Evaluate Vantage

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Merck catches Bristol with surprise PD-1 filing

Jacob Plieth

With yesterday's US filing for MK-3475 Merck & Co stole a march on the mounting competition in immuno-oncology, and must have caught analysts, who had generally not been expecting the anti-PD-1 antibody to be launched until 2016, by surprise.

Little wonder that the group's share price put on 7%, equivalent to a staggering $9.5bn increase in market capitalisation. The focus is bound to remain on additional indications and combination approaches, but for now investors can look to the completion of two key melanoma studies, as well as banking on immunotherapy being the hottest topic at Asco for the third year running.

MK-3475, which Merck had earlier referred to as lambrolizumab, is one of a handful of industry projects targeting PD-1, the so-called programmed death protein expressed on the surface of T-cells. Highly impressive melanoma data have propelled this class up the rankings of the industry's most valuable projects.

Yervoy failures

The rolling BLA Merck submitted yesterday is for Yervoy-refractory advanced melanoma, and the company says it expects it to be completed in the first half of this year. At around this time a phase III trial in Yervoy-naive patients is due to be completed, followed in 2015 by a phase II study in Yervoy failures.

Key studies of Merck & Co's MK-3475

Indication	Status	Detail	Trial ID
Melanoma	Phase III	645 Yervoy-naive pts	NCT01866319
Melanoma	Phase II	510 Yervoy-refractory pts	NCT01704287
Various, including melanoma	Phase I	1,067 pts	NCT01295827
NSCLC	Phase II/III	920 second-line pts	NCT01905657
NSCLC	Phase I	30 pts	NCT01840579
NSCLC	Phase I	24 PD-L1-positive pts	NCT02007070
Renal cell carcinoma	Phase I	228 pts, combo with Votrient	NCT02014636
Various, including TNBC	Phase I	114 pts	NCT01848834
Various	Phase I	71 pts with microsatellite-unstable tumours	NCT01876511
Haematological malignancies	Phase I	100 pts	NCT01953692

Until now Bristol-Myers Squibb's competing project nivolumab was widely acknowledged as the most advanced anti-PD-1 antibody, though in fairness Merck had disclosed far less about MK-3475 than Bristol had about its candidate.

Before yesterday consensus estimates reckoned on a 2016 launch for the Merck antibody, resulting in 2018 sales of $1.2bn. Meanwhile, nivolumab carries 2018 sales estimates of a massive $3.6bn, and an NPV of $21.8bn; Merck might not have leapfrogged over Bristol yesterday, but it might have narrowed the gap.

If *EvaluatePharma's NPV Calculator* tool is used to bring forward the launch of MK-3475 to mid-2015 – though admittedly, without splitting out the separate indications this is a relatively crude measure – forecast 2018 revenue rises to $1.7bn, and the project's NPV rises $1bn to $9.1bn.

Still, in revenue terms the indication to watch is not melanoma but non-small cell lung cancer (*Immunotherapy steps up a gear with lung cancer and combo focus, October 3, 2013*). And ISI Group's Mark Schoenebaum has

been quick to point out that Bristol is well ahead of Merck in developing a melanoma combination with Yervoy – seen as key to improving the side-effect profile while maintaining efficacy.

One thing in Merck's favour is MK-3475's US breakthrough designation – something that nivolumab is not thought to hold. As Gilead Sciences demonstrated recently with idelalisib, however, breakthrough designation does not guarantee priority review, and in any case the FDA will prioritise any project it sees fit.

Bringing up the rear

Of course, Merck and Bristol are not the only players here; AstraZeneca this morning revealed early but significant progress with its anti-PD-L1 antibody MEDI4736. PD-L1 is the corresponding ligand, found on tumours, that binds to PD-1.

While the UK firm is bringing up the rear in this branch of immuno-oncology it is pushing hard to revamp its pipeline, and thus makes an interesting recovery play. It recently started a NSCLC study combining MEDI4736 with its anti-CTLA4 antibody tremelimumab, mirroring Bristol's attempts to combine nivolumab with Yervoy.

A melanoma trial in collaboration with GlaxoSmithKline, combining MEDI4736 with two recently launched Glaxo drugs, the B-Raf kinase inhibitor Tafinar and the MEK inhibitor Mekinist, started dosing this month.

Key studies of AstraZeneca's MEDI4736

Indication	Status	Detail	Trial ID
Solid tumours	Phase I	220 pts, monotherapy	NCT01693562
NSCLC	Phase I	156 pts, combo with tremelimumab	NCT02000947
Melanoma	Phase I	69 pts, combo with dabrafenib and trametinib	NCT02027961

Leerink analysts went as far as to say that, as immuno-oncology evolved towards combination therapy, Astra was a "dark horse" positioned to become a leader. Astute observers will note in the name of its anti-PD-L1 project the MEDI prefix, which stands for Medimmune, the group for which Astra paid $15.6bn in a highly criticised 2007 acquisition.

Remarkably, if immuno-oncology in general and MEDI4736 in particular live up to some of the hype, Medimmune might prove not to have been a waste of money after all.

To contact the writer of this story email Jacob Plieth in London at jacobp@epvantage.com or follow @JacobEPVantage on Twitter