Evaluate Vantage

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Roche takes the Tim-3 battle to Novartis

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The Swiss group has likely been paying attention to industry developments as BCMA and CD40 go out, while Covid-19 and Tim-3 move up.

One day after Novartis delayed the results of sabatolimab, the industry's most advanced anti-Tim-3 asset, Roche has highlighted its move of RG7769/RO7121661, a bispecific combining this mechanism with PD-1, into phase 2.

This is not the only pipeline change it revealed in its second-quarter update today, with earlier industry developments likely spurring the discontinuations of BCMA, CD40 and ophthalmology assets and disappointing investors in Affimed and 4D Molecular. Meanwhile, a hepatitis C antiviral licensed from Atea and repurposed for Covid-19 has moved into phase 3.

That last move is especially interesting as industry's Covid-19 antiviral efforts have come off the boil, with Merck & Co canning MK-7110, and limiting molnupiravir work to outpatients. Roche had licensed RG6422/AT-527 from Atea last October, and phase 2 trials have been enrolling for some time; the new phase 3 study highlighted today seeks to recruit 1,386 outpatients, and compares the antiviral against placebo.

Novel IO

Meanwhile, Roche moved the Tim-3/PD-1 bispecific RG7769 into phase 2 before Novartis yesterday disappointed followers of novel immuno-oncology mechanisms and put the spotlight on Glaxosmithkline's Tim-3 bet with cobolimab. Today's Roche presentation spells out the design of the new trial, called Talios, in refractory oesophageal squamous cell carcinoma.

This has a three-arm design, also including a second active cohort testing the Lag3/PD-1 bispecific RG7769, and comparing this and RG7769 against Opdivo in a blinded fashion. With overall survival as the primary endpoint Telios might even be registrational, and its design appears geared specifically towards showing what Lag3 or Tim-3 blockade can add on top of PD-1, though whether a fixed bispecific is the way to show an incremental benefit will be a big question.

Roche's oncology pipeline has also seen the discontinuation of selicrelumab, which had been in several phase 1 combo studies. This molecule is a CD40 agonist MAb, and its shelving might be linked to Johnson & Johnson's decision two years ago to discontinue the similarly acting ADC-1013/mitazalimab, which it had licensed from Alligator Bioscience.

Still, Roche is not ending its pursuit of this pathway; RG6189, a previously undisclosed bispecific that induces

CD40 stimulation solely in the presence of fibroblast activation protein α (FAP), has moved into a phase 1 Tecentriq combo trial in solid tumours, Roche said today.

These developments will be closely followed by the private biotech Apexigen, whose lead asset, APX005M/sotigalimab, is in phase 2, making it the industry's most advanced CD40 agonist. Mitazalimab also remains in development as Alligator's most advanced project.

Going up, going down: selected Roche pipeline changes

Project	Partner source	Description	Move	Note
RG6422/ AT-527	Atea	Hep C antiviral repurposed for Covid-19	Ph3 start	Merck & Co dropped MK-7110, and narrowed molnupiravir focus, in Apr
RG7769/ RO7121661	Internal	Anti-Tim-3/PD-1 bispecific MAb	Ph2 start	Novartis announced delay to sabatolimab's ph2 CR readout on 21 Jun
RG7876/ selicrelumab	Internal	CD40 agonist MAb	Ph1 combo discontinuation	J&J abandoned Alligator's CD40 agonist MAb mitazalimab in 2019
RG6189/ RO7300490	Internal	CD40/FAP bispecific MAb	Ph1 start	
RG6296/ AFM26	Affimed	Anti-BCMA/CD16A (NK cell engager) bispecific	Ph1 discontinuation	Affimed's NK cell approach has impressed, but note BCMA competition
RG6247/ 4D-110	4D Molecular	AAV gene therapy for choroideraemia	Ph1 discontinuation	Biogen/Nightstar, Adverum & Regenxbio have suffered setbacks with ophthalmology gene therapies
4D-125	4D Molecular	AAV gene therapy X-linked retinitis pigmentosa	Ph1 discontinuation	

Source: company presentations.

The additional discontinuation of RG6296 will disappoint fans of Affimed, which has impressed with its bispecific approach to engaging NK cells. The project is the result of a 2018 tie-up between Affimed and Roche that focused on NK cell engagement.

However, since the antigen-targeting moiety of RG6296 hits BCMA its canning makes perfect sense: BCMA is now a hugely competitive space, involving late-stage Car-T assets showing strong efficacy against multiple myeloma, not to mention other bispecifics and conjugates, and this is probably too much to make an early-stage project worth the investment.

Finally, Roche has also confirmed the scrapping of two gene therapies licensed from 4D Molecular, 4D-110 for choroideraemia and 4D-125 for X-linked retinitis pigmentosa. 4D had announced the termination of the Roche deal last month.

This was driven by a "change in risk-benefit profile". It will not escape anyone's notice that gene therapies for eye disease have had a tough time of it, with Biogen, Adverum and Regenxbio all stumbling on toxicity or lack of efficacy.