Evaluate Vantage

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Plinabulin blooms at last for Beyondspring

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But the vascular disrupting agent's unexpected success in a cancer indication might not be as resounding as it seems.

Beyondspring's claim yesterday that its lead asset, plinabulin, succeeded in phase 3 could be seen as an unexpected victory for vascular disrupting agents, a class that has endured years of clinical failures, and which many had assumed to be dead and buried.

That said, the company now prefers to call plinabulin a "selective immunomodulating microtubule-binding agent", and has played up its associated immune system effects to differentiate it from other failures. And whether the Dublin-3 lung cancer study, whose toplining prompted Beyondspring's 176% surge yesterday, really was a resounding success remains open to debate.

Beyond the not especially convincing <0.04 p value for its primary overall survival endpoint, Dublin-3's most glaring drawback is that it does not represent today's real-world NSCLC setting, which comprises a PD-(L)1 inhibitor, largely in the front line.

85% checkpoint naive

Dublin-3, a second/third-line NSCLC trial, is to support a US filing next year. Yet only 15% of its 559 patients had failed PD-(L)1 blockade, Beyondspring admitted on an analyst call yesterday.

Thus, rather than demonstrating how plinabulin might perform after Keytruda, Dublin-3 had mostly shown its post-chemo effect, compared against patients switched from platinum to docetaxel chemo. 24-month OS was 22.1% for plinabulin plus docetaxel versus 12.5% for docetaxel alone, but Beyondspring did not provide any median OS data beyond a log rank p value of <0.04.

Defending the result, Beyondspring's chief medical officer, Ramon Mohanlal, said: "Even if we have only a relatively small number of patients who had had a prior PD-(L)1 inhibitor the claim still holds that this is a treatment for second and third line generally, irrespective of what [patients] had before."

Worryingly, Mr Mohanlal declined to call the OS effect clinically meaningful, simply saying the hazard ratio was "within expectations".

The reason Dublin-3 fails to reflect the current treatment setting is because it had begun back in 2015, before any anti-PD-(L)1 therapy had been approved for front-line NSCLC. The trial was seen as something of a long shot, plinabulin having already underwhelmed in a phase 2/3 docetaxel combo trial in NSCLC, run by its originator, Nereus Pharmaceuticals.

In 2012 Nereus was sold to Triphase Accelerator, from which Beyondspring bought plinabulin. Beyondspring has largely played up plinabulin's ability to boost neutrophils, and indeed the project is filed for chemotherapy-induced neutropenia, with a November 30 Pdufa date; however, 100% of 2026 sellside forecast $446m revenue is in NSCLC, *Evaluate Pharma* computes.

Demographics representative?

The FDA could additionally take issue with Dublin-3's patient demographics: only 20% of subjects came from US hospitals, so the trial might not reflect a typical US population. But Beyondspring said the FDA was amenable to a US filing as long as pharmacokinetic data for US and eastern patients were similar.

The group called plinabulin a first-in-class selective immunomodulating microtubule-binding agent that induces antigen-presenting cells, distancing it from its earlier vascular disrupting agent (VDA) pharmacology.

Will any other VDA players now take note? *Evaluate Pharma* reveals only two such agents still in development, and even these can barely be called active; Bionomics' BNC105 is in the clinic, but there are no company-sponsored trials ongoing, while Medicinova has deemed its MN-029 non-core, though it has not formally discontinued it.

Apart from that the VDA space is a graveyard whose most abject failure is perhaps Antisoma's vadimezan. Given the numerous red flags around Beyondspring's Dublin-3 study investors would be wise to remain cautious.

Plinabulin, and the vascular disrupting agent graveyard		
Project	**Company**	**Note**
Filed		
Plinabulin	Beyondspring (ex Nereus)	Filed for chemotherapy-induced neutropenia (30 Nov 2021 Pdufa date); ph3 Dublin-3 trial to be used for US filing for 2/3L NSCLC in 2021
Phase 2		
BNC105	Bionomics	Ph1 (US) & ph2 (Australia) investigator-initiated studies ongoing
Phase 1		
MN-029/ denibulin	Medicinova (ex Angiogene)	Two ph1 trials showed safety, v limited efficacy; marked "non-core" in pipeline
Discontinued		
Vadimezan	Antisoma/Novartis	Failed ph3 in NSCLC
Ombrabulin	Sanofi	Failed ph3 in soft tissue sarcoma
Fosbretabulin	Mateon	Ph3 thyroid cancer trial terminated for slow recruitment
ZD6126	Angiogene (ex Astrazeneca)	Scrapped after ph2 by Astra, then by Angiogene
ABT-751	Abbvie	Various ph1 & 2 studies completed or terminated
Verubulin	Myrexis/Epicept	Mixed ph2 glioblastoma data; Myrexis liquidated; Epicept acquired by Immune Pharmaceuticals, also liquidated
Crolibulin	Epicept	Epicept acquired by Immune Pharmaceuticals, liquidated
ICT01-2588	Incanthera	Azademethylcolchicine formulation, part of "project EP0015", but no longer appears in pipeline, said to have been assigned to Ellipses Pharma
OS342/NX101	Oncosynergy	No information
Source: Evaluate Pharma, clinicaltrials.gov & company announcements.		

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