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# AACR – Newlink slipstreams behind Incyte

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After Incyte moved into immuno-oncology's fast track and had analysts hailing the IDO pathway as the next big thing, data unveiled today at the AACR meeting suggested that Newlink Genetics was at least going to try to give its rival a run for its money.

The results, from a melanoma cohort combining Newlink's IDO inhibitor indoximod with Keytruda, show remission rates that compare favourably with established responses to Keytruda alone. IDO inhibition has long been promised as a key emerging immuno-oncology theme, but with barely any data revealed so far investors will hope that this is not another false dawn (see table below).

For now, Newlink investors seem unconvinced, however; the group's stock opened down 19%, perhaps as realisation set in over just how high Incyte had now set the bar.

The IDO field has been complicated by Incyte's numerous non-exclusive alliances on epacadostat, though based on the latest plan to have nine registrational trials under way with this molecule its most important ally seems to be Merck & Co (*Incyte dramatically ups the immuno-oncology combo ante, April 3, 2017*).

Merck, or course, was not involved in the indoximod trial and is not a Newlink partner, beyond making Keytruda available for the study. And Newlink itself has a key partner in the shape of Roche, though that deal concerns not indoximod but a different IDO inhibitor – RG6078.

**Different mechanisms**

At the AACR meeting today the University of Iowa's Dr Yousef Zakharia, presenting data from the Newlink combo trial NLG2103, drew a subtle mechanistic distinction: while indoximod acts directly on immune cells to reverse IDO pathway-mediated suppression, epacadostat and RG6078 are inhibitors of the IDO enzyme. This enzyme breaks down tryptophan, prompting T cells to become inactive; thus blocking this pathway could increase immune response to tumours.

NLG2103 is actually an advanced melanoma trial combining indoximod with several immune checkpoint MAbs – Bristol-Myers Squibb's Yervoy and Opdivo, in addition to Keytruda – with a crossover design. But the AACR data related only to the Keytruda plus indoximod cohort, comprising 60 of 94 patients evaluable as of January.

There were six complete and 25 partial remissions, giving an overall response rate of 52%. Across-study comparisons are of course unreliable, but the efficacy appears favourable versus the registrational melanoma study Keynote-006, which showed a response rate of 33% for Keytruda monotherapy, said Dr Zakharia.

Moreover, while Keynote-006 excluded patients with ocular melanoma – a particularly aggressive and unresponsive subtype – NLG2103 did not. If the Newlink trial's sole remission in nine ocular melanoma patients is excluded the overall response rate is flattered further to 59%.

Surprisingly, patients' baseline PD-L1 status seems not to have been measured, with Dr Zakharia citing the fact that Bristol and Merck use different PD-L1 assays. None of the patients had received prior checkpoint inhibitor therapy.

Until now the only meaningful IDO data had come from a presentation at last year's Esmo meeting in which Incyte's epacadostat plus Opdivo gave a 53% objective response rate in advanced melanoma versus 58% Opdivo plus Yervoy – Bristol's approved combo – but with fewer side effects.

The next stage for indoximod must be a larger, placebo-controlled, study. The moderator of today's AACR press conference, Georgetown Lombardi Comprehensive Cancer Center's Dr Louis Weiner, said if the phase II data were verified in a bigger trial they could put this combination therapy on a similar footing to PD-1/CTLA4 combos.

| Newsflow from trials involving IDO inhibitors | | | | |
|---|---|---|---|---|
| **Project(s)** | **Sponsor(s)** | **Catalyst** | **Trial ID** | **Timing** |
| Epacadostat + Keytruda | Incyte, Merck & Co | Seven pivotal trials planned | NCT02752074 | Announced 31 Mar 2017 |
| Epacadostat + Opdivo | Bristol-Myers Squibb | Two pivotal trials planned | None | Announced 2 Apr 2017 |
| BMS-986205 + Opdivo | Bristol-Myers Squibb | PK/PD data in phase I/II | NCT02658890 | AACR presentation 4 Apr 2017 |
| Indoximod + Keytruda | Newlink | Remission data from NLG2103 trial | NCT02073123 | AACR presentation 4 Apr 2017 |
| Epacadostat + Keytruda | Incyte, Merck & Co | Keynote-037 (cancers beyond melanoma) | NCT02178722 | Possible Asco presentation |
| Epacadostat chemo combo | Incyte | Study initiation | None | Data possible 2017 |
| Epacadostat + Opdivo | Incyte, Bristol-Myers Squibb | Go/no-go decision | NCT02327078 | Possible Asco, Esmo or SITC presentation |
| Epacadostat + durvalumab | Incyte, Astrazeneca | Go/no-go decision | NCT02318277 | Possible Esmo or SITC presentation |
| Indoximod | Newlink | Brain cancer & AML data | NCT02502708 | Data possible 2017 |
| RG6078 + Tecentriq | Roche, Newlink | Safety & early efficacy data | NCT02298153 | AACR, Asco or Esmo presentations |
| *Source: Bernstein, company filings.* | | | | |

Bernstein analysts today wrote that, given Merck and Bristol's aggressive moves to up the ante in IDO/PD-1 combinations, making epacadostat the first "second-generation" immuno-oncology asset to move into phase III, the big pharma companies must already have seen promising data that have yet to be made publicly available.

The proof will come at June's Asco meeting, where data in indications beyond melanoma, including head and neck, lung and renal cancers, could be presented. If these replicate efficacy seen in melanoma Asco could be the "coming-out party" for IDO/PD-1 combinations, Bernstein wrote.

If this is the case investors will hope that AACR has given a taste of things to come, and that Newlink does not get left too far behind Incyte.

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