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No 'ECHO' from the past

# Epacadostat/Keytruda pivotal trial flop sends shivers down IDO pathway

*By Marie Powers, News Editor*

In three sentences, Incyte Corp. and Merck & Co. Inc. threw the immuno-oncology (I-O) world into a tailspin, revealing that the pivotal phase III ECHO-301/KEYNOTE-252 study evaluating Incyte's epacadostat in combination with Merck's Keytruda (pembrolizumab) in individuals with unresectable or metastatic melanoma failed a review by the external data monitoring committee (DMC).

ECHO-301/KEYNOTE-252 missed the primary endpoint of improving progression-free survival (PFS) in the overall population compared to Keytruda monotherapy and was expected to fall short of statistical significance on the co-primary endpoint of overall survival (OS), prompting the companies – following the DMC's recommendation – to halt the study. Merck, of Kenilworth, N.J., and Wilmington, Del.-based Incyte said the safety profile in ECHO-301/KEYNOTE-252 was consistent with previous studies of the combination of Keytruda with epacadostat, an oral indoleamine 2,3-dioxygenase 1 (IDO1) inhibitor.

The trial, which recruited more than 700 participants, was initiated on the back of phase II data suggesting that adding epacadostat to Keytruda might increase efficacy in treating melanoma. (See *BioWorld Today*, June 24, 2016.)

"We Were Wrong," Raymond James analyst Reni Benjamin headlined his take on the news, as analysts, one by one, lined up to express their condolences as precursors to their queries during Incyte's conference call.

Although Merck shares (NYSE:MRK) were off by about 1 percent, closing at $53.95 for a loss of 58 cents, Incyte (NASDAQ:INCY) fell to a two-year low of $63.43 before closing at $64.02 for a loss of $19.05, or 22.9 percent. Nearly 25.7 million shares were exchanged during the sell-off, or about 15 times the stock's three-month moving average.

Hervé Hoppenot, Incyte's chairman, president and CEO, minced no words during the call, acknowledging that "I think now we have to be realistic" in considering the prospect of "a negative impact on the probability of success of the other studies combining epacadostat with the PD-1. The data from this study in melanoma, including the analysis of the biomarker panel, will contribute to our understanding of the role of IDO1 inhibition in combination with PD-1 antagonist."

Hoppenot revealed that the hazard ratio (HR) for PFS was 1 with a confidence interval (CI) of 0.83 to 1.21. For the less mature survival analysis, the HR was 1.13 with a CI of 0.86 to 1.49. The next step in melanoma, he said, is to analyze the data in detail to uncover any difference in benefits observed within subgroups. Due to the extent of the failure, analysts deemed those chances unlikely.

As to other indications, "we, with Merck, will consider making appropriate changes to the ongoing clinical trials of the epacadostat plus Keytruda combination," Hoppenot said. "Whether the results from ECHO-301 have any readthrough to other IDO1-based combinations beyond PD-1 remains an open question. We do intend to continue to investigate the potential of epacadostat in these settings, where preclinical or translational data are compelling."

Benjamin, and other analysts, took a dim view of prospects for epacadostat going forward. "In our view, this event taints the entire epacadostat franchise and therefore we are removing all revenues associated with melanoma and other indications from our models," the Raymond James analyst wrote.

The sentiment was broadly echoed by J.P. Morgan's Cory Kasimov, RBC's Brian Abrahams, Cowen and Co.'s Eric Schmidt and pretty much every other analyst in the I-O space.

## 'Results were unequivocal'

Christiana Bardon, managing partner of the UBS Oncology Impact Fund managed by MPM Capital and founder and managing member of Burrage Capital, saw three important take-homes from the dismal day for I-O.

"Everyone has been looking for the second-generation checkpoint inhibitors because the first-generation are incredibly effective but only in a certain subset of cancers and only in a certain subset of patients," Bardon told *BioWorld*. "But the risk of second-generation checkpoint trials is that a lot of the decision-making has been based on single-arm trial data with PD-1 plus XYZ. The risk of that approach is that it's very, very difficult to make comparisons of combination data without a comparative controlled trial."

The second lesson learned is the need for I-O combination efforts to characterize patient populations more carefully, she said, observing that early epacadostat trials "weren't careful about determining the PD-1 status of patients," leading to "a mixture of patients that can potentially lead to erroneous conclusions."

In Incyte's defense, "early on in clinical development, honestly, we didn't know that all of these different biomarkers were so important," Bardon added. "Now we know that they're extremely important, especially with the Bristol-Myers failure in lung cancer."

Failure of the Bristol-Myers Squibb Co. (BMS) phase III to reach statistical significance on the PFS endpoint in CHECKMATE-026, testing Opdivo (nivolumab) as a monotherapy vs. platinum-based chemo in patients with first-line non-small-cell lung cancer whose tumors expressed PD-L1 at greater than 5 percent was an early shoe-drop for the I-O field. (See *BioWorld Today*, Aug. 8, 2016.)

Shares of BMS (NYSE:BMY) did not escape unscathed Friday, closing at $60.88 for a loss of $1.43, or 2.3 percent.

Incyte will survive, and likely thrive, analysts concluded, as the company refocuses on blockbuster Jakafi (ruxolitinib) and its early stage pipeline.

"Only silver lining in our view is that results were unequivocal and should make future decisions clear," RBC's Abrahams opined. "INCY, epa-free, becomes a lower-risk, though lower-upside, story, with potential for some share bounceback from here on solid fundamentals."

Others in the IDO space might not be so lucky. Shares of Newlink Genetics Corp., which is advancing its IDO1 pathway blocker, indoximod, as a combo candidate in advanced melanoma, were pummeled by the Incyte/Merck news, falling to a historic low of $3.95 before closing Friday at $4.20 for a loss of $3.12, or 42.6 percent. At last year's annual meeting of the American Association for Cancer Research (AACR) in Washington, Newlink reported interim results from the phase II NLG2103 study testing indoximod plus Keytruda in 60 evaluable patients with advanced melanoma, including ocular melanoma, that showed a 52 percent (31/60) overall response rate (ORR) and a 73 percent (44/60) disease control rate (DCR). (See *BioWorld Today*, April 5, 2017.)

Newlink, of Ames, Iowa, is prepping for phase III studies of indoximod in advanced melanoma, both as a monotherapy and in combination with Keytruda, according to Cortellis Clinical Trials Intelligence.

The Incyte/Merck failure prompted Newlink to commence a review of its clinical programs. In a statement, the company called the ECHO-301 trial results "a disappointing result for the IDO field." Despite a differentiated mechanism of action (MOA) for indoximod "that may demonstrate clinical benefit for patients where direct enzymatic inhibitors have not," Newlink said it would examine its programs "in light of Incyte's announcement." The company did not disclose a timetable for providing an update.

Newlink is scheduled to present additional data at this year's AACR meeting, which starts this weekend in Chicago, including a poster presentation on indoximod's MOA and a plenary session presentation on early data of indoximod plus radiation to treat pediatric patients with diffuse intrinsic pontine glioma, a rare brain cancer.

Shares of Armo Biosciences Inc. (NASDAQ:ARMO) also were caught in the IDO cross-fire, closing at $35.89 for a loss of $4.03, or 10.1 percent. Leerink Partners LLC's Jonathan Chang issued a flash note based on a conversation with company executives who sought to highlight key differences between AM0-010 and epacadostat, "including single-agent activity achieved with AM0-010 and mechanistic differences in the approaches," he wrote.

Of more than 40 IDO1 assets cited in Cortellis Competitive Intelligence, only 10 have entered the clinic. ♦