimal dose for belinostat and pralatrexate in combination with cyclophosphamide/vincristine/doxorubicin/prednisone (CHOP) or a CHOP-like regimen. Part 2 will compare the optimal dosages of belinostat plus CHOP and pralatrexate plus CHOP against CHOP alone. The primary endpoint will be progression-free survival, and study completion currently is targeted for February 2030.

For many panelists, this timeline was simply unacceptable given the prolonged period during which both drugs have been available under accelerated approval.

Consumer representative David Mitchell, a myeloma patient and president of Patients for Affordable Drugs, said the period of uncertainty during which the drugs have been available without confirmation of clinical benefit has been exacerbated by the lack of optimized doses to date.

"It feels like we're trying to rationalize this plan, which extends this time out to potentially 2030," Mitchell said. "The current plan to verify clinical benefit is not reasonable given the proposed timelines and the risks to which we are subjecting patients and potentially causing harm."

Seeking A Faster Study

Gita Thanarajasingam, a lymphoma specialist at Mayo Clinic, said she had feasibility and accrual concerns about the recently initiated confirmatory trial, pointing to the chemotherapy backbone in the CHOP arm and the possibility that clinicians may be unwilling to enroll patients with any level of CD30 expression, which could represent 30%-50% of the target patient population.

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“Even if we get this done and the front-line study is negative, I will still wonder is there a role in this as a single-agent therapy … for some PTCL patients or some specific PTCL histologies in the relapsed/refractory setting,” Thanarajasingam said.

“To give these agents their best chance, can we hedge our bets and also complete a smaller study in relapsed/refractory PTCL that would be … something that we could design to be attractive to patients and clinicians for enrollment with a dose-finding component and a part two with a PFS endpoint? This would give an opportunity to define the optimal dose in the relapsed/refractory population and also complete an additional confirmatory study in the population where you can get a quicker readout on survival endpoints,” Thanarajasingam said.

> ***“I would strongly recommend a faster study in a refractory setting to avoid potentially harming patients for an additional seven years. … That's assuming even that the proposed timelines within the confirmatory studies are met.” – University of Colorado’s Chris Lieu***

Chris Lieu, director of gastrointestinal medical oncology at University of Colorado, said he believed that the clinical benefit of pralatrexate and belinostat “is still more likely present than not. We don't want to prevent patients from receiving active therapies that can help them, but we have to have that confirmatory study.”

“Hearing the comments from the experts in the field, I actually have significant concerns about the feasibility of the confirmatory study,” Lieu said. “I would strongly recommend a faster study in a refractory setting to avoid potentially harming patients for an additional seven years. … That's assuming even that the proposed timelines within the confirmatory studies are met.”

Jorge Nieva, section head for solid tumors at the University of Southern California, said he was concerned that the extended duration of the new confirmatory trial “may be a business strategy to sort of run out the clock on the patents for these drugs. And I'm concerned that making the trial as long as possible is somewhat in the economic interests of the company.”

“Because of that, it's not going to get any easier to have a hard timeline or pull these indications after this study has accrued 100 patients or 200 patients,” Nieva said. “I'm also concerned about the company being able to make decisions, such as dropping one of the arms as one of these drugs gets closer to its patent expiration.”

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He requested Acrotech make the drugs available to cooperative study groups to run a second confirmatory trial. “This would allow us to have extra data and, of course, would save the patient population the risk that this trial ends up being closed for lack of feasibility. And we all have an opportunity to continue to learn about these agents.”

Daniel Spratt, chair of radiation oncology at Case Western Reserve University, said the most likely chance of demonstrating clinical efficacy through objective response rates, progression-free survival and potentially even overall survival is if the accelerated approvals are withdrawn and drug access is limited to the clinical trial setting. “I am still perplexed by keeping them approved for six years,” he said.

The Pazdur Moment

Earlier in the meeting during the panel’s clarifying questions for the FDA and sponsor, there was a quintessential “Pazdur moment,” in which the OCE director typically puts a sponsor on the hot seat, highlighting what he sees as glaring weaknesses in an application or a company’s proffered explanation and/or requesting a commitment for a specific future action. (Also see "*The Return of The Pazdur Moment*" - Pink Sheet, 24 Sep, 2017.) In this case, Pazdur made clear his disdain for the development program underlying the prolonged accelerated approvals of pralatrexate and belinostat.

Nicholas Richardson, deputy director for the FDA’s Division of Hematologic Malignancies 2, said the agency often encourages sponsors to have a comprehensive development program and that can include confirmatory trials in different treatment settings. Because of the limited treatments available in the relapsed/refractory PTCL setting, that is something that could explored in terms of a confirmatory trial, he said.

> *“No one with a straight face could say this drug was developed with due diligence.” – FDA’s Richard Pazdur*

“Can I just jump in here? I want to second that point, and would like to have this company discuss this,” Pazdur said.

“The development of this drug, let's face it is, for lack of a better word, not to be over critical, just say suboptimal. And I'm being kind by using suboptimal rather than other words here. I don't want to be back … years later with a negative trial and be in the same situation.”

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Pazdur asked if Acrotech could develop “a more robust program for the determination of clinical benefit, in other words, do two clinical trials, and the second one being in the relapsed/refractory population?”

“It could be a very simple trial. It could be their drug or their drugs … against dealer's choice, so to speak, whatever the physician would choose. We've seen that multiple times in solid tumors, for example, where there is very little effective therapies. And this would not be a competing protocol to the first-line study but would also be there if we have problems and also lead to the confirmation of benefit, perhaps even more rapidly than a first-line setting.”

“I'd like to hear a commitment from the company on this really because, here again, no one could say that this drug was developed with due diligence. No one with a straight face could say this drug was developed with due diligence,” Pazdur continued.

The FDA has authority to require that confirmatory trials for accelerated approval products be completed with due diligence, and the agency has interpreted this requirement to mean that sponsors must conduct such trials promptly to facilitate determination, as soon as possible, of whether the drug provides the expected clinical benefit, the agency said in its meeting briefing document. (Also see "*FDA Panel To Consider Strategies For Timely Completion Of Accelerated Approval Confirmatory Trials*" - Pink Sheet, 15 Nov, 2023.)

“So we're really in a situation where patients are caught in the middle here, and I feel very bad for that situation and very bad for the patients that they don't have this information," Pazdur said. "And I really think it's up to the company to step up and really develop this drug and make sure that we're not here at the year 2028, 2030, 2031 having this discussion.”

“Are you committed to developing the drug in a relapsed/refractory setting to address this issue to give us more confidence in this drug with a shorter timeline?”

“As of now, at this very stage, I would say we are just looking into it,” Acrotech President Ashish Anvekar said. “We have looked at relapsed/refractory. When we have had the discussion on the possibility of the accrual of this trial with the experts in the field, often we have been told that, look, we know the drug works and how do I do a clinical trial in the same indication where I know the drug works? And that has been posed as a challenge. But what I would say is, if there is a possibility of looking at it, we will certainly want to complete this because I think that could be a shorter path.”

“Doing both trials at the same time could be an option,” Anvekar said. “But it's just a little bit difficult for me, as you can appreciate, to make a commitment at this stage.”

Pazdur noted there are many reasons a confirmatory trial could be negative, including lack of

power or not looking at the correct subgroup. Consequently, more information is needed about the drugs.

“Because of the inadequacy of the development program over the 10-plus years here, we really have to step up to the plate,” Pazdur said. “You have a responsibility to do this, and we will hold you to that responsibility.”