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Bellicum’s cells not so controllable after all

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Yesterday’s US clinical hold on Bellicum’s allogeneic stem cell transplant procedure BPX-501 raises numerous issues, perhaps the most burning of which is: just how controllable are these cells?

After all Bellicum’s claim to be able to switch the cells off on demand in the event of unexpected toxicity, by infusing rimiducid, has always been a key feature of the company’s investment case. With details of the hold still sketchy it is hard to draw firm conclusions, though the markets fear the worst, sending the group’s valuation down 35% to not much above its gross cash balance.

Perhaps it is the vagueness of Bellicum’s announcement that spooked investors. All that was initially disclosed was that three cases of encephalopathy – brain injury – “possibly related to BPX-501” had led the FDA to put the US clinical programme for BPX-501 on clinical hold.

Bellicum would not say in which trials these had occurred, and initially did not reveal what had been done to control the side effect, or what the status of the subjects involved was. The only explanation it offered was that these cases were complex, with possible confounding factors including earlier failed transplants, history of immunodeficiency and concurrent infection.

However, the company later confirmed to *EP Vantage* that one patient had died, but that in the other two the encephalopathy resolved. Moreover, it said rimiducid had in fact been administered to trigger the BPX-501 cells’ “off-switch” in the two resolved subjects, but “since it has not been determined whether BPX-501 is a source of the issue, we're unable to determine whether rimiducid could have played a role”.

The sellside also appears to have been briefed: analysts from Wells Fargo said the first patient had died back in November, of respiratory failure, causing a re-examination of six other encephalopathy cases Bellicum had seen, of which two were deemed potentially related to BPX-501.

It seems puzzling that the company put out such a sketchy press release when it clearly had more information.

Partial match

BPX-501 is a procedure designed for use in patients with various diseases who lack a fully matched stem cell donor. This scenario would normally rule out a curative allogeneic transplant, which doctors deem too dangerous on account of the risk of graft-versus-host disease (GvHD).

The procedure comprises donor stem cells and lymphocytes from which GvHD-causing alpha/beta T cells have been removed. The remaining T cells are made to express the off-switch, which can be triggered by infusing rimiducid to cause ablation of the BPX-501 cells should signs of toxicity be seen.

Thus it will be vital to confirm the effect of triggering this switch in the patients with encephalopathy. Why had it not been triggered in the subject who died? To what extent did it do its job in the other two? Bellicum might argue that the switch is designed to counteract GvHD and not encephalopathy, which is not related to GvHD, though in the past it has argued that it could control a wide range of toxicities.

A separate issue is why the FDA has implemented a clinical hold while its EU counterpart has not. Remarkably, given the risks inherent in a fast-developing situation like this, Bellicum yesterday felt confident enough to stress: “The FDA clinical hold does not affect the ongoing BP-004 registration trial in Europe.”

Active studies of BPX-501				
Trial ID	**Enrolment**	**Conditions**	**Location**	**Detail**
NCT02065869 (BP-004)	175	Children with haematological cancers or orphan blood disorders; after initial allo transplant	EU	EU registrational study
NCT03301168 (BP-U-004)	120	Children with haematological cancers or orphan blood disorders; after initial allo transplant	US	On clinical hold
NCT01744223 (BP-001)	36	Adults with haematological cancers; after initial allo transplant	US	On clinical hold
NCT02477878 (BP-008)	24	Post-transplant relapse in adults and children with blood cancers	US	On clinical hold
Source: Clinicaltrials.gov, company statement.				

In response to Bellicum's troubles Kiadis, a rival company working on partial-match allo transplantation, rose 20% this morning; surprisingly, Molmed, a group whose Zalmoxis, a procedure similar to BPX-501, is already approved in the EU, was virtually unmoved.

To be fair, encephalopathy and the related toxicity encephalitis, which is usually due to an infection, are not uncommon in cell therapy trials. In CAR-T therapy, for instance, encephalopathy was implicated in the deaths of one patient given Gilead's Yescarta and another given Juno's JCAR014, while encephalitis was the reason for the deaths of two subjects on Novartis's Kymriah.

Not that a sudden increase in a particular toxicity should not ring alarm bells – as Juno found when its JCAR015 became linked with cerebral oedema, leading to it being discontinued. For Bellicum one fear is that emergence of a side effect not seen to a meaningful extent in 240 other treated subjects might indicate a manufacturing mistake that could take months to rectify, if it can be rectified at all.

If BPX-501 is dead the company does have a CAR-T therapy, BPX-601, and an engineered TCR, BPX-701, in the clinic, but these are very early, and to refocus on them would entail a serious re-evaluation of prospects.

Bellicum has been through its share of troubles, involving slow progress and a management shakeup. Investors must now hope that the clinical hold is resolved quickly.

This story was updated after information was received from Bellicum.

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