Evaluate Vantage

ASH 2021 Conference Round Up

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Ash 2021 movers – IGM steals the show, for all the wrong reasons

BY JACOB PLIETH, MADELEINE ARMSTRONG AND EDWIN ELMHIRST

At a meeting lacking practice-changing studies and featuring many disappointments the downturn in IGM's fortunes stands out.

IGM Biosciences stole the show at the Ash conference for the second year running. Unfortunately for its investors, this year there was no magic rabbit pulled out of the hat like in 2020, and IGM followed an initial dip on its abstract release in November with a 41% crash two days ago as the normally servile sellside largely abandoned the group.

It was not all bad news at Ash, but the meeting seemed more muted this year than in the past, and was characterised by disappointments and a dearth of practice-changing data. Moreover, the period this analysis covers coincided with a year-end downturn in biotech indices, and even the companies that did report positive studies struggled to capitalise.

Thus companies including Fate, Global Blood and Forma, which all reported ostensibly positive data at Ash, finished the meeting firmly in the red. And off even more than IGM was Aptose, whose Hanmi-derived HM43239 raised more mechanistic question than answers, and ALX Oncology, slammed for falling behind in the anti-CD47 race.

X4 Pharmaceuticals beat them all: a phase 1b trial of its CXCR4 antagonist mavorixafor plus Imbruvica in Waldenström's macroglobulinemia was marred by a patient death deemed possibly related to the combination. And the trial is yet to yield data with the highest dose of mavorixafor. X4 crashed 66%.

This analysis compares share prices at market opening on November 4, when non-late-breaking Ash abstracts went live, against close yesterday, the meeting's official last day. It is notable that during this time the Nasdaq biotechnology index fell 11%.

IGM'S PROBLEM

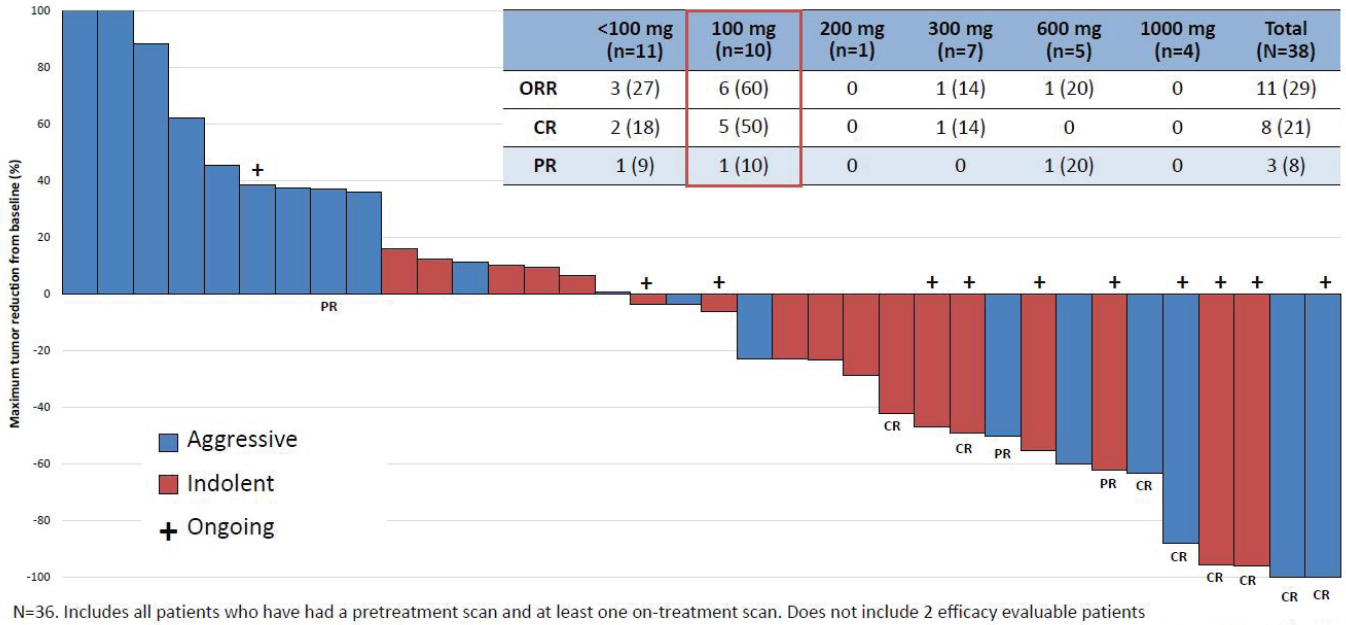
IGM's IgM antibody technology now appears to face an

existential crisis. The company's oncology lead, the anti-CD20 T-cell engager IGM-2323, showed relatively good safety in its lymphoma study, but efficacy was not competitive and limited to a low dose of 100mg.

The fact that there was virtually no activity at doses up to 1g calls into question the project and the technology, and several previously supportive sellsiders downgraded the company. This came after the departure of a key exec, Dan Chen, as chief medical officer, and IGM's formation of non-oncology business units.

Overall NHL cohort: best post-baseline tumor reduction and responses

	<100 mg (n=11)	100 mg (n=10)	200 mg (n=1)	300 mg (n=7)	600 mg (n=5)	1000 mg (n=4)	Total (N=38)
ORR	3 (27)	6 (60)	0	1 (14)	1 (20)	0	11 (29)
CR	2 (18)	5 (50)	0	1 (14)	0	0	8 (21)
PR	1 (9)	1 (10)	0	0	1 (20)	0	3 (8)



N=36. Includes all patients who have had a pretreatment scan and at least one on-treatment scan. Does not include 2 efficacy evaluable patients who came off treatment prior to first scan. Response assessments per Lugano

Data cut off: September 10, 2021

Source: Ash & Dr Elizabeth Budde.

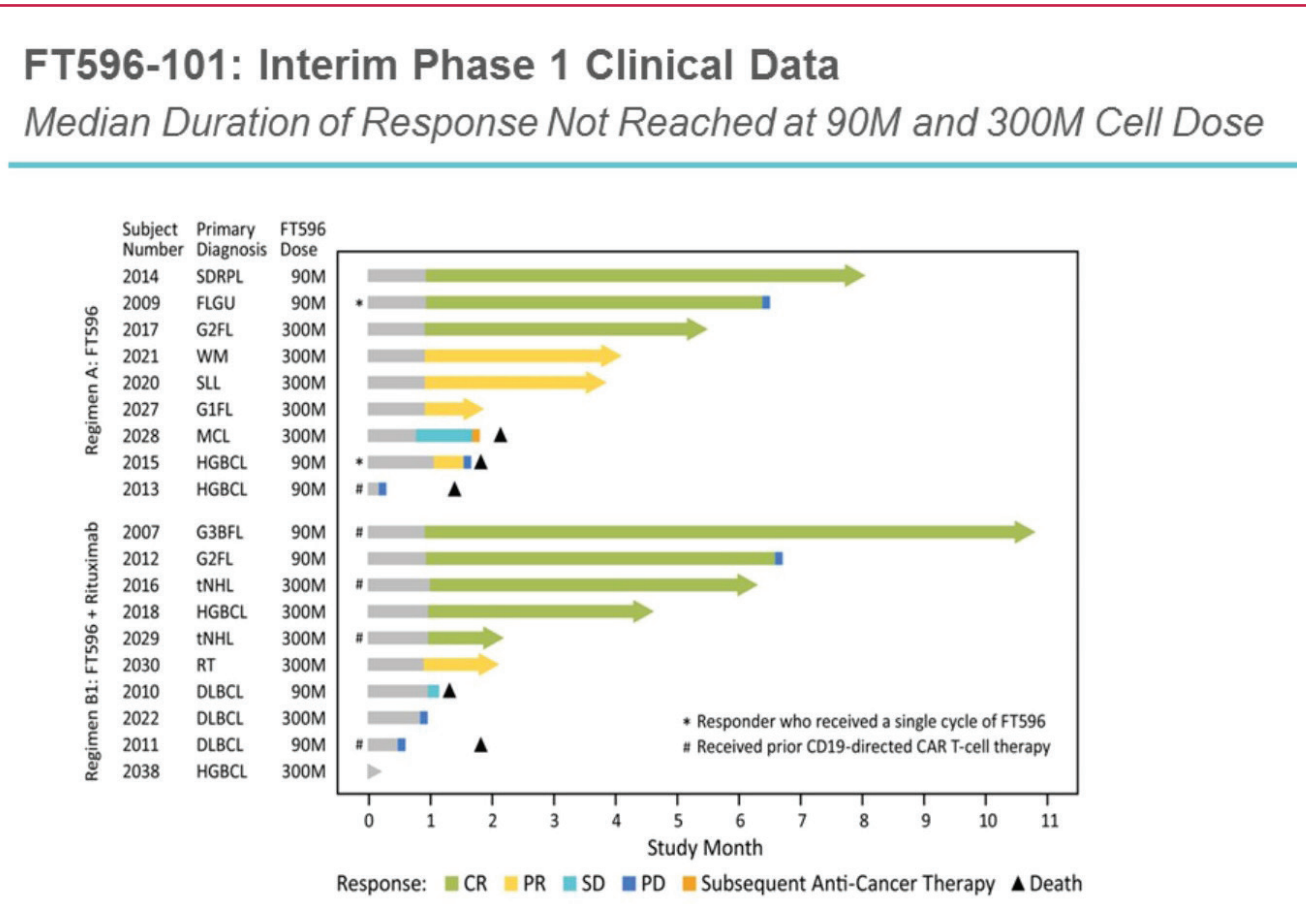
That said, there was good news, and Keros came out on top after its abstract on KER-050 in myelodysplastic syndromes caused a 28% surge in November. Monday's 9% fall took only a little shine off this.

And a few companies were able to use positive Ash data to raise cash. This included Global Blood ($300m convertible) and Legend Biotech ($345m equity); both enjoyed small bumps over the Ash weekend, even if their stocks were down heavily across the entire period in question.

Selected Ash 2021 risers		
Company	**Share price chg***	**Detail**
Keros Therapeutics	16%	Ash 2021 preview – small increases and big falls
2Seventy**	6%	
Celyad	6%	Ash 2021 preview – as competition grows Autolus monetises
Gilead Sciences	5%	Ash 2021 – why Breyanzi and Yescarta might refresh the parts Kymriah cannot reach
OSE Immunotherapeutics	5%	Preclinical efficacy with OSE-127
Incyte	3%	Parsaclisib data supporting US filing
Poseida Therapeutics	3%	P-BCMA-101 (anti-BCMA Car-T) data
Regeneron	3%	First data on BCMA bispecific REGN5458
Bristol Myers Squibb	0%	Ash 2021 – Bristol reveals its sons of Revlimid
Daiichi Sankyo	0%	Pivotal valemetostat data

*December 14 close vs November 3 close; **first day of trading was November 4, 2021.

Long-awaited data on Fate's CD19-directed Car-NK asset FT596 were not bad, the lymphoma cohort now comprising nine monotherapy and 10 Rituxan combo patients, and yielding seven and six remissions respectively. But the focus was always going to be on response durability, which was impossible to gauge given that all but two subjects received multiple FT596 infusions.



Source: Ash & Dr Veronika Bachanova.

Meanwhile, gene therapy companies' annus horribilis continued, and hopes that some could turn the tide with positive Ash updates evaporated. Sangamo had a mixed meeting, with promising data on its sickle cell project, but its haemophilia A asset disappointed.

Rocket Pharmaceuticals did not convince investors with incremental results from 20 patients treated with three of its gene therapy candidates: RP-L102 in Fanconi anaemia, RP-L201 in leukocyte adhesion deficiency-I, and RP-L301 in pyruvate kinase deficiency.

Still, both companies are doing better than Freeline Therapeutics. That group once looked like it might have a haemophilia B gene therapy contender in verbrinacogene setparvovec (FLT180a), but delays to the project have seen the group trade below cash this year. Long-term results from the B-Amaze trial, presented at Ash, merely raised more doubts about the asset.

Patients treated with the highest dose, 8.32x1011vg/kg, showed waning of factor IX levels after a year. Freeline is testing 7.7x1011vg/kg in its dose-confirmation trial, B-Lieve, with interim results due in mid-2022, and will have to hope that these will answer questions about what the optimal dose might be.

Selected Ash 2021 fallers

Company	Share price chg*	Detail
X4 Pharmaceuticals	-66%	See text
Bluebird Bio**	-63%**	Ash 2021 – Bluebird looks to revive Lentiglobin
ALX Oncology	-61%	Ash 2021 preview – small increases and big falls
Aptose Biosciences	-55%	See text
IGM Biosciences	-48%	Ash 2021 preview – small increases and big falls
Gracell Biotechnology	-44%	Ash 2021 – the sun sets on Kymriah, but Novartis has a plan
Global Blood Therapeutics	-38%	Ash 2021 – Global Blood stems the bleeding
Agios Pharmaceuticals	-35%	Ash 2021 – Agios and Forma take different paths in sickle cell disease
Rocket Pharmaceuticals	-34%	See text
Forma Therapeutics	-32%	Ash 2021 – Forma takes on a second Agios drug
Freeline	-27%	See text
Sangamo Therapeutics	-19%	Ash 2021 – Sangamo and Sanofi enter the sickle cell gene editing fray
Genmab	-19%	See text
Precision Biosciences	-18%	Ash 2021 – Precision moves quickly to deal with allo disappointment
Fate Therapeutics	-17%	See text
Syndax Pharmaceuticals	-12%	Ash 2021 preview – small increases and big falls
Legend Biotech	-6%	Update on pivotal Cartitude-1 trial of cilta-cel
Sanofi	-5%	Ash 2021 – Sanofi takes its time with fitusiran
Autolus Therapeutics	-5%	Ash 2021 preview – as competition grows Autolus monetises
Roche	-1%	Ash 2021 – Polivy underwhelms, but stays ahead of Car-T

*December 14 close vs November 3 close; **period takes into account 2Seventy spinout.

Ultimately biopharma stock price movement reflects the market mood as much as the quality of the data presented, and perhaps the bigger takeaway from Ash is just how few of the studies highlighted appeared to be practice-changing.

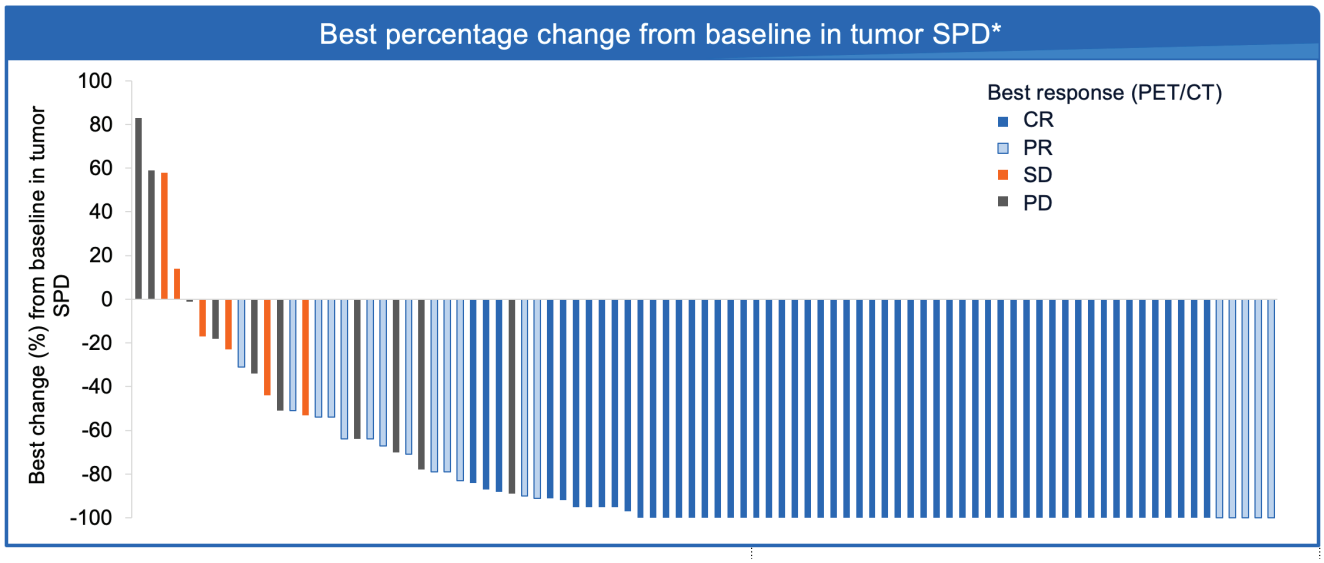
The meeting's big focus, moving Car-T into second-line lymphoma treatment, and the Polarix study of Polivy in front-line lymphoma, have the potential to change practice, but perhaps not until they show convincing overall survival benefits.

That leaves Roche's mosunetuzumab, an anti-CD20 bispecific that shone last year, as perhaps yielding the most impressive waterfall plot of Ash 2021. Its 80% remission rate in third-line or later follicular lymphoma looked even better considering that over 60% of responding patients, and 76% of complete responders, were still progression-free a year later.

This might make mosunetuzumab a shoo-in for approval – US filing is due by the year end – and likely takes some shine off Genmab/Abbvie's rival epcoritamab.

Published on: December 15, 2021

Anti-tumor efficacy



Mosunetuzumab waterfall plot.

Source: Ash & Dr Elizabeth Budde.

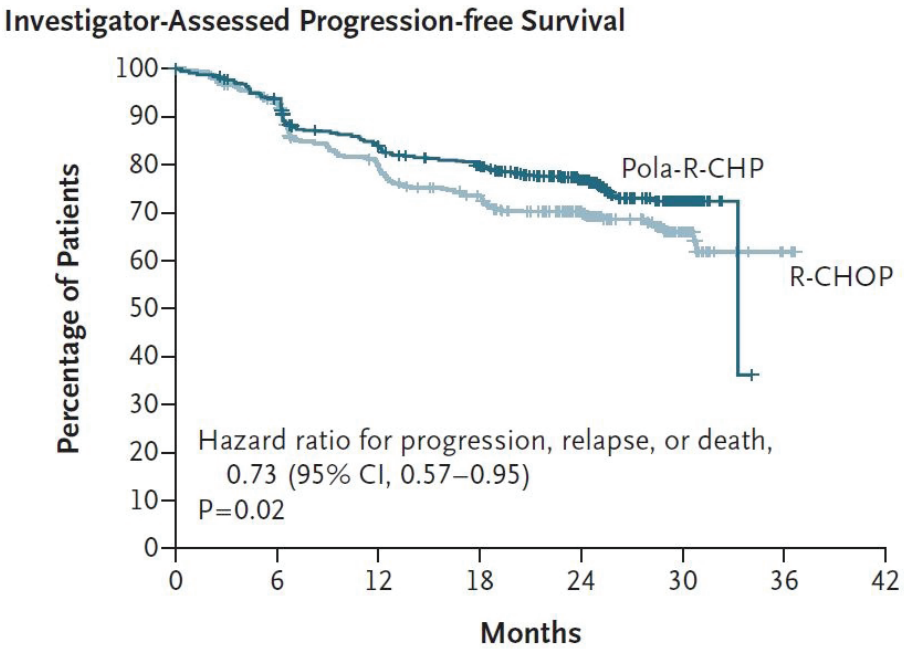
Ash 2021 – Polivy underwhelms, but stays ahead of Car-T

BY JACOB PLIETH

When Polivy scored in the relapsed lymphoma trial that led to its first US approval Roche heralded this antibody-drug conjugate as being as good as Car-T.

Today the group might claim to be a step ahead: as Car-T therapies score in second-line lymphoma Polivy has the front-line setting in its sights, courtesy of the Polarix trial. However, lack of an overall survival advantage hangs heavy over second-line Car-T and front-line Polivy alike: Polarix, unveiled at today's late-breaker session at Ash, showed virtually identical OS curves for Polivy and the modified R-CHOP regimen against which it was compared, with 24-month survival of 88.7% versus 88.6%. The issue is important because analysts reckon front-line use makes up two thirds of Polivy's future sales, put by Evaluate Pharma sellside consensus at $1.6bn in 2026. Polarix's relatively narrow 27% reduction in risk of progression (p=0.02), earlier revealed in the Ash abstract, caused Jefferies to suggest that first-line adoption would be slow. At an Ash press call one of the Polarix investigators, Memorial Sloan Kettering's Dr Gilles Salles, suggested the advent of new lymphoma treatments as a reason for the lack of OS benefit, but also said Polivy-treated subjects had a reduced treatment burden.

Published on: December 14, 2021



No. at Risk

Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

Source: Ash & NEJM.

Ash 2021 – Sanofi takes its time with fitusiran

BY MADELEINE ARMSTRONG

Sanofi reckons it has a universal haemophilia therapy on its hands – but first it needs to test a lower dose.

The choice of Sanofi's fitusiran for both a late-breaking and plenary slot at this year's Ash meeting is puzzling. True, the small interfering RNA could become a universal haemophilia therapy, suitable for both patients with the A and B form of the disease, and those with and without inhibitors.

But the project is far from ready for prime time. Crucially, Sanofi has abandoned the 80mg once-monthly dose featured at Ash in two ostensibly positive presentations, after previous blood clot scares. A lower dose is being tested in ongoing pivotal studies, and the company will have to hope that this new regimen does not mean a compromise on efficacy.

While the Ash presenters talked up the transformative potential of fitusiran, pressing forward with 80mg was not an option, Sanofi's chief medical officer, Dietmar Berger, told Evaluate Vantage. "We had discussions with regulatory authorities. Obviously, we want to bring forward a therapy that's safe and effective – and getting more data is what we want as well."

Shifting the dosage has contributed to delays for the project, which was licensed from Alnylam. Fitusiran's regulatory filings are now expected in 2024, versus a previous estimate of 2022, Sanofi said recently (Delays hit Sanofi, October 28, 2021).

ANTI-ANTITHROMBIN

The universal promise of fitusiran comes from its novel mechanism of action. While conventional haemophilia treatments aim to replace the blood-clotting factors that are lacking in the disease, fitusiran targets antithrombin to restore thrombin generation, thereby rebalancing haemostasis.

However, this mechanism can also lead to an increased risk of blood clots, particularly in patients whose antithrombin levels

are pushed too low. In general, thrombotic events with fitusiran have occurred in patients who had antithrombin of around 10% of normal levels.

Sanofi previously disclosed that its new dosing regimen would aim to get patients' antithrombin levels into the 15-35% range. To achieve that the group is starting with 50mg every other month, Mr Berger said.

"Then antithrombin levels are monitored, and then you dose according to that." If levels drop too far, the fitusiran dose can be lowered to 20mg every other month; on the other side of the coin, the dose can be increased to 50mg monthly if necessary.

Sanofi has switched to the new dosing regimen in the phase 3 Atlas-INH and Atlas-A/B trials, which both featured at Ash.

The company is also generating data with the new dosing schedule in newly diagnosed patients; Mr Berger declined to give more details, apart from saying that this would not involve another large phase 3 study. Neither would he say when the group expects to report data with low-dose fitusiran.

Fitusiran will need to maintain the efficacy reported at Ash – which was consistent with the data already revealed in the abstracts – without the spectre of thrombotic events.

LIVER ENZYME ELEVATIONS

Dosage is not the only issue that Sanofi has to contend with. Liver enzyme elevations were also seen in both trials, although the presenters stressed that these were all mild to moderate and resolved. It is possible that these events could lessen with low-dose fitusiran, Mr Berger said, though he conceded that: "We'll need to see the data."

Could all of this mean that fitusiran, even if approved, might end up as a therapy for those with no other options, such as haemophilia B patients with inhibitors? Sanofi is clearly thinking bigger.

"It has the potential to be broader than that, as it provides unique benefits for patients across the board," replied Mr Berger.

Dr Steven Pipe of the University of Michigan, who presented the Atlas-A/B data, noted that one of these benefits would be freeing patients from the peaks and troughs seen with intravenous factor therapy, and the impact this has on bleeding.

"Fitusiran has the opportunity to transform the day-to-day lives of patients," he told a press briefing. First, though, the low dose has to prove its worth.

Published on: December 14, 2021

Sanofi's phase 3 data with fitusiran

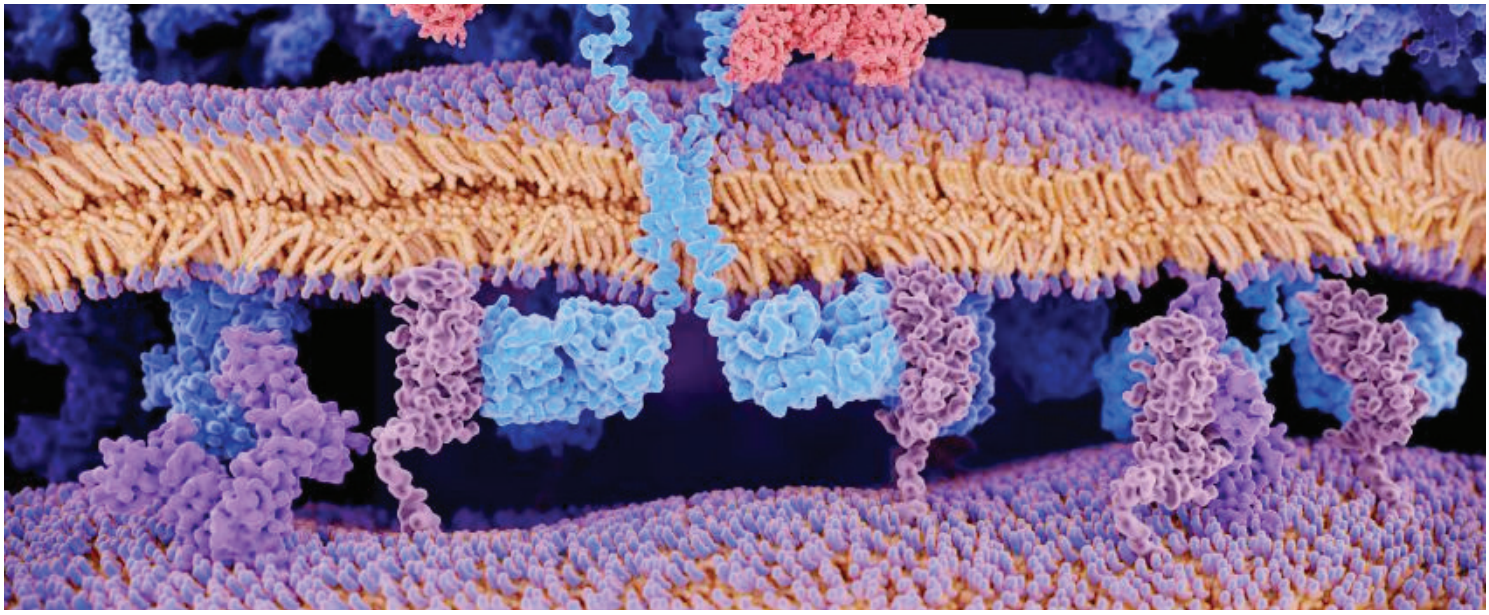
	Atlas-A/B (pts without inhibitors, n=120)		Atlas-INH (pts with inhibitors, n=57)	
	Fitusiran	**Standard of care**	**Fitusiran**	**Standard of care**
Estimated mean ABR	3.1	31.0	1.7	18.1
Reduction in ABR	90%		91%	
P value	<0.0001		<0.0001	
Pts with zero treated bleeds	51%	5%	66%	5%
TEAESIs*	19%	3%	24%	5%
Thromboembolic events	0	0	2 (1 pt discontinued)	0

Standard of care was on-demand factor replacement (Atlas-A/B) or bypassing agents (Atlas-INH). *TEAESI=treatment-emergent adverse events of special interest, includes ALT or AST elevation >3 x upper limit of normal and suspected or confirmed thromboembolism. Source: Ash, Dr Pipe & Dr Young.

Ash 2021 – why Breyanzi and Yescarta might refresh the parts Kymriah cannot reach

BY JACOB PLIETH

Novartis will not pursue Kymriah's use in second-line lymphoma; but have Breyanzi and Yescarta proved enough to be filed in this setting?



With Gilead's Yescarta and Bristol Myers Squibb's Breyanzi showing that Car-T might replace stem cell transplant in second-line lymphoma, one question is why Novartis's Kymriah failed in precisely this setting. Today's Ash late-breaking presentation provided some clues.

Excuses notwithstanding, the bottom line is that Novartis will not file Kymriah for this early use, the Swiss firm confirmed to Evaluate Vantage. A bigger question is whether the strong event-free survival benefit shown in Yescarta and Breyanzi's corresponding successful trials is enough to see these two competitors filed and approved for use in the second-line setting.

Presentation at Ash of detailed data from all three studies in question, Breyanzi's Transform, Yescarta's Zuma-7, and Kymriah's Belinda, has made the possibility of Car-T replacing second-line stem cell transplantation in lymphoma one of the biggest topics of this year's meeting. Each trial compared Car-T against standard of care, meaning chemotherapy followed by transplant in patients who go into remission.

CROSSOVER CONUNDRUM

But a key issue has emerged, in that a majority of patients in the control cohorts of these three trials crossed over to Car-T on disease progression – as part of protocol in Transform and Belinda, and off-protocol in Zuma-7. Thus the EFS metric loses importance if an absence of overall survival benefit suggests that patients relapsing on second-line standard of care can still be rescued by Car-T in its currently approved third-line setting.

The jury is still out on whether this is the case. Both the

successful trials, Transform and Zuma-7, showed an immature OS analysis numerically favouring Breyanzi and Yescarta, the former with widening survival curves, admittedly from an interim analysis.

But Zuma-7's primary investigator, Dr Frederick Locke from Moffitt Cancer Center, told Sunday's Ash plenary session that treatment switching in the standard-of-care cohort was likely confounding a significant OS benefit.

However, for her part University of Colorado Cancer Center's Dr Manali Kamdar, who presented the Transform data on Saturday, said patients who got Breyanzi later (after crossing over from standard of care) did not do as well as those who got it earlier. This appears to back the importance of giving Breyanzi second rather than third line.

However this plays out, it will be up to regulators to determine whether the EFS benefits Bristol and Gilead have shown are enough to secure second-line approvals in the absence of a mature OS analysis. The EFS findings themselves show Yescarta and Breyanzi beating second-line standard of care by a huge margin, cutting risk of progression by over 60%.

Moderating a press briefing, Dr Laurie Sehn of University of British Columbia said it was "inevitable that [Car-T] will become the standard of care" in second-line lymphoma. Without being drawn on which therapy was better, she noted that the Zuma-7 data were very mature, while Transform's was an interim analysis.

Car-T in 2nd-line lymphoma; a cross-trial comparison

	Yescarta (Gilead)	Breyanzi (BMS)	Kymriah (Novartis)
Study	Zuma-7	Transform	Belinda
Baseline disease	Adults within 12mth of adequate 1st-line chemo and intended to proceed to stem cell transplant	Adults, incl with secondary CNS lymphoma, within 12mth of 1st-line therapy, eligible for stem cell transplant	Adults within 12mth of 1st-line chemo
Active bridging?	Optional bridging with steroids (no chemo)	63% got chemo bridging	83% got chemo bridging
Active n	180 (of which 10 not infused)	92 (of which 2 not infused)	162 (of which 6 not infused)
Control arm	Chemo, then stem cell transplant in responders (36% transplanted)	3 chemo cycles, then BEAM + stem cell transplant in responders (47% transplanted)	Chemo, then stem cell transplant in responders (33% transplanted)
Control n	179	92	160
Control crossover?	Yes, off protocol 100 (56%) patients who failed SoC got commercial/investigational Car-T	Yes, 50 (54%) SoC pts not responding crossed over to Breyanzi	Yes, 81 (51%) crossed over to Kymriah; 72 crossover pts were evaluable, and yielded ORR of 40%
EFS	Median 8.3mth vs 2.0mth (HR=0.398; p<0.0001)	Median 10.1mth vs 2.3mth (HR=0.349; P<0.0001)	Median 3.0mth vs 3.0mth (HR=1.07; p=0.69)
OS (immature)	Median NR vs 35.1mth (HR=0.73; p=0.027)	NR vs 16.4mth (HR=0.51; p=0.0257)	16.9mth vs 15.3mth (HR not disclosed, but likely >1.00)
Grade ≥3 CRS	6%	1%	5%
Grade ≥3 neurotox	21%	4%	3%

Source: Ash

BELINDA'S BUST

One Car-T therapy that will not be moving up is Novartis's Kymriah, whose Belinda study was already known to be a bust. Some blame for this has been placed on the fact patients given Kymriah were more sick than those in the control cohort.

But speaking to Vantage Stefan Hendriks, Novartis's head of cell and gene, also said time from randomisation to infusion was longer in Belinda than in the other two trials. This has been an ongoing problem for Novartis, and while it was partly down to Covid-19 and capacity constraints the upshot is that some patients did not get Kymriah in time, and saw their disease get worse.

Investigators said time from leukapheresis to infusion of Car-T cells, including lymphodepletion, was on average 52 days in Belinda, versus just 29 in Zuma-7.

Another quirk was that Novartis capped EFS assessment at 12 weeks. Some patients – Mr Hendriks did not say how many – responded to Kymriah after this point, but because they had stable or progressive disease at 12 weeks they were nevertheless counted as having evented.

Still, Mr Hendricks was clear: "Because of the outcome of [Belinda] we will not submit for a second-line indication." But he said a pivotal second-line lymphoma trial would be carried out with YTB323, a next-generation Car-T that can be manufactured within two days.

BREYANZI SAFER?

Over the weekend discussion turned to fault lines emerging between the two successful studies, Transform and Zuma-7. A key matter appears to be safety: while both trials saw a similar amount of severe all-cause treatment-related adverse events, severe cytokine release syndrome (CRS) and neurotoxicity was lower in Transform than in Zuma-7.

Dr Kamdar said this made Breyanzi "appealing not just from a standpoint of efficacy but also [from its] extremely tolerable safety". Only one Breyanzi patient had grade 3 CRS, and there was no grade 4 or 5 CRS or neurotoxicity. There was one Car-T treatment-related death in each of the two studies.

Other differences were that Transform allowed patients with a broader histology profile than Zuma-7, and it did, like Belinda, allow bridging chemo while the Car-T cells were being produced. Zuma-7 allowed steroids during this phase, but, crucially, not chemo.

In a cutting remark, Dr Locke stated: "We wanted to know: could [Yescarta] be given without the confounding effect of chemotherapy, which we know can cause a response?"

One remaining problem is what to do once a second-line lymphoma patient on Car-T does relapse. Both presenters said there was no appropriate standard of care here, but said a small number of such relapsing patients in both studies ended up getting transplanted; in Zuma-7 this amounted to 19 patients, nine of whom are still alive, said Dr Locke.

No matter, the argument shifts to whether, given Car-T's better efficacy, payers should shell out for this rather than stem cell transplant. Dr Kamdar said it was too early to talk of financial toxicity, but stressed Car-T's potential as a "once and done therapy". Dr Locke said some of the intensive hospital care costs were similar in transplantation and Car-T.

The efficacy data seem pretty clear, so the ball now enters the court of the FDA on whether to approve, and of payers to decide whether to pay up.

Published on: December 14, 2021

Ash 2021 – the sun sets on Kymriah, but Novartis has a plan

BY JACOB PLIETH

Novartis unveils the first clinical backing for a two-day manufacturing technique that it hopes will recharge its Car-T efforts.

Long-drawn-out manufacturing has been a running sore in the development of Kymriah, repeatedly hobbling the Novartis Car-T therapy's efficacy and blunting its utility in rapidly progressing patients. But a new two-day manufacturing technology is ready for prime time, reckons the Swiss group, which used the Ash meeting to splash its clinical effectiveness.

The subjects of the so-called "T-Charge" technique are two second-generation Car-Ts, YTB323 and PHE885, and Ash today saw the first detailed clinical data for both. Stefan Hendriks, Novartis's head of cell and gene, stresses that "we're very confident in Kymriah", but is also clear about the need to develop a "more potent and more durable" Car-T therapy.

For Novartis the need for something like this has been pressing. The Juliet study was notable for the fact that 40% of enrolled patients were never infused with Kymriah, most being lost to disease progression during the protracted manufacturing time; the failed Belinda trial, being presented at an Ash late-breaker tomorrow, is thought to have suffered similarly.

BRIDGING CONFUSION

It has therefore been necessary to use bridging chemo to slow many patients' disease while Kymriah is being manufactured. This in turn has made it difficult to interpret some data, as it can be unclear whether a responding patient is responding to Kymriah or to the bridging therapy.

It will be of interest to some that this problem persists in the phase 1 trial of YTB323, a next-gen CD19-directed Car based on T-Charge that Novartis has unveiled at Ash. Despite YTB323's short manufacturing time many of the 19 lymphoma patients enrolled were bridged, and four (three post-bridging) were in complete remission before YTB323 was even infused.

Thus caution must be used in interpreting the cited three-month overall remission rate of 63%, which includes three of the four complete responders at baseline. However, a commercial product produced within two days would aim to do away with the need for bridging, Mr Hendriks tells Evaluate Vantage.

Meanwhile, the first clinical trial of PHE885, an anti-BCMA Car, has yielded 15 evaluable subjects, and all 11 treated at the highest two of three doses were in remission at one month. However, several relapses had occurred by 3.5 months' median follow-up, Novartis said.

Novartis Car-T projects using T-Charge manufacturing technique		
Project	YTB323	PHE885
Target	CD19*	BCMA
Study	NCT03960840	NCT04318327
Ash abstract	740	3864
Efficacy-evaluable patients	4 at low dose, 15 at high dose	4 at low dose, 10 at mid dose, 1 at high dose
Key efficacy data	3mth ORR 25% in low dose** 3mth ORR 73% at high dose^	1mth ORR 75% at low dose 1mth ORR 100% at mid and high doses combined^^

Notes: *uses the same Car construct as Kymriah; **1 responder was already in CR at infusion; ^2 of the 11 patients were already in CR at infusion after bridging chemo; ^^8 of 14 responders in remission at median 3.5mth follow-up. Source: Ash & Novartis.

As for safety, there was one grade 4 cytokine release syndrome and two grade 3 neurotoxicities in the YTB323 study, and two PHE885 subjects experienced grade 3 cytokine release. Perhaps most importantly, both studies showed that T-Charge could work in practice.

WHAT IS IT?

Still, Mr Hendriks is guarded about precisely what T-Charge involves, and how it makes manufacturing a Car-T product within two days possible. Vein-to-vein times for approved Car-Ts are two to six weeks, with real-world evidence suggesting that Kymriah's is around 44 days, versus 28 days for Gilead's Yescarta.

But the secret to T-Charge's short manufacturing is that cell "expansion is happening in vivo, whereas in the first-generation platform it happens in vitro in the manufacturing setting. That's the big difference," he says.

The key to this lies in the generation of a product based on a different subset of T cells that are relatively young with a high degree of stemness – the quality of self-renewal and proliferation. Thanks to this there is no need for the ex vivo expansion step, and manufactured product can be reinfused quickly, with expansion taking place largely in the patient.

The idea of focusing on a specific T-cell subset is not new, of course: Bristol Myers Squibb's Breyanzi employs an extra cell-sorting process to achieve a defined 50/50 CD4+/CD8+ T-cell ratio, while the Bluebird spin off 2seventy's bb21217 adds a PI3k inhibitor during ex vivo culture to enrich for phenotypically young, memory-like T cells. But these are geared towards greater persistence rather than shorter manufacturing.

Until now the main proponent of quick Car-T production was Gracell, which claims 22 to 36-hour manufacturing with its FastCar process. This involves cell activation and transduction concurrently rather than in sequence, and a similar focus on T cells with memory and stemness and no ex vivo expansion, all in a closed, automated system, just like T-Charge.

Novartis today said T-Charge would serve as the foundation for various new Car-T therapies in its pipeline, and Mr Hendriks sees more projects, using more constructs, following in a "long-term game".

It seems clear that, contrary to earlier rumours, Novartis is not scaling back on cell therapy. It is just that Kymriah might not be at the centre of its efforts for much longer.

Published on: December 13, 2021

Ash 2021 – Sangamo and Sanofi enter the sickle cell gene editing fray

BY MADELEINE ARMSTRONG

SAR445136 could take on Crispr and Vertex's CTX001, but plenty of other groups have the same idea.

For a rare disorder, sickle cell disease has certainly had a lot of interest from biopharma. The latest groups to throw their hats into the ring are Sangamo and Sanofi, which presented promising data with their gene-edited candidate SAR445136 yesterday at Ash.

However, with only four patients' worth of data, it is too soon to say whether SAR445136 could be a real contender. And the companies will be going up against not only Crispr and Vertex, whose CTX001 made a splash at last year's Ash, but a host of other players developing gene-edited projects in sickle cell too.

CRISPR VS ZINC FINGER

SAR445136 works differently from CTX001: the former uses zinc finger nucleases to edit a patient's own stem cells, while CTX001 is based on Crispr/Cas9 technology. However, both projects have the same ultimate goal: reducing the expression of BCL11A, a transcription factor that normally suppresses the production of foetal haemoglobin.

It is hoped that increasing levels of foetal haemoglobin could compensate for the defective haemoglobin found in sickle cell disease.

This approach seems to have legs. The phase 1/2 Precizn-1 study of SAR445136 found that, in the four patients who have received therapy so far, there was a drop in the number of vaso-occlusive crises, the pain events seen in sickle cell disease.

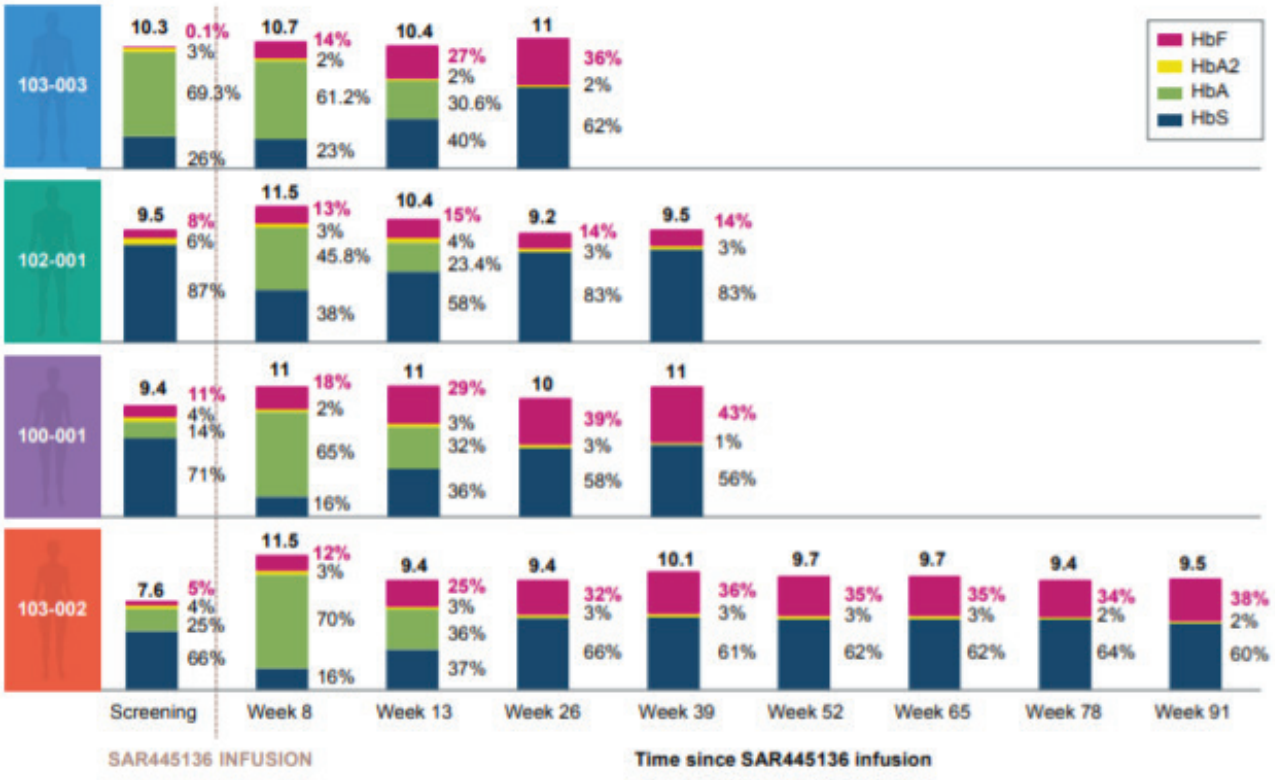
In the two years before SAR445136 infusion, the four patients had 44 VOCs between them; after treatment, only one VOC was seen.

All four patients also had an increase in the proportion of foetal

haemoglobin relative to total haemoglobin levels. However, this was not uniformly impressive: the worst-performing patient on this metric had 14% foetal haemoglobin at six months; this is also the patient who experienced a VOC.

Haemoglobin fractionation following SAR445136 infusion

Figure 3. Total Hb and Hb fractionation in all patients after SAR445136 infusion



Source: Ash.

Based on the data available so far, and with the usual caution about comparing different trials, CTX001 appears to have a slight edge over SAR445136.

At the latest update, at the European Hematology Association meeting in June, seven patients receiving the Crispr/Vertex project remained free of VOCs, with follow-up as long as 22.4 months in one subject.

Cross-trial comparison of gene edited projects for sickle cell disease		
Project	**SAR445136 (BIVV003)**	**CTX001**
Company/ies	Sangamo/Sanofi	Crispr/Vertex
Trial	Precizn-1 (NCT03653247)	Climb SCD-121 (NCT03745287)
N at latest update	4	7
VOCs	1	0
Total Hb (g/dl)	9.2-11.0*	9.7-14.9**
% HbF	14-39%*	40-50%**

*At month 6; **at month 4. Source: Ash 2021 & EHA 2021.

However, long-term data on more patients will be needed on both projects before any firm conclusions can be reached.

This also goes for others trying to gain a foothold in the disease, including Beam Therapeutics, which recently got clearance to start a US study of its first sickle cell project, BEAM-101. The group's base-editing technology is designed to be a more precise version of Crispr/Cas9.

BEAM-101 is also intended to increase foetal haemoglobin, but the company has a preclinical project, BEAM-102, that works differently, converting sickling haemoglobin to a naturally occurring human haemoglobin variant, HbG Makassar.

Graphite Bio claims to go a step further and to correct the underlying genetic mutation that causes sickle cell disease.

Still, all of the projects listed below are autologous, ex vivo therapies that require stem cell transplantation and, therefore, harsh pre-conditioning regimens. This will likely see their use limited to the severely affected patients, even if they get to market. Given these considerations the space is starting to look very crowded.

Published on: December 13, 2021

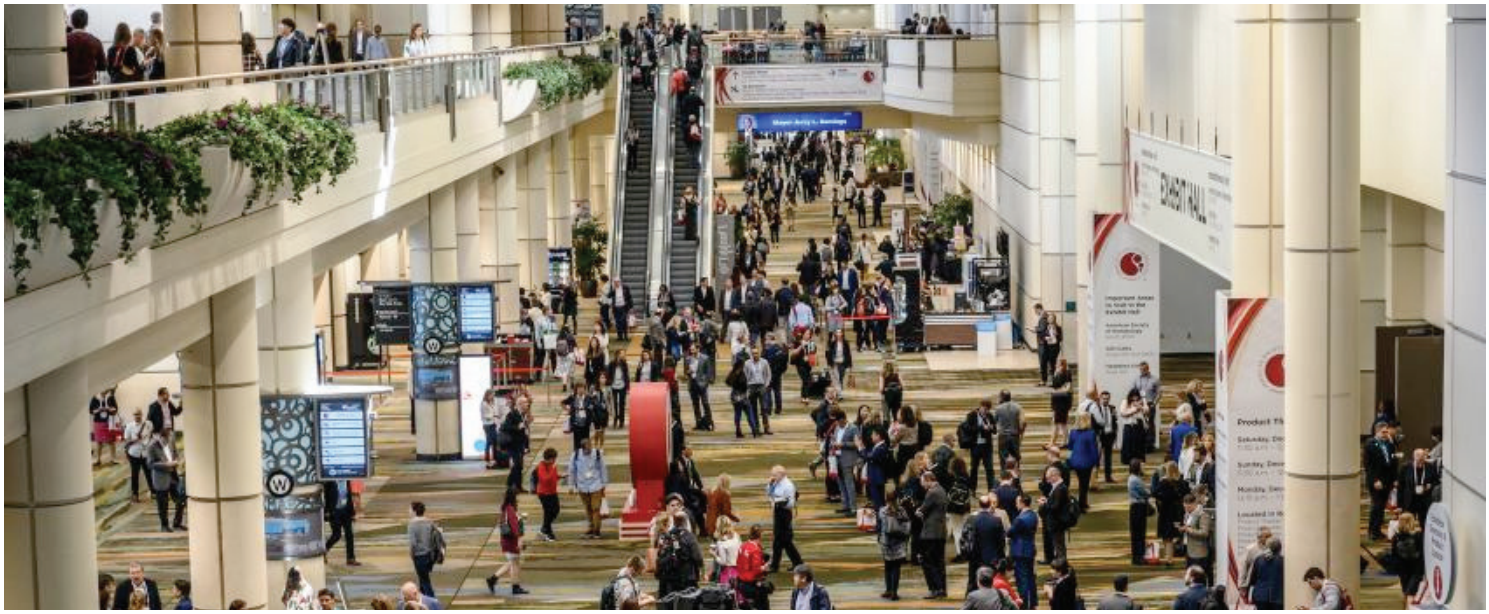
Selected ex vivo gene-edited sickle cell projects in development			
Project	**Company/ies**	**Description**	**Status/trial details**
CTX001	Crispr/Vertex	Crispr/Cas9 gene-edited cell therapy targeting BCL11a	Ph1/2 Climb SCD-121; filing planned late 2022
SAR445136 (BIVV003)	Sangamo/Sanofi	Zinc finger nuclease gene-edited cell therapy targeting BCL11a	Ph1/2 Precizn-1; data on 4 pts at Ash 2021
GPH101	Graphite Bio	Homology-directed repair gene-edited cell therapy targeting underlying beta-globin mutation	Ph1/2 Cedar; initial data due YE 2022
OTQ923 & HIX763	Intellia/Novartis	Crispr/Cas9 gene-edited cell therapy targeting BCL11a	Ph1/2
EDIT-301	Editas	CRISPR/Cas12a gene-edited cell therapy targeting beta-globin to increase foetal haemoglobin	Ph1/2
BEAM-101	Beam Therapeutics	Base-edited cell therapy promoting foetal haemoglobin	Beacon-101; IND cleared Nov 2021
BEAM-102	Beam Therapeutics	Base-edited cell therapy recreating HbG Makassar variant	Preclinical

Source: Evaluate Pharma & clinicaltrials.gov.

Ash 2021 – Global Blood stems the bleeding

BY MADELEINE ARMSTRONG

The company reports decent data with its Oxbryta follow-on, but still has much to prove.



Global Blood Therapeutics believes that it has taken a step towards an oral functional cure for sickle cell disease, with encouraging but early data presented at Ash today with its Oxbryta follow-on GBT021601. Investors were less certain about what to make of the results: the group's stock fell as much as 9% this morning, but ended the day up 5%.

The company met its target of showing haemoglobin modification of 30-40% with daily dosing of '601 in six sickle cell patients, and has room to dose higher. However, results were variable between patients, and reports of several vaso-occlusive crises during therapy also raised concerns.

SMALL N

During a conference call today Global Blood's chief executive, Ted Love, countered that reading too much into the VOCs seen, given the small number of patients and the short duration of the study, "borders on the ridiculous".

He added that the group would not expect to see an immediate impact on VOCs with '601, but that this should improve over time.

Still, the company's first-generation sickle haemoglobin (HbS) polymerisation inhibitor, Oxbryta, did not significantly decrease VOCs in the pivotal Hope study. Instead, the product received accelerated approval on the basis of an increase in haemoglobin levels, a surrogate endpoint. And Global Blood's confirmatory study of Oxbryta does not evaluate VOCs, but instead has transcranial doppler (TCD) flow velocity – an indicator of a patient's risk of stroke – as its primary endpoint.

Therefore, until '601 can show a benefit on VOCs, doubts are likely to remain.

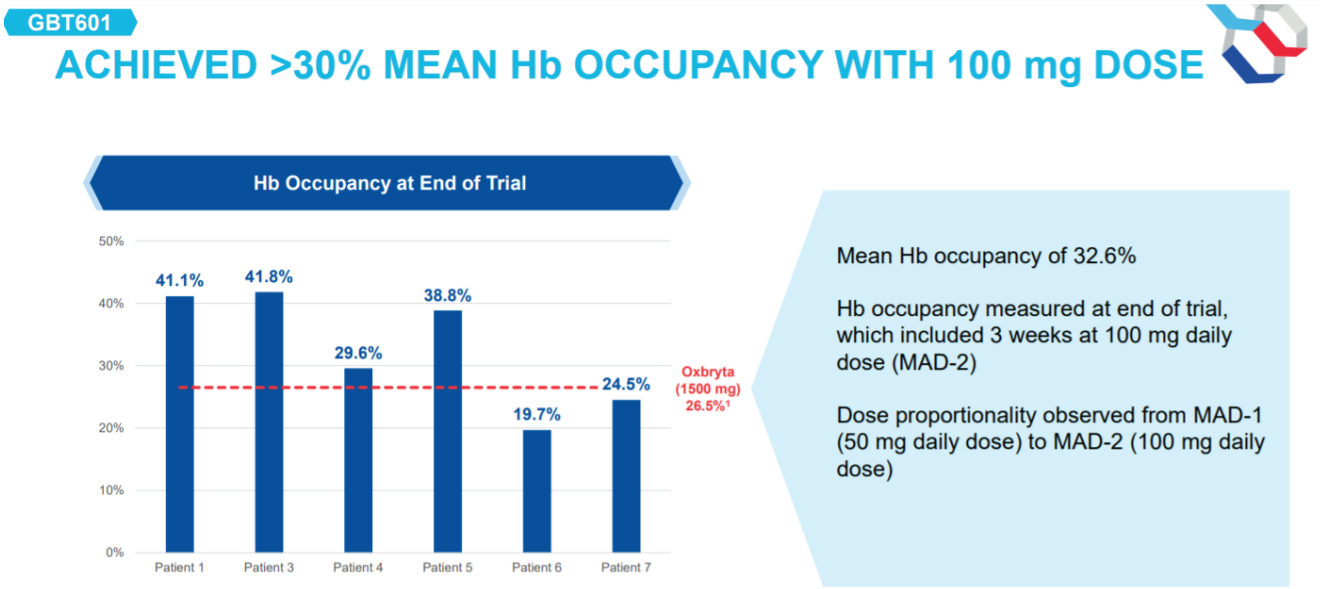
MORE POTENT

The next-gen project works similarly to Oxbryta but is

designed to be more potent – something backed up by the data presented today.

Oxbryta is dosed at 1,500mg/day, while the multiple-ascending dose portion of the phase 1 trial tested '601 at 50mg and 100mg daily, following a loading dose. The sickle cell patients received the 50mg/day dose for five weeks before moving to 100mg/day for three weeks.

At the end of the trial, the mean haemoglobin occupancy rate was 32.6%; occupancy has been shown to correlate with modification. There was also a mean 2.3g/dl increase in haemoglobin.
Source: Ash & company presentation



Source: Ash.

By contrast, Oxbryta has led to haemoglobin modification of around 26%, and a haemoglobin increase of 1.1g/dl.

On the latter measure, '601 also looks better than some potential oral rivals, albeit on the basis of cross-trial comparisons: Agios's mitapivat and Forma's etavopivat have been shown to increase haemoglobin by 1.2g/dl and 1.5g/dl respectively.

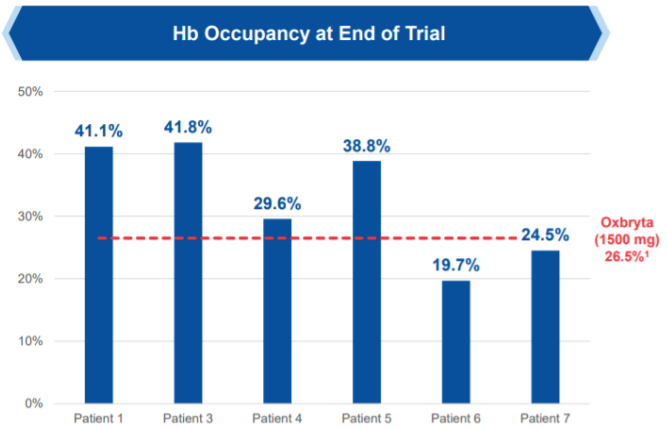
However, the '601 study found a great deal of variability between patients. Perhaps a larger study will make the trends clearer.

Global Blood plans to start a phase 2 trial of '601 in the first half of next year, but is not giving any more details for now.

On dosing, a spokesperson told Evaluate Vantage: "We haven't determined the dose for the next study yet, but we've said we will study higher doses than 100mg but still significantly lower than Oxbryta. The data today suggest that we can achieve even higher occupancy at daily doses well under 500mg."

GBT601

ACHIEVED >30% MEAN Hb OCCUPANCY WITH 100 mg DOSE



Mean Hb occupancy of 32.6%

Hb occupancy measured at end of trial, which included 3 weeks at 100 mg daily dose (MAD-2)

Dose proportionality observed from MAD-1 (50 mg daily dose) to MAD-2 (100 mg daily dose)

Source: Ash & company presentation

Published on: December 13, 2021

Ash 2021 – another factor fade, courtesy of Pfizer and Sangamo

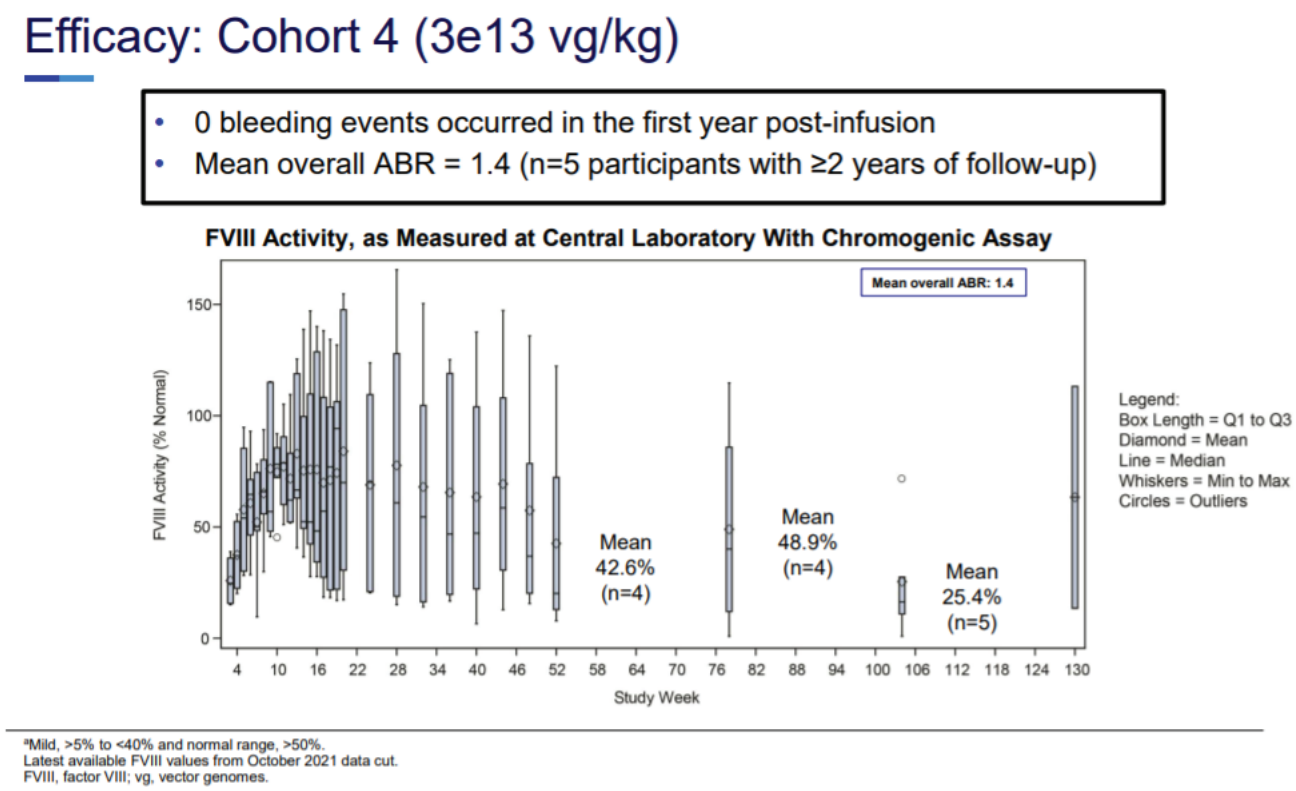
BY MADELEINE ARMSTRONG

Pfizer and Sangamo's haemophilia A gene therapy candidate giroctocogene fitelparvovec was supposed to be more durable than Biomarin's rival project valrox.

This claim has been in doubt for a while, but data presented at Ash yesterday confirmed that, like valrox, girfit is linked with a marked decline in factor VIII levels over the long term. This finding, along with liver enzyme elevations, led Leerink analysts to conclude that the project did not look viable. Updated data from the phase 1/2 Alta trial showed that, among five patients receiving the highest dose of girfit, mean factor VIII levels were 25.4% at two years; this looks less impressive than the two-year results from valrox's phase 1/2 study. Of course, FVIII levels are just a surrogate endpoint, but Alta also saw an emergence of bleeds during year two: one patient had eight bleeds, while another had one. Meanwhile, the phase 3 Affine trial of girfit is on clinical hold after some patients developed FVIII levels over 150%. There are fears that such high levels could lead to blood clots; Pfizer has said that no thrombotic events have occurred, although some patients have been given anticoagulants.

Published on: December 13, 2021

Long-term efficacy of girfit



Source: Ash & Jeremy Rupon (Pfizer)

Ash 2021 – Forma takes on a second Agios drug

BY JACOB PLIETH

Now in Servier's hands, the Agios-discovered Tibsovo could soon face competition from Forma's olutasidenib.

The sellside generally does not expect other IDH1-targeting acute myelogenous leukaemia drugs to displace Servier's Tibsovo, but Forma now has not one but two datasets suggesting that its rival olutasidenib might set out to do just that.

Today's Ash presentation of a Vidaza combo adds to olutasidenib monotherapy data from Asco, and both results are at least as good as the corresponding Tibsovo numbers. "It's hard to make these kinds of comparisons without doing a head-to-head trial," cautions Forma's chief executive, Frank Lee, but he says the data could make olutasidenib a "very, very compelling choice".

If this happens Forma will have taken on Agios twice, having on Saturday unveiled Ash data backing etavopivat, a sickle cell project rivalling Agios's mitapivat. Agios had originated Tibsovo, which is now US-approved as monotherapy for front-line and relapsed IDH1-mutant AML, but has since divested the drug to Servier to focus on non-oncology indications.

At Asco this year Forma had presented olutasidenib monotherapy data showing a 46% remission rate in relapsed IDH1-mutant AML. Tibsovo's label cites a rate of 33% in relapsed patients; though these remission data came from a single-arm study Tibsovo was greenlit under a full approval.

VIDAZA COMBO DUEL

Now the battleground is moving to combinations with Vidaza, and Servier and Forma presented duelling datasets at Ash today. Servier's came from the controlled front-line Agile study, which in May had been halted for efficacy.

Here Tibsovo plus Vidaza beat Vidaza alone in terms of remission rate, which came in at 63% versus 19%. More importantly, there was a statistically significant overall survival

benefit, with an impressive separation in survival curves translating into a 56% reduction in risk of death across any point in Agile (p=0.0005).

The Agile data are important as they might back an EU filing for Tibsovo. The drug had been knocked back in the EU, where regulators had refused to accept an application based on a single-cohort trial.

For its part Forma hopes that its combo might get additional patients into remission if these can tolerate the hypomethylating agent Vidaza, and that a combo might catch some of the co-mutations that can occur along with IDH1, which is seen in about 5-10% of AML patients.

Its Ash presentation included front-line as well as relapsed/refractory disease, and in the former olutasidenib showed a 64% remission rate, albeit in just 11 evaluable subjects. Perhaps more impressive is the relapsed AML cohort, where the combo put 52% of the patients into remission – including 40% of those who had already failed an IDH1 inhibitor like Tibsovo.

Still, Mr Lee said the dataset that would be used to back an initial olutasidenib filing would be the monotherapy cohort presented at Asco, and said very good progress was being made towards a US filing. However, he also said Forma needed a partner to commercialise.

While cross-trial comparisons are dangerous, the monotherapy data for olutasidenib come from a very similar population to that backing Tibsovo's approval. "You can draw a clear conclusion that we have a better response rate and a more durable response rate," Patrick Kelly, Forma's chief medical officer, tells Evaluate Vantage.

Admittedly, things will be tough in the Vidaza combo setting, as Forma's dataset is uncontrolled whereas Servier is showing a comparison for the Tibsovo combo versus Vidaza alone in Agile that demonstrates an overall survival advantage to boot.

Hitting IDH mutations: the competitor landscape

Project	Target	Company	Status	Monotherapy	Vidaza combo
Idhifa (enasidenib)	IDH2	Bristol Myers Squibb (ex Celgene/Agios)	US approved for r/r mIDH2 AML; EU filing for AML pulled Dec 2019	ORR 23% in r/r AML; failed to improve OS in r/r mIDH2 AML; ph2 data for mIDH2 MDS at Asco 2021	ORR 74% in 1L AML vs 36% for Vidaza (n=107, p=0.0003)
Tibsovo (ivosidenib)	IDH1	Servier (ex Agios)	US approved for 1L & r/r mIDH1 AML, & 2L mIDH1 cholangio; EU filing for AML pulled Oct 2020	ORR 43% in 1L AML; ORR 33% in r/r AML	ORR 63% in 1L AML vs 19% for Vidaza (n=146); mOS 24.0mth vs 7.9mth (HR=0.44, p=0.0005)
Vorasidenib	IDH1 & 2	Servier (ex Agios)	Ph3 in mIDH1/2 glioma	Ph1 showed mPFS of 36.8mth in nonenhancing glioma, 3.6mth in enhancing glioma	NA
AB-218 (DS-1001)	IDH1	Anheart (ex Daiichi Sankyo)	Ph2 in 1st-line mIDH1 glioma	No clinical data	NA
Olutasidenib (FT-2102)	IDH1	Forma Therapeutics	Ph1/2 in mIDH1 AML or MDS	ORR 46% in r/r AML (n=123)	ORR 64% (n=11) in 1L AML; ORR 52% in r/r AML (n=52), incl ORR 40% (n=20) in r/r AML after prior IDH1
LY3410738	IDH1	Lilly (ex Loxo)	Ph1 in mIDH1/2 haem & solid tumours	First-in-class covalent IDH1 inhibitor; no clinical data	NA
HMPL-306	IDH1 &	Hutchmed	Ph1 in mIDH1/2 haem & solid tumours	No clinical data	NA
BAY1436032	IDH1	Bayer	Ph1 in mIDH1 solid tumours	ORR 15% (termed disappointing, n=27), mOS 6.6mth, in AML	NA
IDH305	IDH1	Novartis	Likely discontinued	ORR 33% (n=7) in r/r AML	NA

Source: Ash, Asco, product labels & company information.

Mr Kelly pointed to a separate opportunity for olutasidenib, in IDH1-mutant glioma. Interestingly, a separate Agios-originated, Servier-owned project, vorasidenib, is in phase 3 for glioma, but this targets IDH1 as well as IDH2, a mutation olutasidenib does not hit.

In the IDH1-mutant space at least two competitors, Bayer's BAY1436032 and Novartis's IDH305, have fallen by the wayside after showing data that were not competitive against Tibsovo. Perhaps with this in mind Mizuho analysts recently wrote that Tibsovo might be challenged in myelodysplastic syndromes but not in AML.

Do the olutasidenib data show that Forma might actually have an AML drug on its hands? "Absolutely," states Mr Kelly.

Published on: December 13, 2021

Ash 2021 – Bristol reveals its sons of Revlimid

BY JACOB PLIETH

Data in multiple myeloma and non-Hodgkin's lymphoma make Bristol optimistic about follow-ons to Revlimid and Pomalyst.

US patents on Revlimid, the multiple myeloma blockbuster that was a key reason why Bristol Myers Squibb bought Celgene, will start to expire next year. But Celgene also brought a pipeline of follow-on "celmods", and Bristol is now betting on these to help it weather the Revlimid cliff.

The Ash conference this weekend highlighted two of these multiple myeloma wannabes, iberdomide and CC-92480, which Bristol describes as acting similarly to Revlimid but with greater potency. And today brought the first look at clinical efficacy data for a third celmod, CC-99282, which while having the same mechanism of action is "optimised" for lymphoma.

The '282 data will be of interest because they provide the first evidence of the activity of this project – as monotherapy – in a cohort of non-Hodgkin's lymphoma subjects who had failed a median three prior therapies.

The Ash presentation showed a 39% remission rate in 36 subjects. Kristen Hege, a Bristol senior vice-president of early clinical development who joined from the Celgene business, told Evaluate Vantage that this was "very encouraging for a single agent in these highly refractory patients, many of whom had failed transplant and Car-T".

The late-line lymphoma space is becoming competitive, with Car-T establishing itself and various anti-CD20 bispecifics vying for attention. The data could back moving '282 into earlier settings and combining it with other agents, though it is too early to talk about a potentially registrational study.

HOW THEY ACT

"Celmods are small molecules that bind to cereblon [a cellular protein] and lead to the degradation of certain substrates. Key substrates for their activity in multiple myeloma and lymphoma are Ikaros and Aiolos," explains Ms Hege.

Interestingly, imids like Revlimid and Pomalyst work this same way, though it has taken some time since the discovery of these thalidomide analogues to arrive at this pharmacology definition.

"But the next-generation celmods … are much more potent, and are active in patients who have failed on imids," says Ms Hege. "They work in the setting of patients with lower cereblon expression levels, and they lead to much deeper and durable degradation of the substrates."

Data presented at Ash this weekend for iberdomide and '480 appear to bear this out. The phase 2 portion of a fourth-line or later multiple myeloma study of the former yielded 33 remissions in 131 subjects, all of whom had failed Revlimid or Pomalyst.

Winship Cancer Institute's Dr Sagar Lonial described iberdomide as "tumouricidal rather than tumouristatic", and was especially pleased that only five subjects withdrew owing to adverse events, and none for neutropenia – a common problem with imids. Bristol's hope is that this side-effect profile will make iberdomide especially apt for combinations in early-line regimens.

Meanwhile, the idea with CC-92480 is that it is very active in Revlimid/Pomalyst-refractory myeloma, so Bristol is gunning for later-line combo regimens. An Ash poster of a trial in 19 third to fifth-line imid-refractory subjects (37% also refractory to an anti-CD38 MAb) showed 74% responding to a CC-92480/Velcade combo, with maximum tolerated dose still not reached.

Oral small-molecule cereblon E3 ligase modulator (celmod) agents

Project/drug	Substrate	Positioning	Note
Bristol Myers Squibb (ex Celgene)*			
Revlimid (lenalidomide)	Aiolos & Ikaros**	Established 1st-line multiple myeloma therapy, also approved for r/r lymphoma	US patents start expiring 2022
Pomalyst (pomalidomide)	Aiolos & Ikaros	Approved for 3rd-line multiple myeloma	US patents start expiring 2025
Iberdomide (CC-220)	Aiolos & Ikaros	To replace Revlimid as foundation for 1st-line multiple myeloma	Dex combo in 4th+ line: ORR 26% (n=107) in BCMA-naive, ORR 25% (n=24) in post-BCMA
CC-92480	Aiolos & Ikaros	To replace Pomalyst in r/r multiple myeloma	Dex + Velcade combo in 3rd-5th line: ORR 74% (n=19)
CC-99282	Aiolos & Ikaros	Non-Hodgkin's lymphoma	MonoRx 39% ORR (n=36), incl 32% (n=28) in DLBCL & 75% (n=9) in follicular lymphoma
Avadomide (CC-122)	Aiolos & Ikaros	Earlier celmod for lymphoma	Discontinued in favour of CC-99282
CC-91633 (BMS-986397)	CK1α^	AML & MDS	Ph1 started Dec 2021
CC-90009	GSPT1^^	AML	Preclinical
CC-885	GSPT1	AML	Discontinued in favour of CC-90009
C4 Therapeutics			
CFT7455	Aiolos & Ikaros	Multiple myeloma & non-Hodgkin's lymphoma	Ph1 started Apr 2021
Nurix			
NX-2127	BTK & Aiolos#	B-cell malignancies	Ph1 started May 2021
Monte Rosa Therapeutics			
MRT-2359	GSPT1	Myc-driven cancers	IND submission due mid-2022

*Bristol additionally claims five preclinical-stage "novel celmods" targeting undisclosed substrates; **Aiolos (IKZF3) & Ikaros (IKZF1) are zinc finger protein lymphoid transcription factors essential for myeloma cell survival; ^CK1α is casein kinase 1α; ^^GSPT1 is a translation termination factor; #aim is to degrade wild-type & mutant (including C481S) BTK while retaining imid-like activity.

Source: company filings & Ash.

Bristol also has several other celmods in its pipeline, including two for AML: CC-91633 degrades a different substrate, CK1α, and recently started phase 1; CC-90009 is a GSPT1 degrader still in preclinical study.

“When you engage cereblon with different small molecules it can result in the degradation of different substrates, and those different substrates have activity in different diseases,” says Ms Hege. Determining which should be used in which disease is a result of preclinical interrogation of several molecules and observing their activity in different settings.

Bristol’s bold claim is that iberdomide will one day replace Revlimid in front-line multiple myeloma, while CC-92480 will become the new Pomalyst. Sellside consensus compiled by Evaluate Pharma shows Revlimid and Pomalyst generating 2022 sales of $11.3bn and $3.6bn respectively, but in four years these numbers will fall to just $2.2bn and $723m.

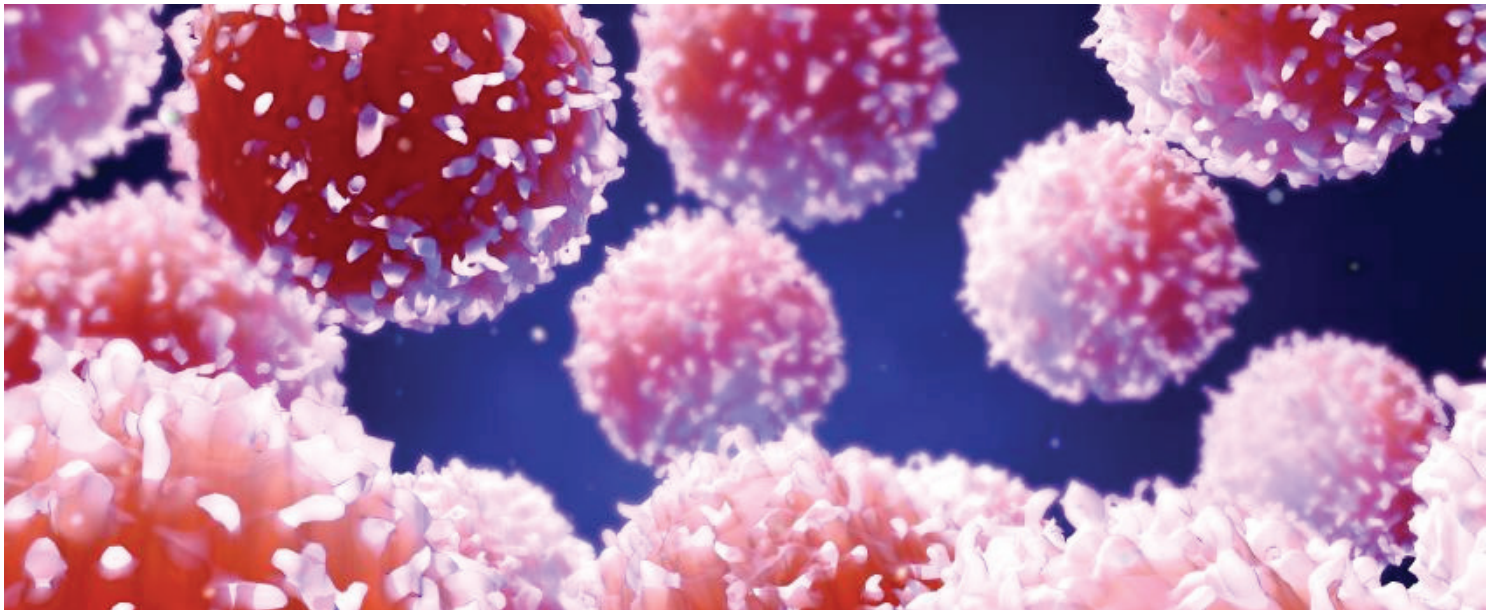
Bristol knows that bold moves are called for, and aims to run a trial demonstrating iberdomide’s head-to-head superiority versus Revlimid in the post-transplant maintenance setting. It has no time to waste.

Published on: December 13, 2021

Ash 2021 – Precision moves quickly to deal with allo disappointment

BY JACOB PLIETH

Like its two competitors Precision shows lack of durability with its allogeneic Car-T approach, but makes a quick move to next-gen assets.



As Precision Biosciences is the third of three players with relatively advanced allogeneic Car-T projects, some investors were looking to its Ash presentation yesterday for signs that this type of therapy is, after all, ready for prime time.

Unfortunately they got no such reassurance, with a lymphoma trial of PBCAR0191 showing that most remitting patients relapse within six months – echoing earlier disappointments with corresponding CD19-directed Cars from Allogene and Crispr. Precision's plan now is to focus PBCAR0191 on Car-relapsed patients while looking to a next-generation asset, PBCAR19B, in the broader population.

This might come as a disappointment to some, who will read this as Precision abandoning PBCAR0191, its lead asset. Their fears will be reinforced by Precision separately admitting yesterday that PBCAR269A, a BCMA-targeting Car for multiply myeloma, was "not comparable with autologous Car-T" in efficacy terms.

PBCAR19B

That said, the company should be congratulated for moving quickly to remedy the situation. In CD19-expressing disease the next-gen PBCAR19B has already begun phase 1 at its first dose level, and the company hopes to present data in mid-2022.

PBCAR19B is a similar allogeneic project to PBCAR0191, but additionally expresses an anti-β2M shRNA, which the company hopes will help it evade rejection by the host's T cells, and an HLA-E transgene to prevent rejection by NK cells. A similar "stealth" Car, PBCAR269B, is in development targeting BCMA but is still in preclinical trials.

As far as the first-generation PBCAR0191 goes, the omens are not good. Precision's Ash presentation yesterday showed

a 71% overall remission rate among 17 evaluable heavily pretreated lymphoma subjects. By six months, however, eight of the 12 responders had relapsed; of the other four, three were ongoing, one after transplant and one at very short duration, while the fourth relapsed at around nine months.

Though the company highlighted relatively good safety in terms of cytokine release and neurotoxicity, there were eight infections in the lymphoma cohort; three led to deaths, one of which was deemed potentially related to PBCAR0191.

Lack of durability is nothing new in allogeneic Car-T, which as a therapy approach has moved painfully slowly through clinical development. In October Crispr trumpeted a 58% ORR among 24 subjects given 100 million CTX110 cells, but by around six months all but three initial responders had relapsed, including an earlier disclosed death.

Unlike Precision, Crispr allowed the redosing of some relapsed patients with CTX110, though questions remain about the viability of such an approach. Allogene had similarly played up redosing in its study of ALLO-501, but now faces much bigger problems, with its entire pipeline on clinical hold after signs of chromosomal abnormalities.

Allogeneic Car-T in lymphoma

Company	Precision Biosciences	Crispr Therapeutics	Allogene
Project	PBCAR0191	CTX110	ALLO-501 (now on clinical hold)
Features	Arcus nuclease editing, Car knocked into Trac locus	Crispr editing, Car knocked into Trac locus, β2M knockout	Talen nuclease editing, CD52 & TCR knockout
Study	NCT03666000	Carbon	Alpha
Evaluable	n=17, incl 5 relapsed on auto CD19 Car-T	n=24 at dose level 2+	n=32 Car-naive
1mth ORR	71% (9 CRs, 3 PRs)	58% (9 CRs, 5 PRs)	75% (11 CRs, 13 PRs)
Relapses	8 of 12 by 6mth	11 of 14 by 6mth (8 redosed)	12 of 24 by 6mth (5 redosed)
CRS	All gr1 & 2	All gr1 & 2	All gr1 & 2
Neurotoxicity	All gr1 & 2 except one gr3	All gr1 & 2 except one gr3	All gr1 & 2 except one gr3
GvHD	None	None	None
Deaths	One (infection) possibly due to PBCAR0191	One (ICANS/HHV 6 encephalitis) due to CTX110	Four (fungal pneumonia, Covid-19, arrhythmia & stroke) treatment-emergent

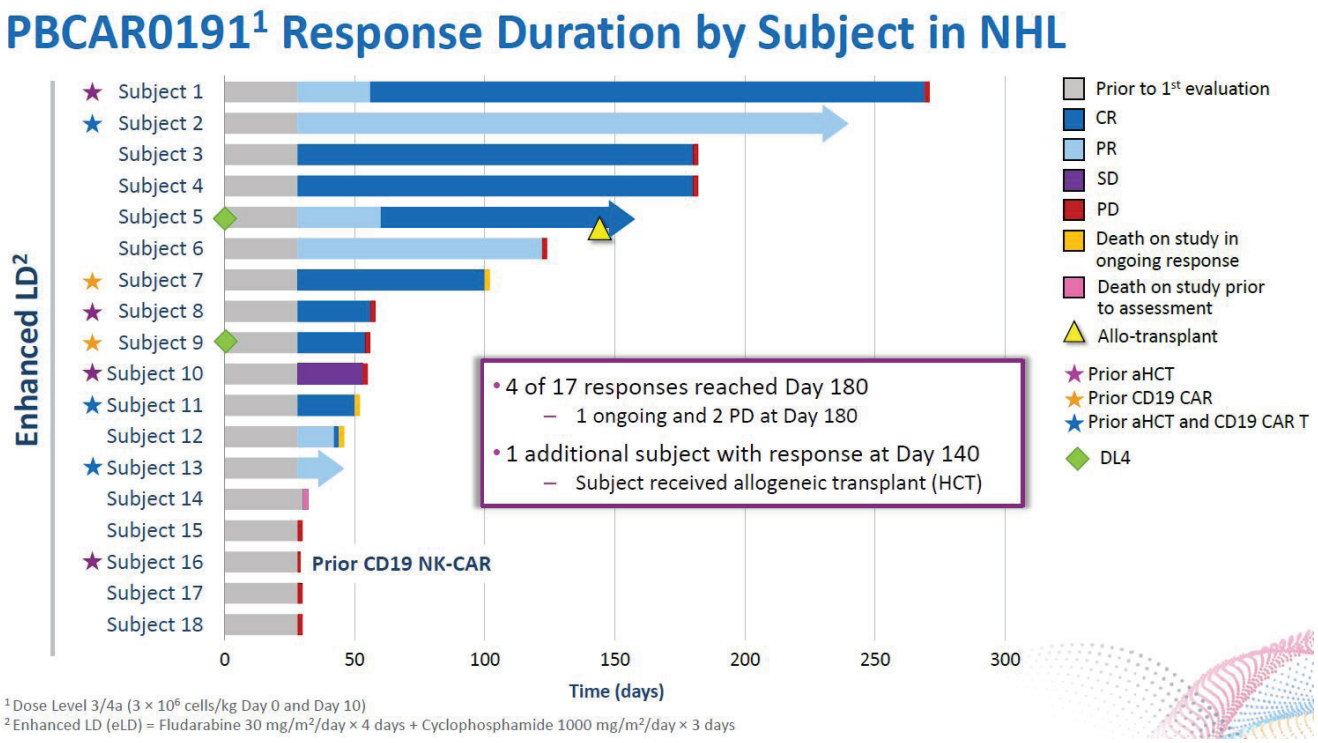
Source: Ash, Asco & company presentations.

All that said, Precision is not giving up on PBCAR0191. On an investor call yesterday the group pointed to a small cohort of six patients with lymphoma or leukaemia who had been given PBCAR0191 after relapsing on an autologous CD19-directed Car, but who were still CD19-positive.

All six went into remission, and though half again relapsed at least two responses were longer than those achieved with the autologous therapy. On this basis the group said this Car-relapsed salvage population could be “uniquely suited” to treatment with an allogeneic product.

In contrast, Allogene’s Asco update of ALLO-501 data focused on a Car-naive lymphoma population. Precision’s view could be backed by the fact that patients relapsing to autologous Car-T therapy often have relatively unfit T cells – a problem an allogeneic product might be able to overcome.

Precision must now prove this in a larger setting, as well as demonstrating the clinical benefit of its next-generation approach next year. Until then Crispr and Allogene will cast rather long shadows.



Source: Precision & Ash.

Published on: December 12, 2021

Ash 2021 – Bluebird looks to revive Lentiglobin

BY MADELEINE ARMSTRONG

Data in sickle cell disease look encouraging, but a filing is a way away.

Bluebird Bio has had a rough 2021, with cancer scares for two of its projects and the withdrawal of Lentiglobin in Europe. But the group will be hoping to put its annus horribilis behind it with promising Lentiglobin data in sickle cell disease, presented at Ash today.

Still, Bluebird does not expect a US filing in sickle cell until the first quarter of 2023, it recently disclosed. By this time it is likely to have been overtaken by Crispr and Vertex, which plan to submit their gene edited sickle cell candidate CTX001 late next year.

True, Lentiglobin could hit the market soon in transfusion-dependent beta-thalassaemia, where it has a Pdufa date of May 20, 2022. Yesterday at Ash Bluebird reported positive long-term data in this setting, with investigators calling it a "potentially curative" one-time therapy.

GROUP C

But sickle cell disease is a much bigger opportunity. Bluebird estimates that around 1,000 beta-thalassaemia patients in the US could benefit from Lentiglobin, versus the 20,000 US sickle cell patients the group is initially targeting.

The sickle cell data, which were published simultaneously in the New England Journal of Medicine, came from group C of the HGB-206 trial. In this cohort, the treatment protocol has been altered in ways intended to increase Lentiglobin's efficacy, and results from this group will form the basis of Bluebird's BLA submission.

Originally the study primarily measured haemoglobin endpoints, but the primary outcome has been changed to the proportion of subjects with complete resolution of severe vaso-occlusive crises (VOCs) six to 18 months after treatment.

The trial has also been tweaked to recruit patients who had experienced at least four VOCs in the two years before enrolment.

Today's results, from a non-prespecified interim analysis, found no severe VOCs in 25 Lentiglobin-treated patients who met this criterion and who had been followed for at least six months. Meanwhile, three of these patients experienced 12 mild VOCs after Lentiglobin infusion.

NO MORE CANCERS

Safety will also be at the top of investors' minds after this study was put on hold earlier this year on a report of acute myeloid leukaemia (Bluebird split looks premature, February 16, 2021). This occurred in group A; Lentiglobin has since been exonerated, and the clinical hold was lifted in June. This followed another case of AML, in 2018, that was also deemed unrelated to therapy.

Reassuringly, no cancers have been seen in group C, although the investigators acknowledged the short follow-up time, ranging from 3.7 to 37.6 months. The changes made to the treatment process in this cohort were designed to reduce the risk of cancers as well as to improve clinical benefit, the authors noted.

As for other adverse events, three were related or possibly related to Lentiglobin, although all of these were described as "non-serious" and resolved a week after onset. There was one death, a cardiac arrest, but this was deemed due to the patient's underlying disease.

There are still unanswered questions for Bluebird, for example around pricing and manufacturing. On the latter point, the company is carrying out the phase 3 HGB-210 study, which will use Lentiglobin manufactured in a commercial facility; product comparability data are due in late 2022.

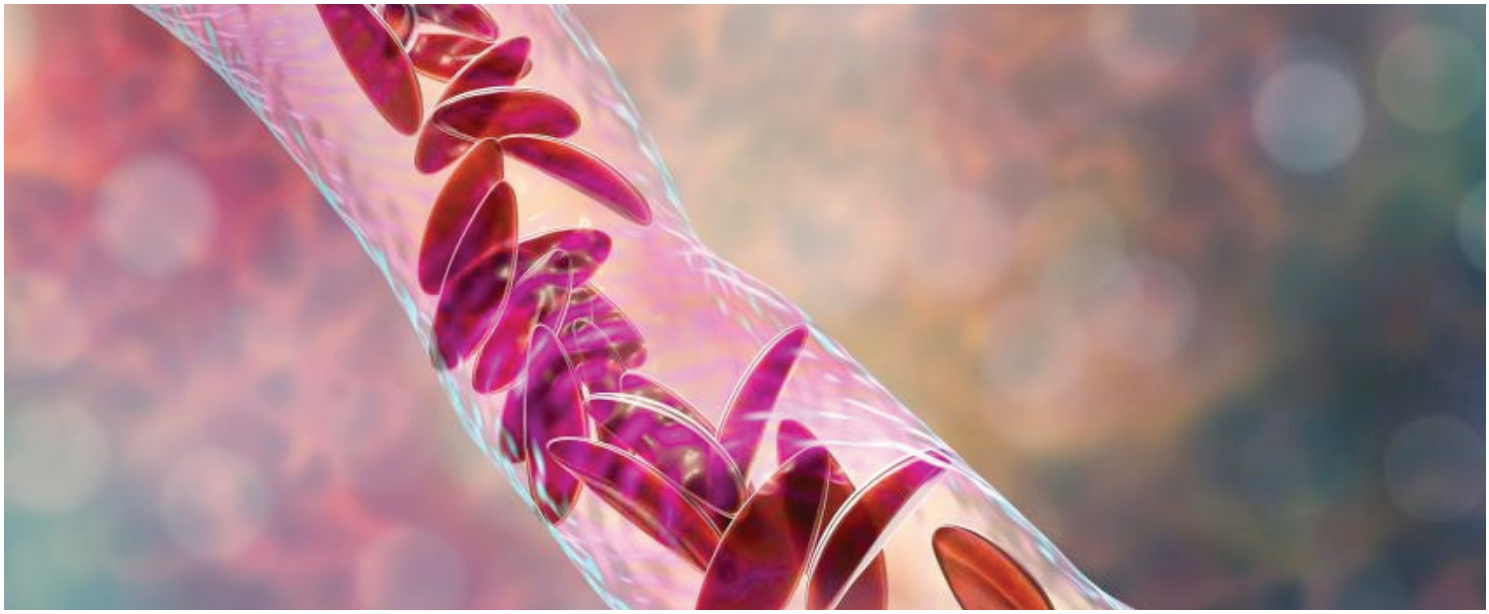
While the path seems to be clearing for Lentiglobin in sickle cell disease, Bluebird still has a long way to go. And even if it can get the asset over the regulatory finish line the next hurdle – making the project a commercial success – looks more daunting yet.

Published on: December 12, 2021

Ash 2021 – Agios and Forma take different paths in sickle cell disease

BY MADELEINE ARMSTRONG

Forma still hopes for accelerated approval of etavopivat, while Agios believes that taking its time with mitapivat will pay off.



Agios and Forma are neck and neck in a race to develop an oral pyruvate kinase R activator for sickle cell disease, but the latter is hoping to pull ahead. Despite recently admitting that the FDA needs data beyond haemoglobin response alone, Forma still believes that an accelerated approval is possible, executives at the Ash meeting told Evaluate Vantage.

Meanwhile, Agios reckons the traditional, full approval route is the way to go. And that group's chief medical officer, Sarah Gheuens, was scathing about the notion that the FDA might allow a quick path to market. "We're not the first drug to market that improves haemoglobin. [Global Blood's] Oxbryta was first. Therefore, every drug that does something similar has a higher hurdle to climb."

Oxybryta got FDA accelerated approval in 2019, after 51% of patients achieved a haemoglobin response, defined as an increase of 1g/dl or more versus baseline, in the pivotal Hope trial. A confirmatory study, Hope Kids 2, is ongoing.

MITAPIVAT VS ETAVOPIVAT

This year's Ash saw data from both Agios and Forma in sickle cell disease, with mitapivat and etavopivat respectively.

The results largely reaffirm the conclusion drawn at Ash 2020, which featured earlier data cuts from the same studies: Forma's compound appears to have a slight edge on efficacy, with the usual caveats about cross-trial comparisons (Ash 2020 – Forma gets an early edge over Agios in sickle cell disease, December 7, 2020).

Cross-trial comparison of PKR activators in sickle cell disease		
Project	**Etavopivat (FT-4202; Forma)**	**Mitapivat (Agios)**
Trial	Ph1 (NCT03815695), 12-wk open-label portion	Ph1 (NCT04000165)*
% haemoglobin responders	73% (11/15)	56% (9/16)
Increase from baseline in Hb	1.5g/dl (mean)	1.2g/dl (mean)**
Total VOCs	3	4
On-treatment VOCs	1	2^

Haemoglobin response defined as haemoglobin increase of ≥1.0g/dl from baseline. *NIH-sponsored trial; **50mg bid dose; ^Both VOCs occurred during dose taper phase. Source: Ash & company presentations.

With both compounds, there remain concerns about vaso-occlusive crises (VOCs), painful events that occur in sickle cell disease. These worries led to drops in Agios and Forma's share prices when the Ash abstracts were released.

However, both groups believe that the VOCs seen in their trials were down to the patients' underlying disease rather than the PKR activators.

"We never claimed to be a full cure," said Agios's Ms Gheuens. "We're trying to provide a reduction – that doesn't mean you're going to see an absence."

Indeed, Forma highlighted an analysis showing that the annualised rate of VOCs dropped to 0.3 during the 12-week open-label portion of its trial versus an annualised rate of 0.93 in these subjects before the trial began.

To complicate matters further, both studies included four-week follow-up periods, during which patients did not receive the project in question. And several of the VOCs happened during these windows – something that Forma's chief medical officer, Patrick Kelly, put down to drug withdrawal.

ACCELERATED VS FULL

Still, Ms Gheuens admitted: "Honestly, I think these worries in the investor community will remain until we present the full dataset of Rise-Up," referring to Agios's phase 2/3 trial in sickle cell.

The phase 3 section of this study has two co-primary endpoints: haemoglobin response and annualised rate of sickle cell crises, both at one year. Agios hopes to get full approval for mitapivat in sickle cell disease in 2026.

Forma has the traditional pathway to fall back on. To this end, the group's pivotal study, Hibiscus, also has co-primary endpoints of haemoglobin response at six months and annualised vaso-occlusive crises at one year, which would support full approval.

But the group is still holding out hope for accelerated approval. "There's no guarantee for accelerated review, but we think it's a worthwhile effort to pursue that, because it means we'll be able to deliver this to patients perhaps a year earlier than via the traditional path," its chief executive, Frank Lee, told Vantage.

Still, hopes for this outcome dimmed during Forma's third-quarter results, when the group said that the FDA had asked for data to support haemoglobin response as a surrogate endpoint. It is unclear yet what these additional data might be.

Ms Gheuens, although confident that Agios is doing the right thing, ultimately believes that "there is easily room for two PK activators in context of sickle cell disease". If the traditional approval path is the way this plays out, it could be some time before this is put to the test.

Published on: December 11, 2021

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