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Incyte’s epacadostat blow-up leaves a trail of destruction

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The Echo-301 trial of Incyte’s epacadostat plus Keytruda in first-line melanoma presented biotech investors with the biggest binary outcome event of 2018. It is therefore impossible to play down the importance – not just to Incyte – of its failure, announced today.

The statistics have laid bare the spectacular nature of the blow-up, raising questions not only about the utility of IDO inhibition, for which epacadostat was the standard bearer, but also about reliance on mid-stage studies and the future of immuno-oncology combinations. While Incyte stock was off 20% this morning Newlink Genetics, which offers 100% exposure to the IDO mechanism, crashed 40%.

Sometime next year Newlink’s NLG2107 trial, a melanoma study analogous to Echo-301 and testing indoximod with either Keytruda or Opdivo, should read out, and the markets can now assign this a zero probability of success. The broader question is whether there is mileage in trying to combine IDO with PD-(L)1 inhibition in any indication.

On a call today Incyte offered analysts few crumbs of comfort. Asked whether the Echo-301 failure had read-through to any other IDO studies – no fewer than eight more pivotal trials involve epacadostat combos – Incyte’s chief executive, Hervé Hoppenot, admitted: “This remains an open question.”

Phase III IDO + PD-(L)1 combo trials			
Study name	**Combo**	**Indication**	**Trial ID**
Epacadostat (Incyte)			
Echo-301	Keytruda	1st-line melanoma	NCT02752074
Echo-302	Keytruda	1st-line renal cell carcinoma	NCT03260894
Echo-303	Keytruda	2nd-line urothelial carcinoma	NCT03374488
Echo-304	Keytruda	1st-line head and neck squamous cell carcinoma	NCT03358472
Echo-305	Keytruda	1st-line NSCLC	NCT03322540
Echo-306	Keytruda +/- chemo	1st-line NSCLC	NCT03322566
Echo-307	Keytruda	1st-line (cisplatin-ineligible) urothelial carcinoma	NCT03361865
Echo-309	Opdivo + chemo	1st-line NSCLC	NCT03348904
Echo-310	Opdivo + chemo	1st-line head and neck squamous cell carcinoma	NCT03342352
BMS-986205 (Bristol-Myers Squibb)			
CA017-055	Opdivo	1st-line melanoma	NCT03329846
CA017-063	Opdivo	1st-line head and neck cancer	NCT03386838
CA017-062	Opdivo +/- chemo	1st-line NSCLC	NCT03417037
Indoximod (Newlink)			
NLG2107	Keytruda or Opdivo	1st-line melanoma	NCT03301636
Source: Clinicaltrials.gov.			

The failure of a trial in a tumour as immunogenic as melanoma, backed by apparently strong mid-stage data, raises fundamental questions about the utility of IDO inhibition. The theory was that blocking this enzyme, which causes T cells to become inactive, could give added benefit on top of checkpoint blockade.

But the statistics behind Echo-301's failure, revealed today, are brutal. Not only did the addition of epacadostat to Keytruda offer zero numerical progression-free survival benefit versus the Merck & Co drug alone, the risk of death numerically favoured Keytruda monotherapy: the hazard ratio for overall survival was 1.13.

Incyte was unable to offer any reassurance about subgroup trends, and did not suggest any obvious confounding factors. It said Keytruda performed in line with other studies, implying a PFS benefit of around six months (*Event – A defining moment for IDO inhibition, February 12, 2018*). A key future analysis to look out for will be cuts according to PD-L1 expression.

Lessons learned?

A post-mortem of Echo-301 should question not only the evidence that had backed combining IDO with checkpoint blockade, but also the logic of all ongoing PD-(L)1 combinations, most of which have yet to deliver convincing results – the early hype notwithstanding.

This should also cause investors yet again to question how much reliance can be placed on ostensibly positive mid-stage data; an uncontrolled phase II study of epacadostat plus Keytruda had delivered an impressive 22.8-month PFS benefit in melanoma patients, fuelling much of the optimism about Echo-301, but this must now be put down to a fluke.

Some might be kicking themselves, as a major hint that the IDO bubble was about to pop was dropped last June, when Roche abandoned the Newlink-partnered navoximod after the Asco meeting. At least the future for Incyte does not look as bleak today as it does for Newlink.

If there is any hope for the remaining epacadostat trials it lies in subgroups, and Incyte today said that it had "more than adequate time to do any endpoint modification, statistical or otherwise", if that was deemed necessary.

Incyte also insisted that the Echo-301 failure would not necessitate a sudden pivot into business development. Even if epacadostat is written off entirely the company has its marketed myelofibrosis drug, Jakafi, as a source of revenue, and its next hope lies in the Lilly-partnered rheumatoid arthritis drug Olumiant.

However, Olumiant is attempting to make a comeback from a US complete response letter, and faces a US advisory panel on April 23. The astonishing failure of Echo-301 just before a high-risk adcom is the last thing that Incyte and the rest of a highly volatile biopharma sector needed right now.