A promising new cancer drug has hit a major setback, raising questions about whether the field is moving too fast

By Ken Garber May. 9, 2018, 3:00 PM

The surprising failure last month of a large clinical trial of a promising cancer immunotherapy drug from the biotech company Incyte has quickly reverberated across the pharmaceutical industry. Three companies have canceled, suspended, or downsized 12 other phase III trials of the compound, epacadostat, or two similar drugs, together slated to enroll more than 5000 patients with a variety of advanced cancers.

The companies say they aren’t dropping the potential drugs, designed to unleash the immune system on cancer cells by blocking an enzyme called indoleamine (2,3)-dioxygenase (IDO). But the retrenching suggests that the frenzy to combine novel drugs with the wildly successful immunotherapies known as checkpoint inhibitors is outpacing the science. The IDO strategy, says neuroimmunologist Michael Platten of the University of Heidelberg in Germany, “has been moved to randomized clinical trials too fast, and now we realize [the enzyme] is still a black box.”

A year ago, the future of IDO inhibitors looked bright. At the June 2017 meeting of the American Society of Clinical Oncology, doctors reported that epacadostat, given with the approved checkpoint inhibitor Opdivo, shrank tumors in 25 of 40 of melanoma patients—roughly double the historical response rate of Opdivo alone. A second epacadostat trial of 63 additional melanoma patients was also impressive, and the drug seemed to work well in other tumor types.

The results from smaller, phase II trials don’t always predict how a cancer drug will do in a randomized phase III trial. But the epacadostat data “were pretty compelling,” says Yale University immuno-oncologist Mario Sznol, who expected to see some benefit to patients. (Sznol was not involved in any of the trials.) Compared with a checkpoint inhibitor alone, however, epacadostat made no difference for the roughly 350 patients receiving both drugs in Incyte’s phase III trial.

“Those results are disappointing and clear,” Incyte Chief Medical Officer Steven Stein in Wilmington, Delaware, said on a conference call announcing an early end to the trial. “The drug didn’t perform.”

Researchers at the company and elsewhere are baffled. Is IDO simply a bad target? Is Incyte’s particular chemical compound flawed? Or were the wrong tumor types or patients treated? “You could go through the whole list of reasons,” Sznol says.

Mass exodus

Three companies have suddenly suspended, canceled, or downsized 13 trials of indoleamine (2,3)-dioxygenase inhibitors (in combination with drugs called checkpoint inhibitors).

<table>
<thead>
<tr>
<th>Company</th>
<th>Drug</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incyte (nine trials)</td>
<td>epacadostat (INCB24360)</td>
<td>Melanoma, lung, head and neck, urothelial, kidney</td>
</tr>
<tr>
<td>Bristol-Myers Squibb (three trials)</td>
<td>BMS-986205</td>
<td>Melanoma, lung, head and neck</td>
</tr>
<tr>
<td>NewLink Genetics (one trial)</td>
<td>indoximod (NLG8189)</td>
<td>Melanoma</td>
</tr>
</tbody>
</table>

The field still generally agrees that IDO makes sense to target, in combination with checkpoint inhibitors. Those drugs release a molecular brake on tumor-killing immune T cells. But the unleashed cells then stimulate the production of IDO, which, in a negative feedback loop, shuts them down again. IDO does this mainly by indirectly activating a protein
inside immune cells called the aryl hydrocarbon receptor (AHR). Suppressing IDO should therefore make checkpoint inhibitors work better.

But much about IDO remains unknown, Platten says. Exactly how IDO stifles the immune system is unresolved, nor is it clear which immune cells are most involved, he says. Even the idea that IDO blunts the antitumor effects of checkpoint inhibitors is suspect. "The evidence that this is really happening in the clinical situation … is very slim," Platten says.

The drug, not the target, might be the problem. Some IDO inhibitors bind the AHR and thus could suppress the immune system, the opposite of the drug's intent. NewLink Genetics reports that its drug does activate the AHR, but in a way that it still believes promotes a strong immune response against tumors. Both Incyte and Eli Lilly and Company say their drugs do not affect the AHR.

Levi Garraway, Eli Lilly's senior vice president of oncology global development and medical affairs in Indianapolis, says that going forward the company will try to select patients who are most likely to respond to IDO inhibitors, using unspecified biomarkers. At a recent cancer meeting, immuno-oncologist Tom Gajewski of the University of Chicago in Illinois noted that biomarker analysis in the IDO trials has been "lagging." The epacadostat trial failure, he added, is "a good wake-up call to make sure all the boxes are checked" for new combination therapies. But companies may still be tempted to press ahead with limited data. "There can be a sense of, 'I'd better act now,'" Garraway says.

Sznol agrees that companies probably moved IDO inhibitors into phase III trials too aggressively. But he cautions against making too much of the epacadostat trial failure. "Sure, the field needs a little bit of cold water—no question," he says. "But it shouldn't reduce the enthusiasm that much. … One negative trial doesn't wipe out all the positive results we've seen up to this point."