Ash 2022

BY JACOB PLIETH, MADELEINE ARMSTRONG AND EDWIN ELMHIRST | DECEMBER 2022

eBOOK

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Arcellx data secure a Gilead buy-in

BY JACOB PLIETH
DECEMBER 10, 2022

Gilead has licensed CART-ddBCMA as this cell therapy continues putting all patients into remission. Can it compete against Carvykti and Tecvayli?

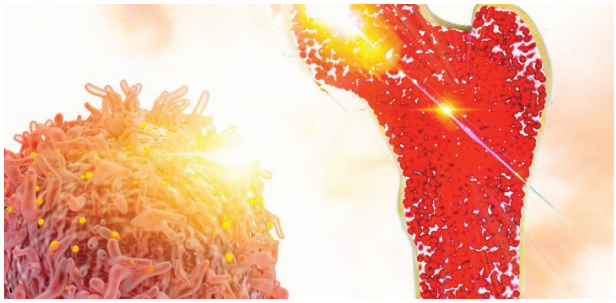
With Arcellx's CART-ddBCMA maintaining its 100% track record of putting multiple myeloma patients into remission, according to data being presented at Ash, Gilead heard enough to sign on the dotted line. Friday's licensing deal saw the big biotech hand across $225m in cash and make a $100m equity investment for rights to the project.

An investor update made available ahead of Arcellx's Ash poster on Sunday sheds more light on the latest cut of the phase 1 CART-ddBCMA study that secured Gilead as a partner. J&J's approved rival BCMA-directed Car-T therapy, Carvykti, has set a high bar which, once again, CART-ddBCMA seems to have met. The Gilead deal adds a key endorsement.

Being competitive in this space is especially hard given the huge number of BCMA-targeting projects in development, and the added availability as of October of J&J's Tecvayli, a T-cell engaging MAb.

BEST IN CLASS?

The last time Arcellx presented CART-ddBCMA data, at Asco in June, it argued that the project, which is autologous but uses an artificial binding domain to hit BCMA, had "best-in-class potential". This was on the basis of efficacy in line with Carvykti in an arguably harder-to-treat population, with possibly better safety to boot.

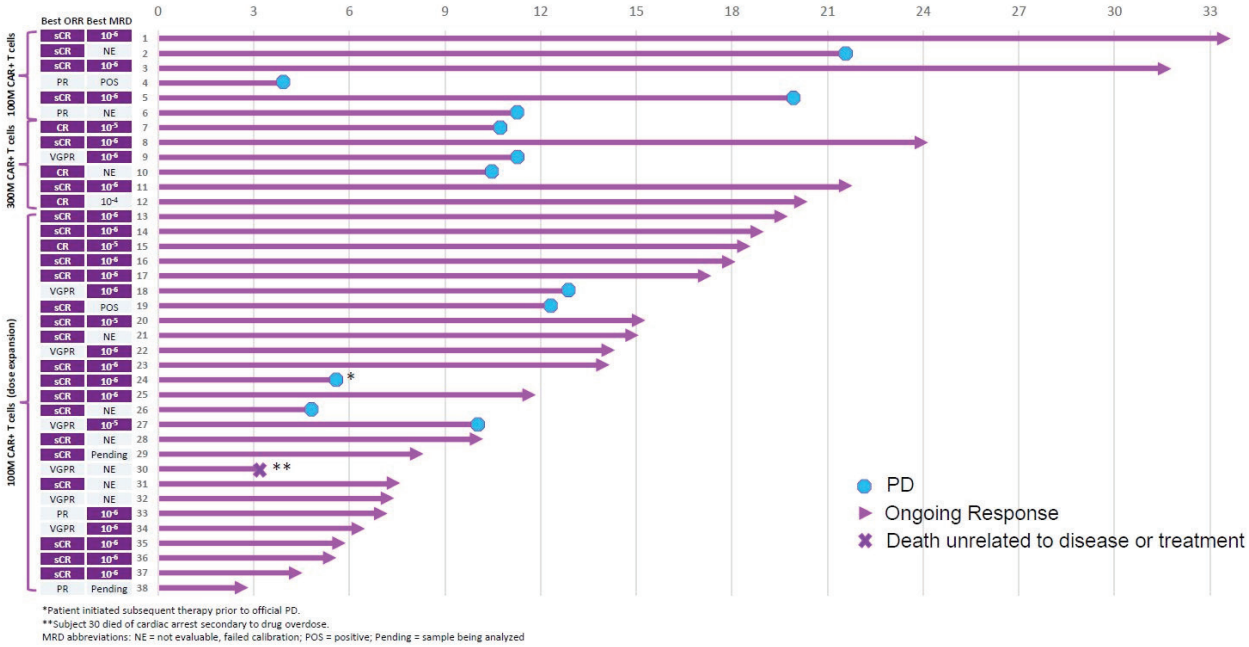


At Ash it is adding seven patients to bring the evaluable dataset to 38 as of an October 31 cutoff. All 31 patients previously detailed had gone into remission, and so have the extra seven patients now presented. And 27 of those 38 responses are complete.

So far so good, and it must also be stressed that safety remains relatively clean: among grade 3 events there is just one cytokine release syndrome and two neurotoxicity cases. This is the same state of play as at the Asco data cutoff.

However, many of the remissions are not proving durable. Close inspection of the swimmers plot shows that 12 patients initially responding to CART-ddBCMA have relapsed, most by around 12 months, and in addition there was one death, though this was unrelated to disease or treatment.

Accordingly, at 18 months the response rate stands at 50% – 11 of 22 patients.



Source: Arcellx presentation.

For more detail in this chart, **click here**.

No matter, Gilead has clearly seen enough. Arcellx says CART-ddBCMA's synthetic binding region – instead of an antibody-derived one – results in more transduced cells being Car-positive than with Carvykti, allowing lower effective cell dosing and less toxicity; the data continue to bear this out.

It is notable that Gilead was until now an outlier among cell therapy players in not having an anti-BCMA therapy. Its legacy company Kite Pharma had been developing such a Car-T project, coded KITE-585, but this never progressed beyond preclinical trials. Gilead canned it after deeming it insufficiently competitive and incurred an $820m write-off as a result.

On Friday Arcellx closed up 29%. Whatever doubts remain about its data, investors should be relieved that of all the developmental BCMA projects Gilead could have chosen, it decided to pick CART-ddBCMA.

Talquetamab heads to the regulators

BY JACOB PLIETH
DECEMBER 10, 2022

The FDA will soon rule on the approvability of the industry's first anti-GPRC5D project, and Ash just saw the data the agency will be reviewing.

Johnson & Johnson is making a bid to own the late-stage multiple myeloma space, in which attention is falling increasingly on approaches beyond BCMA blockade. Yesterday the group filed talquetamab, and today an Ash update revealed the data it has taken to regulators.

A big question is how broad a label the FDA might give the project, a T-cell engager against the novel antigen GPRC5D. J&J's two approved anti-BCMA treatments, the Car-T therapy Carvykti and the T-cell engager Tecvayli, both carry fifth-line labels, but talquetamab's supporting Monumental-1 trial tested this project as early as fourth line.

A similar consideration is whether talquetamab will compete directly against BCMA-directed therapies, or whether it will be used, at least at first, only in those who relapse on the likes of Carvykti and Tecvayli. The former use sets a higher bar to approval than the latter, given a 98% remission rate, and 78% complete response rate, cited by Carvykti's label.

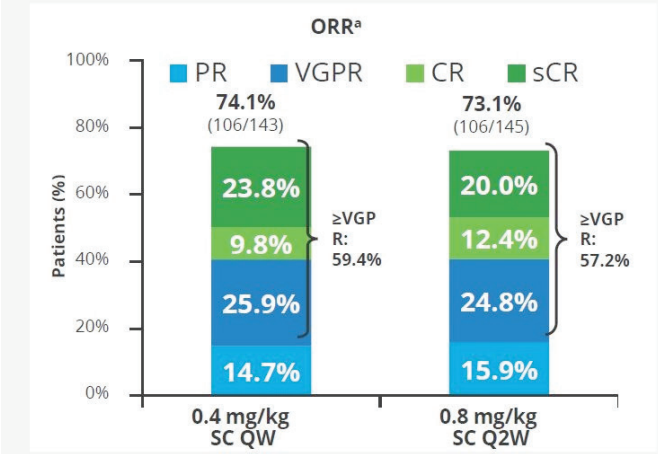
GOING SC

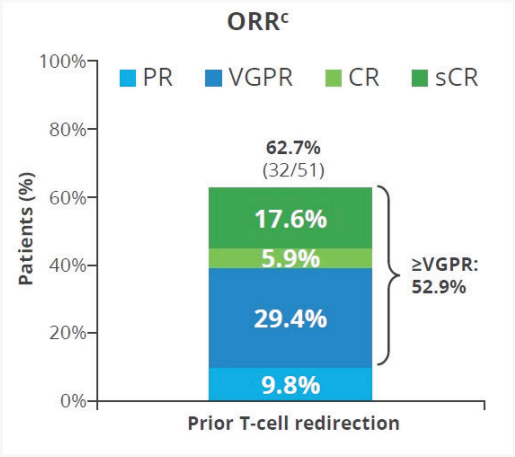
Monumental-1 tested talquetamab in both settings, and the Ash presentation added the study's phase 2 portion for the first time, zeroing in on a total of 288 patients given one of two SC doses, 0.4mg weekly

or 0.8mg every two weeks; the trial had earlier looked at IV dosing, but it is the SC project that was filed yesterday.

The headline number was a 74% overall response rate across the two doses, with 95 of the 212 remissions being deemed complete. Mount Sinai School of Medicine's Dr Ajai Chari, presenting the data at an Ash press briefing this morning, called this result impressive given that until recently 30% ORR in this type of heavily pretreated multiple myeloma population had been considered positive.

Looking only at 51 patients in whom T-cell redirection therapy – in effect meaning bispecifics, ADCs or Car-T therapies targeting BCMA – had failed, the ORR was 63%, including a 24% rate of complete remissions.





- ORR was consistent across subgroups including baseline ISS stage III disease, baseline cytogenetic risk, number of prior therapies, refractoriness to prior therapy, and belantamab exposure, except among patients with baseline plasmacytomas

Data cut-off date: September 12, 2022.

Response rates in all phase 1/2 patients given SC doses (left), and in those after T-cell redirection therapy (right).

Source: Ash & Dr Ajai Chari.

Dr Chari's enthusiasm is understandable, but multiple myeloma treatment has moved quickly recently. This is exemplified by the near-100% response rates seen with Carvykti, and the 68% ORR cited on the label of J&J's own anti-BCMA bispecific, the recently approved Tecvayli.

This comparison is important; if talquetamab were to be restricted to the white space of BCMA failures that would be one thing, but if – as today's data suggest – it is to treat patients who have yet to be exposed to BCMA inhibition then it is anti-BCMA agents against which it must be compared. And on a cross-trial basis talquetamab's efficacy looks not much better than Tecvayli's.

SAFETY ADVANTAGE?

Still, Dr Chari claimed that there was an additional benefit: safety, and specifically a reduced risk of Covid infections, which he said remain a problem for severely immunocompromised haematological malignancy patients.

Monumental-1 was conducted during the Covid pandemic, including during a time before Covid vaccines were available, but the dataset at Ash details only two deaths due to Covid.

The study "was being accrued at a concurrent time to [those testing] the BCMA bispecifics, where there have been many deaths reported from Covid," said Dr Chari. "If you measure Covid antibodies, patients on [talquetamab] are producing antibodies. That's a really different signal than what we've seen before."

So is this down to hitting a different target? "I think so," he told the press briefing. "I think it's partly because of the dirtiness of BCMA."

Asked whether he saw talquetamab being used in BCMA-naive and BCMA-relapsed patients alike, he said yes. Soon it will be the FDA's turn to decide on this matter.

Adicet has a case of déjà vu

BY JACOB PLIETH
DECEMBER 10, 2022

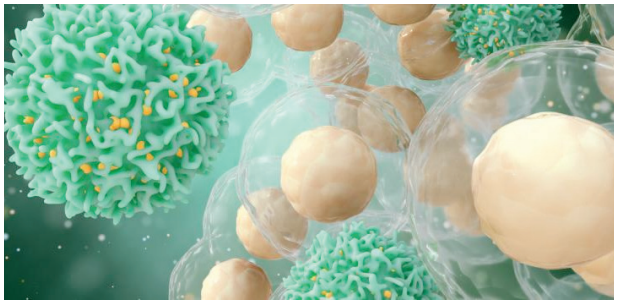
Investors got jittery on Friday, and for good reason: like all allogeneic cell therapy players Adicet is seeing patients relapse.

Just as at this year's Asco, Adicet came into Ash under the weight of investor expectations about a small trial of its off-the-shelf gamma-delta Car-T project ADI-001. And, like at Asco, it will exit Ash desperately trying to convince the markets that the therapy is durable.

However, this time around investors might not be as forgiving. In a dataset that now includes 16 lymphoma subjects it is clear that relapses are a problem: across four dose levels an initial 75% response rate falls to 18% at six months. Pre-Ash jitters saw Adicet lose 13% on Friday, and another fall when the stock opens on Monday cannot be ruled out.

The company's poster is being presented at Ash later today, but is understood to be no different to that seen in the abstract, which has a July 15 cutoff. Instead, the most up-to-date cut has just been put out by press release, relating to a December 5 cutoff – just a few days ago.

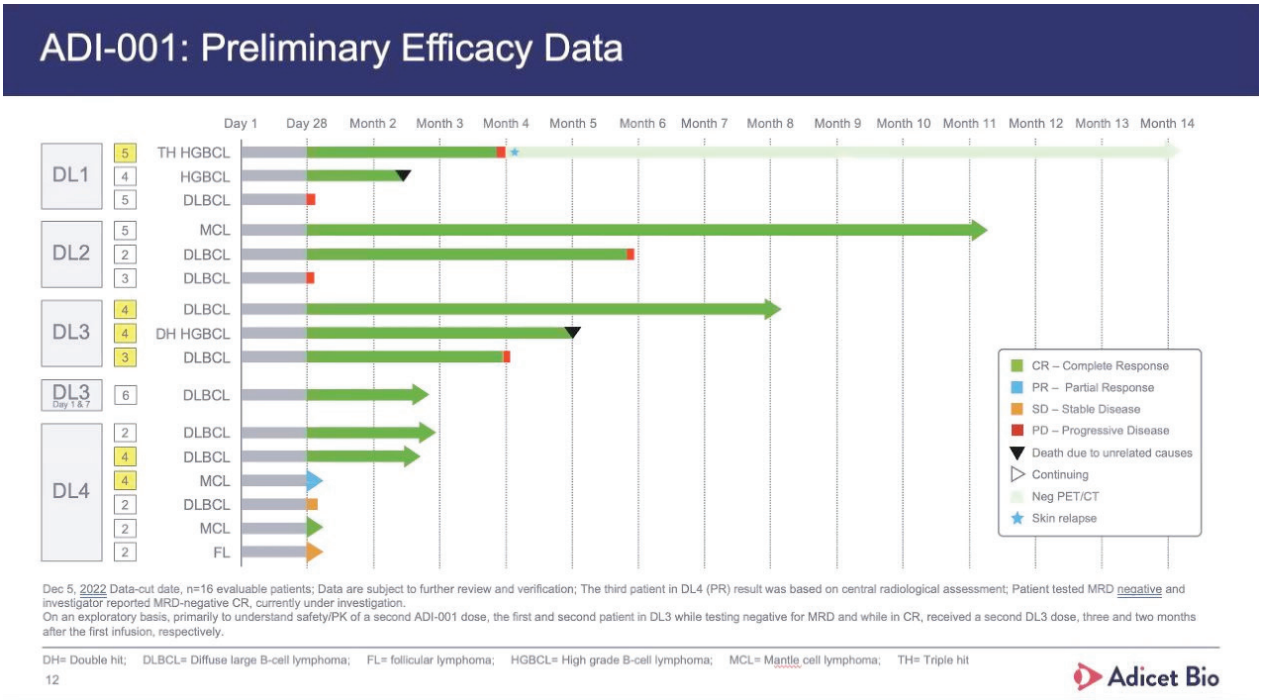
The latest swimmers plot shows a couple of important updates, including a fourth dose level (one



billion cells) comprising six subjects, and one patient at dose level 3 given two lots of 300 million ADI-001 cells, at days one and seven, with just a single lymphodepletion.

However, the most salient feature is relapses – a problem that has taken the wind out of the allogeneic Car-T companies Allogene, Precision Biosciences, Crispr Therapeutics and Caribou.

All but two of the previously detailed nine subjects had relapsed by six months' follow-up; this includes one patient who died of causes unrelated to treatment. Of the seven new subjects, five are in remission, though at very short follow-up.



Source: company presentation.

ADI-001 targets CD20, and is the industry's most advanced Car asset using gamma-delta (rather than the more common alpha-beta) T cells.

It is encouraging that all five CD19 Car-T relapsed lymphoma patients in this trial were put into complete remission, and that safety is clean, with no cytokine release or neurotoxicity at grade 3 or above. But the fact remains that just two patients have durable responses, and one of these has mantle cell lymphoma, a less aggressive disease than the diffuse large B-cell lymphoma that will be the focus for further trials.

Speaking to Evaluate Vantage under embargo yesterday, MD Anderson Cancer Center's Dr Sattva Neelapu, the lead investigator, said that despite the relapses the six-month CR rate was comparable to an autologous anti-CD19 Car-T therapy.

Three patients got double ADI-001 doses, two of these while they were in complete response a few months later, with a second lymphodepletion.

The third patient was treated differently, receiving a planned double ADI-001 dose at days one and seven to explore any potential benefit, Adicet's chief executive, Chen Schor, told Vantage.

How this third patient, who is in CR at around three months, performs in the longer term will be important for gauging whether persistence can be improved. It is highly notable that this third patient was not lymphodepleted a second time – the need to undergo lymphodepletion again would likely hamper the potential to give any cell therapy multiple times.

NO HIGHER

Mr Schor also described the design of a pivotal study, due to start in the second quarter of 2023. This would target large B-cell lymphoma patients in whom Car-T therapy has failed.

However, despite the still clean safety profile at high ADI-001 doses, there is no plan to increase dosing further, perhaps because dose level 4 has not boosted initial responses. The pivotal dose has yet

to be determined, said Mr Schor, but the protocol will likely allow double doses on days one and seven after a single lymphodepletion.

Though Adicet has shown enough to go into a bigger trial, as before it is asking investors to hold out for further results, but this time with more relapses. “We’re very happy with the CR rate … and at dose level 4 we just need to wait for data to mature,” said Mr Schor. “Overall we think we’re on safe ground.”

Argenx faces Vyvgart questions

BY MADELEINE ARMSTRONG
DECEMBER 10, 2022

As the group looks to expand into immune thrombocytopenia, there are several reasons to be cautious.

Immune thrombocytopenia is a disease for which patients could do with more options. Argenx hopes to add to these with Vyvgart, which has bagged a prestigious press slot at this year's Ash meeting.

However, there are outstanding questions about the drug here, including whether a marginal win in the Advance IV study, being presented during a plenary session tomorrow, will be enough to support approval. And, even if Vyvgart gets to market, it is unclear how it might fit into the treatment landscape: Argenx's study enrolled a heavily pretreated population, and oral contenders could be coming.

Argenx is developing intravenous and subcutaneous versions of Vyvgart, and hopes to have both available for all indications currently in development. In ITP, Advance IV tested the intravenous form, and Argenx is awaiting data from the subcutaneous Advance SC trial, due in the second half of 2023, before filing a single package with the FDA.

A spokesperson for Argenx does not anticipate any problems with this approach, despite the fact that the group has previously said that the formulations are seen as different products by regulators.

"ITP is the only indication where the FDA stated two registrational trials would be necessary, so we are conducting the subcutaneous study as the second registrational study," the spokesperson told Evaluate Vantage under embargo before the meeting started.

POST-STEROIDS?

ITP is an autoimmune disorder involving platelet destruction, which leads to excessive bruising and bleeding. The first-line treatment is usually corticosteroids, but most patients cannot tolerate these long-term and can relapse once steroids are tapered, Dr Cynthia Dunbar of National Heart Lung and Blood Institute said during a pre-Ash media briefing.

The next step is spleen removal or thrombopoietin receptor agonists like Novartis's Promacta or Amgen's Nplate. Another second/third-line option is Rituxan, although this has fallen out of favour lately owing to its long-term depletion of patients' antibodies, Dr Dunbar said.

As for how Vyvgart might fit in, it is notable that the Advance IV trial enrolled patients who had failed at least one prior therapy, and 67% of patients had received three or more prior therapies.

At a press conference today, Dr Catherine Broome of Georgetown University, Washington, DC said

Vyvgart could be a "great drug for patients who've not responded to a steroid or thrombopoietin receptor agonist". She estimates that up to 30% of ITP patients fail multiple lines of therapy.

"Whether it will be able to show significant efficacy in a not so heavily pre-treated population remains to be seen," she told Evaluate Vantage in a later interview, but added: "The way the drug works, there shouldn't be a reason why it wouldn't be equally effective in earlier lines of therapy."

Stifel analysts reckon that Vyvgart could bring in sales of over $1bn in ITP, based on the 70% or so patients who relapse after steroids.

ITP ADVANCE

In Advance, patients received IV Vyvgart weekly or every other week, or placebo, for 24 weeks. As previously detailed in the Ash abstract, 22% of those receiving Vyvgart achieved a sustained platelet response, the primary endpoint, versus 5% of the placebo group (Ash 2022 preview – Argenx's expansion plans come into focus, November 10, 2022).

A platelet response was defined as having platelet counts greater than or equal to 50x109/l on at least four of the last six scheduled visits between weeks 19 and 24 of treatment.

The result was statistically significant, with a p value of 0.0316. Stifel has questioned whether this marginal result will support approval, although a bigger issue is probably what this close win might mean for the upcoming Advance SC study of the subcutaneous formulation.

This concern appears to have been behind Argenx's move to increase enrolment in that study, which delayed its readout. It had originally been expected in the first quarter.

Another potential issue is that, in Advance IV, Vyvgart did not lead to a significant decrease in bleeding events. However, Argenx's chief medical officer, Luc Truyen, told Vantage ahead of Ash: "We had relatively low bleeding events at baseline so it was difficult to create a statistically significant delta." He noted a numerical decrease in bleeds with Vyvgart versus placebo.

Dr Dunbar agreed that this finding was not a cause for concern, stressing that Advance was a relatively short study.

In general, Argenx is well ahead of its anti-FcRn rivals. However, the ITP space could soon be evolving and another anti-FcRn player, UCB, recently dropped out of the disease, citing increasing competition. Oral projects pose a particular threat, and one in development is Sanofi's BTK inhibitor rilzabruitnib; however, this has already failed in pemphigus so is far from a dead cert.

Targeting FcRn: clinical-stage projects

Project	Company	Note
Approved		
Vyvgart (efgartigimod)	Argenx	gMG: IV version approved, SC version has Pdufa Mar 20, 2023; ITP: ph3 IV Advance IV data at Ash 2022, Advance SC data due H2 2023; CIDP Adhere due Q1 2023; Pemphigus Address due H2 2023
Phase 3		
Rozanolixizumab	UCB	SC infusion; Mycaring in gMG reported May 2022; development in ITP deprioritised
Nipocalimab	J&J (via Momenta)	IV; ph3 in gMG; ph2/3 in wAIHA & CIDP
Batoclimab (IMVT-1401)	Immunovant	SC; ph3 in gMG & TED; previously linked with cholesterol increases in ph2 Ascend-Go2

CIDP=chronic inflammatory demyelinating polyneuropathy; gMG=generalised myasthenia gravis; ITP=immune thrombocytopenia; TED=thyroid eye disease; wAIHA=warm autoimmune haemolytic anaemia. Source: Evaluate Pharma & clinicaltrials.gov.

Syndax and Kura face off

BY JACOB PLIETH
DECEMBER 11, 2022

Duelling datasets on the companies' rival menin inhibitors show each to have weaknesses and strengths.

Two novel ways of treating acute myelogenous leukaemia squared off against each other at Ash on Saturday, with Syndax and Kura presenting early data on two menin inhibitors, revumenib and ziftomenib respectively.

Some biotech investors have been focusing on these results given that both companies have similar valuations, around $1bn, and offer simple exposure to the success or failure of this mechanistic approach. The take-home message from today's sessions was that Syndax continues to be dogged by cardiac toxicity, but probably targets a broader population than Kura.

Both projects followed a similar journey through the clinic, having initially been tested in broad relapsed/refractory AML populations, before activity was narrowed down to patients with specific mutations. The early trials were then enriched for AML patients harbouring those genetics, namely KMT2A rearrangement and NPM1 mutation.

REMISSION S VS TOXICITY

Syndax is further ahead in development, and its Ash dataset showed a 53% overall response rate among 60 patients with the relevant two mutations. Remissions were better in the KMT2A-rearranged than the NPM1-mutant cohort, but still respectable in each.

Its problem, however, is QTc prolongation, which occurred in over half of all patients, with 13% of subjects experiencing it at grade 3 or higher. This issue first came to light two years ago, and Syndax stock was hammered as a result; with more patients enrolled the incidence of QTc prolongation remains fairly consistent.

Presenting the Syndax data, Dr Ghayas Issa of the University of Texas said QTc prolongation was revumenib's only common severe adverse event and only dose-limiting toxicity, and that it occurred asymptomatically.

As if to hammer home the difference, the presenter of Kura's study, Dr Harry Erba of Duke University Medical Center, said ziftomenib resulted in "no drug-induced QT/QTc prolongation". But Kura's problem is a separate adverse event – differentiation syndrome – which ironically Syndax has not reported in its study to a meaningful extent.

Duel of the menin-KMT2A (MLL) inhibitors				
Company	Syndax		Kura	
Project	Revumenib		Ziftomenib	
Trial	Augment-101		Komet-001	
Data cutoff	31 Mar 2022		24 Oct 2022	
Subgroup	NPM1m	KMT2Ar	NPM1m	KMT2Ar
ORR	5/14 (36%)	27/46 (59%)	10/26 (38%)	3/32 (9%)
QTc prolongation	53% (of which 13% at gr3+)		None reported	
Differentiation syndrome	16% (none at gr3+)		None at gr3+	33% at gr3+

Source: Ash.

A further irony is that Kura has seen severe differentiation syndrome only in patients with KMT2A rearrangement and not in NPM1-mutant AML. And ziftomenib's activity appears limited to the latter genetic subtype (38% ORR) and not the former (9%).

Dr Erba admitted that these findings meant that ziftomenib had no future as monotherapy in KMT2A-rearranged AML, a setting where a combination strategy would instead have to be pursued to optimise the risk/benefit and maximise the time patients can spend on treatment.

Both companies agree that mutant NPM1 is the bigger opportunity, representing some 30% of AML patients, versus around 10% for KMT2A-rearranged disease, so Kura still has something to shoot for. Still, Kura has shown nothing to suggest that it is about to jump ahead of Syndax.

While Kura hopes to start combo studies next year, the pivotal phase 2 portion of Syndax's Augment-101 trial is already enrolling, with a filing planned by the end of 2023.

Following in talquetamab's slipstream

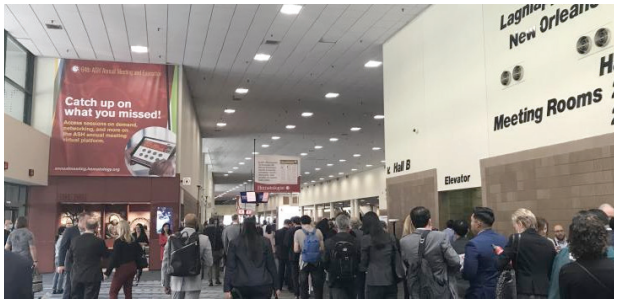
BY JACOB PLIETH
DECEMBER 11, 2022

Roche and Bristol Myers Squibb look to have the industry's next most advanced assets against GPRC5D.

In Johnson & Johnson's talquetamab, which featured at Ash yesterday, the industry might soon have a brand new approach for treating multiple myeloma. But what are other companies doing to develop rival therapies that hit the same target, GPRC5D?

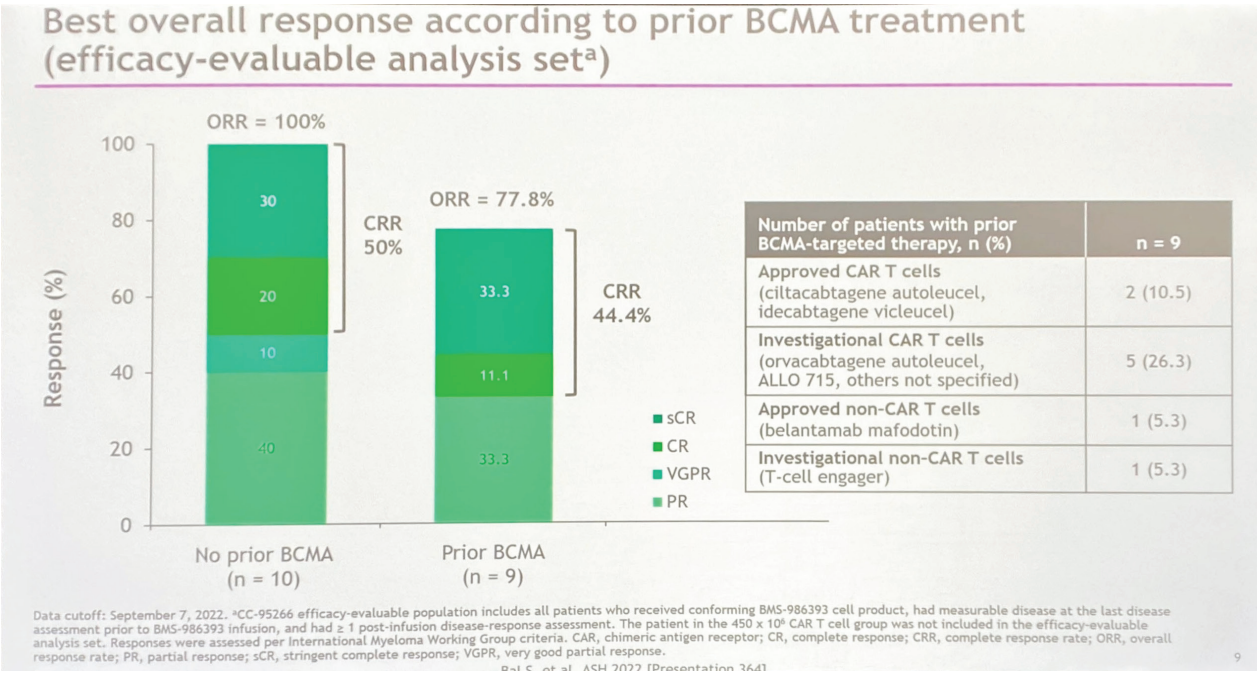
Two Ash sessions provided an answer this weekend. Roche's forimtamig, a me-too T-cell engager bispecific also being studied in IV and SC forms, put up results that appeared to come up short of talquetamab. And Bristol Myers Squibb's Car-T therapy BMS-986393 yielded first-in-human data said to back its potential irrespective of prior BCMA-directed therapy.

It was a legacy Bristol asset that kicked off interest in GPRC5D. Back at Ash 2018 MCARH109, a Car-T against this antigen, was said to have preclinical potential. MCARH109 was then the property of Juno, which had recently been acquired by Celgene, and later Bristol bought out Celgene.



However, BMS-986393 appears to be a different asset. In a relapsed/refractory multiple myeloma population of 33 patients, 18 of whom had received prior anti-BCMA therapy, Bristol reported no treatment-related deaths, and a relatively low 6% rate of severe cytokine release syndrome (CRS).

Across all doses, 17 of 19 efficacy-evaluable subjects went into remission, comprising a 100% ORR in the 10 who had not had prior anti-BCMA therapy, and 78% in the nine who had progressed on Carvykti, ALLO-715, Blenrep or an investigational bispecific.



BMS-986393 efficacy.

Source: Dr Jesus Berdeja & Ash.

J&J's talquetamab has also shown activity in BCMA-naive and experienced patients alike, though whether it will be approved in both is up to the FDA.

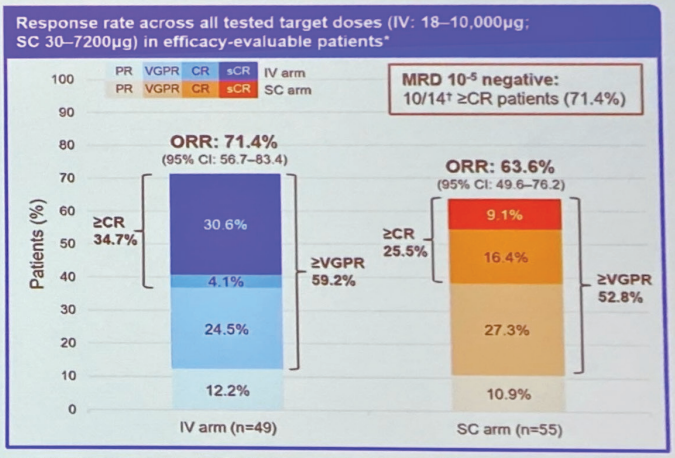
Meanwhile, Roche's forimtamig dataset (the asset had previously been coded RG6234) comprised 50 subjects given an IV and 57 given a SC dose; just over 20% had previously received anti-BCMA therapy. Here severe CRS was higher, at over 30%, and one death in the SC cohort was deemed related to forimtamig.

Response rates were better with IV than with the SC dose, at 71% and 64% respectively, and evaluation and optimisation of both dosing strategies was said to be ongoing. In reality, however, Roche will likely only be able to compete with SC forimtamig, since J&J's talquetamab filing was for two SC doses.

On a cross-trial basis Roche might have some more work to do, as yesterday's Ash data put talquetamab's ORR above the 70% threshold, and the J&J project was associated with only a 2% rate of severe CRS. No other GPRC5D projects appear to be in clinical development in the west.

Forimtamig clinical efficacy

	IV arm (n=49)	SC arm (n=55)
Median follow-up, months (range)	11.6 (0.5–20.6)	8.0 (1.1–15.0)
Median time to first response, months (95% CI)	1.4 (1.2–1.8)	1.6 (1.2–2.1)
Median duration of response, months (range)	10.8 (0.0–17.6)	12.5 (1.2–12.5)
Patients with ongoing response at data cut-off, n/N (%)	23/35 (65.7)	25/35 (71.4)
Patients with prior anti-BCMA and response, n/N (%)	5/10 (50.0)	6/11 (54.5)



Data cut-off: October 21, 2022; *patients who received ≥1 target dose of forimtamig and had at least one baseline and one on-treatment tumor assessment or discontinued due to clinical progression; †of 14 evaluable patients with available BMA at the time of response across all IV and SC doses so far, 10 had MRD-negative CR at 10^{-5}. BMA, bone marrow aspirate; CI, confidence interval; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Source: Dr Carmelo Carlo-Stella & Ash.

Toxicity still looms large for Regeneron's bispecific

BY MADELEINE ARMSTRONG
DECEMBER 11, 2022

Another five treatment-related deaths, despite a dose regimen change, raise questions about whether odronextamab will be able to compete.

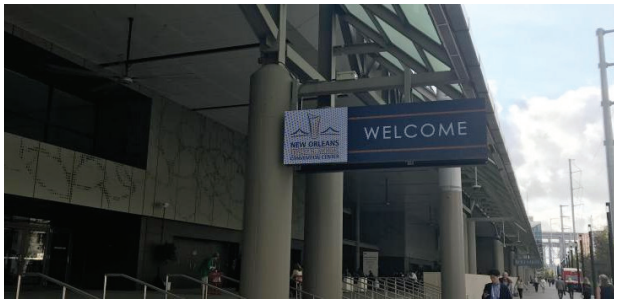
At Ash 2020 presentation of data on Regeneron's CD20-targeting bispecific odronextamab was marred by five treatment-related deaths. Two years later, the company has reported five more fatalities – and this time with a dosing regimen that was meant to reduce toxicity.

Regeneron was already behind Abbvie and Genmab's similarly acting epcoritamab and Roche's glofitamab, and facing questions about how it might compete. The latest disclosure might make it all but impossible for Regeneron to gain a foothold in this space.

All the aforementioned projects are T-cell recruiting CD20xCD3 bispecifics. Epcoritamab looks like the project to beat in terms of efficacy, and in aggressive lymphoma it is also ahead with the regulators: the project has a Pdufa date of May 21, 2023.

Roche is not too far behind – glofitamab impressed at this year's Asco and the company has filed it with the FDA, a spokesperson told Evaluate Vantage. Data from the project's pivotal phase 1/2 trial were presented at Ash today and published in the New England Journal of Medicine.

And another contender is Johnson & Johnson/ Xencor's plamotamab; an Ash poster on Monday



showed an ORR of 52% in DLBCL, putting this project in line with glofitamab, but behind epcoritamab.

Roche has a separate anti-CD20 bispecific, Lunsumio, that is approved in the EU and expecting a US decision by December 29, though this targets the less aggressive disease follicular lymphoma.

PLAYING CATCH-UP

It was in this context that data on odronextamab were presented today, from a cohort of patients in the phase 2 Elm-2 trial with second-line or later diffuse large B-cell lymphoma (DLBCL).

The study was put on partial clinical hold in December 2020 over concerns about cytokine release syndrome in the phase 1 Elm-1 study; the hold was lifted in May 2021 and a longer step-up dosing regimen introduced to try and reduce this

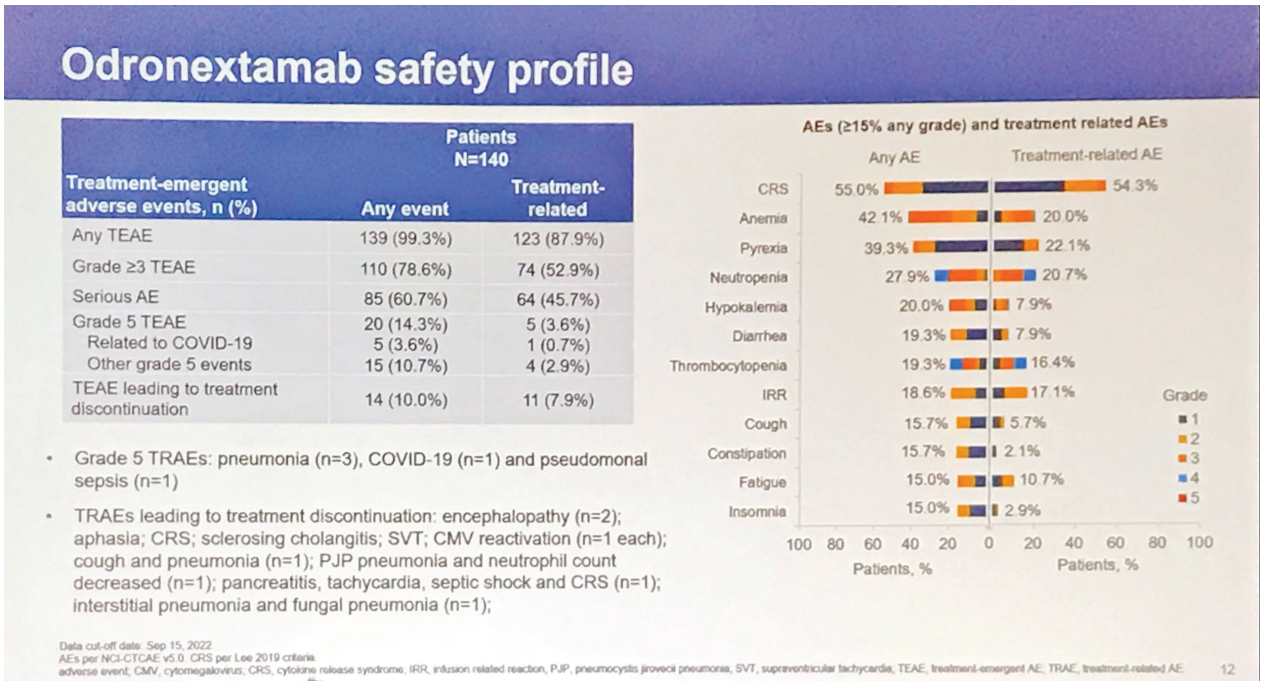
side effect. Notably, the regimen in Elm-2 was modified again during the trial to mitigate this risk even further.

Although cytokine release syndrome rates did look slightly better in Elm-2, this is not the end of concerns over odronextamab's toxicity. Among 140 patients there were five treatment-related deaths in the study, caused by pneumonia in three cases, Covid and pseudomonal sepsis.

Despite this the presenter, Dr Won Seog Kim of the Samsung Medical Center in Seoul, described odronextamab's toxicity profile as "manageable".

There was some good news: among 130 evaluable patients the overall response rate, as assessed by central review, was 49%, and 31% of patients had a complete response. This looks better than the 40% ORR seen in DLBCL in Elm-1.

The question now is whether this will matter with epcoritamab and glofitamab looking at least as good, if not better, in terms of efficacy – and with no treatment-related deaths.



Source: Dr Won Seog Kim & Ash

The sickle cell race hots up

BY MADELEINE ARMSTRONG
DECEMBER 11, 2022

Sangamo emulates Editas, while Crispr/Vertex and Bluebird add weight to their ambitions.

Previous data with Sangamo's sickle cell disease gene editing contender BIVV003 were not enough to keep the group's erstwhile partner Sanofi interested. Sangamo will now hope that it can become a contender here with promising – but very early – data from the first patient treated using a new manufacturing process.

A poster unveiled at Ash on Saturday showed that this patient had foetal haemoglobin levels of 45% at 26 weeks, making BIVV003 look similar to Editas's EDIT-301, which produced similar data in a single patient last week. Meanwhile, the leading players in genetic medicines for sickle cell, Crispr/Vertex and Bluebird, also featured in oral presentations at this year's Ash.

Both Sangamo's BIVV003 and Editas's EDIT-301 are designed to increase foetal haemoglobin to compensate for the defective haemoglobin found in sickle cell disease; Crispr and Vertex's exa-cel has the same aim. Although these are all gene-edited projects they work differently: BIVV003 employs zinc finger nucleases, while EDIT-301 and exa-cel are Crispr-edited assets, but use different nucleases, AsCas12a and Cas9 respectively.

Last year at Ash Sangamo reported data with BIVV003 in four patients that looked decent – but not quite as good as results seen with exa-cel (Ash 2021 – Sangamo and Sanofi enter the sickle cell gene editing fray, December 13, 2021). Then in January Sanofi ended its partnership with Sangamo.

This year's meeting featured longer-term data on the four BIVV003 patients. More importantly, the poster also included a first look at a new manufacturing process that, Sangamo hopes, could improve efficacy.

As well as the foetal haemoglobin finding, the subject using the BIVV003's new manufacturing process has not had any vaso-occlusive crises. It is probably too soon to read much into this given that the patient has only been followed for around six months.

MORE PATIENTS NEEDED

Sangamo will need to replicate these findings in more patients before BIVV003 can be considered a contender – something that Richard Boismenu, a development programme leader at Sangamo, conceded when he spoke to Evaluate Vantage at the Ash meeting.

He maintained that Sanofi had walked away from the deal because it had wanted to focus on allogeneic, rather than autologous therapies like BIVV003.

An unavoidable fact, though, is that Sangamo is behind in a crowded space that could soon be sewn up by Bluebird and Crispr/Vertex.

This is a criticism that could also be levelled at Editas, which last week reported its early data from the Ruby trial of EDIT-301 separately from Ash. The first patient treated saw foetal haemoglobin levels of 45%, and there were no vaso-occlusive crises in two patients followed for five and 1.5 months.

Cross-trial comparison of selected sickle cell projects						
Project	**Company/ies**	**Description**	**Trial**	**Modified Hb levels**	**VOCs**	**Source**
Exagamglogene autotemcel (exa-cel, CTX001)	Crispr/Vertex	Crispr/Cas9 gene-edited cell therapy targeting BCL11A	Climb SCD-121	Mean 43% at 12 mth in 9 pts	0	EHA & Ash 2022 presentation
Lovo-cel	Bluebird	Lentiviral gene therapy that produces anti-sickling Hb, HbAT87Q	HGB-206 study	Mean 45% at 24 mth in 16 pts	1	Ash 2022 presentation
BIVV003 (SAR445136)	Sangamo	Zinc finger nuclease gene-edited cell therapy targeting BCL11A	Precizn-1	11-40% in 4 pts with original manufacturing process; 45% in 1 pt with new manufacturing process	2 (in 1 pt on original manuf process)	Ash 2022 poster
OTQ923 (HIX763)	Intellia/Novartis	Crispr/Cas9 gene-edited cell therapy targeting BCL11A	Ph1/2	16-22% in 2 pts	0	Ash 2022 abstract
EDIT-301	Editas	CRISPR/Cas12a gene-edited cell therapy targeting beta-globin	Ruby	45% in 1 pt	0	Company presentation, Dec 6 2022

Note: all projects except Lovo-cel aim to increase foetal haemoglobin. Source: company presentations & Ash 2022.

The leader in the space is arguably exa-cel; Crispr and Vertex have started a rolling application with the FDA, set to be completed in the first quarter of next year.

The update at Ash on Saturday concerned the same data presented at the EHA meeting in June (EHA 2022 – Crispr still looks bloody good, June 13, 2022).

One concern raised at the time was apparently waning haemoglobin levels, although Dr Haydar Frangoul of the Sarah Cannon Research Institute said during his Ash presentation that there was not enough data to show that this was occurring. "We have not seen any signal to show we're losing efficacy of the treatment," he said.

BLUEBIRD REASSURES

Meanwhile, Bluebird's lovo-cel is not too far behind, with an FDA filing due in the first quarter. This works slightly differently, being a gene therapy that aims to increase levels of an anti-sickling haemoglobin, HbAT87Q.

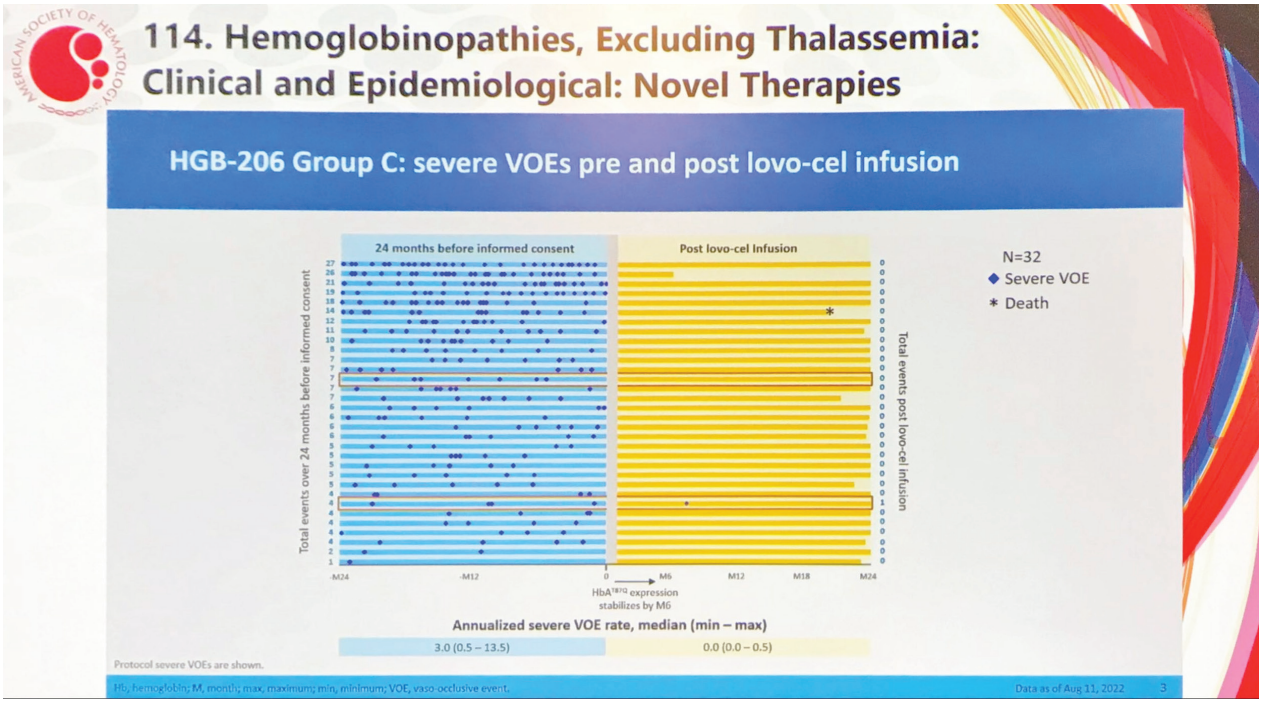
Attendees saw fuller data from part C of the HGB-206 trial of lovo-cel. Among 32 evaluable patients, only one had a severe vaso-occlusive event

following lovo-cel infusion – one event among 29 patients had been detailed in the abstract.

The main focus of the presentation was the two patients – one adult and one child – who suffered anaemia, a side effect that had previously raised concerns about myelodysplastic syndrome.

Presenting the data, Dr Mark Walters of UCSF Benioff Children's Hospitals seemed unconcerned, saying: "The evidence doesn't support an emerging MDS or malignant process."

Lovo-cel is still on partial clinical hold in patients under 18, however. With the sickle cell pipeline behind Bluebird maturing, investors will want to see this lifted as soon as possible.



Source: Dr Mark Walters & Ash

For more detail in this chart, **click here**.

Astra takes two shots at oral complement inhibition

BY MADELEINE ARMSTRONG
DECEMBER 11, 2022

Meanwhile, Roche sees reasons for optimism with its subcutaneous contender.

Astrazeneca is already the dominant force in paroxysmal nocturnal haemoglobinuria, with the intravenous therapies Soliris and Ultomiris. However, competition is mounting, from Apellis's subcutaneous drug Empaveli and Novartis's oral hopeful iptacopan.

Astra is not standing still, with a couple of oral contenders of its own. The most advanced, danicopan, will soon be heading to regulators, but did not feature at this year's Ash; instead it was the next-generation project vemircopan that had data at the conference.

Elsewhere, Roche's subcutaneous PNH asset crovalimab showed encouraging signs in a Chinese study that might bode well for upcoming global phase 3 readouts.

FACTOR D

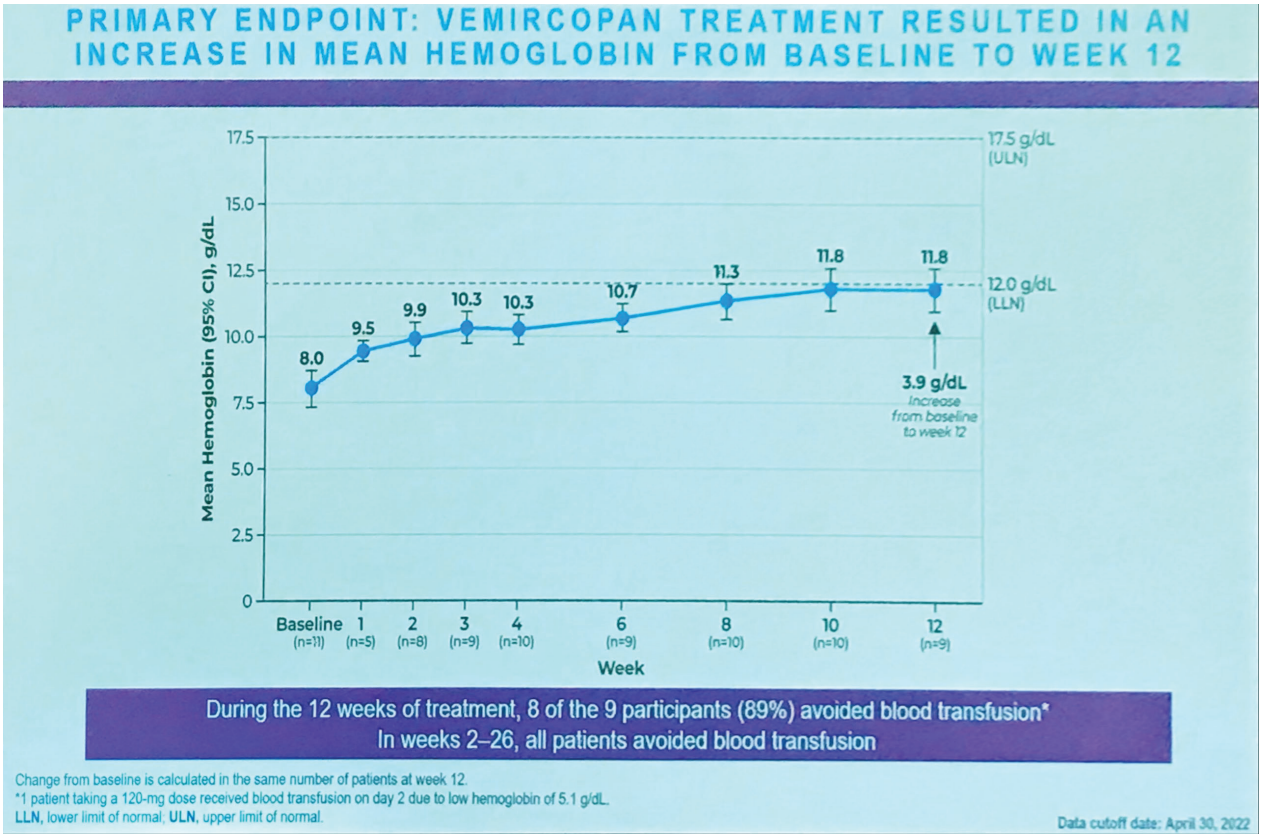
All these drugs hit various parts of the complement cascade to stop the destruction of red blood cells seen in PNH. Both danicopan and vemircopan are oral factor D inhibitors, while iptacopan inhibits factor B.

Danicopan prevailed earlier this year in the phase 3 Alpha study, in which it was used as an add-on to Soliris or Ultomiris in PNH patients with clinically significant extravascular haemolysis. Around 10-20% of patients on these C5 inhibitors develop extravascular haemolysis that can require blood transfusions.

A spokesperson for Astra told Evaluate Vantage before Ash that the group would submit danicopan to regulators "in the coming months", but the project looks set to be limited to this niche. At Ash on Saturday, Dr Peter Browett of the University of Auckland noted that when danicopan had been used as monotherapy a suboptimal effect was seen in some patients, something he put down to an unfavourable PK/PD profile.

Step forward vemircopan, which has greater potency and binding affinity than danicopan. Results from treatment-naive PNH patients in a phase 2 study, who received vemircopan monotherapy, were presented at Ash on Saturday.

The primary endpoint of the uncontrolled study was change in haemoglobin levels from baseline to week 12. An interim analysis found a 3.9g/dl increase, to 11.8g/dl, among nine evaluable patients – as already outlined in the Ash abstract.



Source: Dr Peter Browett & Ash

Still, one patient needed a red blood cell transfusion at day two. And there were questions at Ash about why some patients remained anaemic. Dr Browett suggested that this might be a question of dose – the trial allowed escalation from 120mg to 180mg, and at this higher dose "we saw improved control of haemoglobin and haemolysis".

Astra still has much to do here. And, of the oral players, iptacopan is much further ahead; data from that project's pivotal trial in treatment-experienced patients, Apply-PNH, will feature as an Ash late breaker on Tuesday. Last Thursday Novartis toplined its treatment-naive study, Appoint-PNH, as positive.

CROVALIMAB

Despite this progress on the oral front, Roche must still see a place for subcutaneous options. An Ash presentation on Saturday featured data from Commodore-3, an uncontrolled Chinese trial of that group's crovalimab in treatment-naive patients.

After a loading dose, crovalimab – a C5 inhibitor like Soliris and Ultomiris – is administered once monthly. This should give it the edge over Apellis's Empaveli, a C3 inhibitor given via a twice-weekly, 30-minute subcutaneous infusion.

Commodore-3 had two co-primary endpoints, proportion of patients with haemolysis control and transfusion avoidance, which were achieved by 79% and 51% of patients respectively, again in line with the abstract.

There was one treatment-related adverse event, of grade 3 bacteremia; this patient later died of a subdural haematoma following a fall, but this was deemed unrelated to crovalimab.

Roche has already filed the project in China, but a sterner test awaits with data from the global Commodore-1 and 2 studies, which both pit crovalimab against Soliris in treatment-experienced and naive patients respectively. Commodore-2 completes next year, so Roche's chances will soon become clearer.

Fast production fails to cure Car-T's problem

BY JACOB PLIETH
DECEMBER 11, 2022

Novartis and Gracell's two-day manufactured Cars do not solve cell therapy's biggest bottleneck – yet.

One of the biggest problems cell therapies face in the west is lack of manufacturing capacity. Data presented at Ash by Novartis and Gracell suggested that manufacturing time can be cut drastically, from a few weeks to two days, but the elephant in the room remains: patients still have to wait weeks or months before they receive therapy.

This was made clear in trials of Novartis's YTB323, an anti-CD19 construct, and of Gracell's GC012F, a bispecific Car against BCMA and CD19. They are manufactured using a virtually identical process that employs concurrent activation and transduction, and in vivo cell expansion; Novartis and Gracell respectively call the technology T-Charge and Fastcar.

The selling point of what Novartis calls a pioneering technique providing reliable and rapid manufacturing is that cells can be ready within one or two days rather than the more common two or three weeks. However, it then takes a further period of time before the cells are purified, frozen and released for reinfusion.

HOW LONG?

This shortcoming was laid bare at Sunday's Ash session when the presenter, Dr Pere Barba of Vall d'Hebron University Hospital, repeatedly dodged questions about what the vein-to-vein time was in a phase 1 lymphoma study of the T-Charge-manufactured YTB323 (rapcabtagene autoleucel).

After insisting that a clinical trial setting was suboptimal to assess this, Dr Barba eventually admitted that vein-to-vein time – the time taken from apheresis to cell reinfusion – was "similar" to the industry norm for autologous Car-T therapies, implying two to six weeks.

This is only part of the problem. Current capacity constraints mean that, once a patient is deemed a candidate for Car-T therapy, it then takes weeks before a slot can be booked for their cells to be manufactured. Dr Barba said some patients were kept waiting for so long that they had to be bridged with chemo, and indeed some went into remission as a result; this had become evident at last year's presentation.

Dr Barba presented a swimmers plot of responses that pointedly omitted patients' time between enrolment and dosing. At Ash 2021 this was shown to be between two and three months, with one patient waiting as long as six months. Against this

backdrop shaving a week or two off manufacturing time seems paltry.

"TEMPORARY"

Speaking to Evaluate Vantage at Ash Gracell admitted that the cell therapy space had several problems to tackle, but insisted that the capacity shortage was "temporary. Once the industry catches up to patient demand then the key issue [will be] how do you get a therapy to patients faster?"

This is where shorter manufacturing comes in, and Gracell's chief medical officer, Wendy Li, said the Chinese company had come out with Fastcar years before Novartis splashed T-Charge in 2021.

Ms Li cited an impressive vein-to-vein time of 12-15 days in the GC012F multiple myeloma study. However, as this was conducted in China it will have been subject to different capacity constrains versus those that have become common in the west.

Just like in the Novartis study patients were enrolled a long time before receiving treatment. Though the Gracell trial did not use bridging chemo, its confounding factor was that all patients got induction therapy of Revlimid/Velcade/dexamethasone over a couple of months.

This alone put most of them into remission by the time the GC012F cells were dosed, making it difficult to put the 100% ORR (and 88% complete response rate) claimed at Ash down to the Car-T cells. The trial was billed as a first-line study, but the use of induction means that it was done in something more akin to a first-line maintenance setting.

Ms Li explained the nuance, saying the typical treatment would have involved six cycles of induction, so what this trial was investigating was Car-T on top of a reduced induction regimen, and no stem cell transplant. Just two cycles alone would have yielded short-lived responses, she claimed, so what was important was that GC012F deepened remissions.

What vein-to-vein times Fastcar can achieve in the west might become apparent soon enough: Gracell aims to file a US IND shortly.

Affimed feels the pain

BY JACOB PLIETH
DECEMBER 12, 2022

Affimed investors find that what goes up must come down, though the stock owes only part of its fall to an Ash presentation.

Affimed was one of the early winners of the Ash abstract drop last month, but today it felt the pain. As the markets opened on the first trading day of the haematology conference the shares were off 38%, while other Ash-relevant stocks like Adicet, Fate, Kura, Caribou and Allogene were nursing losses of 37%, 15%, 14%, 11% and 11% respectively.

With a few important caveats, however, the dataset Affimed had touted going into Ash – an MD Anderson-sponsored study of AFM13 combined with NK cells – more or less held up. It was results of a separate Affimed-sponsored study of AFM13 monotherapy, press released and not presented at the conference, that might have been more responsible for investors fleeing.

The study, Redirect, was testing AFM13, an NK cell-redirecting anti-CD30 MAb, in CD30-positive peripheral T-cell lymphoma (PTCL). On Saturday Affimed press released a respectable 32% overall response rate from 108 efficacy-evaluable patients.

But poor persistence was a setback. Median duration of response was 2.3 months, below the 8.4 months and 9.4 months seen with Beleodaq and Folotyn in separate trials, though median PFS of 3.5 months and OS of 13.8 months were more in line with those established drugs.

Wells Fargo analysts called the survival data confounding, and removed AFM13 monotherapy in PTCL from their models because the duration

of response came up short of their internal target of 8-9 months. Affimed itself said it would now focus on combining AFM13 with AB-101 NK cells, which it recently secured via a deal with Artiva Biotherapeutics.

NO SURPRISE

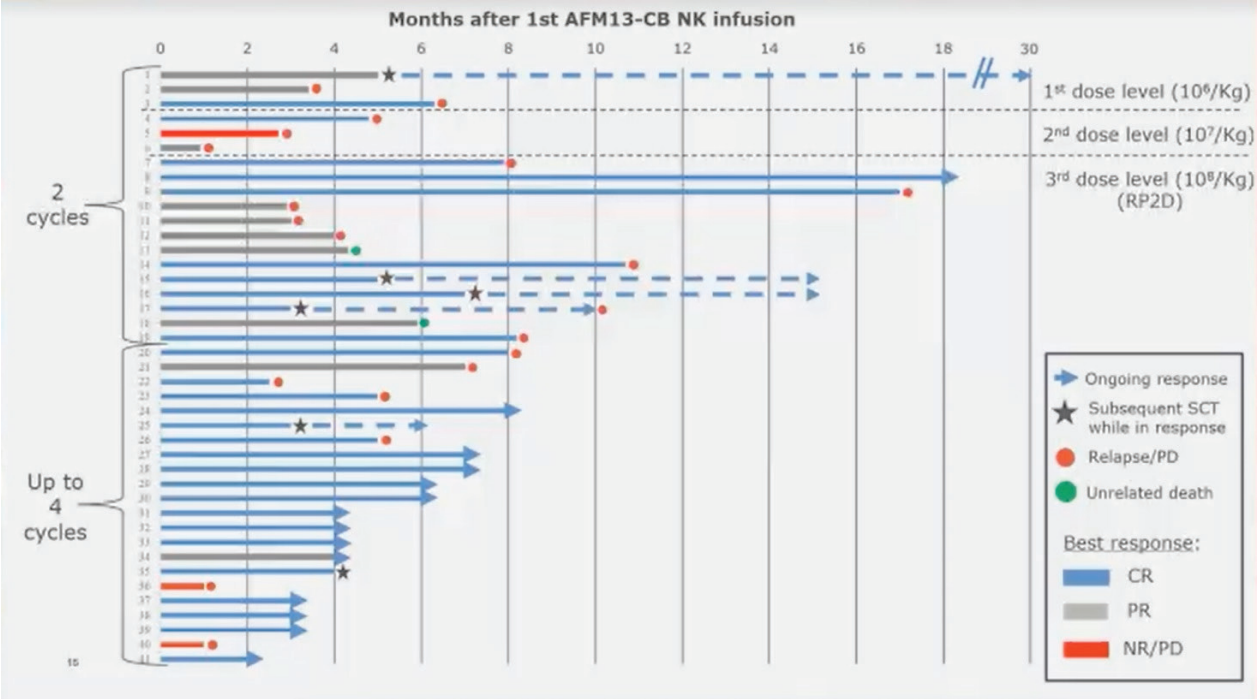
In reality none of this should have come as a surprise. AFM13 has long been seen as mediocre in monotherapy, and it was only the early results of MD Anderson's trial combining it with NK cells that revealed the approach's promise.

The basis for this is that many lymphoma patients are said to lack sufficiently potent NK cells of their own; give them a fresh source of NK cells and you solve this problem. This view drove Affimed's Artiva deal, and the updated results of the MD Anderson trial, in CD30-positive lymphoma, have now informed Affimed's strategy in PTCL.

Those MD Anderson data featured at Ash on Saturday, and comprised 41 patients, all of whom were refractory to or intolerant of Seagen's Adcetris.

Initial responses across all doses were 93% overall, with a 66% rate of complete remissions.

However, here too AFM13 faces durability questions. The data were split into 19 patients who had received two cycles of therapy, and 22 who had received up to four cycles, and only four of the 10 complete responders seen in the former group were still in remission at 12 months – two having received stem cell transplants.



Source: Dr Yago Nieto & Ash.

Meanwhile, most of the remissions seen in the second group are ongoing, but are of short duration. "When we go up to four cycles we're hoping that duration of responses will increase," said the presenting investigator, Dr Yago Nieto.

He also revealed that two deaths had occurred in the study, one due to Covid and the other to stroke. Despite cell therapies' documented links with susceptibility to infections and brain haemorrhage, these two grade 5 events were deemed unrelated to treatment, said Dr Nieto.

If durability remains unproven, so does the efficacy Affimed might see in a future company-sponsored trial. It is assumed that when Affimed co-administers AFM13 with Artiva's AB-101 cells the finished product will behave at least as well as the co-complexed AFM13/NK cells used by MD Anderson, but this has yet to be shown clinically.

And Affimed's own combo study is still some way off: the company has yet to hear back from the FDA, but expects to file an IND in the first half of next year to start a registrational trial of AFM13 plus AB-101 in Hodgkin lymphoma and CD30-positive PTCL.

Orchard gets a Sanfilippo boost

BY MADELEINE ARMSTRONG
DECEMBER 13, 2022

Promising but early data with OTL-201 could see the group compete against the likes of Ultragenyx and Lysogene.

There are no approved therapies for the rare lysosomal storage disorder Sanfilippo syndrome, or mucopolysaccharidosis type III. Several gene therapy players are hoping to change this, though – and one of these, Orchard Therapeutics, had promising early data at Ash on Monday.

The group's lentiviral vector-based project OTL-201 produced cognitive benefits in four of five very young patients with the disease subtype known as MPS type IIIA. The company acknowledges that longer follow-up will be needed but investors were encouraged, sending Orchard's stock up 14% yesterday.

However, an after-hours investor event raised questions over how long development might take – Orchard is planning on following the current cohort for three years before outlining its next steps.

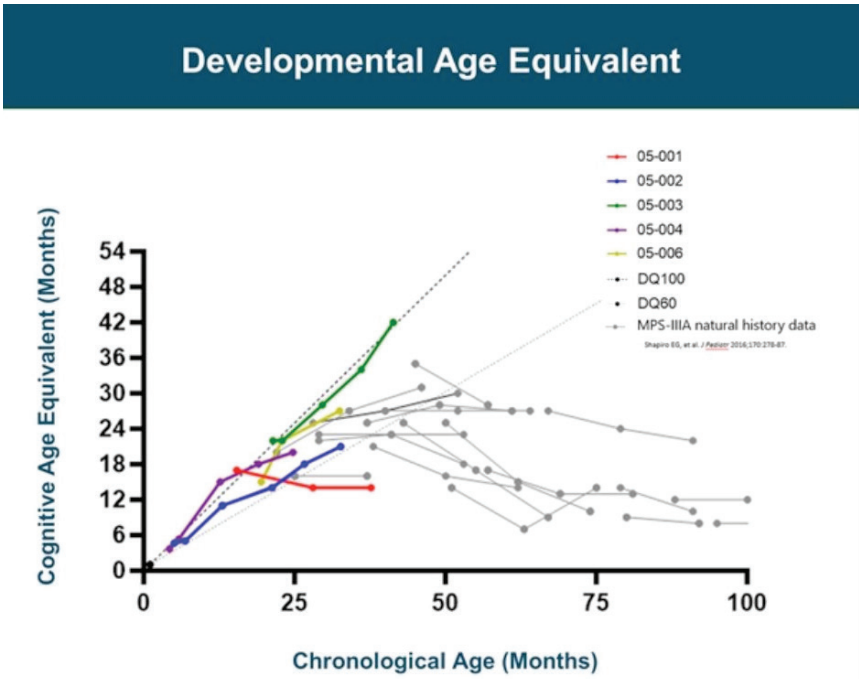
MPS IIIA is caused by mutations in the SGSH gene that codes for an enzyme that breaks down mucopolysaccharides. In the disease, these build up and cause neurodegeneration and resulting behavioural problems. Most patients initially develop normally, with regression only becoming apparent from around two years old, and patients have a life expectancy of 10-20 years.

Orchard could eventually be up against Lysogene, which recently reported mixed phase 2/3 data on LYS-SAF302, and Ultragenyx, which earlier this year licensed the phase 1/2 project UX111 from Abeona. LYS-SAF302, which was partnered with Sarepta before that group walked away in January, showed a cognitive benefit in patients younger than 30 months, but not in patients above this age.

The phase 1/2 study of OTL-201, sponsored by the University of Manchester, only enrolled patients aged 24 months or younger – but in this group results were striking, with four patients showing a gain of cognitive skills in line with development in healthy children.

The final patient "has not gained skills, but has not lost skills", said Professor Rob Wynn of the University of Manchester, presenting the data.

Cognitive outcomes with OTL-201



Source: Professor Rob Wynn & Ash.

Still, there was no clear correlation between SGSH enzyme levels and clinical outcomes; indeed, Professor Wynn noted that "the child that's done the best actually had the lowest CSF enzyme levels".

There were six serious adverse events, although four were thought to be due to the conditioning regimen and one down to underlying disease.

Orchard, which is nursing a tiny $62m market cap, has enough cash to get it to the second quarter of 2024. On this point it has the edge over Lysogene, which has made no secret of its need for funding.

Pirtobrutinib leads the post-Imbruvica charge

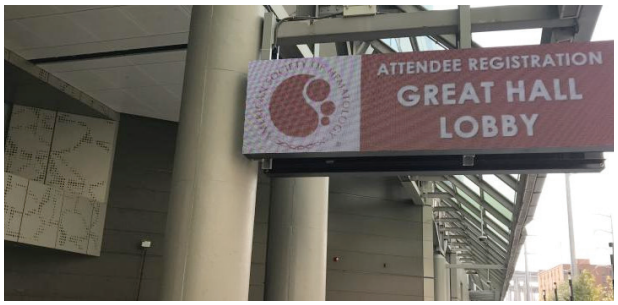
BY JACOB PLIETH
DECEMBER 14, 2022

Lilly's non-covalent BTK inhibitor shines yet again, blunting the impact of early data with Nurix's BTK degrader.

If yesterday's Ash late-breaker on Beigene's Brukinsa signalled a changing of the guard in primary BTK inhibition, earlier data from Lilly's pirtobrutinib and Nurix's NX-2127 highlighted potential new options for patients who relapse on current BTK drugs.

Nurix specialises in target degradation, a field that has seen the Serds post mixed success in breast cancer, but in which NX-2127, Nurix's lead asset, looks active, according to an early Ash dataset. Whether this really matters is unclear given that pirtobrutinib appears to have the immediate opportunity in BTK inhibitor-relapsed patients sewn up, and this could see Nurix relegated to an even later-line setting.

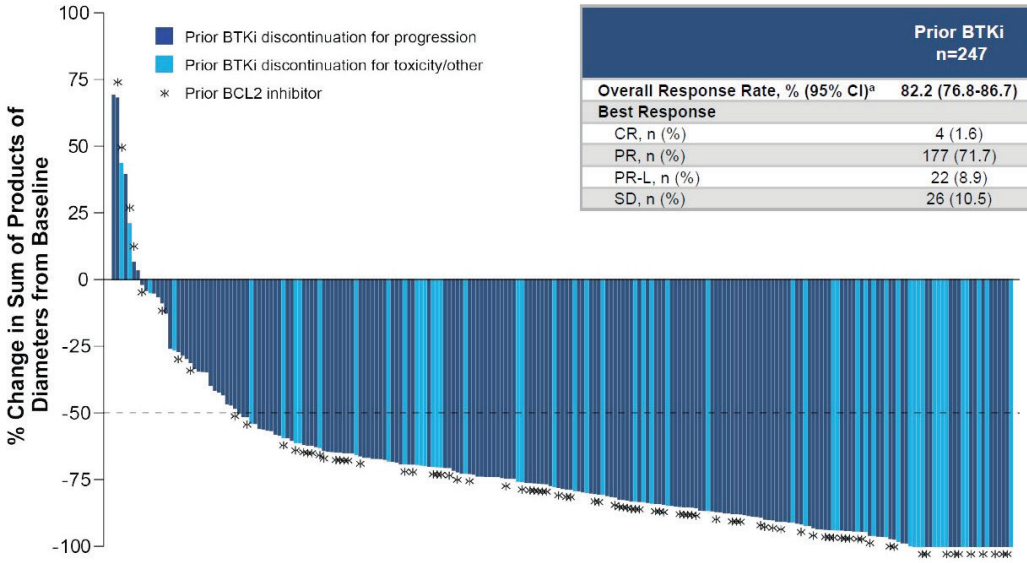
Pirtobrutinib is a non-covalent BTK inhibitor said to work after patients develop resistance mutations to covalently acting BTK drugs like Imbruvica, Calquence and Brukinsa, and made a big splash at Ash 2020. This year Lilly completed a rolling US filing for mantle cell lymphoma patients who relapse after prior BTK blockade, and first approval is expected in early 2023.



Still, mantle cell lymphoma is a relatively small use, and the big prize is chronic lymphoblastic leukaemia (CLL), the major indication for Imbruvica and other first-generation BTKs. It was an update of the CLL subset of pirtobrutinib's Bruin study that featured as the Lilly project's biggest Ash dataset.

This comprised an expansion cohort of 247 patients who had received a prior BTK inhibitor, and the group put up a stunning waterfall plot, showing tumour shrinkage in all but six patients, and an 82% overall remission rate. Not only that, but 100 of these patients had failed Abbvie's highly efficacious Bcl-2 inhibitor Venclexta as well as BTK blockade, and the ORR held up in these too, at 79%.

Pirtobrutinib Efficacy in CLL/SLL Patients who Received Prior BTKi Treatment



	Prior BTKi n=247	Prior BTKi+BCL2i n=100
Overall Response Rate, % (95% CI)[a]	**82.2 (76.8-86.7)**	**79.0 (69.7-86.5)**
Best Response		
CR, n (%)	4 (1.6)	0 (0.0)
PR, n (%)	177 (71.7)	70 (70.0)
PR-L, n (%)	22 (8.9)	9 (9.0)
SD, n (%)	26 (10.5)	11 (11.0)

Data cutoff date of 29 July 2022. Data for 24 patients are not shown in the waterfall plot due to no measurable target lesions identified by CT at baseline, discontinuation prior to first response assessment, or lack of adequate imaging in follow-up. [a]ORR includes patients with a best response of CR, PR, and PR-L. Response status per iwCLL 2018 according to independent review committee assessment.

Source: Dr Anthony Mato & Ash.

It was difficult for Nurix to compete against this kind of result, though a phase 1 trial of NK-2127 did show this BTK degrader to be active: an efficacy population of 15 post-BTK inhibitor patients with CLL presented at Ash on Monday showed five remissions.

This is all very well from an academic perspective, but Lilly's data puts up a significant roadblock; if pirtobrutinib is approved in CLL patients who fail covalent BTK therapy, as seems likely, what purpose is served by bringing forward a BTK degrader for the same use, however active the latter is proved to be mechanistically?

This must now be the main question for NX-2127, which carries a hefty sellside consensus for 2028 sales of $870m, according to Evaluate Pharma. This is only slightly short of pirtobrutinib's total of $1.1bn.

None of this is to say that NX-2127 has no future, but its use could be restricted to a very late setting. The Ash dataset includes five patients who had failed not only a covalent BTK inhibitor and Venclexta, but also a non-covalent BTK agent. One of these reported a partial response, ongoing at 12 months.

This is clearly an extremely early, albeit positive, signal. But, if this is a sign of NX-2127's future applicability, then that $870m number will have to come down. Already Nurix investors assume that the forecast is wildly optimistic, given that the market valuation of the entire group sits at $570m.

A further consideration is safety: 35% of CLL patients in the NX-2127 trial discontinued owing to an adverse event, versus just 3% of those treated with pirtobrutinib.

Glycomimetics shakes off its sickle cell past

BY MADELEINE ARMSTRONG, JACOB PLIETH AND EDWIN ELMHIRST
DECEMBER 14, 2022

Meanwhile, there was bad blood between cell therapy players and their investors.

As the dust settles on an Ash meeting that threatened to be overshadowed by sightings of Taylor Swift, which companies had a conference beyond their wildest dreams, and which still have a way to go to get out of the woods?

Evaluate Vantage's annual look at the winners and losers of the meeting show the small cap player Glycomimetics making a comeback, while lentiviral vector-based gene therapies are also having a resurgence courtesy of Bluebird and Rocket. On the other side of the ledger, many cell therapy players floundered, and promising early sickle cell data were not enough to save Sangamo.

This analysis compares share prices at market opening on November 3, when non-late-breaking Ash abstracts went live, against close yesterday, the meeting's official last day.

GLYCOMIMETICS RETURNS

Three years ago Glycomimetics' then-lead project, rivipansel, failed in sickle cell disease. That development saw the group pivot to uproleselan, an E-selectin inhibitor, and Ash posters revealed this to yield a 62% ORR in secondary AML, while in front-line AML an azacytidine plus Venclexta combo put five of eight subjects into complete remission. Gycomimetics' 207% gain makes this company

the clear winner looking over the entire Ash period, though another micro-cap player, Harpoon Therapeutics, also saw some success. Harpoon was at one point up 100% on Monday on data showing a 77% ORR in multiple myeloma patients given the highest doses of its anti-BCMA trispecific HPN217, but the stock ended the day up only 22%, crashed 37% the next day, and ended up just 7% over the period.

Arcellx will also be celebrating a successful meeting; that group's move was ultimately down to its deal with Gilead on Friday, though this was spurred by data being presented at Ash.

Meanwhile, Bluebird investors will hope that a positive safety update on lovo-cel in sickle cell disease will bode well for that project's regulatory future. Rocket was also flying the flag for lentiviral-based gene therapies with updates on three

programmes, but data were largely incremental.

In the CD20-targeting bispecific space, Genmab and Abbvie's epcoritamab still looks like the one to beat, although Xencor had early data showing its contender, plamotamab, could be as good as Roche's glofitamab.

And Beigene was rewarded by investors for a late-breaker on its BTK inhibitor Brukinsa in chronic lymphoblastic leukaemia. This space could soon be shaken up soon by Lilly's non-covalent project pirtobrutinib; stellar data raised questions about how Nurix's BTK degrader NX-2127 might fit in, and the latter's stock fell 4% over the Ash period.

Selected Ash 2022 risers		
Company	**Share price chg***	**Detail**
Glycomimetics	207%	Uproleselan (E-selectin inhibitor); 62% ORR in secondary AML
Arcellx	40%	Arcellx data secure a Gilead buy-in
Bluebird	30%	The sickle cell race hots up
Rocket	19%	Ash 2022 preview – Argenx's expansion plans come into focus
Aptose	18%	Ash 2022 preview – Affimed and Aptose score
Beigene	17%	Ash 2022 preview – Brukinsa has the edge over Calquence
Genmab	9%	Multiple datasets on epcoritamab
In8bio	9%	INB-100 (gamma-delta T-cell therapy); 4/4 CRs in ph1 cohort 1 in AML
Syndax	8%	Syndax and Kura face off
Harpoon	7%	HPN217 (anti-BCMA trispecific); 77% ORR in multiple myeloma
Xencor	4%	Toxicity still looms large for Regeneron's bispecific
Argenx	3%	Argenx faces Vyvgart questions

*December 13 close vs November 2 close.

Meanwhile, Ash fallers were led by Adicet, which became the latest allogeneic cell therapy player to be hit by the problem of patient relapses. An identical problem hit Caribou, though its data were actually presented at an investor event rather than at Ash.

Also hit with relapse problems was Affimed, which turned an initial surge triggered by its Ash abstract into an overall fall on the data, as questions were raised about the durability of its NK-cell engager AFM13 and about how data from an academic study would translate into a more robust, company-sponsored effort.

Among other allogeneic cell therapy disappointments, Allogene fell after a low-key Ash presence, for which it tried to make up by hosting a late November R&D day of little consequence. Ash saw clinical data for its BCMA-targeting Car-T therapy, which put up a seemingly uncompetitive ORR of 68%, with many responders relapsing.

Fate also reported disappointing multiple myeloma data with a BCMA-targeting project, namely with the iPSC-derived Car-NK therapy FT576. This managed just two partial responses, one among six monotherapy subjects and the other in a cohort of three patients on a Darzalex combo. And the menin inhibitor battle ended with a win for Syndax and a loss for Kura, though in reality both companies face opportunities and threats.

As usual the Ash weekend ended with a selloff, though the presence of many risers and an uptick in deal-making should give investors some confidence as the 2023 JP Morgan healthcare conference looms. Will Taylor Swift be sighted at the Westin St Francis in January? Watch this (blank) space.

Selected Ash 2022 fallers		
Company	**Share price chg***	**Detail**
Adicet	-37%	Adicet has a case of déjà vu
Affimed	-29%	Affimed feels the pain
Gracell	-25%	Fast production fails to cure Car-T's problem
Allogene	-21%	ALLO-715 efficacy underwhelming
Fate	-18%	FT576 efficacy underwhelming
Sangamo	-18%	The sickle cell race hots up
Magenta	-14%	MGTA-117 data
Caribou	-13%	Antler trial update (not at Ash) revealed another patient relapsed on CB-010
Kura	-12%	Syndax and Kura face off
Immunogen	-7%	38% ORR at ph2 pivekimab sunirine dose, but durability seems underwhelming
Nurix	-4%	Pirtobrutinib leads the post-Imbruvica charge
Orchard	-2%	Orchard gets a Sanfilippo boost

*December 13 close vs November 2 close.

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