Evaluate Vantage

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ICML roundup – New dogs for old tricks

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Away from the limelight of the Juliet study of Novartis's CAR-T lead, CTL019, this week's International Conference on Malignant Lymphoma played host to several novel approaches targeting tried and tested pharmacological pathways.

Indeed, one of these, ADC Therapeutics' ADCT-402, targets the same CD19 antigen as CTL019, and might in time give CAR-T a run for its money. Data on other approaches, from Servier challenging Venclexta, and from Seattle Genetics and Cellestia Biotech against CD37 and the Notch pathway respectively, turned ICML from a relatively low-key get-together in a Swiss holiday town into one of the year's more important scientific meetings.

Of course, all the results were early, so it would be premature to read too much into them. But they provided a clear path forward for some of biotech's unsung assets.

Tumour lysis

The Servier data concerned the novel Bcl2 inhibitor S 55746, discovered in collaboration with Vernalis and licensed to Novartis. The industry's first anti-Bcl2 asset, Abbvie and Roche's Venclexta, was launched last year with much fanfare as one of the most promising drugs for CLL.

However, its development was dogged by tumour lysis syndrome – perhaps a reflection of strong efficacy – and this point was stressed by Dr Steven Le Gouill, of Nantes University Hospital, who presented early data from a first-in-human trial of S 55746 in relapsed/refractory B-cell lymphoma.

No dose-limiting toxicities and no tumour lysis syndrome have been seen with S 55746 so far, he told ICML on Wednesday, suggesting further dose escalation and combinations as a logical future strategy. So far, however, there have only been hints of efficacy, with one complete and three partial remissions among 30 patients evaluable on May 1.

Greater promise was shown by ADC Therapeutics' antibody-drug conjugate ADCT-402, the first clinical results on which were presented by Dr Brad Kahl of Washington University, St Louis. Its dose-escalation study has so far enrolled 65 B-cell lymphoma subjects, and in 48 of those evaluable at May 10 the best response rate was running at an impressive 15 CRs and nine PRs.

Efficacy was driven by diffuse large B-cell lymphoma patients, and Dr Kahl stressed ADCT-402's relatively clean safety profile so far, with just one dose-limiting toxicity (worsening thrombocytopenia), and no cytokine release – a known problem of CAR-T therapy. ADC, a private Swiss biotech, raised $105m last October.

CD19 is the antigen targeted by the first wave of CAR-T projects (*ICML – Novartis's non-infusion mystery centres on Juliet's design, June 14, 2017*). The anti-CD19 antibody-drug conjugate approach of ADCT-402 is – like Amgen's anti-CD19 bispecific Blincyto – unlikely to match CAR-T's efficacy, but could be cheaper and thus be used earlier, limiting the patients in whom CAR-T could subsequently be used.

Dr Ahmed Sawas, of Columbia University, presented early data on a separate antibody-drug conjugate, Seattle Genetics/Astellas's AGS67E, showing single-agent activity in 53 heavily pretreated non-Hodgkin's lymphoma subjects that amounted to seven CRs and nine PRs.

This project targets CD37; other approaches against this antigen include the MAbs BI 836826 and otlertuzumab, from Boehringer/Xencor and Aptevo Therapeutics respectively, and Nordic Nanovector's antibody-radionuclide conjugate Betalutin.

Notching up a new trial

Meanwhile, another Swiss start-up, Cellestia Biotech, which raised CHF8m ($8m) in January, looks set to begin first-in-human trials of its lead asset, CB-103, in September or October.

CB-103 is a transcription factor inhibitor of Notch signalling, which could give it broader activity than MAbs against individual Notch receptors, or approaches versus DLL 3/4 or gamma-secretase, which are also involved

in Notch signalling. The planned dose-escalation trial will enrol subjects with various Notch-positive tumours, said Dirk Weber, Cellestia's chief medical officer.

And, while Innate Pharma's investment case centres on its Bristol-Myers Squibb-partnered anti-KIR MAb lirilumab, ICML heard supporting data for its next-furthest advanced asset, IPH4102, which targets the checkpoint KIR3DL2. An escalation trial in cutaneous T-cell lymphoma saw one CR and 9 PRs in 24 subjects.

The benefit was driven by patients with Sezary syndrome, where overall best remission was 47%, and the next stage will involve expansion cohorts in 30 additional subjects, including 15 with Sezary syndrome.

All these studies are early, but investors will no doubt pay close attention to updates as companies seek out better ways of targeting existing pathways.

Selected studies highlighted at ICML			
Project	**Company**	**Study**	**Trial ID**
ADCT-402	ADC Therapeutics	Dose escalation in B-cell NHL	NCT02669017
S 55746	Servier/Vernalis/Novartis	Dose escalation in B-cell NHL	NCT02920697
AGS67E	Seattle Genetics/Astellas	Dose escalation in advanced lymphoid malignancies	NCT02175433
IPH4102	Innate Pharma	Dose escalation in CTCL	NCT02593045
CB-103	Cellestia Biotech	Starting in Sep/Oct 2017	NA