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Asco 2018 – German Merck's run at US Merck and other updates

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Immuno-oncology is one area where Merck & Co could see a challenge from its historic parent company.

Keytruda has seen off all challengers so far and secured its place as the first-choice drug in most non-small lung cancer (NSCLC) cases. But this does not mean that competitors will not try to knock it off its perch. A contender could be emerging from the German Merck, with its bifunctional agent M7824 showing signs that, at least in advanced disease, it has a shot at matching Keytruda.

But German Merck still has work to do. Thanks to Keytruda, second-line disease is irrelevant for therapies acting on the PD-1 pathway, including M7824, so the company will almost certainly need to prove its candidate's worth in first-line disease, perhaps even in a head-to-head trial. Meanwhile, other closely watched biotech presentations at Asco came from Jounce, Celgene and Celldex, along with Roche's assessment of taselisib.

Ready for phase III

For its part, Merck KGaA can for now bask in the glow of positive second-line NSCLC results with M7824, a bifunctional fusion protein binding PD-L1 and TGF-beta. In an immunotherapy-naive population, researchers measured a response in 11 of 27 patients (40.7%) expressing PD-L1 at greater than 1%, and in five of seven patients (71.4%) with high expression of PD-L1 at the recommended phase II dose of 1,200mg every two weeks.

By comparison, Keytruda's second-line trials scored an objective response rate (ORR) of around 30% in high expressers and around 19% in those with 1% expression or more. And Opdivo saw a 20% ORR in squamous disease and 19% in non-squamous.

"[Our] response rates are numerically better than any other immunotherapy presented in the last few years," Merck KGaA's R&D head, Luciano Rossetti, said. "Based on the consistent observation with the dose response, and the robustness of the data and the durability of these responses, we're very excited about the potential in lung cancer."

It is clearly too soon to declare a Merck-against-Merck race, but with these results the German company would be unwise to not at least try to match its American counterpart. Besting Keytruda in the first-line setting is probably M7824's only chance of becoming a meaningful player, so it would be a surprise to see it tested

anywhere else.

The German group will be making public the design of its pivotal NSCLC programme this summer, Mr Rossetti told *EP Vantage*.

PI3K in solid tumours

Meanwhile, Roche's attempts to push PI3K inhibition into solid tumours has come to naught. Underwhelming responses in the Sandpiper study prompted a decision not to file taselisib for approval in hormone receptor-positive, HER2-negative breast cancer, a disappointing outcome for physicians who struggle to treat patients with a PIK3CA gene mutation. This drives disease in almost half of patients with hormone receptor-positive breast cancer.

The combination of taselisib and fulvestrant added two months of progression-free survival to fulvestrant alone – taking it to 7.4 months – but at the cost of significant extra toxicity. Discussants at the conference concluded that the molecule was simply not hitting its target hard enough, and said they hold out hope that different agents might have better results.

Still, CDK4/6 inhibitors like Ibrance have also proved effective in these patients, so it is arguable whether this presents an attractive area for other researchers. Roche at least will not take too much of a hit; sellside forecasts only amounted to $332m in 2024, according to *EvaluatePharma*.

Still no Jounce bounce

Jounce's presentation on its Icos antibody JTX-2011 was apparently more damaging than the original abstract drop let on (*Asco preview – No Icos bounce for Jounce, May 17, 2011*).

Shares tumbled another 35% in early trading today following the Saturday data readout, which showed one partial response in a gastric cancer patient with JTX-2011 monotherapy. And when the project was combined with Opdivo there was one response in gastric cancer and one response in triple-negative breast cancer. No responses were recorded in non-small cell lung cancer or head and neck squamous cell cancer.

The presenters suggested moving on by switching the anti-PD-1 mechanism with CTLA4 – which has some biological rationale. But given the substantial toxicities of the anti-CTLA4 antibodies, such a strategy is unlikely to substantially raise hopes for this project.

Celldex meanwhile was hoping for a bounceback after glembatumumab vedotin flamed out in breast cancer in April. Asco data from varlilumab's combo studies with Opdivo have not yet helped Celldex get back to the minimum $1-per-share price for Nasdaq listed companies, but they might represent a new beginning – shares rose 4% in early trading today.

The company hopes that varlilumab, a TNF receptor superfamily member 7 antibody, can convert non-immunogenic tumour cells into ones that are amenable to treatment with checkpoint inhibition. In combination with Opdivo, the strategy is showing promising signs, with seven of 56 ovarian cancer patients in phase II dosing cohorts seeing a shrinkage in their target lesions – four of those had been PD-L1 negative at enrolment.

Finally Celgene, which is a company in need of a win. While data from the CAR-T project JCAR017 did not necessarily wow, the results at least should improve confidence in the company's takeout of Juno. Asco saw an update from JCAR017's phase I/II Transcend trial in diffuse large B-cell lymphoma and transformed follicular lymphoma – data are now available from 37 patients, up from the 14-patient presentation at Ash in December.

The latest update showed a 49% objective response rate, with complete responses in 46% of patients at six months after treatment, and near zero reports of grade 3 or above cytokine release syndrome (CRS) and a low 8% neurotoxicity rate at grade 3 or above.

It is still early for this agent, but if the safety data hold up it could be viewed as the best-in-class treatment – Novartis's Kymriah and Yescarta had serious CRS rates of 23% and 13%, and neurotoxicity of 12% and 28%, respectively.

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