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Mystic falls at the first hurdle

Jacob Plieth

Give Astrazeneca executives full marks for putting on brave faces. The failure of the group's Mystic trial – its single most important event of 2017 – was summed up on this morning's press call by its chief executive, Pascal Soriot, saying: "It's too early to conclude that Mystic is not positive."

Of course he has a point: today's failure concerns progression-free survival, an endpoint that other immuno-oncology studies have shown does not always predict overall survival. But the odds of a positive OS benefit have lengthened considerably, and many investors and some sellsiders have already thrown in the towel.

Analysts at Citi wrote today that the lack of a PFS benefit, and additional confounding factors such as patient crossover in Mystic, made them "very doubtful that the trial [would] meet its OS endpoint".

That OS readout, in various cuts of the first-line NSCLC data concerning Imfinzi plus tremelimumab and Imfinzi monotherapy, is due in the first half of 2018 (*What to expect from Astra's big binary event of 2017, June 30, 2017*).

And while today's announcement from Astra was short on detail, one important point has emerged, namely that 25% PD-L1 expression was being used as the first cutoff for the PFS data. With this failing to show a benefit for the combo over doublet chemo, analyses in broader cutoffs become irrelevant.

Progression, but not as we know it

One hope concerns the phenomenon of pseudoprogression. This occurs when a treated tumour first continues growing – with the patient classified as a progressor in the PFS analysis – before shrinking and ultimately causing overall survival to be extended.

This has been seen in studies of Imfinzi's competitors, including Bristol-Myers Squibb's Opdivo and Roche's Tecentriq.

Then there is the possibility that cuts of the Mystic data by narrower PD-L1 expression levels, for instance 50%, might yield something positive. These would of course only be exploratory; Astra's chief medical officer, Sean Bohen, said other analyses were being carried out, but he would not reveal the data yet.

The potential future upside scenarios aside, there is clearly far more to be negative than positive about today, as reflected in investors panicking and sending Astra's stock down 15% this morning.

For one thing, Astra confirmed that the PFS analysis at 25% PD-L1 expression was also flunked by Imfinzi monotherapy. This was a secondary endpoint, and its failure should confirm doubts about tremelimumab, the anti-CTLA4 asset Astra got as a castoff from Pfizer; investors might ask themselves whether tremelimumab can add any benefit over Imfinzi monotherapy.

Moreover, Mr Bohen this morning scotched the idea of pseudoprogression, calling it an "uncommon phenomenon not likely to have confounded" the Mystic PFS readout. If this is the case OS hopes simply rest on late separation of the survival curves.

This in itself could be in doubt given the possible crossing of progressing patients over to other therapies, confounding a survival benefit. Mr Soriot said Astra had reduced this risk; patient crossover within the study is not permitted, but this does not preclude patients moving on to other efficacious drugs outside the setting of Mystic.

Investors might also ask themselves why Astra chose to sign today's deal with Merck to study Lynparza in combination with Keytruda, rather than retaining all of Lynparza's upside and putting its faith in an Imfinzi combo alone (*Astrazeneca muddies the water as Mystic fails, July 27, 2017*). Is this its first admission that Imfinzi is not all it was cracked up to be?

All over bar the shouting?

Perhaps the broadest doubt of all is whether Merck's US approval for Keytruda plus chemo in first-line NSCLC

patients irrespective of PD-L1 expression renders further Mystic analyses irrelevant.

There is a chance for Imfinzi monotherapy to show a survival benefit next year in patients at the 25% expression level – a co-primary endpoint – giving Astra an advantage against Keytruda monotherapy, which in first-line is approved at the narrower 50% cutoff. However, some analysts expect Astra to rely on 50% expression here, which would vastly reduce the relevance of a positive readout.

Bristol's Opdivo failed in the Checkmate-026 trial to show a survival benefit in an aggressively broad cut of patients with 5% PD-L1 expression. In tandem with the Mystic failure Bristol fell 6% this morning, presumably as investors saw Keytruda's grip tighten further on first-line lung cancer; Merck was up 5%.

Whatever hope still remains for Mystic, the market has decided that Astra executives are now clutching at straws.

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

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