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Interview – German Merck doubles down on dual-acting cancer agents

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Pfizer and Merck KGaA successfully got the PD-L1 antibody Bavencio over the US FDA's finish line thanks to its orphan indication of Merkel cell carcinoma. As commercialisation proceeds, the German group is now thinking of the future of immuno-oncology by locking up bispecific assets.

During Asco, Merck announced a deal with the UK group F-star for a suite of bispecific antibodies, including a Lag-3/PD-L1 asset that is "close to the clinic," says Merck's global research & development head Luciano Rossetti. Dual acting projects are quicker to develop than PD-1 combinations, since with combos each element must first be tested separately; in addition, they could offer an alternative to two very expensive agents in an environment where "financial toxicity" has become an oft-repeated term.

"That gives you advantage in development and perhaps even makes the payer happy," Mr Rossetti said in an interview on the sidelines of Asco.

Moving swiftly

The F-star deal follows the announcement that Merck is trialling its own bispecific fusion protein, M7824, which acts on PD-1 and TGF beta (*Interview – German Merck unveils its secret weapon, January 9, 2017*). Mr Rossetti says the project is moving more swiftly than Bavencio – first human trials began in late 2015, and today it has enrolled 600 patients in 14 expansion cohorts.

For now, Merck is moving these projects independently of the Pfizer alliance, revenue from which will be its biggest growth driver. Key to that is Bavencio, the fourth of five antibodies acting on the PD-1 pathway to receive US approval and the least loved among sellside analysts. Yet collaborators Pfizer and Merck KGaA see opportunities to strike in what is a crowded and competitive space.

Snagging a win in the rare disease Merkel cell carcinoma was one way to speed development, Mr Rossetti says. But now the pace of research is growing even faster as hundreds of PD-1 combination trials are underway, and Mr Rossetti says the Pfizer-Merck alliance is responding.

"By combining [Bavencio] with assets that are unique to Pfizer or Merck we can create some very good opportunities," he tells *EP Vantage*. "I don't think the door is closed."

Mr Rossetti names ovarian cancer as one opportunity, and evidence to support its use here could be found in the Javelin Ovarian 100 and 200 trials. The former uses Bavencio as a single agent or in combination with carboplatin/paclitaxel as a maintenance therapy following platinum-based chemotherapy in newly diagnosed patients; the latter tests Bavencio alone or in combination with doxorubicin in patients with platinum-resistant disease.

Earlier combinations include HDAC inhibitor entinostat and FAK inhibitor defactinib, the latter of which Pfizer out-licensed to Verastem.

Something special

Renal cell carcinoma is another opportunity: combined with Pfizer's Inlyta, Bavencio produced a 55% response rates in a phase Ib study. As a result, the partners have launched Javelin Renal 101, a head-to-head test against Pfizer's Sutent, a blockbuster nearing the end of its market exclusivity, in advanced disease.

Non-small cell lung cancer has turned into the most competitive area of all, with Merck & Co's Keytruda having firmly established itself as the agent to beat in both front-line and progressive disease. Yet even there, Mr Rossetti sees the potential to offer something special.

Data from the Javelin Solid Tumor trial suggested a better response rate in NSCLC patients with greater exposure to Bavencio. Because the Javelin Lung 100 trial needed to be modified owing to changes in the standard of care, Merck and Pfizer decided to add an arm in which patients were dosed with Bavencio once a week for the first 12 weeks rather than once every other week, which so far has increased exposure fourfold,

he says.

“This is a test of a hypothesis that Bavencio might be special,” he says.

Keytruda’s success as a monotherapy and combination in NSCLC means Bavencio will need to be very special. Then again, in an indication forecast to be worth nearly $27bn in 2022, it is a chance worth taking.

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