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Another checkpoint combo blow-up fuels Darzalex doubts



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Genmab had hoped to add billions to sales of its multiple myeloma blockbuster, Darzalex, by pushing into solid tumours. Instead, the discontinuation of a study testing the drug alongside Roche's Tecentriq in non-small cell lung cancer wiped \$2.4bn off the Danish company's market cap yesterday.

It was probably not the setback per se that caused the mass exodus – the trial in question was in second-line disease, an increasingly irrelevant setting – but rather the fact that the pairing of Darzalex and PD-(L)1s looks dead in the water. This does not bode well for other Darzalex combination trials, including several with Bristol-Myers Squibb's Opdivo (see table below).

Worse Luc

The phase I/II Callisto trial, aka Luc2001, of Darzalex plus Tecentriq had been due to read out in the second half of 2018, giving an early indication of whether the combo might have utility in solid tumours.

But the study was discontinued over the weekend because of a lack of effect and, more worryingly, an increase in deaths in the combination arm. Berenberg analysts said it was still unclear whether the deaths with Darzalex plus Tecentriq had been caused by adverse events or progressive disease, but the future of this combination looks bleak.

A second combination trial, MMY2036, testing Darzalex plus Johnson & Johnson's anti-PD-1 antibody JNJ-63723283 in multiple myeloma, has also been halted.

As for whether any more Darzalex-PD-(L)1 combo trials might meet a similar fate, Genmab would only say that it had contacted its partners "to discuss ceasing enrolment and dosing of the combination while the data is being further investigated".

A spokesperson for Genmab told *EP Vantage* that the company would not give more details as it could not speak for Johnson & Johnson, its partner on Darzalex. J&J is developing and commercialising the drug under an exclusive licensing deal signed in 2012 – the company had not responded to a request for more information on the remaining combo trials at the time of publication.

Darzalex/PD-(L)1 combo trials

Trial	Setting	Combination	ID	Status
LUC2001/Callisto	2L NSCLC	+ Tecentriq	NCT03023423	Discontinued
MMY2036	Relapsed/refractory MM	+ JNJ-63723283	NCT03357952	Discontinued
Checkmate-142	Colon cancer	+ Opdivo	NCT02060188	Primary completion Dec 2018
Keynote-668	Relapsed/refractory MM	+ Keytruda	NCT03221634	Primary completion Mar 2019
Checkmate-358	Virus-associated tumours	+ Opdivo	NCT02488759	Primary completion May 2019
-	Metastatic pancreatic, NSCLC, TNBC	+ Opdivo	NCT03098550	Primary completion Jun 2019
-	Relapsed/refractory MM	+ Opdivo	NCT01592370	Primary completion Jun 2020
-	Relapsed/refractory MM	+ Tecentriq	NCT02431208	Primary completion Sep 2020

Source: [Clinicaltrials.gov](https://clinicaltrials.gov) & [EvaluatePharma](https://www.evaluatepharma.com).

Bernstein analysts do not hold out much hope for the remaining trials. They assume the worst for the Darzalex-Opdivo combo, posing the question: "Why would Opdivo be very different versus Tecentriq?"

They had given Darzalex a 50:50 chance in solid tumours, citing strong preclinical data supporting the combo approach.

Genmab's chief executive, Jan van de Winkel, previously told *EP Vantage* that CD38 inhibition with Darzalex might help overcome resistance to PD-(L)1 blockade, with CD38-positive immune-suppressing cells seen in various solid cancers ([Interview - Genmab aims at multiple new markets for Darzalex, February 19, 2018](#)).

Still, the Bernstein analysts conceded that human data supporting the combination in solid tumours were lacking. And though the sellside had not factored solid tumour indications into their projections for Darzalex, confirmation that this huge opportunity will come to nothing was clearly a disappointment to some.

On the cards?

The writing was arguably on the wall for this combination strategy last year when the FDA placed on hold various combination trials of AstraZeneca's PD-L1 inhibitor Imfinzi in blood cancers, including two studies involving Darzalex.

These trials, FusionMM-003 and FusionMM-005, were being carried out under a partnership with Celgene, and have since been discontinued. At the time of the cancellation, Celgene blamed the trial halts on [deaths seen with the combination](#) of another PD-1 inhibitor, Merck & Co's Keytruda, with Celgene's Revlimid and Pomalyst in multiple myeloma trials.

Any hope that Darzalex's different mechanism of action might have allowed it to avoid the PD-(L)1 combo safety concerns have been dashed by the latest news.

Still, even without this combination setting Darzalex is expected to be hugely successful in multiple myeloma – the indication accounts for the entire \$6bn of *EvaluatePharma's* consensus forecast in 2024. And Genmab has more important readouts coming up, with the first-line Maia and Cassiopeia trials due to report this year.

Knock-out results will help rebuild confidence in the company, but any hint of disappointment – or any more safety worries – would be another big blow to sentiment.

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