Evaluate Vantage

August 10, 2018

Upcoming events – US approval verdicts for Opdivo and Galafold

Jacob Plieth

The Bristol-Myers Squibb and Amicus drugs face approval decisions next week.

Welcome to your weekly digest of approaching regulatory and clinical readouts. Next week should see the US regulator decide on two approvals, with Bristol-Myers Squibb looking for Opdivo to become the first ever anti-PD-(L)1 antibody to secure a US label for small-cell lung cancer.

And Amicus could finally reach the end of a tortuous approval road for Galafold in the US, with the FDA due to announce its verdict on the Fabry disease treatment by August 13.

Small-cell first

The FDA action date for Bristol's SCLC filing, based on the Checkmate-032 trial, falls on August 16.

Bristol is seeking a third-line label, and interestingly is focused on Opdivo monotherapy. Checkmate-032 included monotherapy as well as Yervoy combination arms, and recruited subjects with various tumour types; those with SCLC had failed two or more lines of therapy.

Data from the trial have emerged in dribs and drabs, and at the last Asco meeting the combo arm was said to have yielded overall remission of 23%. A previous data cut gave 25% remission for the combo and 11% for monotherapy.

No data are available split by subjects' PD-L1 status, something that could be important in the FDA's deliberations about labelling. Merck & Co's Keynote-158 trial of Keytruda in progressed SCLC clearly showed responses being driven by PD-L1 positivity (*Asco 2018 – Small cell lung data underwhelm but big readouts approach, June 5, 2018*).

After progress made by checkpoint blockers in NSCLC the more difficult-to-treat SCLC represents a key extension, though it is still early days.

More important studies are ongoing in first-line SCLC: at Esmo Roche is expected to present data from Impower-133, which is already said to have been positive for overall and progression-free survival, while Merck and Astrazeneca are due to unveil their respective Keynote-604 and Caspian trials next year. Another study, Bristol's Checkmate-451, focuses on first-line maintenance.

Given the poor prognosis for SCLC patients, and the fact that survival rates have not improved for decades, it

would be unusual for the FDA not to grant Opdivo a third-line approval next week.

Study	Drug	Design	Trial ID
Checkmate-032	Opdivo +/- Yervoy	Various relapsed tumours and dose levels	NCT01928394
Keynote-158	Keytruda	Various relapsed tumours, single-arm	NCT02628067

Into the fold

Meanwhile, Galafold has been on the market in Europe since 2016, but at that time US regulators were unconvinced by Amicus's clinical data, which relied on a surrogate endpoint to prove effectiveness.

Unlike the enzyme-replacement therapies that remain treatment mainstays for Fabry disease in the US, Galafold is an oral small molecule that works by stabilising the dysfunctional alpha-Gal A enzyme found in Fabry patients. This dysfunction causes a glycolipid, GL3, to accumulate in organs.

Amicus's initial pivotal efficacy study measured the effect on GL3, but back in 2016 the FDA wanted a whole new study using harder endpoints. Last year that decision was reversed: Amicus managed to persuade the regulator that real-world data collected in Europe would answer its questions, and an NDA was finally submitted.

Amicus is apparently optimistic about a green light, already having its US sales team in place, and earlier this month lifted its annual revenue guidance for Galafold, based partly on expected US launch. The company expects Galafold sales to reach $80-90m this year, while sellside analysts see revenue of $534m by 2024, according to consensus data from *EvaluatePharma*.

The failure of a phase III epidermolysis bullosa project late last year means that Amicus will be punished by investors if its US ambitions for Galafold are not realised this time around, especially as the company's clinical pipeline amounts to a project for Pompe disease that is awaiting regulatory clearance to push into pivotal studies. Galafold revenues from the world's biggest drugs market would come in handy.

Fabry disease market outlook

			Annual sales ($m)		
Product	**Company**	**Pharma class**	**2018**	**2021e**	**2024e**
Fabrazyme	Sanofi	Alpha galactosidase ERT	889	1,045	1,196
Galafold*	Amicus Therapeutics	Alpha galactosidase chaperone	85	306	534
Replagal	Shire/Sumitomo Dainippon	Alpha galactosidase ERT	596	590	559
Pegunigalsidase Alfa	Protalix Biotherapeutics	Alpha galactosidase ERT	–	82	147
Lucerastat	Idorsia	Glucosylceramide synthase inhibitor	–	22	53
Total market incl others			**1,572**	**2,061**	**2,555**

*Notes: ERT = enzyme replacement therapy. *Galafold only treats an amenable genetic mutation, found in 35-50% of patients. Source: EvaluatePharma.*