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Astrazeneca gets personal

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A collaboration this week with the blood testing specialist Capitainer underlines the big pharma's ambition to have a diagnostic linked with every pipeline project.

Personalised medicine has long been a popular biopharma catchphrase. And Astrazeneca is going further than many, setting a bold aim to have a diagnostic linked to each asset in its pipeline.

It is not just cancer that gets the personalised treatment, with big readouts approaching for several of the company's biomarker-driven projects in asthma and Nash. The group reckons there could be a reward for identifying which patients might do best on a drug: "hopefully, payers reward you with a better price", it tells *Evaluate Vantage*.

The effort is considerable: within Astra's respiratory and immunology portfolio 93% of its early-to-mid-stage projects – from discovery to phase 2 – are already paired with a biomarker, says Adam Platt, head of translational science and experimental medicine in that division.

This approach could also influence Astra's deal-making, as the group hopes to see at least the promise of a personalised approach before signing on the dotted line. Might this be limiting in terms of targets? Mr Platt does not think so: "I haven't met a molecule I haven't been able to find a precision medicine hypothesis for."

On Monday the group underlined this strategy, partnering with Capitainer, a private company specialising in devices that allow patients to collect cell-free blood at home – technology that should make testing easier.

This presumably small transaction adds to a $2m up-front deal in November with C4X that gave the big pharma rights to Nrf2 activators being developed initially for COPD that are set to go down a precision medicine path.

IL-33

Still, much later-stage tests of Astra's biomarker-driven strategy are approaching. The first will come in another respiratory disease: phase 2 data are due later this year on tozorakimab, an anti-IL-33 MAb, in asthma.

However, attempts to hit this target have fallen short in the past, with the failure of a phase 2 COPD study of Sanofi and Regeneron's itepekimab; those groups found a benefit in a subgroup of former smokers, and have pushed on into phase 3 in these patients; results are expected in 2024. Development in asthma was abandoned in 2021.

Astra, meanwhile, is homing in on early-onset asthma, where IL-33 is thought to play a role, and is also looking

at a gene signature designed to identify which patients have IL-33-driven disease and, therefore, are most likely to respond to tozorakimab.

The group has yet to determine the threshold for IL-33 “high” or “low” according to this gene score, but hopes to nail this down in the phase 2 all-comers trial. This should clarify what proportion of asthma patients, if any, could benefit from IL-33 inhibition.

The company is already trialling tozorakimab in the phase 3 Oberon and Titania trials in former smokers with COPD; here, as well as the gene score, it is looking at another, as-yet-undisclosed biomarker.

Roche is also in this arena with astegolimab, which inhibits the binding of IL-33 to ST2; this is in the phase 3 Arnasa trial, in both former and current smokers.

Flap

Not too far behind is another asthma project, atuliflapon, an inhibitor of 5-lipoxygenase-activating protein (Flap); this is involved in the production of leukotrienes, which have a role in inflammation. Astra is taking a slightly different approach here, looking at a urine biomarker; namely a metabolite from the leukotriene pathway.

Again, the group hopes to set a threshold of the metabolite over which patients are most likely to respond. However, measuring urine markers can be tricky, given that these are not always stable and can be affected by things like food intake and exercise, Mr Platt concedes.

There are other reasons for caution: work on this class by other companies, including GSK, seems to have petered out. And Astra last year discontinued development of atuliflapon in coronary artery and chronic kidney disease, citing “efficacy/safety”.

Nash

Finally, Astra is expecting data on another precision project this year: AZD2693, an Ionis-originated antisense oligonucleotide against PNPLA3 being developed in Nash.

Patients with mutations in the *PNPLA3* gene generate a non-functional protein, which cannot do its usual job of breaking down fats and hinders other fat-removing proteins. AZD2693 is designed to stop production of the dysfunctional PNPLA3 protein, and Astra plans to target the 30-40% of Nash patients who have two risk alleles.

Still, this asset is at a much earlier stage, in phase 1. Safety will therefore be key, although the company will also look at liver fat reductions.

Overall, while individual projects have it all to do, Astra is convinced that precision medicine is the right approach. Mr Platt points to the heterogeneity of diseases like rheumatoid arthritis and inflammatory bowel disease, as well as things like asthma and COPD. “It isn't one size fits all any more. The way to be competitive is to show greater efficacy in a smaller group."

Upcoming tests of Astrazeneca's biomarker strategy due in 2023

Project	Description	Setting	Trial details
Tozorakimab	Anti-IL-33 MAb	Asthma (also in development for COPD, DKD & atopic dermatitis)	Ph2 Frontier-3
Atuliflapon (AZD5718)	Flap inhibitor	Asthma	Ph2 Flash
AZD2693*	PNPLA3-targeting antisense	Nash	Ph1 in healthy volunteers & Nash pts

**Partnered with Ionis; DKD=diabetic kidney disease. Source: Evaluate Pharma, clinicaltrials.com & company communications.*

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