Ash 2022 Preview

BY JACOB PLIETH AND MADELEINE ARMSTRONG | NOVEMBER 2022

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Contents

Want to get a bit more detail on our team's thoughts? Listen to Jacob Plieth and Madeleine Armstrong discuss the abstracts to look out for with biotech investor Brad Loncar here.

Affimed and Aptose score

BY JACOB PLIETH
NOVEMBER 04, 2022

In oncology settings outside multiple myeloma investors have picked two early winners.

After leaving investors waiting at Asco Adicet will come into December's Ash meeting with much to prove. However, the markets will have to wait a bit longer, until Ash itself, because the abstract unveiled yesterday on ADI-001 reveals little about this gamma-delta Car-T therapy's durability.

Instead, biotech investors picked out Aptose as the early winner of yesterday's Ash abstract drop: the micro-cap ended the day up 27% on hopes for its Hanmi-derived kinase inhibitor tuspetinib. However, it was Affimed that made a claim to having one of the meeting's most convincing efficacy datasets, with its NK-cell engager AFM13.

Affimed ended yesterday up 9%. AFM13, which targets CD30, already impressed at last year's AACR meeting, when MD Anderson's trial combining it with NK cells sent 17 of 19 lymphoma patients into remission, and yesterday Affimed secured a source of off-the-shelf NK cells, striking a deal giving it access to Artiva's AB-101.

The clinical side was complemented by an Ash abstract detailing a dataset that now boasts a 97% overall response rate at AFM13's recommended phase 2 dose, with 17 of 24 patients in complete remission.

AWAITING ADICET

For Adicet the big reveal had come at Asco, when ADI-001, which targets CD20, put six of eight lymphoma subjects into remission. Things then became complicated, as two responders relapsed, though with Adicet claiming that one of these was not a bona fide relapse the company largely avoided a backlash, with investors happy to await longer-term data.

Ash should bring just that, and for the time being the abstract puts long-term remissions at two – assuming Adicet's arguments about the irrelevance of a skin relapse are believed – though another patient has now relapsed at six months. The remaining two short-term remissions continue, and have been joined by a third; this dataset has a July cutoff, and it is vital for Adicet to avoid showing significantly more relapses at next month's update.

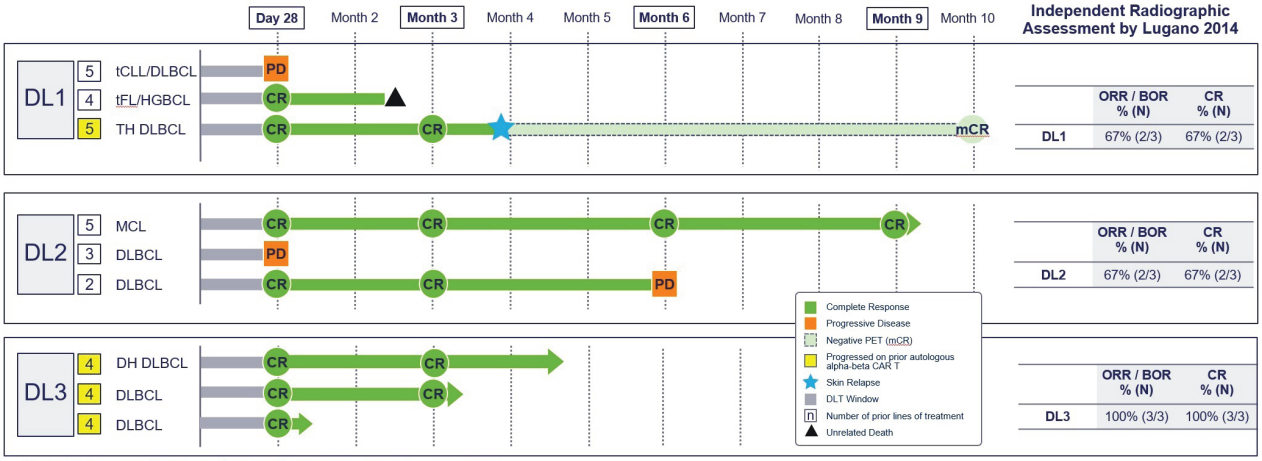


Figure 2. Preliminary Efficacy and Durability Results. Data cut-off date: 15 Jul 2022

TH=triple hit; DH=double hit; DLBCL=diffuse large B-cell lymphoma; tCLL=transformed chronic lymphocytic leukemia; HGBCL=high grade B-cell lymphoma; MCL=mantle cell lymphoma

ADI-001 in adults with B-cell malignancies. Source: Ash.

As an approach, of course, CD20-targeting has featured prominently at the previous three Ash conferences, and the 2022 instalment maintains this trend.

However, the market for T-cell engagers is becoming fiercely competitive: Roche's Lunsumio is available for follicular lymphoma in the EU and has a December 29 US Pdufa date, while its separate asset, glofitamab, is awaiting EU approval. Abbvie/Genmab's epcoritamab, having put up what could be best-in-class data, was filed in the US and EU for third-line non-Hodgkin's lymphoma a week ago.

Ash includes data on these and a fourth CD20 T-cell engager, Xencor's plamotamab, as well as a fifth, Regeneron's odronextamab. The last of those is notable for having been associated with treatment-related deaths, and spent time on clinical hold. Its Ash abstract sees Regeneron pinning hopes on step-up dosing as a means of avoiding serious cytokine release syndrome.

Notable by its absence is another CD20 bispecific, IGM's imvotamab. The lack of a competitive efficacy profile of this asset made IGM one of the biggest fallers of Ash 2021, and this year the company's presence is limited to preclinical work. IGM stock lost 8% yesterday as the group launched a $400m shelf financing.

Selected Ash oncology presentations excluding multiple myeloma					
Project	**Mechanism**	**Company**	**Abstract**	**Cutoff**	**Data**
AFM13	CD30 NK engager	Affimed	168	31 Jul	ORR 97%, 17/24 CR
ADI-001	CD20 gammadelta Car-T	Adicet	2018	15 Jul	7/9 CRs, 1 new relapse
Glofitamab	CD20 T-cell engager combo	Roche	4259	7 Jun	Combo with RO7227166 (CD19x4-1BBL with no monoRx actvity)
Odronextamab	CD20 T-cell engager	Regeneron	444	20 Apr	Pivotal DLBCL study: 52% ORR, 2 deaths
Plamotamab	CD20 T-cell engager	Xencor	4262	25 Jul	NHL: 9/19 ORR
INB-100	Unmodified gammadelta T cells	In8bio	3323	?	No advance on July data
AUTO4	Anti-TRBC1 Car	Autolus	4634	?	5/9 complete metabolic responses; 73 patients screened for TRBC1 to identify 10 to dose
Azercabtagene zapreleucel (PBCAR0191)	Allo CD19 Car-T (1st-gen)	Precision Bio	2005	?	Company investigating signal in transplant-relapsed patients after disappointing at Ash 2021
CTX110	Allo CD19 Car-T	Crispr	4629	22 Apr	56% ORR, 11/32 CR across 4 doses
YTB323 (rapcabtagene autoleucel)	CD19 Car-T (2-day manufacture)	Novartis	439	31 Mar	65% CR rate for dose level 2, some confounded by bridging chemo
Ziftomenib (KO-539)	MLL inhibitor	Kura	64	?	5/12 ORR in genetically driven leukaemias
SNDX-5613	MLL inhibitor	Syndax	376	?	32/60 ORR in genetically driven leukaemias
Tuspetinib (HM43239)	Kinase inhibitor (Flt3, Syk, cKit, Jak & others)	Aptose (ex Hanmi)	2758	14 Jul	AML: 16% ORR, 7/50 CRs
Imetelstat	Telomerase inhibitor	Geron	459	?	Ph3 Imerge study: focus on 11 patients (57 enrolled) who achieved >1yr transfusion independence
Emavusertib (CA-4948)	Irak-4 inhibitor	Curis	4077	Dec 2021	Clinical hold lifted in Aug
Favezelimab	Lag3 MAb	Merck & Co	2910	?	Keytruda combo, cHL 73% ORR

Source: Ash.

Also falling yesterday on a financing deal, for $150m, including a $125m term loan, was Kura, whose MLL inhibitor ziftomenib will be held up against Syndax's similarly acting SNDX-5613. The latter disappointed last year, though it is probably too soon to call a winner.

No such problems for Aptose, a micro cap that had earlier tried to play in the non-covalent BTK arena with luxeptinib, an asset it later decided was a "cluster-selective" kinase inhibitor that also hit Flt3, PDGFR-alpha, CSF1R, Akt, Ras, Erk, Stat and Syk. The group put on 27% yesterday on hopes of another multi-kinase molecule, tuspetinib, which inhibits Flt3, Syk, cKit and Jak and was licensed from Hanmi last year. An Ash abstract shows a 16% ORR in Flr3-mutated and wild-type AML patients, though most responses appear to have been achieved with the lowest tuspetinib dose.

GERON'S RETURN

Finally, those investors who have been around long enough to remember the last time Ash took place in New Orleans, in 2013, will recall the controversial splash that a myelofibrosis doctor tried to make at the time with Geron's imetelstat.

Now Geron and imetelstat are back, having endured a clinical hold, and a licensing deal with Johnson & Johnson that was scrapped after data from J&J's Imbark trial failed to replicate the earlier academic success. Geron has managed to finance and undertake the phase 2/3 Imerge study, focusing on low-risk myelodysplastic syndromes, and this features at Ash.

An abstract focuses on 11 patients who achieved over one year's transfusion independence, an effect Stifel reckons differentiates imetelstat from Bristol's Reblozyl, for instance. Reblozyl this week scored in the first-line Commands trial, a finding that has put pressure on Geron stock, though Stifel notes that imetelstat targets later-line, post-Reblozyl patients.

Comprehensive topline Imerge data are due in January, with US and EU filings later in the year. Imetelstat might – or might not – be about to stage one of biotech's more amazing turnarounds.

The Ash conference is due to take on December 10-13 in New Orleans, Louisiana. Late-breaking abstracts will be revealed on November 22.

A new multiple myeloma mechanism makes a splash

BY JACOB PLIETH
NOVEMBER 04, 2022

Talquetamab gets top billing in Ash's press programme, but the data raise important issues about the role of targeting GPRC5D.

The appearance of Johnson & Johnson's talquetamab in this year's Ash press programme will highlight GPRC5D blockade as an important new mechanism in treating multiple myeloma.

Hitting GPRC5D made its first splash as part of a preclinical Juno/Celgene Car-T therapy back at Ash 2018, and though it took a long time for this asset to enter the clinic it too appears at this year's Ash. The meeting, most of whose abstracts went live yesterday, also features the usual crowd of BCMA therapies, but the large talquetamab dataset will no doubt raise numerous questions when presented in full.

The headline number is that 73% of the 143 patients given talquetamab at its phase 2 dose in the MonumenTAL-1 trial went into remission, according to the May data cutoff cited in the Ash abstract.

However, close analysis of the swimmers plot reveals that 53 of the 104 responders relapsed, most well within 12 months. Only six remissions appear to be ongoing at over a year.

RELAPSES

When talquetamab data were presented at Ash two years ago targeting GPRC5D was highlighted as a way of rescuing patients who had relapsed on anti-BCMA therapy. However, while the phase 1

stage of MonumenTAL-1 included these patients, the pooled data being presented at Ash comprise only patients with no prior exposure to "T-cell redirecting therapies".

A separate trial, MonumenTAL-5, does include – and stratify for – patients who have, as well as those who have not, received BCMA therapies. But the MonumenTAL-1 Ash dataset's relatively early setting means that it needs to be held up against BCMA therapies, including Blenrep, Carvykti, Abecma and, as of last month J&J's own Tecvayli – a tough comparison.

Other GPRC5D-directed therapies at Ash include Bristol Myers Squibb's Car-T BMS-986393, which is likely related to the MCARH109 project unveiled at Ash 2018, at which point it was linked to the Bristol legacy company Celgene. And Fate's FT555, which has a preclinical Ash poster, has been revealed as an anti-GPRC5D Car-NK therapy.

Ash 2022: selected multiple myeloma presentations					
Project	**Mechanism**	**Company**	**Abstract**	**Cutoff**	**Data**
ALLO-715	Allo BCMA Car-T	Allogene	2019	22 Jun	Focus on dose level: ORR 15/21
CART-ddBCMA	BCMA Car-T (synthetic ScFv)	Arcellx	3313	3 May	Same data as Asco 2022
GC012F	BCMA/CD19 dual Car-T (2-day manufacturing)	Gracell	366	25 Jul	1st-line: 100% ORR, 9/13 CR
FT576	BCMA Car-NK	Fate	2004	18 Jul	No efficacy data
Elranatamab	BCMA T-cell engager	Pfizer	159	?	Potentially pivotal MagnetisMM-3 trial: 61% ORR
Linvoseltamab (REGN5458)	BCMA T-cell engager	Regeneron	4555	28 Jan	75% ORR at high doses
HPN217	BCMA trispecific	Harpoon/Abbvie	3240	27 Jun	Efficacy & durability to be presented at Ash
Talquetamab	GPRC5D T-cell engager	J&J	157	16 May	73% ORR @0.4 mg/kg QW; 51% relapse rate; no post-BCMA patients
RG6234 (RO7425781)	GPRC5D T-cell engager	Roche	161	8 Jun	IV: 71% ORR; SC: 60% ORR
BMS-986393 (CC-95266)	GPRC5D Car-T	Bristol Myers Squibb	364	24 May	86% ORR, 44% patients post-BCMA

Source: Ash.

All Ash abstracts except the late-breakers are now live, though the early data cutoffs in most mean that investors must wait until the meeting itself to see up-to-date results.

Thus a presentation of Fate's anti-BCMA Car-NK project FT576 for now reveals no efficacy findings, and neither do abstracts on Fate's FT596 (anti-CD19 Car-NK) and FT538 (CD38-knockout Car-NK cells for multiple myeloma).

Those looking at the burgeoning BCMA space will take interest in data on Pfizer's elranatamab and Regeneron's linvoseltamab – like Tecvayli these are bispecific T-cell engagers.

And investors appear to have already picked an early winner: Gracell closed up 11% after its fast-manufactured, dual anti-BCMA/CD19 Car GC012F was claimed to have yielded a 100% remission rate, though the swimmers plot contains ambiguity about the patients' pre-infusion status. Arcellx rose 4%, though its abstract on CART-ddBCMA, with a May cutoff, offers no advance on data presented at Asco.

On the debit side, Allogene fell 6%. The company has an unusually low-key presence at Ash, the highlight of which is an abstract claiming a 71% ORR in patients given a high dose of its allogeneic anti-BCMA Car ALLO-715. Perhaps to make up for missing the Ash submission deadline, Allogene is instead directing investors to an "R&D showcase" event on November 29.

The Ash conference is due to take on December 10-13 in New Orleans, Louisiana.

Waiting for Editas

BY MADELEINE ARMSTRONG
NOVEMBER 09, 2022

Data on the group's sickle cell project do not feature in the regular abstracts, while Bluebird walks away from its short hairpin contender.

2022 promised to be a big year for sickle cell disease, and this year's Ash meeting will see updated results on Crispr and Vertex's already impressive exa-cel, more data on Bluebird's lovo-cel, and results from a handful of patients treated with therapies from the likes of Sangamo and Novartis.

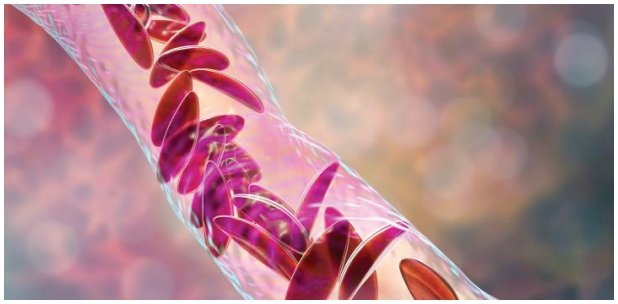
One group that does not feature in the regular abstracts is Editas, despite it promising both a presence at Ash and initial data on EDIT-301 in sickle cell disease. It is possible that Editas has bagged a coveted late-breaker slot; however, only two patients have been treated so far in the phase 1/2 Ruby trial. Editas had not responded to a question about its Ash presence at the time of publication.

Meanwhile, Bluebird Bio has told *Evaluate Vantage* that it is "winding down" its work on a short hairpin RNA project targeting BCL11A, which first came to prominence at Ash 2019. More data from an investigator-led pilot trial will feature at this year's meeting, and an academic phase 2 study is now recruiting.

RACE FOR THE PRIZE

This project was always well behind in the race to get a gene-based medicine approved for sickle cell disease, and Bluebird's focus will now be on lovo-cel, which is vying with Crispr Therapeutics/Vertex's exagamglogene autotemcel.

Exa-cel looks to be slightly ahead: Crispr is to start a rolling submission in the US this month, while Bluebird maintains that it is still on track to file lovo-



cel in the first quarter, despite its partial clinical hold in under-18s following a case of anaemia. Bluebird said during its third-quarter results that it was still working to resolve this.

The Ash abstract on lovo-cel had some good news on this front: it details two cases of persistent anaemia in part C of the HGB-206 trial, but does not conclude that these were myelodysplastic syndrome. Worries over malignancies put the same study on a fairly short-lived hold in early 2021.

The FDA has shown that it is comfortable with the risk/benefit profile of this project, approving it as Zynteglo for beta-thalassaemia in August. Bluebird will have to hope that the agency has a similar attitude in sickle cell.

For Crispr, meanwhile, the main focus at Ash is on its allogeneic CD19 Car-T project CTX110, but the group will also have data on exa-cel in both sickle cell disease and beta-thalassaemia. The results in the abstract echo those presented at EHA in July, so investors will be looking for more patients and longer follow-up at Ash.

Selected Ash sickle cell and beta-thalassaemia abstracts				
Project	**Description**	**Company/ies**	**Abstract**	**Details**
Lovo-cel	Beta-globin gene therapy	Bluebird	11	28 of 29 SCD pts had no VOCs in part C of ph1/2 HGB-206 study; 2 pts with persistent anaemia not classed as MDS
Exagamglogene autotemcel (exa-cel, CTX001)	Ex vivo Crispr/Cas9 gene-edited therapy against BCL11A	Crispr/Vertex	12	No VOCs in 31 pts in Climb SCD-121; same as EHA 2022
			2137	42 of 44 pts in Climb Thal-111 transfusion free; same as EHA 2022
OTQ923 (HIX763)	Crispr/Cas9 gene-edited cell therapy targeting BCL11A	Intellia/Novartis	786	HbF levels of 16-22% in 2 SCD pts in ph1/2
BIVV003 (SAR445136)	Zinc finger nuclease gene-edited cell therapy targeting BCL11A	Sangamo	2140	HbF levels of 12-41% in 4 SCD pts in Precizn-1; 5th subject treated with new manufacturing method
Zynteglo (beti-cel)	Beta-globin gene therapy	Bluebird	2348	Beta-thal, long-term outcomes
			3665	Beta-thal, long-term patient-reported outcomes
ET-01	Crispr/Cas9 gene-edited cell therapy targeting BCL11A	Edigene (China)	4778	HbF increase from 3-90g/l in 1 beta-thal pt in EDI-001*
BCL11A shRNA	Short hairpin RNA targeting BCL11A	Academic (ex-Bluebird)	4784	HbF levels of 21-42% in 7 SCD pts in ph1*

*Investigator-sponsored trial; HbF=foetal haemoglobin; SCD=sickle cell disease; VOC=vaso-occlusive crisis. Source: Ash.

Decent data with Sangamo's sickle cell contender BIVV003 at last year's Ash did not stop the group's partner, Sanofi, from walking away in January. Sangamo is back this year with more results from the Precizn-1 trial, which is to include a first look at patients treated using a new manufacturing process.

Stifel analysts reckon that, to compete, BIVV003 will need to show "near-perfect elimination" of vaso-occlusive crises – something the project has not managed to do so far.

Like exa-cel, BIVV003 is designed to reduce the expression of BCL11A, thereby increasing levels of foetal haemoglobin, which is thought to compensate for the defective haemoglobin found in beta-thalassaemia and sickle cell disease.

OTQ923, being developed by Novartis and Intellia, also harnesses this mechanism, and investors will get a first look at data on this project at Ash. The abstract, with a cut-off date of July, includes just two patients treated so far.

Some other prominent groups with ex vivo gene-edited sickle cell projects do not feature at Ash, however. One is the base-editing specialist Beam, which has yet to enrol the first patient into the Beacon trial of Beam-101; the group this week deprioritised its follow-on asset, Beam-102.

Meanwhile, Graphite Bio had once been expecting proof-of-concept data this year with its lead project, nulabeglogene autogedtemcel (GPH101), but in March said this would not come until 2023. All eyes are now on Editas.

The Ash conference is due to take on December 10-13 in New Orleans, Louisiana.

Argenx's expansion plans come into focus

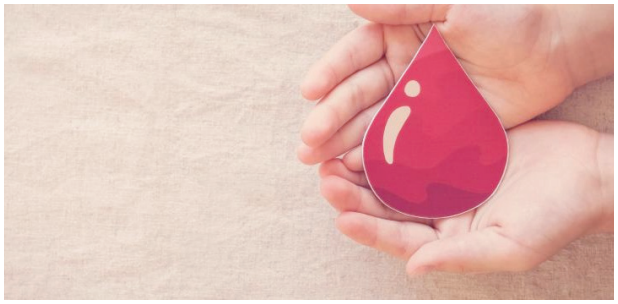
BY MADELEINE ARMSTRONG
NOVEMBER 10, 2022

Vyvgart gets a prestigious press slot for its next potential use, while Sangamo's haemophilia A gene therapy mimics Biomarin's valrox again.

Argenx's Vyvgart is expected to become a mega-blockbuster, but much still depends on the FcRN antagonist's ability to expand beyond its current use, generalised myasthenia gravis. A study in immune thrombocytopenia (ITP) features in the press programme at this year's Ash meeting, suggesting excitement around this approach.

Meanwhile, other non-oncology projects to watch at the conference include Roche's crovalimab; Ash attendees are set to see the first phase 3 data on the anti-complement C5 antibody in the increasingly crowded indication of paroxysmal nocturnal haemoglobinuria (PNH). Still, these will come from a single-arm study in China, and more important readouts are approaching.

In the haemophilia A gene therapy space there will be a rare glimpse at Roche's SPK-8011, acquired via Spark. And Sangamo's Pfizer-partnered giroctocogene fitelparvovec continues to emulate Biomarin's valrox by showing another fade in factor VIII levels at three years.



At least gir-fit appears to be back on track following the cases of very high FVIII levels that spurred a clinical hold of the pivotal Affine trial. The hold was lifted in September, and readout is due in the first half of 2024.

SPK-8011, meanwhile, does not appear to have started phase 3, although the project still featured in Roche's most recent pipeline update.

Some are trying to get around the lack of durability problems that have been seen with factor VIII gene therapies. Poseida, better known for the Car-T portfolio that it recently licensed to Roche, will have preclinical data at Ash on its Takeda-partnered candidate, P-FVIII-101, which uses its non-viral Piggybac delivery system.

Selected Ash non-oncology abstracts				
Project	**Description**	**Company/ies**	**Abstract**	**Details**
Vyvgart (efgartigimod)	FcRN antagonist	Argenx	3	Advance in ITP; 22% response rate vs 5% with placebo
Crovalimab (RG6107)	Complement C5 inhibitor	Roche	293	Commodore-3 single-arm Chinese PNH trial; 79% haemolysis control
SPK-8011	FVIII gene therapy	Roche (Spark)	783	Up to 5-yr data from ph1/2 & LTE in haemophilia A
Giroctocogene fitelparvovec (SB-525)	FVIII gene therapy	Sangamo/Pfizer	3461	3-yr data from ph1/2 Alta in haemophilia A; FVIII levels continue to fade
P-FVIII-101	FVIII gene therapy (using PiggyBac delivery)	Poseida/Takeda	400	Preclinical data
OTL-201	SGSH gene therapy	Orchard	782	Ph1/2 in MPS-IIIA; 5 pts; first neurocognitive data due
RP-L301	PKLR gene	Rocket	2138	RP-L301-0119; 2 adults with PKD had normal-range Hb 18mth post-infusion
RP-L201	ITGB2 gene therapy	Rocket	3460	RP-L201-0318; 100% OS at 1 yr in 9 pts with LAD-I (previously disclosed)
RP-L102	FANCA gene therapy	Rocket	4775	Efficacy seen in 5 of 9 pts with Fanconi anaemia across trials

LAD-I=Leukocyte adhesion deficiency-I; MPS=mucopolysaccharidosis; PKD=pyruvate kinase deficiency. Source: Ash.

Poseida has a long way to go, unlike Argenx, which will hope to add another string to its bow soon. The Vyvgart data come from the Advance trial of the intravenous formulation of the drug; this was toplined as positive in May.

The company says there is no clear standard of care for ITP, which causes excessive bruising and bleeding; current options include steroids and the blood cancer drug Rituxan. Patients in Advance were heavily pretreated, with 67% receiving three or more prior therapies.

Of 118 chronic ITP patients, 22% of those receiving Vyvgart achieved a sustained platelet response, the primary endpoint, versus 5% of the placebo group, according to the abstract. Still, Vyvgart did not significantly decrease the incidence of WHO-classified bleeding events, a secondary outcome.

A study of the subcutaneous formulation of Vyvgart in ITP is set to report in the second half of next year. In the nearer term, the Adhere trial in another new indication, chronic inflammatory demyelinating polyneuropathy, could unlock a "multibillion-dollar market" according to SVB analysts.

PNH PUSH

If ITP is an underserved disease, PNH is shaping up to be the opposite, with various players aiming to take a bite out of the current market leader, Astrazeneca.

Roche is one of these hopefuls. It has already filed crovalimab in China on the back of the uncontrolled Commodore-3 study, data from which will be presented at Ash.

However, the bigger test will come in the global Commodore-1 and 2 trials, which aim to show non-inferiority of subcutaneous crovalimab versus Astra's intravenous Soliris. Whether this will be enough, with oral options like Novartis's iptacopan coming, is a big question. Roche plans US and EU filings for crovalimab next year.

Elsewhere, the beleaguered gene therapy specialist Orchard is promising the first cognitive outcomes data on OTL-201, a gene therapy for Sanfilippo syndrome type A; biomarker data have previously been reported.

And Rocket will have data on its three lentiviral projects, including two that are set to be filed next year: RP-L102 in Fanconi anaemia and RP-L201 in leukocyte adhesion deficiency-I. In pyruvate kinase deficiency there will be adult data on RP-L301; investors will have to wait for next year to see if results can be replicated in children, and a pivotal trial is due to start next year.

The Ash conference is due to take on December 10-13 in New Orleans, Louisiana.

Brukinsa has the edge over Calquence

BY JACOB PLIETH
NOVEMBER 23, 2022

Brukinsa's head-to-head victory over Imbruvica is confirmed, and the Beigene BTK inhibitor looks better than Calquence too.

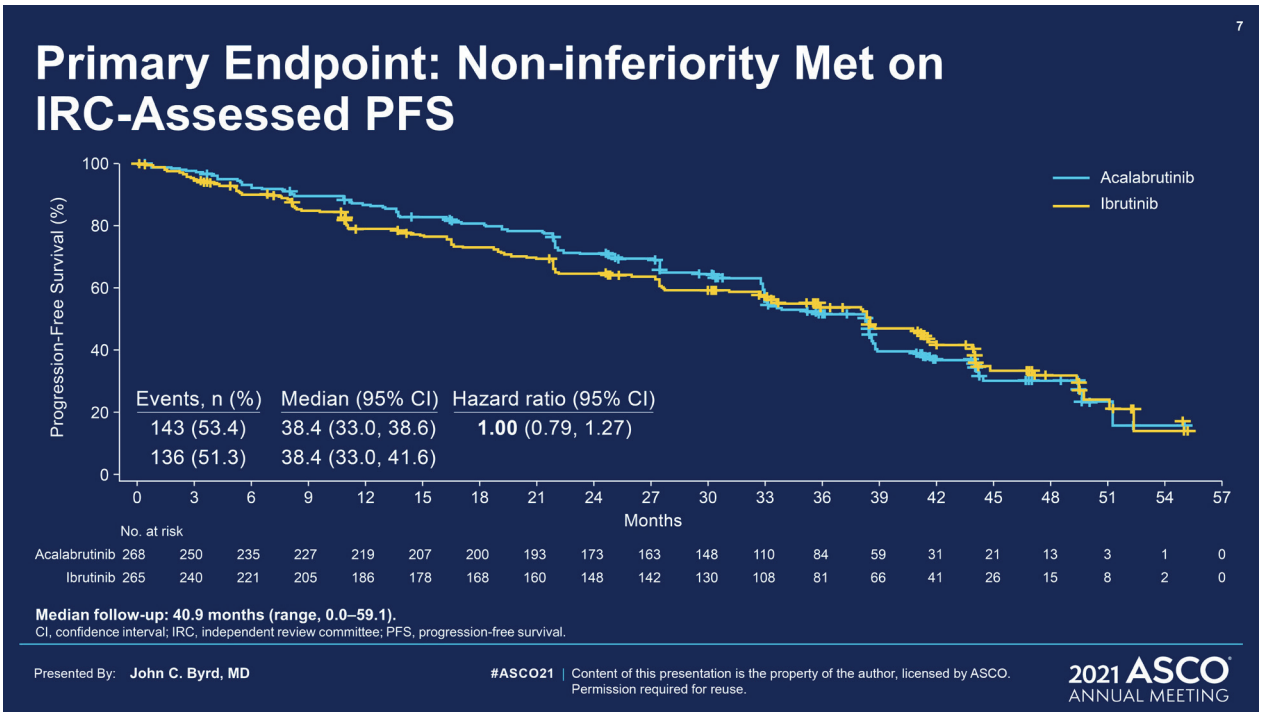
When Astrazeneca's Calquence challenged Imbruvica's most important setting of chronic lymphoblastic leukaemia it became the BTK inhibitor that others had to beat. Yesterday an Ash late-breaker suggested that Beigene's Brukinsa had done precisely this – at least on a cross-trial basis.

Beigene's Alpine trial features among six just unveiled Ash late-breaking abstracts, and shows the extent to which Brukinsa has beaten Imbruvica head to head. Nevertheless, Beigene shares fell 9%, possibly on concerns over whether the PFS benefit would hold up longer term; or maybe Beigene investors just saw this as a clearing event for a stock that had climbed 55% since October 11.

That surge had been triggered when Beigene first toplined Alpine, a trial in relapsed/refractory CLL. Momentum continued when six days ago the EU approved Brukinsa in first-line and r/r CLL, on the basis of the Sequoia and Alpine trials respectively; median PFS and some other safety data from Alpine remained under wraps, however, and have only emerged in the Ash abstract.

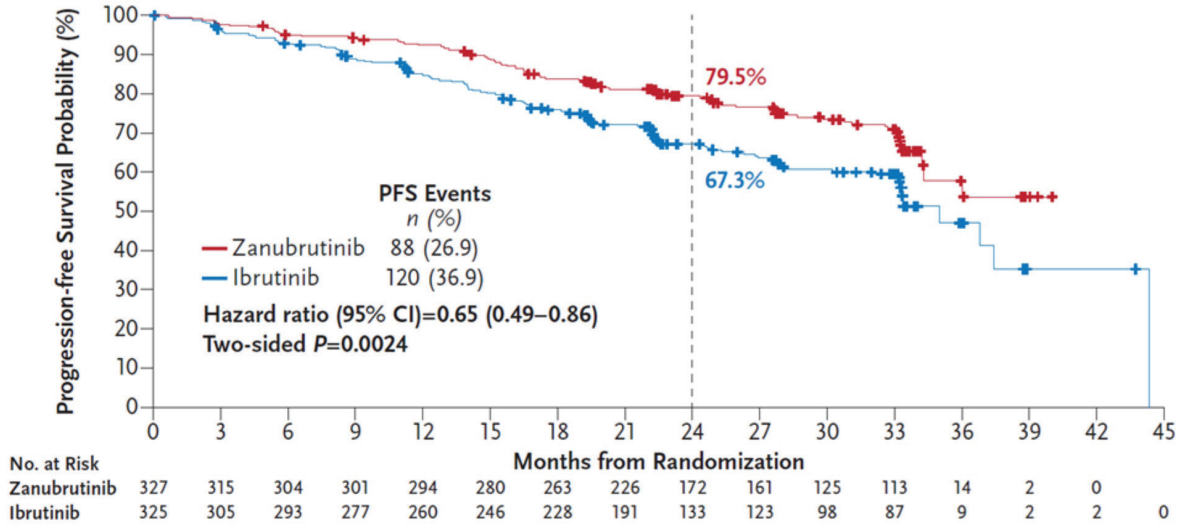
The stage is set for a fierce battle between the three US-approved BTK inhibitors. So far only Johnson & Johnson's Imbruvica and Calquence carry CLL on their labels, but the FDA is to decide on Beigene's Brukinsa filing by January 20. The Ash abstract suggests that approval is a no-brainer.

In Alpine Brukinsa cut risk of progression by 35% versus Imbruvica, meeting a threshold for superiority with a p value of 0.0024. In Astra's corresponding Elevate-RR study Calquence only managed to show non-inferiority versus Imbruvica, with identical median PFS values; as of an August cutoff Brukinsa has yet to reach median PFS for in Alpine, but its 24-month PFS rate of 80% beats Calquence's 70% in Elevate-RR.



PFS curves for Calquence vs Imbruvica in Elevate-RR, presented at Asco 2021.

Figure 1: IRC-Assessed Progression-Free Survival (ITT Population)



PFS curves for Brukinsa vs Imbruvica in Alpine, to be presented at Ash 2022.

Another key win for Brukinsa is a strong PFS advantage over Imbruvica in CLL patients with the intractable 17p deletion mutation; here Calquence had shown no advantage versus the J&J drug.

If there is a concern about the Alpine data it is that the PFS benefit might not hold up with longer-term follow-up. The PFS curves show a fair amount of censoring before the medians, but this does not appear to be disproportionate in one cohort versus the other. No OS data are given in the abstract.

It was OS that impressed in Astra's Elevate-RR study: though this was non-significant Calquence patients were 18% less likely to die than those on Imbruvica. This might have been thanks to Calquence's better safety profile versus Imbruvica, which is associated with toxicities such as atrial fibrillation.

However, here too Brukinsa has an edge. Its 5% atrial fibrillation rate in Alpine beat Imbruvica's 13%, and is better on a cross-trial basis than Calquence's 9%. In Elevate-RR Calquence was no better than Imbruvica on severe atrial fibrillation (though the patient numbers were low), and information on this metric in Alpine will be keenly awaited at Ash.

As for how the BTK market plays out, much will clearly depend on the three companies' pricing strategies. Sellside consensus compiled by *Evaluate Pharma* suggests that Calquence will nearly catch up with Imbruvica's $5.5bn sales in 2028, but that Brukinsa will lag this, with a 2028 revenue forecast of just $2.5bn.

Beigene will clearly want to turn the tables, and the Ash data support such hopes.

The Ash conference is due to take on December 10-13 in New Orleans, Louisiana.

BTK inhibitors in r/r CLL, head-to-head vs Imbruvica		
	Calquence (Astrazeneca)	**Brukinsa (Beigene)**
Trial	Elevate-RR	Alpine
mPFS	38.4mth vs 38.4mth (HR=1.00)*	NE vs 35.0mth (HR=0.65)**
24-mth PFS	~70% vs ~65%	80% vs 67%
mPFS in 17p del patients	HR=1.00	HR=0.52
ORR	81% vs 77%	86% vs 76%
mOS	NE vs NE (HR=0.82)	Not given
Atrial fib/flutter, any grade	9.4% vs 16.0%	5.2% vs 13.3%
Atrial fib/flutter, grade ≥3	4.9% vs 3.8%	Not given
Source	Asco 2021 (15 Sep 2020 cutoff)	Ash 2022 (8 Aug 2022 cutoff)

Notes: *met criterion for non-inferiority (upper bound of 2-sided 95% CI for HR <1.429; ** demonstrated superiority (p=0.0024). NE=not estimable; HR=hazard ratio.

Novartis has Apellis in its sights

BY MADELEINE ARMSTRONG
NOVEMBER 23, 2022

Iptacopan looks as good as Empaveli in PNH, with the added bonus of being oral.

Solo launches are always tricky for biotechs, and Apellis has had a tougher task than most. Its paroxysmal nocturnal haemoglobinuria therapy, Empaveli, is up against an entrenched big pharma, Astrazeneca.

Now Apellis looks set to get squeezed from the other side, with a new PNH contender on the horizon from Novartis. The Swiss group's oral project, iptacopan, has bagged a prestigious Ash late-breaker slot, showing that there is excitement over this novel approach.

The bad news for Apellis is that iptacopan looks as good, if not better than Empaveli on a cross-trial basis. Furthermore, iptacopan, being a twice-daily pill, is more convenient than Empaveli, which is given via a twice-weekly, 30-minute subcutaneous infusion.

APPLY

The data being presented at Ash come from the Apply-PNH study, which evaluated iptacopan versus standard of care, Astra's Soliris or Ultomiris, in patients who still had anaemia despite previously receiving standard of care. This was defined in the study as haemoglobin levels of less than 10g/dl.

This makes Apply-PNH broadly analogous to Pegasus, the phase 3 trial of Empaveli in treatment-experienced patients.

Apply-PNH met its two co-primary endpoints, showing superiority to standard of care, as Novartis had already disclosed – and the Ash abstract gives the magnitude of the benefit. After 24 weeks 82% of ipatcopan-treated patients had at least a 2g/dl increase in haemoglobin levels, versus 2% with standard of care. And 69% and 2% of patients respectively had haemoglobin levels of 12g/dl or more.

It is on secondary endpoints that the cross-trial comparison against Empaveli can be made, and here iptacopan looks to have a slight edge, although the usual caveats about carrying out these kinds of analyses apply.

Cross-trial comparison of iptacopan vs Empaveli				
	Apply-PNH		Pegasus	
Project	**Iptacopan**	**Placebo**	**Empaveli**	**Placebo**
Change from baseline in Hb (g/dl)*	+3.59	-0.04	+2.37	-1.47
Transfusion avoidance	96%	26%	85%	15%

*Primary endpoint of Pegasus. Apply-PNH at 24 weeks, Pegasus at 16 weeks.

Source: Ash 2022 & product label.

As for adverse events, one patient on iptacopan had a transient ischaemic attack, but this was considered unrelated to the drug. The abstract reveals nothing else remarkable, with headache and diarrhoea more common with iptacopan, and infections more common with Soliris/Ultomiris. Both have a black-box warning for infection.

FIRST VS SECOND LINE

Empaveli is approved in treatment-naive as well as experienced patients, although so far sales have mainly been driven by the latter. Apellis carried out a treatment-naive trial, Prince, and is trying to get those data added to Empaveli's label, which could help a shift towards newly diagnosed patients. The FDA is due to make a decision by February 2023.

Novartis, which estimates that around 40% of PNH patients remain under the haemoglobin 10g/dl threshold despite current therapy, also hopes that iptacopan will become a first-line PNH therapy. The group is carrying out the single-arm Appoint-PNH trial in treatment-naive patients; results are expected by year-end.

Novartis is far from alone in the PNH space. Astra also has an oral contender, danicopan, and said in September that it had hit in the Alpha trial, evaluating the project as an add-on to Soliris or Ultomiris.

Danicopan does not feature in this year's Ash but Astra's earlier-stage oral project, vemircopan (ALXN2050), does. Vemircopan is also a factor D inhibitor, but looks to be more potent than danicopan.

Biocryst is another oral player, but its project BCX9930 went on partial clinical hold earlier this year following cases of elevated serum creatinine levels. Trials have since resumed, but with a reduced dose.

Marketed/late-stage projects for PNH			
Project	**Company**	**Description**	**Status**
Marketed			
Soliris	Astrazeneca (via Alexion)	IV anti-complement C5 MAb (every 2 wks)	Approved for PNH & aHUS, REMS programme
Ultomiris	Astrazeneca (via Alexion)	IV anti-complement C5 MAb (every 8 wks)	Approved for PNH, REMS programme
Empaveli	Apellis/Sobi	Subcutaneous complement C3 inhibitor (twice weekly)	Approved for PNH, REMS programme
Phase 3			
Iptacopan (LNP023)	Novartis	Oral complement factor B inhibitor	Data at Ash 2022 from Apply-PNH (treatment-experienced); data from Appoint-PNH (treatment-naive) due 2022
Crovalimab (RG6107)	Roche	Subcutaneous complement C5 inhibitor	Data at Ash 2022 from Commodore-3 China study; global Commodore-1 (treatment-experienced) & Commodore-2 (treatment-naive) complete 2025 & 2023 respectively
Danicopan (ALXN2040)	Astrazeneca	Oral complement factor D inhibitor	Claimed topline hit in Alpha, Soliris/Ultomiris add-on, Sep 2022
ABP 959	Amgen	Soliris biosimilar	Claimed topline hit in Dahlia Aug 2022
BCX9930	Biocryst	Oral complement factor D inhibitor	Redeem-1 (treatment-experienced) & Redeem-2 (treatment-naive), clinical hold lifted Aug 2022
Cemdisiran	Alnylam	Subcutaneous siRNA complement C5 inhibitor	Pozelimab combo; Access-1 (treatment-naive) & Access-2 (treatment-experienced); ph2 data at Ash 2022
Pozelimab	Regeneron	Subcutaneous anti-complement C5 antibody	Cemdisiran combo; see above

Source: Evaluate Pharma & clinicaltrials.gov.

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