Evaluate Vantage

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# Upcoming events: Eylea combinations and Array's play for melanoma

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Welcome to your weekly digest of approaching regulatory and clinical readouts. Regeneron Pharmaceuticals and Bayer are expecting soon to see the first data from follow-on projects to their blockbuster eye drug Eylea.

Meanwhile, Array Biopharma is set to report topline phase III results with its Braf/Mek inhibitor combination encorafenib and binimetinib in Braf-positive melanoma in the third quarter.

**Eye to the future**

Regeneron Pharmaceuticals' bid to manage the lifecycle of Eylea, its biggest seller, has begun just four years after its launch. The New York-based group has two Bayer-partnered Eylea combinations in phase II, and one of these trials should yield results in coming weeks.

The first therapy, REGN2176-3, combines Eylea's active ingredient, aflibercept, with rinucumab, an antibody blocking platelet-derived growth factor receptor beta, for wet age-related macular degeneration (AMD). Platelet-derived growth factor plays a role in blood vessel formation, an excess of which leads to the fluid leakage characteristic of wet AMD, causing damage to retinal cells.

Aflibercept blocks vascular endothelial growth factor, which also spurs blood vessel growth, so the hope is that by adding a second agent to the mix Regeneron and Bayer can improve on Eylea – or achieve similar efficacy with even fewer intravitreal injections. The phase II Capella trial for REGN2176-3 attempts to show just that.

The partners have enrolled 500 patients randomised to two different dosing regimens of the combination project or Eylea alone, with the primary endpoint set as the change in best corrected visual acuity at 12 weeks. Regeneron says topline data are expected by the end of the year.

Eylea won approval based on non-inferiority to Roche's Lucentis but with less frequent dosing.

Earlier this year Regeneron and Bayer agreed to advance yet another Eylea-based combination, REGN910-3, into phase II. This adds to Eylea nesvacumab, which targets another protein involved in blood vessel growth, angiopoietin-2. Earlier this year, this project started phase II trials in AMD and diabetic macular oedema, which are expected to read out next year.

Eylea's global patents expire between 2020 and 2026, so Regeneron and Bayer are trying to get a headstart on generic competition.

**Columbus's day**

The phase III Columbus trial has a primary endpoint of progression-free survival at two years, with Array hoping to show a benefit with encorafenib/binimetinib versus Roche's Braf inhibitor Zelboraf alone.

A second part of the study will test the combination against encorafenib monotherapy; results from this section are due later.

Assuming that data are positive, Array's combo is set to be third to market behind Novartis's Tafinlar/Mekinist and Roche's Zelboraf/Cotellic – however, encorafenib/binimetinib could differentiate itself with a better safety and tolerability profile, Leerink analysts believe.

The incidence of side effects like fever and rash – known to be a problem with the existing combination products – was low in phase I/II trials with encorafenib/binimetinib.

**Post-PD-1**

The Columbus study also included patients who had progressed on checkpoint inhibitors, which could give encorafenib/binimetinib an edge if this makes it onto its label. PD-1 inhibitors like Bristol-Myers Squibb's Opdivo and Merck & Co's Keytruda are set to dominate the melanoma space, so this would not be a trivial advantage.

In spite of the growth of checkpoint inhibitors, FDA-approved Braf/Mek inhibitors still make up a big chunk of the market, with the Leerink analysts estimating that they will be used in 35% of patients with Braf-mutated first-line metastatic melanoma and putting 2016 worldwide annual sales for the class at $800m.

To get a piece of this market, Array will need to show comparable efficacy to the already approved combinations and hope its side-effect profile remains clean.

Binimetinib/encorafenib is also about to go into phase III in Braf-mutant colorectal cancer in collaboration with Merck KGaA (*Asco 2016 – Array to test Braf/Mek combo in colorectal cancer, June 5, 2016*).

Array is also testing binimetinib alone in Nras-mutant melanoma, and presented positive results from the Nemo study at this year's Asco, with a filing expected shortly.

| **Project** | **Study** | **Trial ID** |
|---|---|---|
| REGN2176-3 | Capella | NCT02418754 |
| REGN910-3 | Onyx | NCT02713204 |
| REGN910-3 | Ruby | NCT02712008 |
| Binimetinib/encorafenib | Columbus | NCT01909453 |
| Binimetinib/encorafenib | Beacon CRC | N/A |

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