Asco 2022: Reasons to be cheerful?

BY JACOB PLIETH, AMY BROWN, EDWIN ELMHIRST AND MADELEINE ARMSTRONG | JUNE 2022

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Evaluate Vantage

Introduction

Despite the parlous state of the biotech markets this year's Asco abstract drop still managed to drive some stock prices higher, ahead of the meeting. But of course the proof is in the pudding – or more accurately – in the pudding's data. Hopes were high for a number of long-awaited trial results and thousands of the world's leading oncology specialists gathered to share their news and find out what their colleagues (and competitors) had to say.

Oncology continues to attract a huge slice of pharma's R&D spend and the eyes of investors were on the big players as well as the smaller biotechs. The stakes are high for a number of companies which are in desperate need of good news about their pipelines.

So what happened? Inevitably it was a rather mixed bag but there were plenty of reasons to be cheerful, including what's looking like a hat trick for Daiichi Sankyo. The big news was Enhertu, partnered with Astrazeneca, in Her2-low breast cancer. The antibody-drug conjugate showed an impressive survival benefit over chemotherapy in patients currently considered to be Her2-negative, potentially opening up a huge new market for the drug.

At the other end of the spectrum was the Skyscraper-02 trial, which was confirmed to be complete dud. The future is far from certain for Tigit blockade, and Roche and other developers pursuing this mechanism need to prove they are not throwing good money after bad.

In the first in-person Asco conference in two years held from 3rd - 7th June, and with a rare standing ovation featured, there's a huge amount to cover. In this eBook, we've summarised the highs, lows, near-misses and TBCs – settle in.

Contents

Daiichi's third conjugate progresses in breast and lung

BY AMY BROWN

Daiichi Sankyo licensed to Astrazeneca its two most advanced antibody-drug conjugates – Enhertu and datopotamab deruxtecan – but it has kept a third, patritumab deruxtecan, for itself.

That project targets Her3, which is thought to play a role in certain breast and lung cancers, with new data in both presented at Asco. In the former several partial responses across the various cohorts make for encouraging reading, although with Enhertu expected to impress in a Her2-low population over the weekend patritumab's potential in breast cancer could already be narrowing. EGFR-mutated NSCLC is the biggest hope for the project, however, with a potentially pivotal phase 2 trial already ongoing; there is evidence that Her3 expression is associated with resistance to tyrosine kinase inhibitors. Asco will see impressive response rates achieved across patients with a broad range of driver genomic alterations, and in some with no identified drivers. On safety, interstitial lung disease once again reared its head, with one death in the breast cancer trial, showing that, of the Daiichi ADCs, it is not just Enhertu that must overcome this toxicity. Her3 also needs confirming as a truly viable cancer target, of course, and such data remain some way off.

Daiichi's third ADC: the latest results on patritumab deruxtecan

Her3-expressing metastatic breast cancer – a phase 1/2 trial

	HR+/Her2 negative, Her3 high or Her3 low (n=113)	*TNBC Her3 high (n=53)*	*Her2+ and Her3 high (n=14)*
ORR	30.1%	22.6%	42.9%
PRs	30.1% (34)	22.6% (12)	42.9% (6)
mPFS	7.4 months	5.5 months	11.0 months
mOS	14.6 months	14.6 months	19.5 months

Targeting TKI resistance in advanced EGFR-mutated NSCLC – a phase 1/2 trial

	Identified driver genomic alterations other than EGFR (n=21)	*Without identified driver genomic alterations (n=26)*
ORR	28.60%	26.90%
CR	0	1
PRs	6	6
mOS	9.4 months	9.6 months

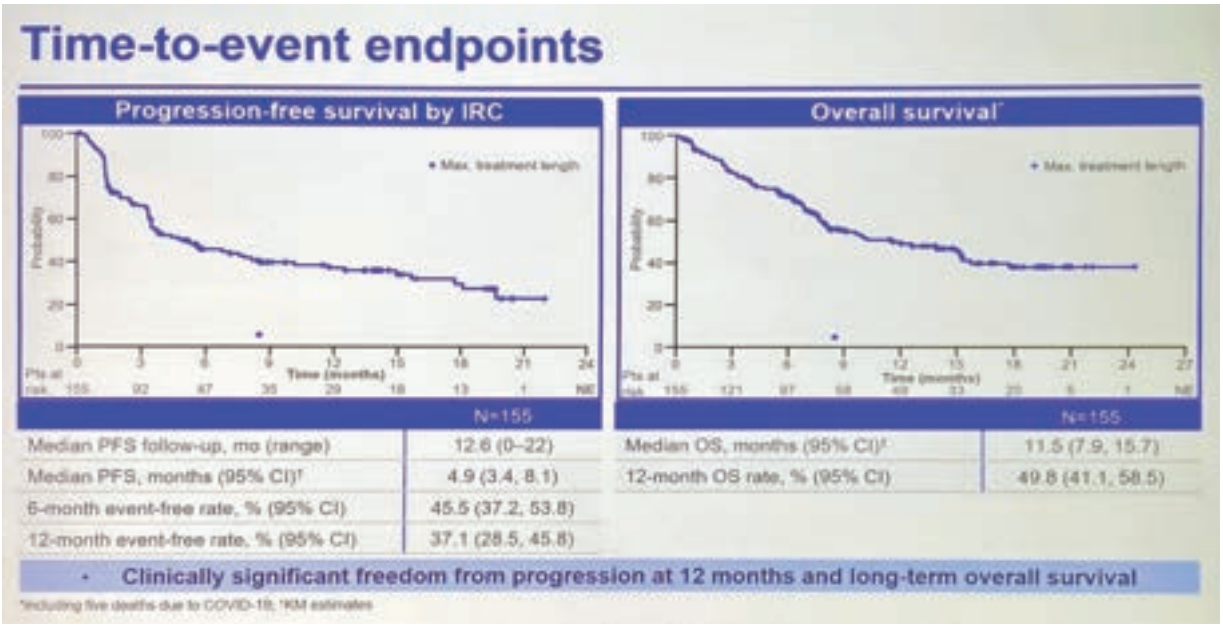
Source: company press release.

Roche bids for the CD20 bispecific prize

BY JACOB PLIETH

Abbvie/Genmab's epcoritamab is the anti-CD20 bispecific that has impressed the most so far, but Roche is not far behind.

Asco heard of the pivotal lymphoma dataset for glofitamab that Roche will soon take to the FDA: at Roche's favoured step-up 2.5/10/30mg dose in DLBCL the overall remission rate is 52%, with 18.4-month median duration of response. Complete remissions, the primary endpoint of study NP30179, are at 39%, and a look at the survival curves reveals a benefit that Peter MacCallum Cancer Centre's Dr Michael Dickinson called "clinically significant". The data are all the more impressive since 34% of patients were after Car-T therapy, and the CR rate in these was 35%. The study includes less aggressive lymphomas, but Roche is zeroing in on these DLBCL subjects, including those with transformed follicular lymphoma, for a US filing expected in the third quarter; an EU submission has already been made. Mosunetuzumab, a separate Roche anti-CD20 T-cell engager, is filed in the US and approved in the EU for less aggressive follicular lymphoma. The glofitamab data are an advance on the 41% ORR Roche reported with lower doses a year ago, but for many epcoritamab's 63% figure is the one to beat.



Source: Dr Michael Dickinson & Asco.

The Tropical wind blows cold for Trodelvy

BY AMY BROWN

A slim survival benefit puts Gilead's hopes of label expansion for Trodelvy on hold.

Gilead has spent the past few weeks lowering expectations around the Tropics-02 trial, and the full data, unveiled in an Asco late-breaker, show why. The 1.5-month median progression-free survival benefit achieved by Trodelvy over chemotherapy might be statistically significant, but it will be tough to argue that this represents a real breakthrough for these breast cancer patients.

The trial was known to have hit on PFS, and investors had initially been hoping to see at least a 2.5-month advantage, but assumptions tumbled after Gilead refused to say whether the result was clinically relevant. The group can contend that a 34% reduction in the risk of progression is meaningful, but a similarly weak showing on overall survival does not help its case.

The full Tropics-02 dataset will be presented at the conference later, but summary data being discussed at a press briefing this morning revealed median PFS of 5.5 months for Trodelvy and 4.0 months for the chemo patients (p=0.0003). With some analysts braced for the delta to fall below one month this result might actually not be as bad as some had feared.

The result was defended by reviewing physicians at an Asco press conference this morning, with Dr Jane Meisel of Emory School of Medicine, pointing out that three times as many patients in the Trodelvy arm were alive at 12 months, 21% vs 7% for chemo.

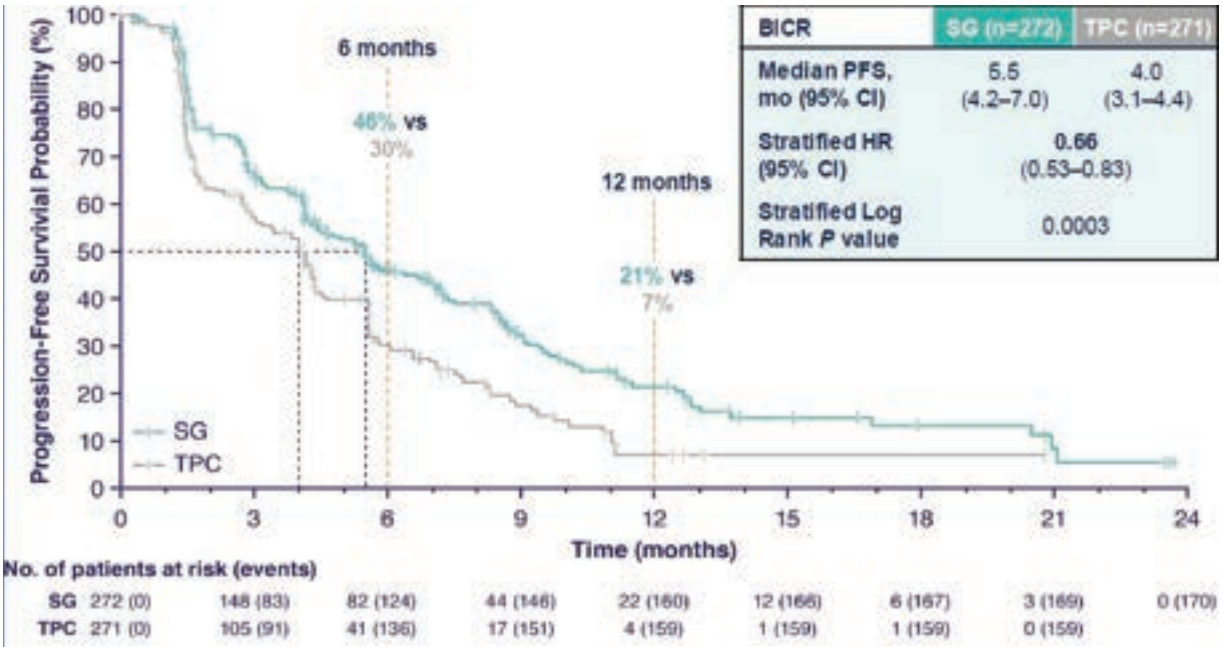
"That PFS may not seem clinically significant but it is important to look at those landmark analyses," she said. "Being able to offer someone with such heavily pre-treated disease an option that allows a one in five chance of not progressing at one year is still huge from a clinical perspective."

But this result is still much weaker than hoped, which can perhaps partly be explained by the control arm performing slightly better than expected. Other features of the data include a high level of patient censoring ahead of the medians – investigators pointed out that the trial enrolled due the Covid pandemic – while the survival curves suggest that Trodelvy needs to be better targeted at those with a higher chance of a strong response.

"The medians fail us to some degree when there's a segment of patients who will progressive rapidly and you can't predict that," Dr Hope Rugo, the Tropics-02 lead investigator, told the Asco press conference.

On overall survival Trodelvy has also yet to make

Tropics-02: KM-curve for progression free survival (primary endpoint)



Source: Dr Hope Rugo, Asco press briefing.

a mark, albeit in an immature dataset that could possibly improve over time. At this interim readout the Trodelvy arm generated 13.9 months of median OS versus 12.3 months for the chemo arm. Gilead had already admitted that OS was not significant, and a hazard ratio of 0.84 and p value of 0.143 reveals the extent of the miss.

The trial was powered for a hazard ratio of 0.73, based on OS of 16.5 months vs 12 months in the two arms.

Jefferies wrote recently that doctors they spoke to wanted to see a trend of at least a few months on overall survival to get optimistic. That has yet to emerge, which probably helps explain why Gilead has not said when it might file for approval on this data.

The official reviewer for Asco, Dr Veronique Dieras of Centre Eugène Marquis, also expressed reservations about the result. “Questions still to be answered before considering [Trodelvy] as an option in this population,” she concluded.

MOOT POINT?

Unfortunately for Gilead there is another twist in this tale. This is because of a potential overlap in the populations recruited for Tropics-02 and Destiny-Breast04, the latest Enhertu study.

Tropics-02 was conducted in third-line, ER-positive, Her2-negative breast cancer, while Destiny-Breast04 recruited similarly late-line patients deemed to be Her2-low (irrespective of ER status).

But the definitions that lie behind Her2-negative in the former and Her2-low in the latter reveal an important overlap: both studies included tumours scored 1+ by immunohistochemistry, or IHC2+ with a negative in-situ hybridisation (ISH) score. Tropics-02 also included IHC 0 tumours.

This means that Enhertu’s performance in ER-positive patients can be compared against the Trodelvy result, the normal caveats of cross-trial comparison notwithstanding.

The Tropics-02 data cut by IHC score is not yet

available, Dr Rugo said. But she pointed out that 35% of hormone receptor positive breast cancers are Her2 negative.

If Enhertu performs as strongly as expected, this could be the niche left for Trodelvy in this setting. Astra and Daiichi have already said that both PFS and OS endpoints were hit and the trial has won a plenary presentation spot. It seems likely that Enhertu will redefine the way breast cancer hitherto deemed "Her2-negative" is treated.

There are of course important differences between the trials. Gilead insists that the Tropics-02 patients were more advanced and therefore represent a more challenging patient group. The two antibody-drug conjugates are also targeted differently – Enhertu at Her2 and Trodelvy at Trop-2.

But Gilead is apparently well aware of this threat. A $2.7bn impairment charge taken last quarter against the Immunomedics acquisition, the source of Trodelvy, was blamed on the potential for a delayed launch in the Tropics-02 setting and "the possibility of a reduced market share in late-line patients given the emerging competitive landscape".

Abbvie goes back to basics with navitoclax

BY JACOB PLIETH

Abbvie's decades-old work into Bcl-2 inhibition gave rise to Venclexta, but the group has gone back to studying a Venclexta predecessor compound.

The coming 12 months should see the results of two pivotal trials of Abbvie's navitoclax in myelofibrosis, events that the group hopes will back approval of this Bcl inhibitor by the end of 2023.

In the meantime, data just discussed at Asco from a single-cohort study have set the expectations, with navitoclax's efficacy in combination with Novartis/Incyte's Jakafi, the standard of care, outperforming Jakafi alone on a cross-trial basis. True, navitoclax will not become a blockbuster, but its development path – the project was an early iteration of the drug that became Venclexta – is an interesting study in serendipity.

Navitoclax and Venclexta alike are the result of decades of work into Bcl-2 inhibition, but the former had gone on hiatus while Abbvie and its partner Roche focused efforts on the latter, a blockbuster drug that now forms a major part of the armamentarium in chronic lymphoblastic and acute myelogenous leukaemias.

GOING PIVOTAL

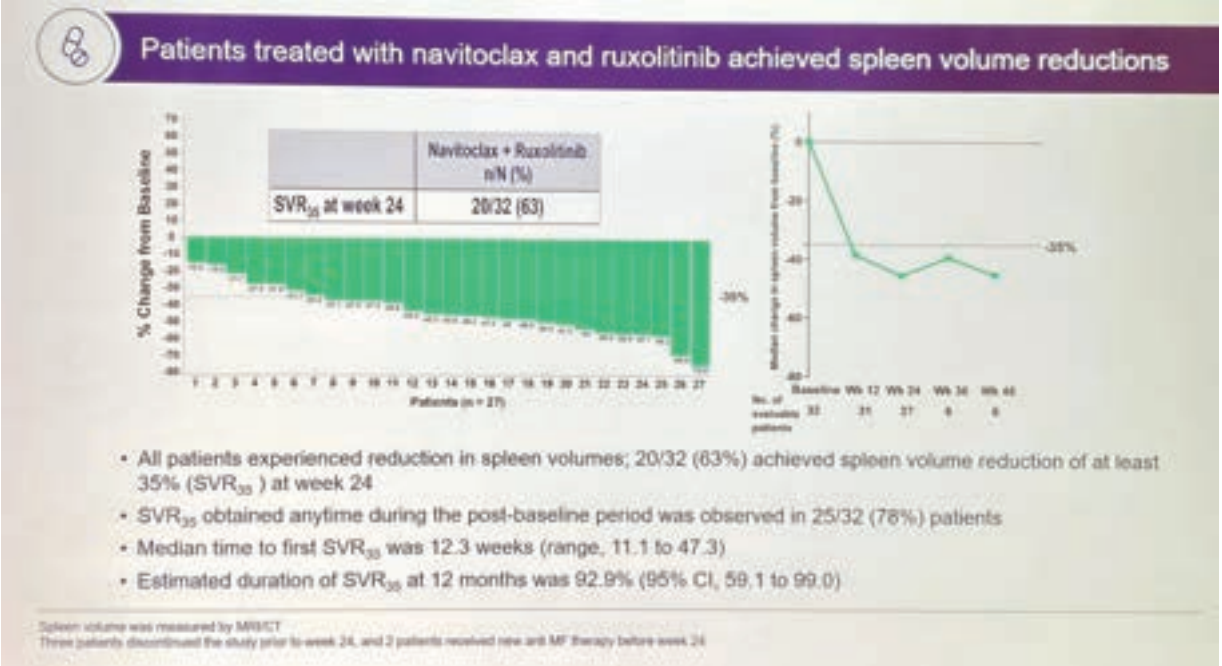
It was not until two years ago that pivotal trials of navitoclax got under way. Transform-1 tests the project's Jakafi combination versus Jakafi alone in front-line myelofibrosis, while Transform-2 pits the combo against best available therapy in relapsed/refractory disease.

Data from the phase 2 Refine study discussed at Asco concern Jak-naive patients, and complement results from the same trial but in relapsed disease, published in the Journal of Clinical Oncology recently.

In the Asco dataset spleen volume reduction of at least 35% at week 24 was achieved by 63% of the 32 evaluable patients given navitoclax plus Jakafi. For comparison Jakafi's label cites efficacy on the same endpoint of 42% in one study, and 29% in another, so – at least on a cross-trial basis – addition of navitoclax seems beneficial.

There was a toxicity price, however, with high rates of thrombocytopenia (47%), anaemia (34%) and neutropenia (25%) at grade 3 and above, and three deaths – two unrelated to treatment and one unknown.

Promising while this might seem, when the poster was discussed at an oral Asco session Memorial Sloan Kettering's Dr Kamal Menghrajani poured some cold water on navitoclax. She said it was unclear whether spleen volume reduction would translate into a survival benefit, and suggested that what myelofibrosis needed was not multiple mechanistic pathways but a more potent Jak2 inhibitor than Jakafi.



Source: Dr Kamal Menghrajani & Asco.

But why navitoclax, and why myelofibrosis? For the answer you need to go back 23 years, when Abbott, as Abbvie was then known, partnered with Idun Pharmaceuticals to develop cancer drugs that work by apoptosis, including Bcl-2 inhibitors. Idun was later bought by Pfizer, which sold it to Conatus, now part of Histogen.

But in 2007 Abbott struck a second deal, with Roche, to develop compounds including the Bcl-2 inhibitor ABT-263 and follow-ons. It is not clear whether any of this work was derived from Idun, and whether Histogen retains an interest, but ABT-263 is the molecule now known as navitoclax.

Still, though navitoclax moved into the clinic in CLL it became associated with thrombocytopenia as a result of binding not only Bcl-2 but also Bcl-XL, a protein platelets rely on for survival. Navitoclax was found to have modest activity, largely because it could not be dosed high enough.

Instead, Roche and Abbvie brought a third party to the table, the Walter and Eliza Hall Institute of Medical Research, and navitoclax was re-engineered to give rise to ABT-199, an improved inhibitor with more specificity for Bcl-2.

Navitoclax went to the back burner. ABT-199 was prioritised, to be approved as Venclexta, first for CLL and then for AML, bringing in sales of $1.8bn last year. 2028 revenue is set to approach $4bn, according to Evaluate Pharma sellside consensus.

But in 2017 Abbvie went back to navitoclax and put it into trials in myelofibrosis, seeking to take advantage

of its action on platelets and on Bcl-XL. This is the state of play today.

The competitor pipeline in Bcl-2 inhibition remains quite thin, numbering discontinued assets like Teva's obatoclax, found to have little clinical activity, and early Abbvie projects like ABT-737, which lacked oral bioavailability. Ascentage Pharma's lisaftoclax is in phase 2, and big pharma groups with an interest include Novartis and Lilly.

As for navitoclax, that no longer appears in Roche's pipeline.

Selected inhibitors of Bcl-2			
Project	**Company**	**Mechanism**	**Clinical trial**
Marketed			
Venclexta (ABT-199)	Roche/ Abbvie	Bcl-2 selective	CLL14
			Viale-A (AML)
Phase 3			
Navitoclax (ABT-263/ RG7433)	Abbvie/ Roche	Also hits Bcl-XL	Transform-1 (Jakafi combo vs Jakafi in MF)
			Transform-2 (Jakafi combo vs BAT in MF)
Phase 2			
Lisaftoclax (APG-2575)	Ascentage Pharma/ Innovent	Bcl-2 selective	NCT05147467 (CLL)
			NCT04496349 (T-cell leukaemia)
Phase 1/2			
Pelcitoclax (APG-1252)	Ascentage Pharma	Also hits Bcl-XL	NCT05186012 (lymphoma)
			NCT04354727 (MF)
AZD0466	Astrazeneca	Also hits Bcl-XL	NCT04865419 (haem cancers)
ZN-d5	Zentalis	Bcl-2 selective	NCT05199337 (light-chain amyloidosis)
Phase 1			
S65487/ VOB560	Servier/ Novartis	Bcl-2 selective	NCT04702425 (MIK665 combo in haem cancers)
TQB3909	Sino Biopharmaceutical	Bcl-2 selective	NCT04975204
LOXO-338/ FCN-338	Lilly (ex Fosun)	Bcl-2 selective	NCT05024045 (haem cancers)
LP-118	Newave Pharmaceutical	Also hits Bcl-XL	NCT04771572 (haem cancers incl MF)

CLL=chronic lymphoblastic leukaemia; MF=myelofibrosis.

Source: Evaluate Pharma & clinicaltrials.gov.

Merck's follow-on immuno-oncology plan hits a myositis problem

BY JACOB PLIETH

ILT3 blockade shows no monotherapy activity while a combo runs into toxicity issues, but Merck presses on.

Expect Immune-Onc, NGM Biopharmaceuticals and Biond Biologics to be casting a nervous eye over the data for Merck & Co's anti-ILT3 antibody MK-0482 just presented at Asco. The results offer little reason for optimism, so the pressure is on the smaller biotechs, which are following similar approaches, to show that Merck's problems are specific to its MAb.

The data could knock a hole in Merck's hopes that hitting ILT3 could give it a new immuno-oncology mechanism, notwithstanding the group's decision to press on with a Keytruda combo. MK-0482 has shown no monotherapy activity, and particularly concerning is myositis as a toxicity that led to one patient death.

Merck cautioned that what it presented were first-in-human data from a dose-finding study. Eric Rubin, the group's senior vice-president of early-stage oncology, called the results "promising at this stage", and said lack of monotherapy activity was not necessarily a problem, citing Lag3 as one oncology mechanism that was relatively inactive until combined with PD-1 blockade.

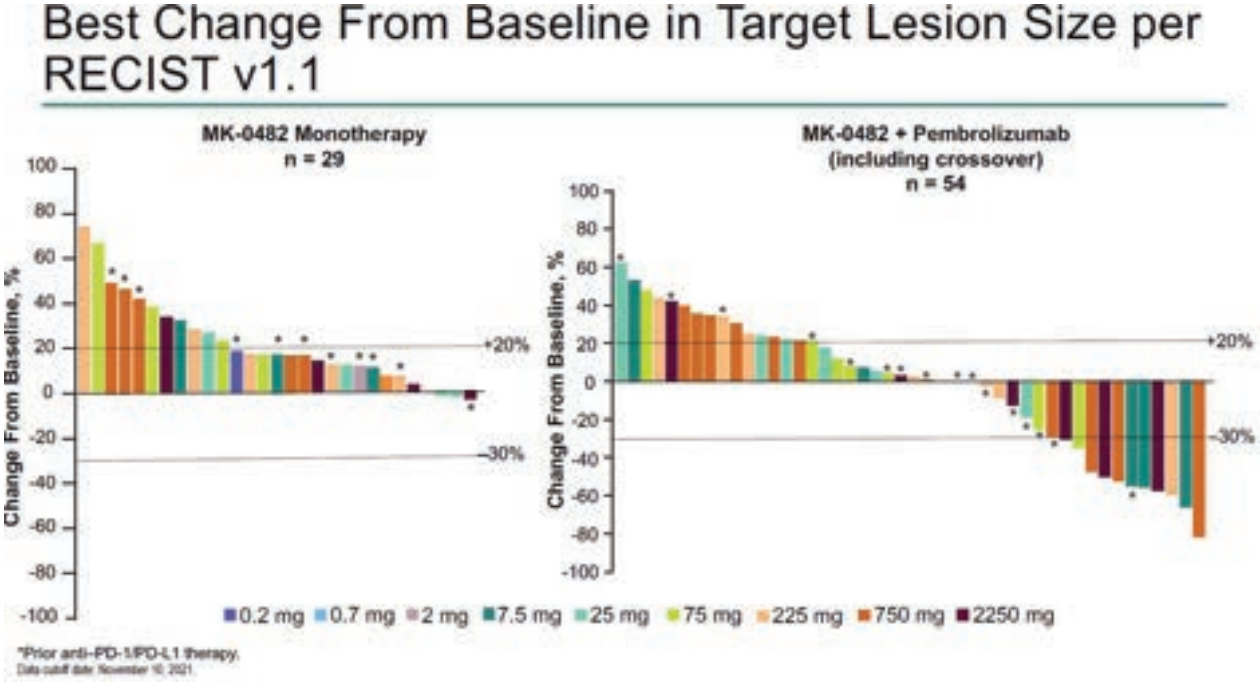
IMMUNOSUPPRESSION

ILT3, also known as LILRB4, is a receptor expressed on myeloid-derived suppressor cells, which are thought to be a key driver of immunosuppression in the tumour microenvironment.

MK-0482 represents one approach Merck is taking to complement the activity of Keytruda. The company also has a molecule coded MK-4830, partnered with Agenus, that targets the related ILT4 protein and is also in phase 2.

But for now the best that can be said about the ILT3 approach is that the jury is still out. The data presented at Asco showed zero remissions in 29 solid tumour subjects given MK-0482 monotherapy, while 54 receiving the MAb plus Keytruda yielded a 15% rate of responses, all partial.

The Asco abstract had shown two cases of myositis, a rare muscle disorder, one of which was fatal. The Asco presentation revealed both to have occurred in the Keytruda combination cohort, a fact that perhaps offers Merck a ray of hope.



Source: Dr Martin Gutierrez & Asco.

"Keytruda can cause myositis," Mr Rubin told Evaluate Vantage. "The question is whether [MK-0482] is somehow adding to the myositis that you would see with Keytruda."

He accepted that the toxicity was not common, but suggested that seeing two cases in a small trial like this could be down to bad luck, adding: "It's still too early to understand whether the safety profile is really different to that of Keytruda. The other immune adverse events do not really look much different to what we would expect with Keytruda."

Merck will now go into dose expansion in a number of solid tumours with 750mg MK-0482 plus 200mg Keytruda every three weeks, based on what the primary investigator, Dr Martin Gutierrez of Hackensack University Medical Center, called the totality of data. Another approach is to explore triple combinations that include chemo, said Mr Rubin.

Selected inhibitors of Bcl-2			
Project	**Mechanism**	**Company**	**Clinical trial**
Phase 2			
MK-4830	Anti-ILT4 MAb	Agenus/ Merck & Co	Several, including Keytruda combo trials Keymaker-U01A, B & C, & Keynote-B99
MK-0482	Anti-ILT3 MAb	Merck & Co	Keytruda combos Keymaker-U01B & C
Phase 1/2			
NGM707	Anti-ILT2 x ILT4 MAb	NGM Biopharmaceuticals	MonoRx & Keytruda combo
BND-22/ SAR444881	Anti-ILT2R MAb	Biond/ Sanofi	MonoRx & Keytruda or Erbitux combo
JTX-8064	Anti-ILT4 MAb	Jounce	MonoRx & pimivalimab combo
Phase 1			
IO-202	Anti-ILT3 MAb	Immune-Onc Therapeutics	Keytruda combo
NGM831	Anti-ILT3 MAb	NGM Biopharmaceuticals	MonoRx & Keytruda combo
IO-108	Anti-ILT4 MAb	Immune-Onc Therapeutics	MonoRx & Keytruda combo
Preclinical			
AGEN1571	Anti-ILT2 MAb	Agenus	IND cleared
CDX585	Anti-ILT4 x PD-1 MAb	Biosion	Preclinical
BND-35	Anti-ILT3 MAb	Biond Biologics	Preclinical

Source: Evaluate Pharma & clinicaltrials.gov.

Other clinical-stage anti-ILT3 MAbs include Immune-Onc's IO-202 and NGM's NGM831, while Biond's BND-35 is still at the preclinical stage.

Merck's data will be relevant also for companies pursuing related approaches. For instance, Jounce is in the clinic with a MAb targeting ILT4, while Agenus had an anti-ILT2 MAb in addition to the anti-ILT4 it has licensed to Merck.

Previously Tolerx had worked preclinically on MAbs targeting ILT2, ILT4 and ILT5, but the company was wound up after its diabetes project failed phase 3 in 2011.

Merus gets some competition

BY MADELEINE ARMSTRONG

Response rates with zenocutuzumab hold up, but Elevation Oncology's rival project looks similar.

First, the good news for Merus: its Her2/Her3-targeting bispecific, zenocutuzumab, looks just as good, if not slightly better, than it did a year ago. And the group is hopeful that data presented at Asco, in NRG1-fusion driven cancers, will help support a tumour-agnostic filing towards the end of this year or early 2023.

Now for the not so good news: a rival project from Elevation Oncology has produced similar overall response rates, albeit in a small number of patients so far. In a tiny niche like NRG1 fusions, competition could be a big deal.

Elevation will present early results on its project, the Her3-targeting MAb seribantumab, at Asco on Tuesday, but it has already detailed the full dataset via press release, a spokesperson told Evaluate Vantage.

The seribantumab results call into question something that Merus has long maintained: that its dual approach, docking onto Her2 and then blocking Her3, could be more potent than monoclonal antibodies (Asco 2021 – Merus's slight improvement might not win over investors, June 4, 2021).

However, Merus's chief executive, Bill Lundberg, maintained this claim when Evaluate Vantage spoke to him on the sidelines of Asco. "We think we have the potential not only to be first in class, but potentially best in class in this setting."

He noted that patients in Merus's Enrgy trial and early-access programme received a median of two prior therapies, compared with a median of one in Elevation's Crestone trial. This raises the possibility that patients in Crestone were less sick, which could have flattered seribantumab's performance.

Cross-trial comparison of zenocutuzumab & seribantumab

	Zenocutuzumab: Enrgy & Early Access Program		**Seribantumab: Crestone**
	Asco 2021 presentation	**Asco 2022 presentation**	**Asco 2022 presentation**
Cutoff	Apr 13, 2021	April 12, 2022	April 18, 2022
ORR – overall	31% (14/45)*	34% (27/79)	33% (4/12)**
ORR – pancreatic cancer	42% (5/12)	42% (8/19)	0% (0/1)
ORR – NSCLC	29% (7/24)*	35% (16/46)	36% (4/11)**
ORR – other solid tumours	22% (2/9)	18% (3/17)	N/A

*Included one PR confirmed after cutoff date; **Includes 2 CRs. Source: Asco & company releases.

And Mr Lundberg added: "We're a couple of years ahead."

SMALL MARKET

In NRG1 fusion cancers this head start could make a difference. Merus currently estimates that 0.5-1.5% of pancreatic cancer and 0.3-3% of lung cancer patients have NRG1 fusions, but Mr Lundberg noted these numbers are based partly on epidemiologic studies using old sequencing methods.

"We think the numbers could increase over time with better diagnosis," he said. "But it's not going to dramatically be tenfold higher. We think it's several thousand patients per year in the US."

For now, Merus is not saying how many patients it will need for a US filing, only that it has reached agreement on this with the FDA. "And we believe we'll have sufficient patients with sufficient clinical follow-up around the middle of this year."

It is not clear yet whether this could support an accelerated or full approval; Mr Lundberg said this would be up to the FDA. The group is currently considering whether to go it alone or sell zenocutuzumab via a partner, assuming it does get the nod.

COMPETITION

Still, Mr Lundberg admitted that the anti-Her3 space is getting crowded. As well as Elevation, Hummingbird Bioscience's HMBD-001 recently went into the clinic in Her3-positive solid tumours, including NRG1 fusion-driven cancers.

Meanwhile, Aveo Oncology still has hopes of reviving AV-203, despite it being ditched by two partners: Biogen in 2014 and China's Canbridge in 2021. Aveo is also developing a Her3-targeting antibody radio-conjugate alongside Actinium.

GSK's GSK2849330 has also produced intriguing results in NRG1 fusion cancers, but is not currently listed on the company's pipeline.

And Daiichi's Her3-targeting antibody-drug conjugate patritumab deruxtecan produced encouraging results in breast and lung cancers at Asco, but the company does not appear to be focusing on NRG1 fusions.

Merus will need to keep its first-mover advantage if it wants to make the most of this niche.

Her3-targeting projects with potential in NRG1 fusion cancers

Project	Company	Description	Details
Zenocutuzumab	Merus	Anti-Her2/Her3 bispecific	Filing due late 2022/early 2023 based on ph1/2 Enrgy & EAP
Seribantumab	Elevation Oncology	Anti-Her3 MAb	Early data from ph1/2 Crestone at Asco 2022; trial could be basis for AA
HMBD-001	Hummingbird Bioscience	Anti-Her3 MAb	First pt dosed in ph1/2* in Dec 2021
GSK2849330	GSK	Anti-Her3 MAb	Ph1 completed 2017, one of two NRG1 fusion pts had partial response
AV-203	Aveo Oncology	Anti-Her3 MAb	Ph1 completed 2014, one of two NRG1 fusion pts had a partial response

*Investigator-sponsored, study enrols pts with Her3-expressing tumours, including NRG1 fusion pts. AA=Accelerated approval; EAP=Early access programme.

Source: Evaluate Pharma & clinicaltrials.gov.

Carvykti casts a long shadow

BY JACOB PLIETH

Arcellx, Gracell and Oricell work hard to prove that there is still space for new Car-T therapies in multiple myeloma.

For Arcellx investors, who backed the group's audacious $124m flotation in February, in the middle of a biotech slump, Asco was a key test. Judging by new data for the group's lead Car-T project the enthusiasm was not entirely misplaced.

Arcellx was not the only company with Car-T data in multiple myeloma at Asco. Also featured oral presentations on Gracell's fast-manufactured dual-acting project and on a novel follow-on approach from the venture capital-backed Chinese group Oricell. As impressive as many of these data are, however, Johnson & Johnson's Carvykti casts a long shadow.

Indeed, Carvykti's Cartitude-1 trial, on the basis of which this anti-BCMA Car-T therapy was approved in fifth-line multiple myeloma, seems insurmountable on efficacy: response rate was 98%, including a 78% rate of complete responses. On a cross-trial basis this beat the other two approved BCMA-directed products, Bristol Myers Squibb's Abecma and GSK's Blenrep.

And the Asco update of Cartitude-1 reported PFS and OS rates, at 28 months' follow-up, of 55% and 70% respectively. The big chink in the armour of all three approved therapies is toxicity; Carvykti carries a black box warning of cytokine release, neurotoxicity, macrophage-activation syndrome, Parkinsonism – of which one new case has been seen in Cartitude-1 – and Guillain-Barré syndrome.

ARCELLX

Perhaps this is where Arcellx comes in. Dr Matthew Frigault, of Massachusetts General Hospital, reported just one case of grade 3 cytokine release, and two grade 3 neurotoxicities, among 31 multiple myeloma patients given CART-ddBCMA.

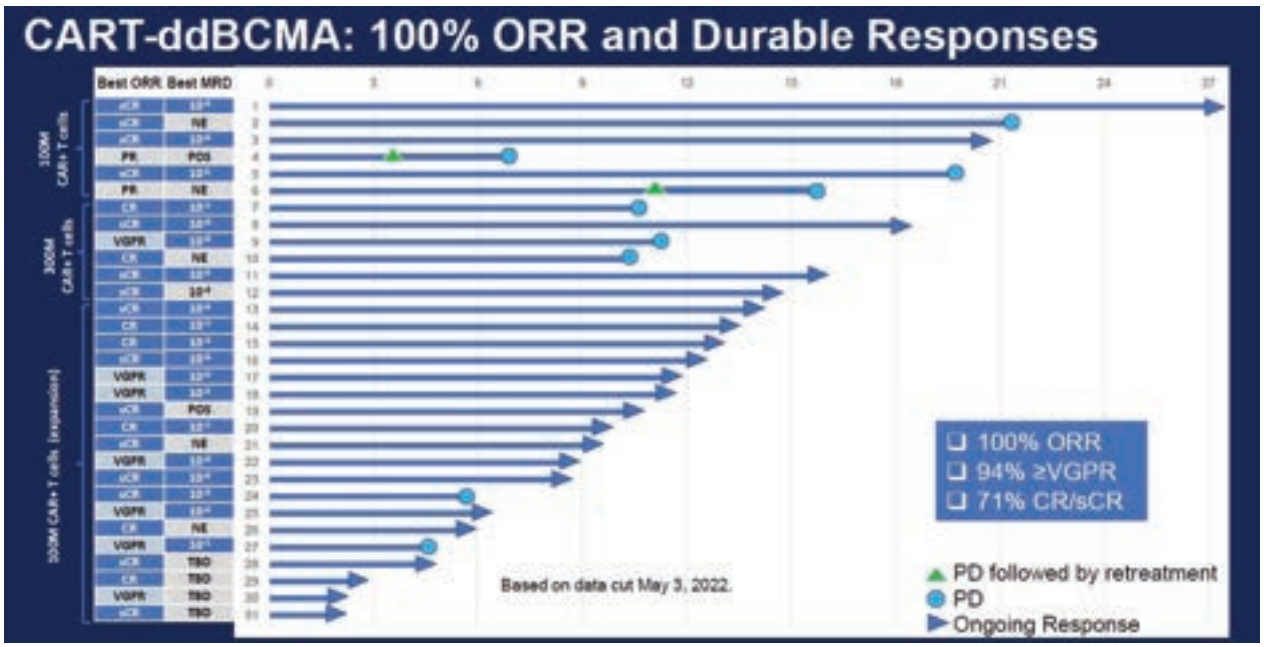
As for efficacy, all 31 patients went into remission, with a 71% complete response rate, though there were nine relapses by the May 3 data cutoff. CART-ddBCMA has "best-in-class potential", Rami Elghandour, Arcellx's chief executive, told Evaluate Vantage.

He highlighted CART-ddBCMA's activity in extramedullary disease, a negative prognostic factor, claiming: "We're largely achieving very similar result to [Carvykti], in a much harder to treat patient population, with arguably a very attractive safety profile."

In terms of design, what makes CART-ddBCMA different is its use of a synthetic binding region instead of an antibody-derived one; this, says Mr Elghandour, results in more transduced cells being Car-positive than with Carvykti, so the cell dose can be lower. And he cites reduced tonic signalling, meaning that the Car-T cells remain relatively fresh.

Interestingly, CART-ddBCMA is being positioned as a product in its own right rather than as a test of this technology, and Arcellx has designed a pivotal study, to start by the year end, in a similar population to Cartitude-1. The BCMA market can support multiple players, Mr Elghandour insists.

If so this is good news for Gracell, which is touting a fast-manufactured multiple myeloma Car-T asset



Source: Dr Matthew Frigault & Asco.

that targets CD19 as well as BCMA, in an attempt to counteract BCMA antigen-negative relapse.

This project, GC012F, has generated an 83% ORR among 28 patients, and all 27 patients evaluable for MRD status were negative; 87.5% of eight patients evaluable at 12 months remained MRD-negative. The longest ongoing responses are over 29 months out, Dr Juan Du, of Shanghai Chang Zheng Hospital, told Asco.

Perhaps in this small population Gracell can make a case for this dual antigen targeting approach. CD19 might seem an unusual second antigen to hit in multiple myeloma, but a 2015 NEJM paper famously described a case report of a multiple myeloma patient who went into sustained complete remission after getting Kymriah, despite lacking CD19 on most malignant cells. It was hypothesised that the remission was brought about because Kymriah targeted rare, CD19-expressing myeloma precursor cells.

NOVEL ANTIGEN

It was Oricell that brought to Asco data on a novel antigen, specifically GPRC5D, which is hit by its Car-T project OriCAR017.

Its study enrols patients with GPRC5D expression on at least 20% of their multiple myeloma cells, 10 of whom appear at an April 30 data cut. All 10 are reported to have gone into remission (six complete responses) across three doses; five of the patients had relapsed on BCMA-targeted Car-T cell therapy.

Still, there is already competition building here, too. Johnson & Johnson's bispecific talquetamab is probably the most advanced GPRC5D-targeting agent, and posted impressive data at Ash 2020. In 50 evaluable subjects given over 20µg/kg the ORR was 66%, and in the 13 who had received 405µg/kg subcutaneously, which has been set as the phase II dose, ORR was 69%.

While Oricell remains a little-known private Chinese group, Arcellx is basking in its status as a newly minted listed biotech. "Good companies, even in difficult times, are able to go public and are able to fund raise," said Mr Elghandour. "I think I'd rather be public than private."

Investors clutch at the Tigit straws

BY JACOB PLIETH

Roche's SCLC study is an unmitigated disaster, but investors holding out for success in NSCLC are thrown a crumb of comfort.

Tigit blockade, already facing existential questions after the failure of Roche's tiragolumab in non-small cell lung cancer, took another hit. A late-breaker at Asco has laid bare the unmitigated disaster of tiragolumab's other flop, in the more intractable small-cell lung cancer setting.

Just how bad is it? In Skyscraper-02, the SCLC trial, adding tiragolumab to Tecentriq actually worsened progression-free survival numerically. However, a key disclosure about Skyskraper-02's statistical analysis plan has raised hopes that Skyscraper-01, the failed NSCLC study, might not be dead and buried just yet.

How this pans out is crucial not only for Roche, which has invested hugely in Tigit, but for numerous smaller biotechs working on this mechanism who had been hoping for some crumbs of comfort from Skyscraper-02.

APPORTIONING ALPHA

Importantly, nothing has been revealed about Skyscraper-01, the front-line NSCLC study, beyond its miss at interim analysis on PFS and a numerical trend favouring an OS benefit. That trial tests tiragolumab plus Tecentriq versus Tecentriq alone in PD-L1 ≥50% expressers.

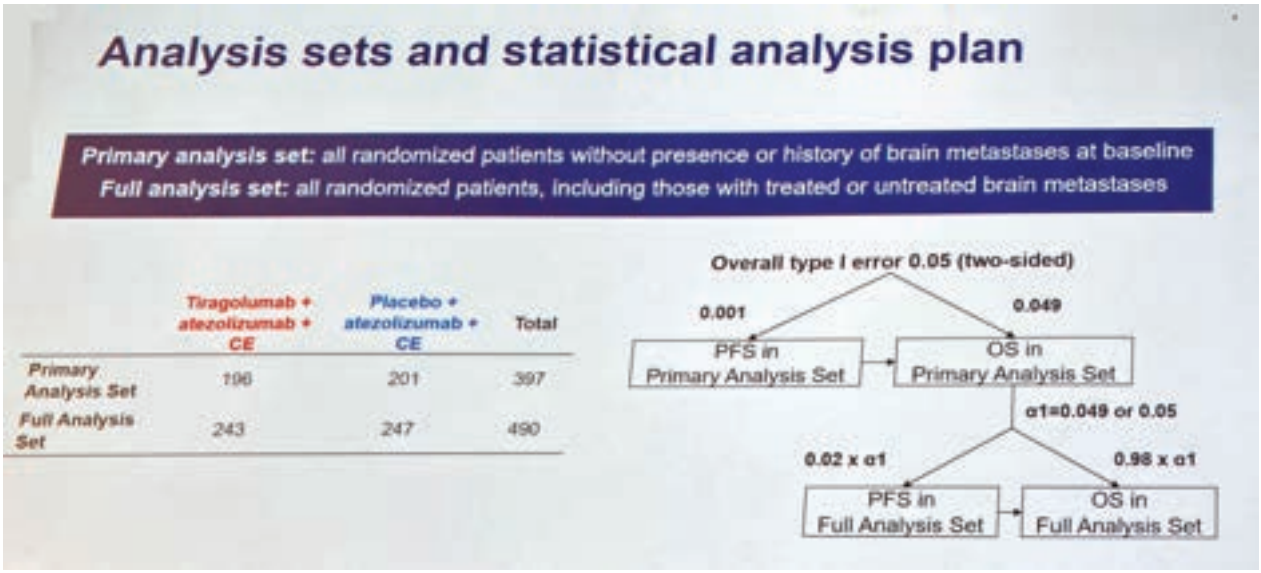
The central question is what the numerical PFS miss looks like, and how Roche has divided up statistical power in Skyscraper-01. The standard of statistical significance at p=0.05 is typically split for multiple analyses across multiple endpoints.

Indeed, Evaluate Vantage understands that whisper numbers among optimistic investors are that Skyscraper-01's PFS result has yielded a p value well below 0.05, but that this nevertheless missed statistical significance, which had been set at a much more aggressive level.

Even more important is how much statistical power remains to show an OS benefit at a subsequent interim analysis. As far as PFS goes, of course, whatever powering – or "alpha" – was apportioned to this endpoint at first interim has been spent.

So why do the latest Skyscraper-02 data add optimism? The key is this SCLC study's statistical design, posted at the Asco late-breaker by Memorial Sloan Kettering's Dr Charles Rudin. Revealingly, almost the entirety of the alpha at p=0.05 was assigned to OS, meaning that a very tough p value of 0.001 needed to be cleared to declare a statistical win on PFS.

No one is suggesting that Skyscraper-01 has an identical statistical design. And clearly there is no



Source: Dr Charles Rudin & Asco.

salvaging anything from tiragolumab's SCLC study, which was a flop on all counts.

But it is nevertheless possible that Roche has apportioned the majority of the alpha in Skyscraper-01 to OS. In a note to clients Evercore ISI's Umer Raffat wrote: "These tidbits raise our confidence that there is a real chance Roche can hit on a subsequent OS analysis of Skyscaper-01 in NSCLC; next interim [due] possibly later in the year."

THERAPEUTICALLY IRRELEVANT?

As for Skyscraper-02, there was no attempt by Dr Rudin to gloss over the disaster. Perhaps damningly for Merck & Co, he stated: "Targeting Tigit in SCLC does not appear to be therapeutically relevant."

Merck had started Keyvibe-008, a broadly similar front-line SCLC trial with its Tigit MAb vibostolimab plus Keytruda, at precisely the same time that Skyscraper-02 was toplined as a flop. However, speaking to Evaluate Vantage Eric Rubin, Merck's senior vice-president of early-stage oncology, said: "Roche's failure isn't going to detract from our interest in [vibostolimab]."

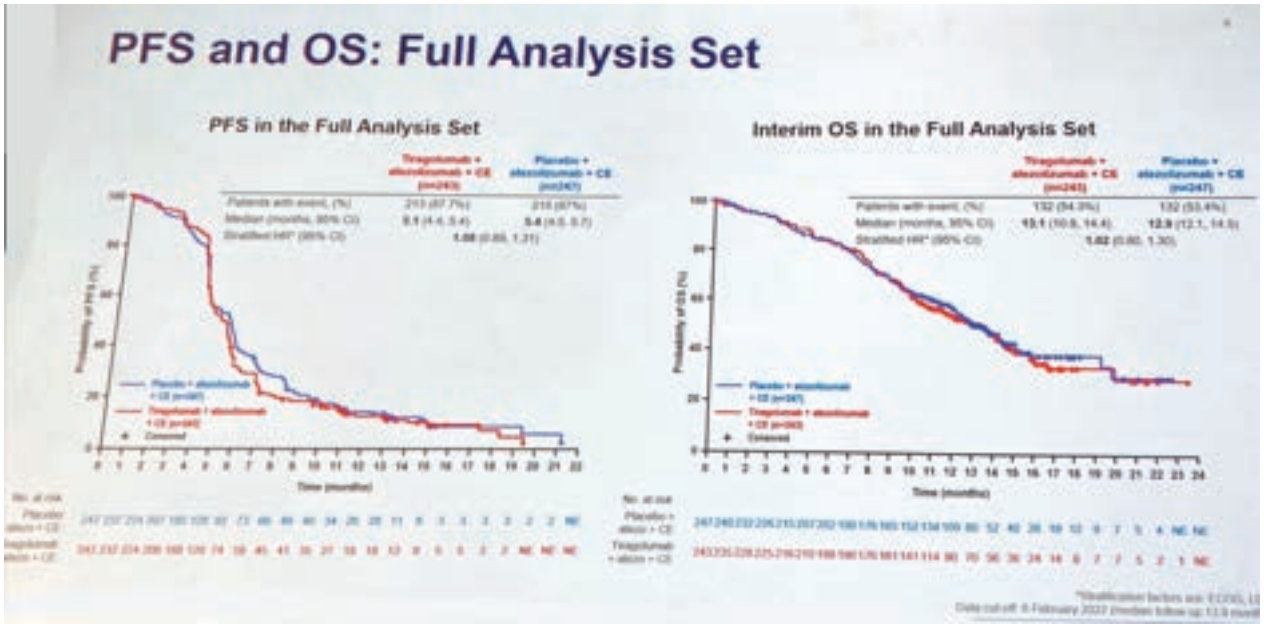
Of more importance will be Merck's work in NSCLC, where the Keyvibe-003 vibostolimab plus Keytruda trial is ongoing. Mr Rubin drew a distinction between Skyscraper-01 and Keyvibe-003, saying that Roche's Tecentriq comparator arm restricted enrolment to patients expressing PD-L1 at 50% or above, in line with Tecentriq's monotherapy label.

Because Keytruda is approved in PD-L1 ≥1% expressers, and comprises the comparator in Keyvibe-003, Merck can test its Tigit combo in the broader population. "It may be easier to detect a combination effect in lower biomarker positives rather than at the higher level, where the PD-1s are pretty effective by themselves," said Mr Rubin.

He added that in single-arm NSCLC trials "we saw a nice effect" in 1-49% PD-L1 expressers, where Roche notably did not see efficacy in the mid-stage Cityscape trial. A third player, Beigene, is studying its Tigit ociperlimab plus tislelizumab versus Keytruda in the PD-L1 ≥50% population in the Advantig-302 trial, its chief medical officer, Mark Lanasa, told Vantage.

Thus at least Roche has some clinical rationale for continuing to pursue Tigit blockade in NSCLC.

Not so in SCLC. After Dr Rudin's presentation the Asco discussant, Penn State Cancer Institute's Dr Chandra Prakash, slated Skyscraper-02 for being a phase 3 study designed solely on the basis of preclinical findings, with "no evidence of clinical activity in SCLC".



Source: Dr Charles Rudin & Asco.

Enhertu asks, how low can you go?

BY AMY BROWN AND JACOB PLIETH

Another strong readout could redefine how Her2-negative breast cancer is treated, though a declared victory in triple-negatives is less clear.

Enhertu has already delivered several outstanding results in Her2-positive breast cancer, and its latest performance does not disappoint. The antibody-drug conjugate has now shown an impressive survival benefit over chemotherapy in patients considered Her2-negative, with the data holding up even in those with the very lowest expression.

In Destiny-Breast04 Enhertu almost doubled median progression-free survival to 10.1 months over chemotherapy in women with Her2-low, estrogen receptor-positive tumours, equivalent to a 49% reduction in the risk of progression, newly released data at Asco show. Around half of all breast cancers are considered Her2 low, meaning that a major label expansion is likely on the way for the drug.

Investigators' claim that a result was seen irrespective of estrogen receptor (ER) status is more questionable, however. Largely this is because this cohort, also known as triple-negative disease, only recruited around 60 patients, and no statistical powering was assigned to it. And a snafu that saw Asco releasing incorrect data in the abstract also raises eyebrows.

Redefining Her2-negative disease: the topline Destiny-Breast04 results

	ER-positive*		All patients		ER-negative	
	Enhertu (n=331)	Chemo (n=163)	Enhertu (n=373)	Chemo (n=184)	Enhertu (n=40)	Chemo (n=18)
mPFS (mth)	10.1	5.4	9.9	5.1	8.5	2.9
	HR 0.51 (p<0.001)		HR 0.50 (p<0.001)		HR 0.46	
mOS (mth)	23.9	17.5	23.4	16.8	18.2	8.3
	HR 0.64 (p=0.003)		HR 0.64 (p=0.003)		HR 0.48	

*Cohort for primary endpoint. Numbers in the two cohorts do not add up to all patients because of mis-stratification error.

Source: NEJM & company communications.

Daiichi told Evaluate Vantage that five patients were initially misclassified as ER-negative. In the abstract these remain assigned to the ER-negative group; by the time the data were presented at Asco and published in the NEJM they had been removed, and as luck would have it their removal flattered the result in the ER-negative group.

Daiichi insists that reanalysing patients' ER status had been pre-planned, and that this was not done in response to what the initial readout had shown.

"This agent is not influenced by whether you are ER positive or negative," Gilles Gallant, head of oncology development for the Japanese drug maker, said in an interview.

Dr Jane Lowe Meisel of Emory School of Medicine said that it was tough to know whether Enhertu was having a real benefit in the ER-negative group, because of the small number of patients recruited.

"But we have biological plausibility and a lot of reasons to think it actually works. It is an option that I would discuss with a [triple negative] patient," she said at an Asco press conference this morning.

Destiny-Breast04 recruited an advanced population that had progressed on one or two lines of chemo and were no longer benefiting from endocrine therapy. More than a third had also been failed by CDK4/6 inhibition. Her2-low was defined as having an immunohistochemistry (IHC) score of 1+, or IHC2+ with a negative in-situ hybridisation score (ISH-).

Current guidelines dictate that these patients should be considered Her2-negative, largely because of the lack of benefit shown in this group by other Her2-targeted drugs.

Patients in the study were stratified by IHC score, and a benefit was seen regardless of this, with hazard ratios of 0.48 and 0.55 for IHC 1+ and 2+/ISH- respectively. A clear survival benefit over control, which was physician's choice of chemo, was seen across every subgroup, according to the New England of Medicine.

It was already known that the trial had also hit on overall survival, and a 6.4-month advantage is likely to be applauded by physicians when the full data are presented at Asco later today. The PFS result largely meets expectations in the financial community, and although some were hoping to see a 50% improvement in OS it would be hard to describe this result as disappointing.

Analysts reckon the Her2-low opportunity to be worth $2-3bn in annual revenue at peak, contributing around a third of Enhertu's total peak sales.

It should be noted that the drug's biggest toxicity, interstitial lung disease, once again reared its head, causing three deaths in the study. Rates of ILD, particularly high grade events, have been coming down in Enhertu trials, thanks to more intensive monitoring and education. The side effect is arguably the biggest barrier for Astra and Daiichi to overcome as they try to move the drug into earlier treatment lines.

FATAL BYSTANDER

Enhertu's high antibody to drug ratio and strong "bystander effect", meaning that it kills nearby cells as well as those directly hit by the ADC, are thought to contribute to its efficacy in patients with relatively few tumour cells that display the Her2 target.

It seems that IHC scoring might no longer be the best method to select patients who might benefit from Enhertu. Daiichi and Astra are trialling a different assay in a follow-up Her2-low study called Destiny-Breast06, which also includes a Her2-0 cohort.

"If you are Her2-0 it doesn't mean you have zero receptor. It means less than 10% of cells take the stain, so there is presence of the receptor," said Daiichi's Mr Gallant. "The big question, and we haven't determined this yet, is how low [on Her2 expression] can we go?".

But it is clear that Destiny-Breast04 has already done the heavy lifting. The trial could establish Enhertu as the first targeted agent for a population whose only option previously was chemotherapy, and prompt previous definitions of Her2-negative cancers to be thrown out of the window.

The spirit of Rova-T struggles to live on

BY JACOB PLIETH

DLL3, a pariah antigen after the implosion of Abbvie's Rova-T, holds the interest of a handful of industry players.

When Abbvie's Rova-T crashed and burned many might have assumed that DLL3 blockade was finished as an oncology drug mechanism. Not so: through an Asco poster covering its T-cell engager HPN328, Harpoon Therapeutics continued a tenuous bid to join Amgen and Boehringer Ingelheim among a small group of companies working clinically on this mechanism of action.

Still, Harpoon's data are very early, and there is little to celebrate just yet: there is just one confirmed partial response, and hopes that a second might be confirmed have fallen on stony ground. With the group 85% below its IPO price, and 90% off its peak a year ago, investors clearly need more data to be convinced.

Some will take heart in the lack of severe cytokine release or neurotoxicity of any sort, facts that do at least allow HPN328 to be dosed higher in future. And, at least in SCLC, which had been the intended use for Rova-T, the data point in the right direction: among 18 patients with various tumours, four of the six SCLC subjects given high HPN328 doses showed a decrease in the sum of their target lesions.

But at a December cutoff Harpoon had reported a second, unconfirmed, partial response, which is now classified as stable disease. A further patient, also with SCLC, with partial response at their target lesion is classified a progressive disease after new asymptomatic brain metastases were identified, the waterfall plot in Asco's poster reveals.

NOT ALONE

Rova-T was canned after failing in phase 3 for SCLC, suggesting that the $5.8bn Abbvie had spent in 2016 to buy its originator, Stemcentrx, was money down the drain.

Still, some see the problem with Rova-T as having been not the target but the design of Stemcentrx's project, an antibody-drug conjugate. Indeed, Harpoon is not the only company pursuing this target.

Boehringer Ingelheim and Amgen each have clinical-stage T-cell engagers targeting DLL3, and the latter's tarlatamab had SCLC data at last year's Asco showing a 20% confirmed overall remission rate. This seemed impressive given that the 64 patients in question had not been preselected for DLL3 expression, and that this was still at the dose-escalation stage.

A phase 1 study of Amgen's AMG 119, a Car-T therapy against DLL3, was suspended last year after enrolling just six subjects. A phase 2 tarlatamab trial, in SCLC patients progressed after at least one platinum regimen and one other therapy line, began in December.

Oncology assets targeting the DLL3 antigen				
Project	**Company**	**Mechanism**	**Trial**	**Focus**
Tarlatamab (AMG 757)	Amgen	Bispecific T-cell engager	Dellphi-301 (ph2)	3rd-line SCLC
HPN328	Harpoon Therapeutics	Trispecific T-cell engager	NCT04471727 (ph1/2)	SCLC & DLL3-expressing solid tumours
BI 764532	Boehringer Ingelheim	Bispecific T-cell engager	NCT04429087 (ph1)	DLL3-expressing solid tumours
AMG 119	Amgen	Autologous Car-T therapy	NCT03392064 (ph1 suspended)	2nd-line SCLC
AMV300	Amphivena Therapeutics	Bivalent bispecific T-cell engager	NA	SCLC & neuroendocrine tumours
Unnamed	Allogene	Allogeneic Car-T therapy	NA	SCLC (discovery poster at AACR 2020)

Source: Evaluate Pharma & clinicaltrials.gov.

Adicet works hard to avoid the allo Car-T scenario

BY JACOB PLIETH

Long-awaited gamma-delta Car-T data sees the response rate fall to 20% at six months, but when is a relapse not a relapse?

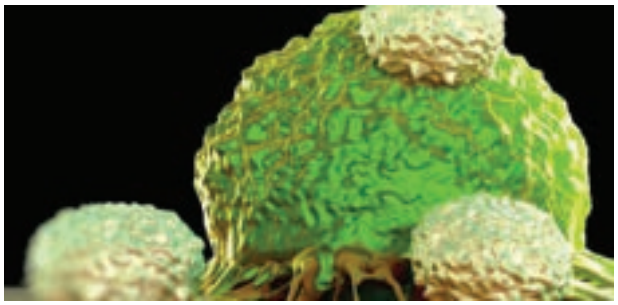
Adicet's fate rests on showing that its off-the-shelf gamma-delta Car-T project ADI-001 is durable, and on avoiding the relapses that have paralysed allogeneic Car-T developers. So the fact that only one in five patients is still in remission at six months, revealed at Asco, does not look good.

However, there is nuance to this update, which added a further two lymphoma subjects to those disclosed in an abstract that prompted Adicet to climb 10% last month. Investor focus will fall on two subjects no longer in remission – one because they died of Covid and the other with a skin relapse that Adicet insists cleared up with a minor intervention.

First the good news: ADI-001 continues to put lymphoma patients into remission. The Adicet study initially saw three of four lymphoma subjects develop complete responses, a rate that rose to four of six in the Asco abstract.

Today the ORR remained compelling, with six of eight subjects in complete remission. All patients had aggressive lymphomas – follicular lymphoma was not allowed at inclusion. Three had relapsed on autologous Car-T therapy, and all three went into remission after getting ADI-001 cells.

But there the story gets complicated. One of the patients in remission developed Covid before month three and died. Another remained in complete remission until month four, at which point they

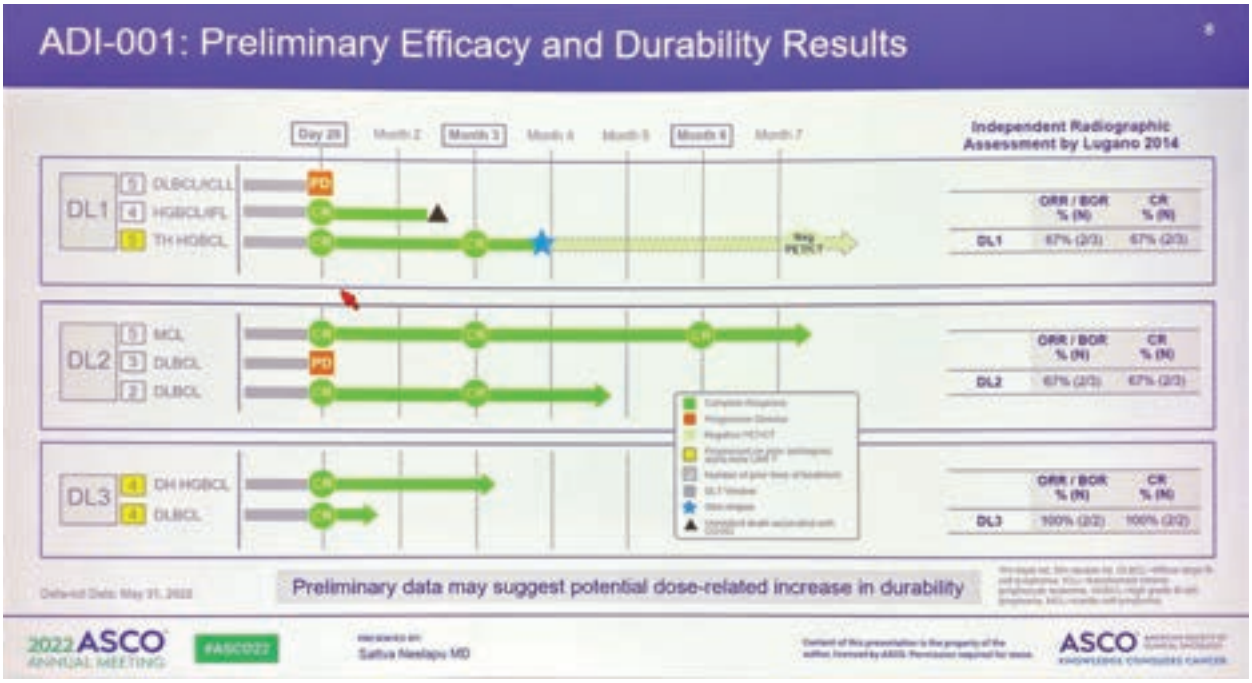


suffered a skin relapse, MD Anderson Cancer Center's Dr Sattva Neelapu told Asco this morning.

Adicet worked hard to play this down, stating that the skin lesion resolved with local radiotherapy, and that "the patient continues to be cancer-free" at 7.5 months, as measured by PET/CT scan.

But its headline claim that two patients "remain cancer-free" after six months does not tell the whole story: the aforementioned patient did relapse, and counting the two initial non-responders only one of five patients evaluable at six months is in complete remission.

On the plus side safety seemed good, with no cytokine release or neurotoxicity at grade 3 or higher in any of the three ADI-001 doses used. Indeed, Dr Neelapu said dose escalation in this study was continuing, and that given the safety the protocol had been amended to add a higher fourth dose before recommending which should be used in phase 2.



Source: Dr Sattva Neelapu & Asco.

CD20

ADI-001 hits CD20, and it is interesting that Adicet picked this as its first target; CD20 has been exploited by the likes of Rituxan and Gazyva, but as a Car-T target it has been beset with toxicity concerns, notwithstanding some impressive efficacy reports.

The key potential advantage of using a gamma-delta approach is that these cells do not cause a graft-versus-host response, and so can be given off the shelf.

Discussing the data, Fred Hutchinson Cancer Research Center's Dr Brian Till said gamma-delta Car-Ts against CD19 would likely also be developed, but said more had to be learned about the susceptibility of these types of cells to exhaustion from chronic antigen exposure, and their dependence on the IL-2 cytokine.

However, he did not directly address the issue of relapse to which, mechanistically, gamma-delta T cells could be prone just as much as allogeneic Car-Ts; notably, relapses have derailed the allogeneic Car-T players Allogene, Precision and Crispr.

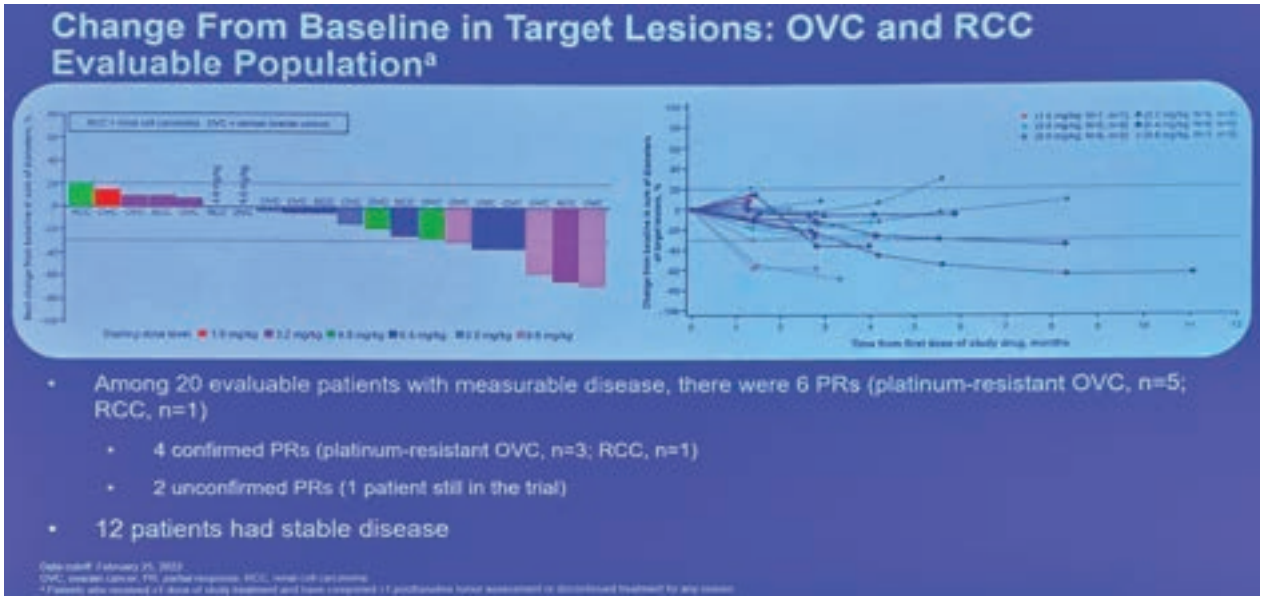
Perhaps the best Adicet can say coming out of Asco is that more time, and more treated patients, are needed to gauge whether there is a relapse problem or not. The debate over durability is not about to go away.

A novel target rounds out Daiichi's triple

BY JACOB PLIETH AND AMY BROWN

Did Daiichi Sankyo's antibody-drug conjugates win Asco?

Data on the Japanese group's Her3-targeted patritumab deruxtecan served as a prelude to Enhertu's practice-changing Destiny Breast04 result, widely acclaimed as the most important dataset of this year's meeting. For an encore, Daiichi presented the first human data on DS-6000, an ADC targeting CDH6, which could help validate this mechanism. CDH6, or human cadherin-6, is a protein thought to be overexpressed in ovarian and renal cell cancers. A phase 1 study yielded 20 evaluable patients at a February data cutoff, six of whom have developed partial remissions, Asco heard. Two are unconfirmed, however; of the four confirmed three were in platinum-resistant ovarian cancer. There were some dose-limiting toxicities, and one high-dose patient discontinued because of pneumonitis. Though retrospective analysis of patients' CDH6 expression has yet to be performed, these early data give some hope in a highly refractory population for a new target that has no other clinical-stage assets in the competitor pipeline, according to Evaluate Pharma. Daiichi told Evaluate Vantage that DS-6000 was "one of our rising stars", and said the approach differed from that taken by Novartis's HKT288, an anti-CDH6 ADC scuppered by toxicity not long ago.



Source: Dr Erika Hamilton & Asco.

Looking beyond Enhertu in Her2-low cancer

BY AMY BROWN

Enhertu continues to show that it can hit Her2-expressing cancer cells that other drugs cannot reach, priming the Daiichi Sankyo and Astrazeneca asset for dominance across the Her2 space.

That means serious competition for players in what now must be called Her2 high. Roche has the most to lose here, although newer products will also suffer – the launch of Seagen's Her2 kinase inhibitor Tukysa has already been stopped in its tracks after a mere two years by Enhertu's arrival. In the newly defined Her2-low space there will also be repercussions. The impressive Destiny-Breast04 data likely consign Gilead's Trodelvy to a last-resort option, given this ADC's weaker showing in Tropics-02. What of others eyeing this niche? Not many active trials can be found on clinicaltrials.gov of agents specifically going after Her2 low. Most are ADCs – step forward again Seagen, which paid $200m up front for ex-Asia rights to Remegen's Her2-targeted ADC, disitamab vedotin. Meanwhile, a trispecific from Sanofi and a radiotherapeutic from Bayer provide different mechanistic approaches to watch. Safety is Enhertu's weak spot so there is room for improvement here; on efficacy, though, a high bar has been set.

Aiming low: selected active trials seeking Her2-low patients			
Project	**Mechanism**	**Company**	**Details**
Disitamab vedotin (RC48)	Anti-Her2 ADC	Seagen/Remegen	Remegen has a ph3 breast cancer trial ongoing in China recruiting Her2 low only; Seagen has said it plans to start a ph3 in Her2 low
Zanidatamab + evorpacept	Anti-Her2 MAb	Zymeworks + ALX Oncology	Ph1/2 trial has Her2-low cohort
MRG002	Anti-Her2 ADC	Shanghai Miracogen	Ph2 breast cancer trial ongoing in China recruiting Her2 low only
Cinrebafusp alfa (PRS-343)	Anti-Her2 x 4-1BB bispecific	Pieris	A ph2 gastric or GEJ adenocarcinoma trial has a Her2-low cohort (Tukysa combo)
Trastuzumab duocarmazine (SYD985)	Anti-Her2 ADC	Byondis/Medac	Ph1 trial has a Her2-low cohort
SAR443216	Anti-CD3xCD28xHER2 trispecific	Sanofi	Ph1b trial has Her2-low cohorts
BAY2701439	Thorium-227-Her2 MAb conjugate	Bayer	Ph1 trial has a Her2-low cohort
IBI315	Her2xPD-1 bispecific	Innovent	Ph1 trial possibly has Her-low cohort, company has said it intends to move into Her2 low
Runimotamab (RG6194)	Her2xCD3 bispecific	Roche	Potential for low Her2 cohort in large phase 1 trial (Her2 criteria undefined)
ARX788	Anti-Her2 ADC	Ambrx	Ph1b has a Her2-low cohort
A166	Anti-Her2 ADC	Sichuan Kelun/Sorrento	Ph1/2 trial allows low Her2 expression

Source: clinicaltrials.gov, company communications, Evaluate Pharma & Journal of Clinical Oncology.

PMV's therapeutic window slams shut

BY JACOB PLIETH

Liver and other toxicities threaten to scupper another attempt to reactivate mutated p53, the "guardian of the genome".

What goes up must come down, as PMV Pharmaceuticals investors discovered at Asco. As one of the biggest gainers at the time of the Asco abstract drop the company came into the conference with much to prove. Unfortunately, a presentation suggested that its p53 reactivator PC14586 might not have a viable therapeutic window.

Nevertheless, both the presenter of the study in question, Pynnacle, and its Asco discussant hailed the result as proving that p53 was becoming druggable. But this ignores toxicities that threaten the most active PC14586 dose, and with PMVP stock off 22% today the company might soon be joining others that have failed with this highly intractable target.

On the positive side, the Pynnacle study presenter, Dr Ekaterina Dumbrava of MD Anderson, cited eight partial remissions among 31 subjects with p53-mutant cancers given PC14586 at high doses of 1.15-2.5g daily and 1.5g twice daily. There were no responses in the 10 given lower 150-600mg once-daily doses.

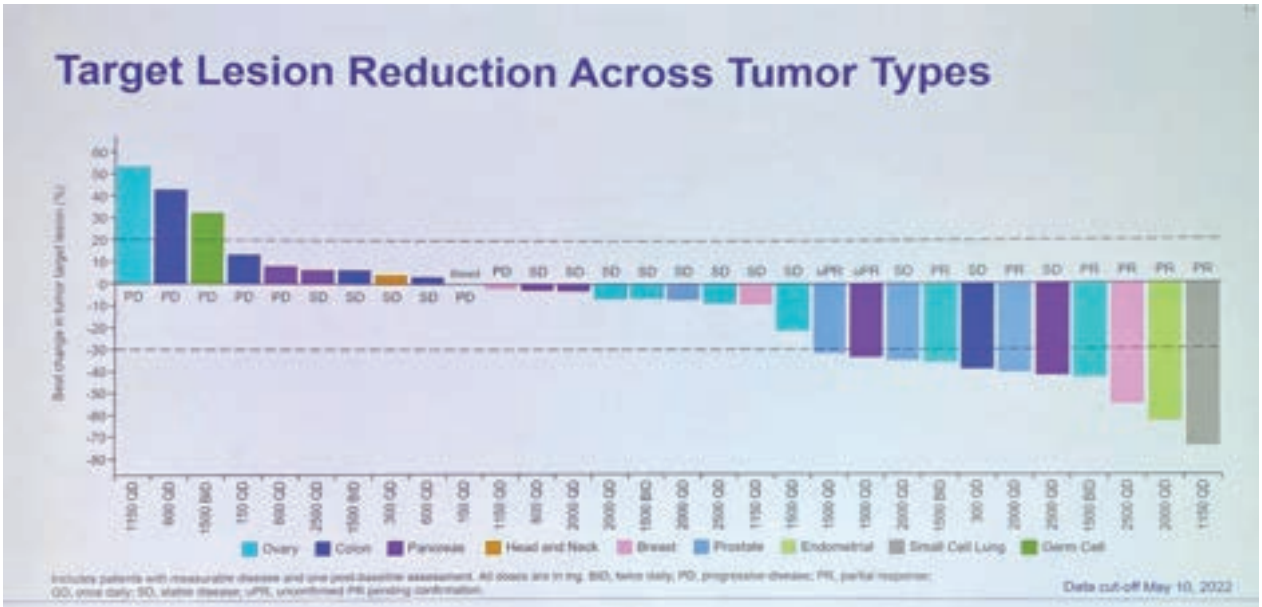
However, across the 41-patient set she cited liver enzyme increases – nine involving aspartate aminotransferase and eight alanine aminotransferase. There were also severe cases of hypokalaemia and pneumonitis, and two dose-limiting toxicities at 1.5g twice daily: one grade 3 AST/ALT increase and one grade 3 acute kidney injury.

And this is where the PMV story unravels. A close look at the waterfall plot reveals two of the eight remissions to be unconfirmed – both appearing to be at the borderline of what can be classified as a PR. And of the six confirmed PRs, five were achieved with the highest PC14586 dosing of 2-2.5g daily or 1.5g twice daily.

The discussant, Dr Irene Brana of Vall d'Hebron Institute of Oncology, gave a resounding "yes" to the question of whether p53 can now be drugged. Whether this can be achieved at a dose that does not cause unacceptable toxicity is the question PMV now has to grapple with.

p53 was first identified in 1979, and has been a "holy grail" in oncology drug discovery; it is a tumour suppressor protein with a central function in numerous critical cell processes, and is sometimes called the "guardian of the genome". Its inactivation – either by mutation of the TP53 gene or by other means – is estimated to be a factor in over half of all cancers.

But targeting it has proved elusive. PC14586 is said to work by stabilising a key p53 mutation, and thus restoring this protein's normal function.



Source: Dr Ekaterina Dumbrava & Asco.

MDM2 AMPLIFICATION

p53 can also become inactivated by other factors, such as overexpression of the MDM2 protein. MDM2 is a negative regulator of p53, and cancers driven by this process are called p53 wild-type, since here p53 remains unmutated.

This calls for an entirely separate mechanistic approach. And this is where companies including Kartos Therapeutics and Boehringer Ingelheim come in with MDM2 antagonists, specifically navtemadlin and BI 907828 respectively. Both assets also featured at Asco oral sessions over the weekend.

Navtemadlin yielded early data from p53 wild-type Merkel cell carcinoma patients who had failed PD-(L)1 blockade. Most of its activity seemed to be in those who had not received chemotherapy, with six PRs (one of which was unconfirmed) seen across 15 subjects. In 14 post-chemo subjects there were just two unconfirmed remissions, though one non-responder was later found to have a p53 mutation.

Meanwhile, BI 907828 showed some activity in p53 wild-type liposarcoma, specifically in de-differentiated disease (four PRs in 28 subjects) and well-differentiated disease (four PRs in 15). Boehringer is now enrolling patients into the phase 2/3 Brightline-1 study in front-line de-differentiated liposarcoma, while Kartos plans to begin pivotal dose-expansion at the recommended phase 2 dose in the second half.

Other MDM2 inhibitors in clinical trials include Ascentage's APG-115, Rain Therapeutics/Daiichi Sankyo's milademetan, Novartis's siredmadlin, Aileron's ALRN-6924 and Astex's ASTX295.

Still, those interested in mutated p53-driven cancer will recall Aprea, a group that had styled itself as the p53 reactivation company. Its lead asset, eprenetapopt, flunked phase 3 in front-line p53-mutant myelodysplastic syndromes and then was hit with two clinical holds.

Aprea became a listed shell into which the private group Atrin reversed last month. Though work on p53 is no longer a primary focus APR-548, an improved form of eprenetapopt, is in phase 1. Meanwhile, another company that had focused on p53 was the private San Diego group Actavalon, which no longer seems to be active.

The big worry for PMV investors is that their company now risks joining Aprea and Actavalon on the list of p53 reactivation disappointments.

Can Daiichi do it again?

BY AMY BROWN

The Japanese drug maker has four more conjugates coming behind Enhertu, and plans to keep future successes to itself.

Thanks to Enhertu's successes, the next antibody-drug conjugates emerging from Daiichi Sankyo's pipeline are being closely watched. Four more are in the clinic and only one of them has been partnered – and the Japanese developer hopes to keep it that way.

It made sense to bring Astrazeneca on board three years ago because of the resources needed to develop Enhertu and datopotamab deruxtecan, the second ADC partnered with the UK pharma giant. "But we've grown since that deal so maybe we won't need as much help [with the next projects]," Gilles Gallant, head of oncology development for Daiichi, tells Evaluate Vantage.

"We may change our mind, but it's something we think we can manage on our own," he says, speaking on the sidelines of the Asco meeting.

The group's remaining unencumbered assets are still early stage so there is little real incentive for the company to sell out now. These next ADCs also target smaller populations so are perhaps more viable to keep in house anyway.

They also still need to prove their worth. Encouraging new data were seen at this year's Asco on the most advanced, patritumab deruxtecan, which targets Her3.

"Her3 is a very different receptor to Her2," says Mr Gallant. "It has not been very successfully hit with antibodies because it's an incomplete receptor. Inside the cell it doesn't have the same kinase

activity as Her2. But with an ADC we only need the external parts [of the receptor] to get the active drug externalised."

In breast cancer Her3 is thought to be involved in resistance to Her2 inhibitors. Enhertu's strong results in broad Her2-low population arguably dent patritumab's potential, although Mr Gallant says that opens up the possibility of dosing the drugs sequentially.

"That's the future of these agents. If we can work out how to sequence them, we should be able to extend duration of response and hopefully overall survival," he says.

The biggest opportunity for patritumab is non-small cell lung cancer, however; Her3 is expressed in most EGFR-mutated tumours. All eyes are on Herthena-Lung01, a potentially pivotal phase 2 trial in a very late-line, EGFR-positive population, who have been failed by TKIs, including Tagrisso, and chemo.

An earlier phase 1 trial found response rates of 39% and median PFS of 8.2 months. Daiichi might have stated a desire to go it alone with patritumab but

the owner of Tagrisso, which just happens to be Astrazeneca, will be watching closely.

"This is a population with complete unmet need, and we're really looking forward to the results," Mr Gallant says.

Daiichi's ADCs			
Product	**Target**	**Company**	**Main tumour focus**
Enhertu	Her2	8	Breast
Datopotamab deruxtecan (DS-1062)	Trop2	4	Lung
Patritumab deruxtecan (U3-1402)	Her3	8	Lung
DS-6000	CDH6	8	Renal, ovarian
DS-7300	B7-H3	4	TBC (solid tumour trial ongoing)

DAR = drug to antibody ratio. Note: all use a deruxtecan payload and cleavable linker. Source: Company website, Berenberg research.

Coming after patritumab is DS-6000, which Mr Gallant describes as "one of our rising stars". Early data in ovarian and renal cell cancer at Asco revealed encouraging responses, albeit in only 20 patients.

DS-6000 aims at CDH6, or human cadherin-6, and appears to be the only project directed at this target in the clinic. Novartis abandoned an anti-CDH6 ADC a few years ago due to toxicity.

"You have to remember that these targets we're using, we only need the ADC to bring the drug into the cell. So when Novartis tried with CDH6, they tried to block the target. That's not we're trying to do. It's a completely different mechanism of action," Mr Gallant says.

The final ADC is the B7-H3-directed DS-7300 which along with DS-6000 Mr Gallant describes as "the most exciting drugs in our pipeline". Daiichi is not alone here, however; Macrogenics has pursued B7-H3 with various mechanisms in recent years, not always successfully, and several others are working on the target.

The next big test of Daiichi's ADC technology will come from datopotamab, however. The pivotal Tropion-Lung01 trial, being conducted in a broad second-line NSCLC setting, is due to read out early next year. Agents like Keytruda might have reshaped first-line NSCLC but the IO-failure space remains wide open.

Hopes are already very high for datopotamab. Analysts at Berenberg are forecasting peak sales of $10bn, $2.9bn from the second-line lung setting.

Daiichi's ADCs: the trials to watch		
Product	**Trial**	**Details**
Datopotamab deruxtecan	Tropion-Lung01	Ph3 2nd/3rd-line NSCLC, data due H1'23
Patritumab deruxtecan (U3-1402)	Herthena-Lung01	Potentially pivotal ph2 in late-line EGFR+ NSCLC. Data due around YE'22
DS-6000	Ph1 in renal and ovarian	Further cuts of the data to emerge 2022/23
DS-7300	Ph 1/2 in solid tumours	Further cuts of the data to emerge 2022/23, early data reported at Esmo last year
DS-7300	Ph2 in SCLC	Recently initiated

Source: Company communications, clinicaltrials.gov.

Another hit will cement Daiichi's reputation in the ADC space. However its success with this technology is no fluke. Enhertu and the follow-on projects are the result of decades of research into the technology, initiated by scientists at Daiichi before that company merged with Sankyo in 2007.

The payload, deruxtecan, is a derivative of exatecan, which Daiichi abandoned as a cancer agent in the late 1990s on lack of efficacy. Deruxtecan was found to be extremely potent with high cell membrane permeability, allowing it to diffuse easily into neighbouring cells.

Stable linkers were also developed to prevent the payload from being released early into the circulation. Daiichi's linkers are broken down by lysosomal enzymes that are upregulated specifically in tumours.

The company also managed to push the drug-to-antibody ratio higher than has been achieved elsewhere. So with Enhertu, this means that each Her2 antibody molecule delivers more payload molecules than other ADCs, with a DAR of 8 to Kadcyla's 3.5.

This all adds up a powerful, localised payload with a strong bystander effect; a short-half life is the final ingredient, which helps limit side effects.

Toxicity remains Enhertu's major downside, however, in the shape of interstitial lung disease. Fatal cases are still being seen in clinical trials despite concerted containment efforts. Some analysts believe that the ILD risk will prevent the Daiichi ADC from moving into front-line settings.

Safety is probably also the biggest risk to the follow on projects, and is also the angle future competitors are likely to take. The Japanese company needs to make sure it stays out in front.

Asco 2022 movers – cell therapy wins, but it's not the whole story

BY JACOB PLIETH, MADELEINE ARMSTRONG AND EDWIN ELMHIRST

Despite the often dismal mood over the weekend, the Asco conference provided rich pickings for some biotech investors.

It is probably fair to characterise the mood over the Asco conference as negative, at least among biotech investors, who are struggling with plunging market valuations and saw a number of companies sell off after data presentations over the weekend.

But an Evaluate Vantage analysis comparing share prices at the end of Asco against when the abstracts went live throws up impressive gainers, notably the cell therapy players Arcellx and Adicet, and a strong showing from Merus and biotechs involved in Tigit blockade. Some might see in this signs that the market crash is bottoming out, though what it does not capture is moves during the meeting, like Astrazeneca's perverse fall on presentation of Asco's most momentous dataset.

That was of course the groundbreaking data from the Destiny-Breast04 study of Enhertu, the ADC Astra licensed from Daiichi Sankyo. But it is key to remember that this study was toplined back in February, since when both companies enjoyed strong run-ups into Asco. As such the slight selloff merely shows that expectations had been priced in.

Specifically this analysis compares share prices at market close on Tuesday, formally Asco's last day, against May 26, when all regular abstracts went live after market close. But late-breakers only went live on the morning of their presentation, and many regular

presentations contained new data that were not in the abstracts. This analysis therefore does not capture stock fluctuations that occurred during this period.

KRAS AGAIN

A good example is Mirati, which during this Asco period appears as a virtually irrelevant 1% gainer. However, the stock had crashed in response to the May 26 abstract, when questions were raised about the durability of its Kras G12C inhibitor adagrasib in second-line lung cancer.

But Mirati recovered the losses when a late-breaker showed a 32% ORR in brain metastases, spurring hopes of differentiation versus Amgen's rival product Lumakras. A separate update from the phase 2 Krystal-7 trial, with an adagrasib/Keytruda combo in first-line NSCLC, also impressed analysts – particularly its 77% ORR in patients with ≥50% PD-L1 expression. Amgen now has a bar to hit when it presents its own combo data in late summer.

Arcellx sold off on Tuesday after presenting an important update on its BCMA-directed Car-T therapy CART-ddBCMA, but over the whole Asco period was an impressive 77% gainer. The stock is trading above its February IPO price at last.

Biggest Asco 2022 risers		
Company	**Share price chg**	**Note**
Arcellx	+77%	Carvykti casts a long shadow
Merus	+60%	Merus gets some competition
Mereo	+32%	Investors clutch at the Tigit straws
Adicet	+29%	Adicet works hard to avoid the allo Car-T scenario
Harpoon	+26%	The spirit of Rova-T struggles to live on
Legend Biotech	+21%	Carvykti casts a long shadow
Adaptimmune	+11%	Lete-cel in MRCLS: 2/10 PRs with reduced dose, 4/10 PRs with standard dose; 1 fatal cardiac arrest
Gracell	+7%	Carvykti casts a long shadow
Surface Oncology	+4%	1/27 PR for SRF388 monotherapy, 1/9 PR for SRF388 + Keytruda combo
Mirati	+1%	Great expectations for Adicet, Arcellx and PMV

Note: market close May 26 to Jun 7.

Another cell therapy company, the gamma-delta Car-T player Adicet, also had a good Asco, despite leaving durability questions unanswered. And, concerns over a Parkinsonism side effect aside, an update to the Cartitude-1 trial cemented Carvykti's unassailable status in the first wave of BCMA-directed therapies, and lifted Legend Biotech.

A curious thing happened regarding Tigit blockade. Roche's SCLC study Skyscraper-02 was revealed to be an unmitigated disaster, but an important detail regarding statistical analysis emboldened those betting that Skyscraper-01, a study in the more important setting of front-line NSCLC that failed at first interim analysis, could still yield a positive readout.

With Tigit expectations at rock bottom this lifted the stocks of Iteos and Arcus, two Tigit players without significant Asco updates, as well as that of Mereo, a distressed company that did present a poster on its anti-Tigit MAb etigilimab.

In a battle in NRG1 fusion cancers Merus came out on top, helped by a head start over its closest competitor, Elevation Oncology. Elevation came out swinging, with its chief executive, Shawn Leland, telling Evaluate Vantage that its MAb seribantumab could have broader activity than Merus's bispecific zenocutuzumab. Elevation will report data in more patients next year, but over the Asco period this micro-cap biotech slumped.

Biggest Asco 2022 fallers		
Company	**Share price chg**	**Note**
Elevation Oncology	-35%	Merus gets some competition
Springworks	-25%	Great expectations for Adicet, Arcellx and PMV
PMV Pharmaceuticals	-18%	PMV's therapeutic window slams shut
Affimed	-6%	Affimed suffers withdrawal symptoms
Roche	-4%	Roche bids for the CD20 bispecific prize
Takeda	-4%	3/32 confirmed PRs for subasumstat + Keytruda; 2/43 DLTs; 1 pt with TRAE
Sanofi	-3%	Turning Point and Libtayo steal some pre-Asco thunder
Daiichi Sankyo	-3%	A novel target rounds out Daiichi's triple
Gilead Sciences	-3%	The Tropical wind blows cold for Trodelvy
Astrazeneca	-2%	Looking beyond Enhertu in Her2-low cancer

Note: market close May 26 to Jun 7.

Although PMV Pharmaceuticals enjoyed an Asco abstract bump it came down to earth over questions that its p53 reactivator PC14586 might lack a therapeutic window, and the stock ended down over the Asco period.

Sanofi had data at the meeting but its move was probably down to a Libtayo development that did not concern Asco, while conversely Affimed was off after ultimately being unable to present a promised paper.

But, in terms of sentiment, it was perhaps Gilead that had the worst Asco. First came a late-breaker detailing Trodelvy's Tropics-02 study – to be fair this was not as bad as the biggest doom-mongers had feared – and then Destiny-Breast04 threatened to relegate that drug to a tiny breast cancer niche.

The icing on the cake came with the anti-CD47 MAb magrolimab, which has recently had its clinical hold lifted, but which continued to disappoint. Azacitidine combos in both high-risk myelodysplastic syndromes and AML produced waning complete response rates versus earlier data cuts.

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