Evaluate Vantage's Top 10 Most-Read

VOLUME 1 | 2022

ARTICLE PACK

Evaluate Vantage

Introduction

Know what's happening – and what it means for your organisation and market.

To help you stay on top of market-moving news and identify the important themes in a sea of information and data, we have rounded up our Top 10 Reads from Evaluate Vantage: the publication that brings you independent, data-driven daily news and analysis on **pharma, biotech** and **medtech**.

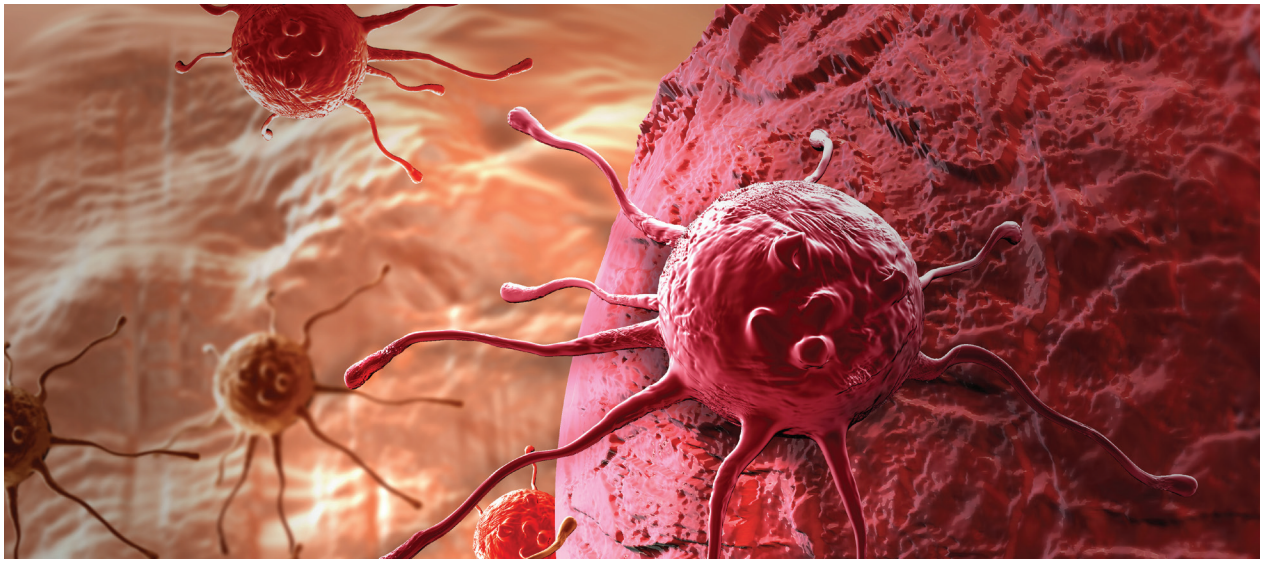
Read this selection of stories that captured the most interest among our readers recently, to discover which developments and products could have a big impact going forward, and access expert analyses on the issues driving thinking or practice changes in the sector.

Contents

AACR 2022 – the first biopharma catalysts emerge

BY JACOB PLIETH

Last night's big reveal from AACR has given biopharma investors the first clues about what to expect from this year's conference, which starts in New Orleans on April 8.



Though apart from posters AACR has published only the abstract titles for now, several look noteworthy, including a clinical update on Affimed's NK cell engager AFM13, which had wowed last year's meeting, and a look at human data with Astrazeneca's son of Lynparza, AZD5305, and PD-1/CTLA-4 bispecific MEDI5752. A few private biotechs will be thrust into the spotlight, with late-breakers (likely featuring preclinical data) from the cell therapy players Elpis Biopharmaceuticals and Myeloid Therapeutics, as well as Caribou Biosciences. An oral clinical presentation will feature TTX-030, an Abbvie-partnered anti-CD39 MAb that Tizona had spun out into the private entity Trishula after Gilead took a 49.9% stake in Tizona. And AACR's biggest late-stage dataset might be Bristol Myers Squibb's Checkmate-816 trial of Opdivo plus chemo in neoadjuvant NSCLC, though for many this will have little beyond academic interest: Opdivo secured US approval based on this study last week, just four days after the FDA accepted its filing.

Selected presentations at AACR 2022				
Company	**Project**	**Mechanism**	**Study**	**Abstract**
Biontech	BNT211	Anti-CLDN6 Car-T	CLDN6+ve solid tumours	CT002
Affimed	NK cells + AFM13	Anti-CD30xCD16A NK cell engager	CD30+ve lymphoma	CT003
Bayer	Elimusertib	ATR inhibitor	Solid tumours with DDR defects	CT006
Astrazeneca	AZD5305	Next-gen Parp1 inhibitor	Petra trial, Brca1/2, Palb2 or Rad51C/D mut	CT007
Bristol Myers Squibb	Opdivo	Anti-PD-1 + chemo	Checkmate-816, neoadj NSCLC	CT012
Highlight Therapeutics	BO-112	RNAi + Keytruda	Spotlight-203, PD-1-refractory melanoma cohort	CT014
Trishula/Abbvie	TTX-030	Anti-CD39 MAb + chemo	1L gastric/GEJ	CT015
Astrazeneca	MEDI5752	Anti-PD-1/CTLA-4 bispecific	First-in-human solid tumour study	CT016
Genocea	GEN-011	Neoantigen-directed T cells	Titan-1 study	CT153
Bicycle	BT8009	Anti-nectin-4	Nectin-4 expressing tumours	CT025
C4	CFT7455	IKZF1/3 degrader	First-in-human multiple myeloma study	CT186
Gracell	GC-0502	Allo anti-CD19/CD7 Car-T	B-cell ALL	CT196
Adaptimmune	ADP-A2M4	Anti-Mage-A4 TCR	Mage-A4 +ve tumours	LB001
Elpis Biopharmaceuticals	EPC-001	Fully human anti-CD19/CD22 tandem Car	Preclinical	LB002
Myeloid Therapeutics	?	ATAK receptors, novel Cars	Preclinical	LB005
Caribou Biosciences	CB-011	Allo anti-BCMA Car-T with HLA-E transgene	Preclinical	LB009

Source: AACR.

Another strike for biotech: China

BY JACOB PLIETH AND EDWIN ELMHIRST

Use of an auditor that cannot be inspected by the US regulator takes centre stage as Chinese biotech stocks fall.

Already reeling from general waning investor sentiment, biotech now has another problem. China-based companies traded on US exchanges are coming under pressure over the perceived risk that they might be delisted because of a rule recently implemented by the SEC.

The issue relates to the accountancy firm that each company uses to audit financials; where such a firm is based in China it typically cannot be inspected by the US regulator – and this could be grounds for delisting. Though the risk is theoretical and just five companies have so far been identified the fear is that the list will grow as annual reports are filed, and that the SEC cuts its grace period for non-compliers.

At present this grace period is three years. This means that biotechs the SEC has identified as non-compliers when they filed their 2021 accounts – currently Beigene, Zai Lab and Hutchmed – would only be delisted from Nasdaq if the regulator was also unable to inspect the firms that audited their 2022 and 2023 financials.

However, in a statement today Hutchmed cautioned: “Legislation is being considered in the US to shorten the number of non-inspection years from three years to two.”

HOLDING COMPANIES ACCOUNTABLE

How did this all come about? The problem had been brewing since December 2020, when the US Holding Foreign Companies Accountable Act came into law.

This requires the SEC to identify US-listed companies that are audited by firms located in a foreign jurisdiction that makes it impossible for them to be inspected by the Public Company Accounting Oversight Board (PCAOB). The statute is part of a US push to access information protected by national law, especially China's.

What happened this week was that the SEC published its list of the first five non-compliant companies. Purely by dint of being the first to file annual reports, Beigene, Zai and Hutchmed featured as the first three biotechs to be identified as non-compliant.

But there was investor selling across the board, and the Loncar China Biopharma exchange-traded fund closed down 3% yesterday. Curiously, the fallers included Lianbio, off 10%; Lanbio today issued a statement stressing that it was compliant with the new law, and that it had a US-based auditor that is currently inspected by the PCAOB.

Moreover, the audits involved are understood not to be especially onerous. "There's a moderate to high probability that this gets worked out in the year ahead," Brad Loncar, chief executive of Loncar Investments, told Evaluate Vantage, adding that it was not in China's interest to allow its companies to be delisted from the US.

"Ironically, I think the way the stocks have plunged will bring China and the US closer to the table to work it out, so [the selloff] yesterday might end up being productive in some ways," he said.

Trading in selected US-listed Chinese companies on March 10, 2022

Company	Share price chg	On SEC's provisional non-compliance list?	Statement
I-Mab	-13.8%	No	None
Lianbio	-10.1%	No	Says principal auditor is located in New York, and inspected by PCAOB
Zai Lab	-9.0%	Yes	Confirms auditor cannot be inspected by PCAOB; working to engage independent auditor that satisfies PCAOB requirements
Connect Biopharma	-8.7%	No	None
Hutchmed	-6.5%	Yes	Confirms potential delisting in 2024, unless PCAOB can conduct full inspection of auditor; notes US might shorten allowed non-inspection period from 3 to 2 years
Beigene	-5.9%	Yes	None
Legend Biotech	-3.7%	No	None
Gracell	-1.7%	No	None
Adagene	-1.6%	No	None
Sinovac	None*	No	None
China Pharma Holdings	Unchanged	No	None
Universe Pharmaceuticals	+0.8%	No	None
Genetron	+1.4%	No	None

Note: *Trading in Sinovac stock has been halted since 2019.

Source: Stock exchange & company information.

For its part, China's securities regulator said it respected the SEC's strengthened supervision of "relevant accounting firms to improve the quality of listed company financial information", but strongly opposed what it called "the politicisation of securities supervision".

"We are willing to solve the problem ... through regulatory cooperation. China's Securities Regulatory Commission and Ministry of Finance have continued to communicate with the PCAOB and have made positive progress," it said.

Still, given the cautious biotech investment climate, many will want to know what the worst-case scenario is. Importantly, Beigene, Zai and Hutchmed have secondary listings, so their stock can be converted between each listing, and cancellation of shares on Nasdaq would not erase holders' ownership, no matter how bad the optics of such a move would be.

"I expect others like I-Mab, which don't yet have a secondary listing, to [secure one] ASAP as an insurance policy," said Mr Loncar. "The fact that I-Mab doesn't yet have one is the reason why its stock was hit the hardest yesterday."

Amgen hold-up gives Mirati a vital lifeline

BY JACOB PLIETH

A possible timing crunch threatening Mirati's delayed Kras inhibitor might not now happen.

Six months might not seem like much, but for Mirati every second of it will count. Readout of Amgen's confirmatory lung cancer trial of Lumakras, yesterday delayed from the first to the second half of this year, buys vital breathing space for Mirati as it scrambles to get its rival adagrasib onto the market.

Since Mirati is a year behind Amgen, the possibility of Lumakras being formally approved, based on the confirmatory data, jeopardised adagrasib's chances of gaining an accelerated label. Mirati earlier rejected the suggestion that there was a risk, but recent precedent shows the threat to be real; the group must now execute quickly.

When Evaluate Vantage two weeks asked Mirati's chief executive, David Meek, whether Lumakras confirmatory data and full approval threatened adagrasib he stated: "No, we don't think so. The FDA is well aware of the timelines of both programmes. We have breakthrough therapy designation [and] we were granted real-time oncology review, so we fully expect our approval."

Still, investors need look no further than last October for an example of a very similar timing crunch. Then Agenus had to pull an accelerated filing under priority review for balstilimab in cervical cancer after the FDA granted Merck & Co's

Keytruda full approval, making a conditional green light for a similarly acting rival in the same setting unsustainable.

THE TIMELINE

For Mirati the timeline is crucial. Until yesterday's delay Amgen had been due to reveal results of Lumakras's confirmatory Codebreak-200 trial before the mid-year point, which is when Mirati expects adagrasib to be approved.

But even this Mirati expectation is extremely bullish: though the adagrasib NDA has been submitted it has yet to be reviewed and accepted, something Mirati expects imminently. If the FDA raises no questions, grants the filing priority review and accepts it now, a six-month cycle would put August as the action date for approval.

Thus Mirati is banking not only on flawless execution and priority review but also on a super-fast turnaround, as had happened for Lumakras, which was greenlit in the space of just three and a half months. However, a standard 10-month review is a possibility, and would put the adagrasib action date into November.

This bear case could see the FDA reviewing Lumakras's confirmatory dataset before adagrasib's Pdufa date, even with Amgen's delay.

Timeline of the duelling Kras G12C inhibitors in lung cancer

	Lumakras (Amgen)	Adagrasib (Mirati)
Accelerated filing for 2L Kras G12C+ve NSCLC accepted	Feb 2021	Feb 2022*
Goal action date	Aug 2021	Aug/Nov 2022*^
Accelerated US approval	May 2021	Jul-Nov 2022*
Confirmatory study readout	Delayed from H1 to H2 2022 (Codebreak-200)*	H2 2023 (Krystal-12)*
Full US approval	2022/23*	2023/24*

Note: *Expected; ^Aug if priority review is granted, Nov if it is not.

Source: Company statements.

While Mirati has gained a valuable lifeline its investors will recall the crucial months it has already lost; adagrasib and Lumakras had been on similar timelines, with the former sometimes showing superior efficacy on a cross-trial basis, but while Amgen moved fast to get its asset before the regulator Mirati became embroiled in a C-suite overhaul.

How does Mirati now catch up? "We are coming in later, we are well aware of that," said Mr Meek. But adagrasib is "a different agent, with a 24-hour half life, which enables near complete inhibition of mutant Kras G12C. Response rates across the board are higher with adagrasib relative to other G12C inhibitors."

He also cited adagrasib's CNS activity, and the project's activity in colorectal cancer shows another point of departure from Lumakras. Still, the first filing is in NSCLC, while Mirati continues to "finetune" the colorectal cancer approval pathway with the FDA.

Interestingly, while Mr Meek denied the threat Amgen's confirmatory data pose to adagrasib, he said they would "present challenges to follow-on Kras G12C inhibitors; they're not going to be able to pursue the conditional marketing authorisation accelerated pathway, at least in second-line lung cancer."

For Amgen a delay to Codebreak-200 matters much less than Lumakras's 2021 sales, which some analysts yesterday saw as light. For Mirati to take advantage of the bullet it might just have dodged it cannot afford any further delays.

Looking beyond Roche's Tigit bombshell

BY JACOB PLIETH

The failure of Skyscraper-01 calls into question Roche's vast investment in Tigit blockade, but is there broader significance?

Boom! That was the sound of another immuno-oncology mechanism blowing up. In fairness, it would be premature to say with certainty that today's failure of Roche's tiragolumab in the Skyscraper-01 trial – one of 2022's biggest catalysts – is the death knell for Tigit blockade, but it surely is not a good sign.

Judging by the market's early reaction, investors in Arcus and Iteos, two players with large exposure to Tigit, fear that this mechanism will soon join IDO and IL-2 among immuno-oncology's expensive flops.

Here, Evaluate Vantage has tried to cut through the hubris and assess what is known and what is not, and what this all means.

WHAT DO WE KNOW?

In Skyscraper-01, in PD-L1-high front-line NSCLC patients, tiragolumab plus Tecentriq failed to beat Tecentriq in terms of progression-free survival, although there was a numerical benefit. Analysis of overall survival, the co-primary endpoint, is immature. This is the second pivotal trial in the Skyscraper programme to fail, with eight more yet to read out.

WERE THERE ANY WARNING SIGNS?

The failure of Skyscraper-02 was one, though this was easily dismissed given the intractable nature of SCLC. There were three other, bigger canaries in the coalmine, all from the Cityscape study that also tested Roche's combo against Tecentriq in first-line NSCLC.

This did show tiragolumab adding efficacy in terms of remissions and PFS over Tecentriq, but only in high PD-L1 expressers; the effect was flattered by Tecentriq monotherapy underperforming versus the Impower-110 trial; and there was no link between efficacy and Tigit expression. Ultimately, these facts cast doubt over what Tigit blockade was bringing to the party.

SO WHAT WAS ROCHE THINKING WHEN IT EMBARKED ON THIS MASSIVE PROGRAMME?

When in January 2020 Roche quietly put tiragolumab into the first of 10 Skyscraper studies investors assumed that it must have had convincing data in house. However, beyond the subsequent Cityscape results, with the drawbacks outlined above, little else has emerged to back the enthusiasm for a programme that currently has an enrolment target of 8,365 patients.

ARE THERE ANY POSITIVES?

The lack of statistical significance despite a numerical improvement suggests that Skyscraper-01 might have been underpowered, and the lack of a PFS benefit need not translate into a fail on overall survival. A setback in lung cancers does not necessarily mean that tiragolumab is a bust in other settings, and each anti-Tigit MAb works slightly differently.

HOW BAD ARE THE OMENS FOR OTHER TIGIT PROJECTS?

Full Skyscraper-01 data are needed before drawing firm conclusions, but things do not look great, especially as no other Tigit player has been able to rival Roche's earlier Cityscape dataset, or show meaningful single-agent activity. On the other hand, not all Tigit MAbs are alike, with differences in binding sites, IgG type and Fc functionality.

Clinical-stage projects targeting Tigit				
Project	**Company**	**MAb type**	**Key study**	**Total enrolment target**
Phase 3				
Tiragolumab	Roche	IgG1, Fc active	Skyscraper-01 (failed)	8,365
Vibostolimab	Merck & Co	IgG1, Fc active	Keyvibe-003	5,331
Ociperlimab	Novartis/ Beigene	IgG1, Fc active	NCT04866017	2,892
Domvanalimab	Gilead/ Arcus	IgG1, Fc silent	Arc-7 (ph2)	1,932
Phase 2				
EOS-448	Glaxosmithkline/ Iteos	IgG1, Fc active	NCT03739710	841
BMS-986207	Bristol Myers Squibb	IgG1, Fc silent	NCT05005273	657
Phase 1/2				
Etigilimab	Mereo (ex Oncomed; Celgene turned down option)	IgG1, Fc active	NCT04761198	158
AZD2936	Astrazeneca (ex Compugen)	IgG4, PD-1 bispecific	Artemide-01	147
Phase 1				
SGN-TGT	Seagen	IgG1, Fc enhanced	NCT04254107	397
JS006	Coherus/ Junshi	IgG4, incl Fc silent & active molecules	NCT05061628	384
IBI939	Innovent	?	NCT04353830	332
M6223	Merck KGaA	IgG1, Fc active	Javelin Bladder Medley	287
AB308	Arcus	IgG1, Fc active	NCT04772989	160
COM902	Compugen	IgG4, Fc silent	NCT04354246	90
AGEN1777	Bristol Myers Squibb/ Agenus	Fc enhanced bispecific	NCT05025085	75

Source: Evaluate Pharma & clinicaltrials.gov.

WHICH COMPANIES ARE THE MOST EXPOSED?

Arcus, Iteos and Compugen offer nearly pure-play exposure to Tigit, and today opened off 29%, 19% and 3% respectively.

But it is also important to remember that several big biopharma business development departments will be feeling the heat. Gilead handed across $750m to Arcus last November, after Glaxo paid $625m for Iteos's EOS-448; later Novartis paid $300m for an option on Beigene's ociperlimab.

Among in-house assets Merck & Co has vibostolimab in the pivotal Keyvibe programme, some of whose studies mirror the design of the Skyscraper trials, and which is seeking to enrol 5,331 patients in total.

WHAT DATA SHOULD INVESTORS LOOK TO NEXT?

Before Roche reports full data from Skyscraper-01 investors will be able to scrutinise the failed Skyscraper-02 study, courtesy of an Asco late-breaker on June 5 (LBA8507). At a stroke this has been transformed into one of Asco's key presentations, given that it might shed light on this morning's failure and on Tigit blockade in general.

After that it will be the turn of the industry's next-biggest Tigit catalyst – data from Arcus/Gilead's domvanalimab in Arc-7, a first-line NSCLC study with a broadly similar design to Skyscraper-01 and Keyvibe-003. However, after three opaque updates it is anyone's guess how much data will actually be revealed.

Given the history of disastrous biz dev moves under Gilead's belt, that company's chief executive, Daniel O'Day, will today be sitting very nervously.

What now for low-cost PD-(L)1 competition?

BY JACOB PLIETH

The prospects for Chinese competitors, ongoing controversy in cervical cancer and a super-fast approval take centre stage.

Welcome to the third in a series of periodic Evaluate Vantage updates on developments in the PD-(L)1 inhibitor space, whose focus is sintilimab's savaging at a February 10 US adcom.

A 14-1 vote against the Innovent/Lilly drug and in favour of additional trial(s) virtually assured its rejection by the FDA. The bigger question for investors and for healthcare systems is whether this also scuppers the chances of other PD-(L)1 newcomers seeking to undercut the current US incumbents and bring about price competition at last.

As well as identifying the key upcoming catalysts facing immuno-oncology players in the US, EU, China and Japan, the report surveys the past three months' clinical trial development. These include an important success for Astrazeneca's tremelimumab, and the fast-changing landscape in adjuvant and neoadjuvant treatment of lung cancer.

Indeed, this setting in recent weeks featured one of the fastest US approvals on record: Bristol Myers Squibb's filing for Opdivo plus chemo as a treatment for neoadjuvant lung cancer was approved just four days after filing, over four months before its goal Pdufa date.

Less positive news came from Sanofi/Regeneron, which cancelled a follow-on US filing for Libtayo in second-line cervical cancer. This update details further clinical and regulatory catalysts, with comprehensive tables, and developments in January-March, including:

- Key upcoming catalysts for low-cost competitors.
- Recent US approvals and upcoming Pdufa dates.
- Recent approvals in China, including that of the 12th anti-PD-(L)1 antibody.
- Development-stage anti-PD-1/PD-L1 MAbs in China.
- Clinical developments in liver, bile duct, lung and other cancers.
- Upcoming regulatory catalysts in the EU and Japan.

The **EVALUATE VANTAGE PD(L)ANNER** – March 2022 provides news, insights and analysis on the PD-(L)1 antibody landscape. Among other issues, we focus on potential pricing changes, provide an update on what's happening in China and other markets, and share our views on the results of recent studies.

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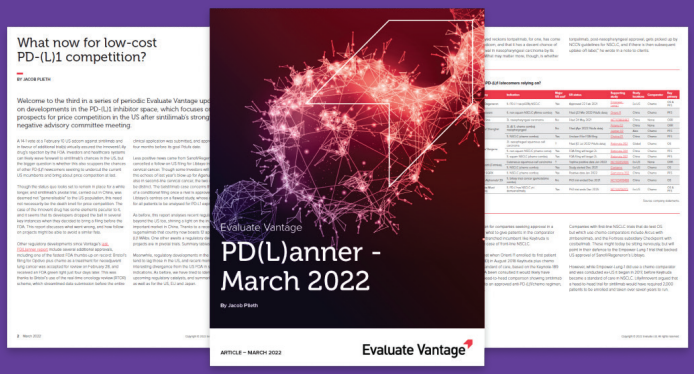

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Genetic medicine: the next generation

BY MADELEINE ARMSTRONG

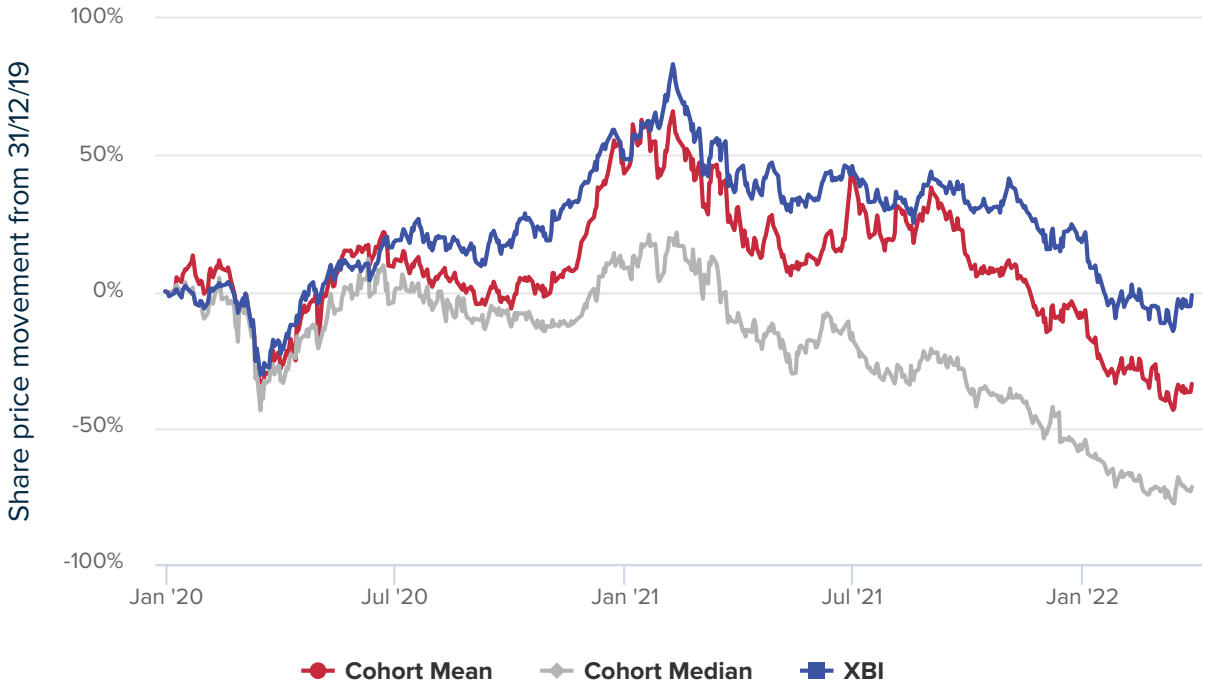
A new report from Evaluate Vantage looks at new approaches aiming to solve problems facing the current generation of genetic medicines.

Once upon a time, a gene therapy player could release data on a handful of subjects and see its share price rocket. The sector was riding high after the landmark approvals of Luxturna and Zolgensma, and big pharma was keen to buy in. Valuations surged as investors clamoured for a piece of the pie.

Those days are long gone, as a just-published Evaluate Vantage report spells out. The US biotech bear market has been particularly tough on gene therapy and editing groups, whose multi-billion-dollar valuations always looked rich considering that the technologies involved were mostly unproven.

Indeed, the chart below, which includes a cohort of 35 genetic medicine companies, shows just how hard the sector's fall from grace has been.

The rise and fall of gene therapy stocks



Note: Cohort comprised of 35 listed biotechs with a primary focus on genetic medicines

The nascent field has had its fair share of problems, from worries about toxicity and lack of durability to questions about the size of the market for these expensive therapies. The conclusion that investors seem to have reached, for now, is that reality has not lived up to the hype.

However, genetic medicine groups are not yet ready to throw in the towel, and some players are working on technologies that, they believe, will address the problems with the current generation of therapies.

This free report from Evaluate Vantage profiles several very early-stage groups that are all trying to do something different. Topics discussed in the report include:

- The limitations of delivery via adeno-associated viral (AAV) vectors, including immunogenicity, lack of durability, and complex manufacturing;
- how companies are trying to address these problems by using different delivery methods, for example lipid nanoparticles and inert scaffolds, designed to allow redosing;
- how these methods could broaden the reach of genetic medicine to include diseases that involve large genes, currently not addressable with AAV vector-based projects;
- whether genetic medicines could one day be used for common disorders, from cardiovascular to infectious diseases;
- how non-viral delivery could make manufacturing simpler and more scalable;
- and the importance of price if genetic medicine is ever going to become mainstream.

The companies profiled are:

- Generation Bio, which is using lipid nanoparticles to deliver close-ended DNA, for rare and common disorders alike;
- Code Bio, whose “plug and play” approach employs a DNA scaffold, specific targeting molecules and various payloads, from gene therapy to RNA interference to gene editing;
- Verve Therapeutics, which hopes to bring gene editing to the masses with its base-editing project hitting PCSK9;
- Excision Biotherapeutics, which is using Crispr/Cas9 to target, and hopefully cure, infectious diseases like HIV;
- and Saliogen Therapeutics, which has coined the term “gene coding” to define its ambitious approach, which it claims can allow the insertion of unlimited amounts of DNA directly into the host genome.

For a view from the frontlines, Evaluate Vantage spoke to executives at companies that are working on new gene therapies about how they are overcoming the challenges that beset the first generation.

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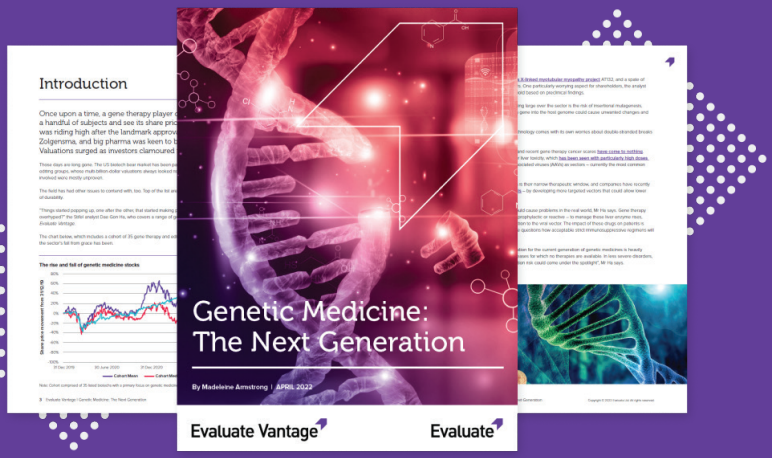

Thought-provoking insights and commentary on all the key issues

Understand what’s happening in the world of pharma, biotech and medtech with Evaluate Vantage’s independent, data-driven news and analysis.

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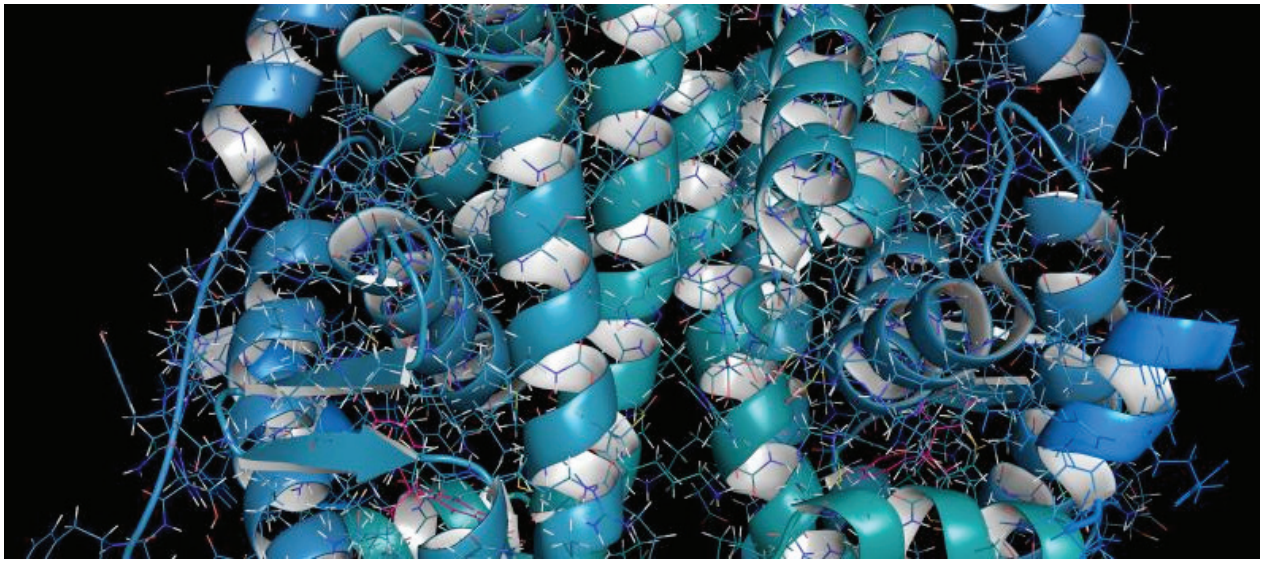
Close encounters of the Serd kind

BY JACOB PLIETH

All-comer Serd studies in pretreated breast cancer look doomed, so why do Astra and Lilly persist? And why isn't Radius seizing its advantage?



The idea of treating breast cancer with selective oestrogen receptor degraders, or Serds, has undergone a divergence. The pretreated setting looks increasingly driven by ESR1 mutation, but rather than focus on this the big pharma players are turning instead to front-line combination use.

An even stranger fact is that Radius Pharma, the only company so far that managed to design a second-line study geared at showing a benefit in ESR1-mutant disease – and which succeeded as a result – is not pursuing the first-line setting. Unless Radius moves quickly it will not have the upper hand for long.

Radius has this advantage as a result of the Emerald trial of its Serd, elacestrant, which succeeded in second-line ER-positive, Her2-negative breast cancer largely thanks to having been enriched for ESR1 mutation. There was a statistical PFS benefit versus standard of care (including Faslodex) in ESR1-positive patients, and these also drove a PFS benefit in all-comers.

Conversely, two subsequent studies in a similar setting – but not enriched for ESR1 – have failed recently. In March Sanofi's amcenestrant flunked the Ameera-3 trial, and last week Roche's giredestrant failed in Acelera.

DOOMED TO FAIL

Based on this trend the two remaining registrational Serd studies in the second-line setting now look doomed to fail; Astrazeneca's Serena-2 trial of camizestrant reads out in the second half, while Lilly's Ember-3 study of imlunestrant has a completion date of mid-2023. Neither enriches for ESR1 mutation, or tests for a benefit in this group as a primary endpoint.

Instead of amending trial designs the big pharmas are instead looking to position Serds in earlier settings of ER-positive Her2-negative breast cancer.

On April 28 Sanofi's head of R&D, John Reed, said: "From the beginning we felt that the sweet spot for Serds was going to be in early lines of therapy. We took a swing in the late line [with amcenestrant], knowing the risks associated."

On the same day Jake Van Naarden, head of Lilly's Loxo division, stated: "The ultimate impact [for imlunestrant] is adjuvant, and we're working on a trial design that we will share later in the year." The company suggested that the failed second-line trials were underpowered.

For its part, Astra says there are differences between the projects. It is continuing with the now fully enrolled Serena-2 study, in which it expects 30-40% of patients to be ESR1-positive, and cites an earlier trial that showed camizestrant's clinical activity in patients with and without ESR1 mutation.

BEATING FASLODEX

To understand why this debate has even arisen it is important to go back to the launch of the first Serd, Astra's Faslodex. This now off-patent drug had poor bioavailability and was delivered intramuscularly, and only received a second-line label.

However, toxicity and poor bioavailability aside, there is no theoretical reason why Faslodex should not work first line, where the oestrogen receptor is thought to be an even bigger driver of disease than in later therapy lines, where resistance builds up.

Crucially, in patients with ESR1 mutations Faslodex is thought not to work as well as newer Serds. This might explain Radius's success in the Emerald study: elacestrant and Faslodex alike might have proved efficacious in ESR1 wild-type patients, but the Radius project won out in those with ESR1 mutation.

More evidence of such a benefit comes from Roche's failed Acelera trial: on April 25 Bill Anderson, the Swiss group's head of pharma, said giredestrant yielded better progression-free survival versus standard of care in patients with baseline ESR1 mutations than in all-comers.

Sanofi says "most patients become ER-independent in their cancer journey", and along with Roche and Astra is playing up the relevance of front-line studies that are already under way. With no need to beat Faslodex in these early lines the key for novel Serds will be to come out better than aromatase inhibition, in combination with other front-line drugs like Ibrance.

Oral Serds in late-stage development for ER+ve/Her2-ve breast cancer						
	Elacestrant	**Amcenestrant**	**Giredestrant**	**Camizestrant**		**Imlunestrant**
Company	Radius Health/ Menarini	Sanofi	Roche	Astrazeneca		Lilly
2nd-line study	Emerald	Ameera-3	Acelera	Serena-2		Ember-3
Enrichment for ESR1 mutation?	Yes	No	No	No		No
Result	Succeeded in ESR1mut & all-comers	Failed	Failed	Due H2 2022		Ends Jun 2023
1st-line study	None (Menarini's responsibility)	Ameera-5	Persevera	Serena-4	Serena-6	None
Design		Ibrance combo, vs Ibrance + aromatase inh				
Enrichment for ESR1 mutation?		No	No	No	Yes	
Data		Ends Jan 2024	Ends Apr 2024	Ends Nov 2025	Ends Sep 2023	
Adjuvant study	None (Menarini's responsibility)	Ameera-6	Lidera	None		None (design to be revealed in 2022)
Design		Vs tamoxifen	Vs doc's choice			
Enrichment for ESR1 mutation?		No	No			
Data		Ends Dec 2026	Ends Dec 2025			

Source: Evaluate Pharma & clinicaltrials.gov.

The debate about patient enrichment concerns earlier-stage biotechs too, including Arvinas and Zentalis; Stifel analysts recently wrote that the monotherapy setting looked increasingly like an ESR1-mutant story, and no doubt when these companies get around to designing registrational trials they will bear this in mind.

It is remarkable that so far only Radius has been able to score a second-line success. Roche, for instance, has been playing the Serd game for years with zero success so far; in 2014 it spent $725m buying Seragon, but both of this group's lead Serd assets, RG6046 and RG6047, ended up in the bin. Giredestrant is the group's third attempt.

But Radius now faces a big problem of its own. It is not running early-line elacestrant studies, saying these are the responsibility of its partner Menarini, and is focusing on getting its project approved second-line, where a filing is due in the current quarter.

Should any of Radius's rivals score in the first-line setting elacestrant could see its second-line window close just as fast as it had opened.

This story has been amended to correct the design of Ameera-6.

Biogen goes back to 1995 to grab mosunetuzumab

BY JACOB PLIETH AND AMY BROWN

The company has yet again cashed in on a decades-old Roche deal that few might even remember.

It might come as a surprise to all but the most avid readers of US regulatory filings that Biogen owns a significant stake in Roche's anti-CD20 franchise, including Ocrevus. Investors were reminded of this 27-year-old arrangement yesterday when Biogen exercised an option to license the Swiss group's anti-CD20 bispecific mosunetuzumab.

The deal has already enabled Biogen to collect billions from these products, including Rituxan, which since becoming the first ever MAb approved to treat cancer has generated cumulative sales of over $100bn. Biogen also collects cash on Gazyva and Ocrevus; it will now do so on mosunetuzumab, and could in future repeat the trick with other Roche assets, including glofitamab.

In a sense mosunetuzumab will help offset the declining cash Biogen gets from a share of Rituxan and Gazyva's profits, which have been hit by biosimilars and other competitors. Still, by far the biggest contributor to Biogen's CD20 revenue line will be royalties on the multiple sclerosis blockbuster Ocrevus; extrapolating from Evaluate Pharma consensus forecasts these might exceed $1bn over at least each of the next six years.

The fruit of Roche & Biogen's 27-year CD20 marriage ($m)					
	2018	**2020**	**2022e**	**2024e**	**2026e**
The current arrangement...					
Rituxan US sales	4,289	3,022	1,192	810	640
Gazyva US sales	195	312	399	561	697
Profit on Rituxan & Gazyva US sales	3,815	2,901	1,384	1,193	1,163
Biogen's share of the above	1,432	1,080	512	441	430
Biogen co-promotion profits on Rituxan in Canada	70	52	0	0	0
Ocrevus global sales	2,406	4,614	6,242	7,127	7,639
Biogen royalty on Ocrevus	478	845	1,124	1,283	1,375
Total booked by Biogen	**1,980**	**1,978**	**1,636**	**1,724**	**1,805**
...and possible future Roche products?					
Mosunetuzumab global sales	0	0	68	248	525
Biogen has opted in to mosunetuzumab, and will receive a low to mid-30% US profit share plus low single-digit ex-US royalties					
Glofitamab global sales	0	0	0	71	236

Source: Evaluate Pharma & SEC filings.

These forecasts have mosunetuzumab, which could be filed this year for follicular lymphoma, hitting 2026 sales of $525m, though the sellside sees $1bn at peak. Under the opt-in exercised yesterday Biogen paid $30m, and will contribute to development costs incurred in 2021, in return for a low to mid-30% share of US profits, plus a low single-digit ex-US royalty.

Though this might look like Biogen moving away from neurology and into oncology, the group has denied this to analysts. As such this is likely a financial exercise – seizing on a legacy tie-up to secure a large revenue line for a relatively small outlay.

But how did this all come about? For the answer you have to go back to 1995, when Idec Pharmaceuticals struck an anti-CD20 antibody discovery deal with Roche's Genentech unit.

This originally focused on molecules coded Y2B8 and In2B8, which later became Zevalin, Idec's radiolabelled anti-CD20 MAb that was the first US-approved radio-immunotherapy; and C2B8, which in Roche's hands became the blockbuster Rituxan. In 2003 Idec underwent a $6.8bn merger with Biogen, assigning rights to the current Biogen entity.

CERTAIN ADDITIONAL PRODUCTS

Meanwhile the deal underwent several amendments, perhaps the most significant of which was an expansion to include "certain additional products whose mechanism of action is initiated by interaction with CD20, including ... the humanised molecule created by Genentech known as G2H7".

It is not clear whether G2H7 became Gazyva or Ocrevus, but either way Biogen now has rights to both of these. And now it owns a share of mosunetuzumab, a project that impressed at each of the last two Ash meetings, and one of the most promising bispecifics looking to push the increasingly competitive CD20 space forward once more.

Interestingly, mosunetuzumab is not the only late-stage anti-CD20 T-cell engaging MAb in development at Roche's Genentech division; the other is glofitamab.

While mosunetuzumab uses a straight "1+1" format, glofitamab has a more complex "2+1" structure, with a silent Fc region to increase its half life. One question for Roche has been whether it would end up prioritising one asset over the other, though

Biogen opting in to mosunetuzumab will probably not influence the Swiss group's thinking.

This is because the 1995 deal's key amendment gives Biogen certain broad rights to anti-CD20 assets beyond "G2H7", including "new products", as well as a right of negotiation for third-party anti-CD20 products. Such assets might include glofitamab as well a RG6035, a brain-shuttle anti-CD20 in phase 1 for multiple sclerosis.

Roche said it was too early to speculate on RG6035, but confirmed to Vantage that Biogen "may have the opportunity to participate in the US commercialization of glofitamab, the details of which have yet to be negotiated".

The biggest launches of 2022: a reboot

BY AMY BROWN

New Alzheimer's launches are all but ruled out, so projects from Lilly, Alynlam and Roche top 2022's biggest hopes.

Before the fallout from Biogen's ongoing travails quashed the prospect of a fast-growing market for novel Alzheimer's therapies, anti-amyloid-beta MAbs from Lilly and Roche sat among 2022's biggest potential launches. Not any more.

Evaluate Vantage's latest look at the projects approaching the market this year that are considered by the sellside to have the largest commercial potential still finds Lilly way out in front with tirzepatide. But the diabetes asset is now flanked by a wider range of prospects, with Alnylam's amyloidosis hope vutrisiran and Roche's macular degeneration bispecific standing out.

That last drug is Vabysmo, containing the active ingredient faricimab, which has already secured a green light from the FDA. Grabbing a share of what is a highly competitive market might be harder than these punchy numbers suggest, however. As Bernstein analysts noted recently, the product is not yet available in a pre-filled syringe, while its benefits versus Eylea are far from clear.

It is also worth noting that there were several big approvals in the closing days of 2021 that could arguably be considered 2022 launches. This includes Argenx's Vyvgart, which became the first FcRn antagonist to win US approval, and Amgen

and Astrazeneca's Tezspire, an antibody for severe asthma. Both are forecast to be in blockbuster territory by 2026.

Elsewhere, Pfizer's contender in the Jak inhibitor class, Cibinqo, received approval in the all-important US market in January, a couple of months after getting the nod in Europe. Evaluate Vantage has restricted the below analysis to first-time 2022 approvals, however.

Blockbusters in waiting? Big arrivals on the horizon for 2022				
Product	**Company**	**Description**	**Status**	**2026e sales**
Tirzepatide	Lilly	GLP-1/GIP dual agonist for type 2 diabetes & obesity	Approvals expected around mid-year in US, EU & Japan	$5.4bn
Vutrisiran	Alnylam	RNAi therapy for ATTR amyloidosis	Pdufa Apr 14, 2022; EU approval expected Q4 2022	$1.8bn
Vabysmo	Roche	Anti-VEGF-A & ANG 2 bispecific for wet age-related macular degeneration & diabetic macular oedema	Approved in US in Jan, decisions expected in EU & Japan later this year	$1.8bn
Carvykti	Johnson & Johnson	Anti-BCMA Car-T for multiple myeloma	Pdufa Feb 28, 2022 (extended by 3mth); EU approval expected Q1 2022	$1.7bn
Adagrasib	Mirati	KRAS G12C inhibitor for NSCLC	Acceptance of FDA filing pending; Aug Pdufa date possible	$1.7bn
Mavacamten	Bristol Myers Squibb	Cardiac myosin inhibitor for cardiomyopathy	Pdufa Apr 28, 2022 (extended by 3mth); EU approval expected H2 2022	$1.7bn
Deucravacitinib	Bristol Myers Squibb	Tyk2 inhibitor for psoriasis & other autoimmune conditions	Pdufa Sep 10, 2022; EU approval expected Q4 2022	$1.7bn
Ublituximab	TG Therapeutics	Anti-CD20 MAb for multiple sclerosis	Pdufa Sep 28, 2022	$1.6bn
Lenacapavir	Gilead	Long-acting HIV-1 capsid inhibitor, initially targeting heavily pretreated patients	Pdufa Feb 28, 2022, EU approval expected early 2022	$877m
177Lu-PSMA-617	Novartis	PSMA-directed, Lu-labelled radioligand, for prostate cancer	FDA decision expected H1, EU decision H2	$851m

Source: Evaluate Pharma.

This analysis was previously conducted for our 2022 Preview, which is available as a free download. Back then, Lilly and Roche Alzheimer's projects donanemab and ganterenumab featured as this year's biggest launches. But with Roche effectively putting speculation of an accelerated approval submission to bed, and Lilly saying its application would be delayed, the prospect of these agents becoming available imminently is very low.

Another project that no longer features is Reata's bardoxolone, which received a savaging from an FDA advisory committee in December, prompting panel members to vote unanimously against its approval.

On the other hand, there are other potential blockbusters that might yet make it to market this year, though the timing is tight. One is Apellis's geographic atrophy project APL-2, or pegcetacoplan, which the group has promised to file in the second quarter; a speedy and hitch-free FDA review remains the bull case, of course.

Elsewhere, some analysts reckon Nektar's bempegaldesleukin, partnered with Bristol Myers Squibb, might have a chance of approval this year. This depends on success in the crucial Pivot trial, and not many have faith in that happening.

At least Bristol has two other projects to fall back

on – three if relatlimab is counted, since forecasts for the Lag3 inhibitor sit at $437m, according to Evaluate Pharma consensus. It is worth noting that consensus for deucravacitinib has come down substantially in the past few months, amid concerns that the FDA's caution around the safety of the Jak inhibitors might extend to the Tyk2 class.

It remains true, however, that projects owned by smaller developers should be treated with the most caution. Take Mirati, which has fumbled adagrasib's programme at a time when doubts are growing about the potential for the Kras inhibitor class.

Consensus around TG Therapeutics' ublituximab is also highly debateable. If approved, this anti-CD20 MAb will compete in a crowded market, while missteps by the company elsewhere could be interpreted as lowering the chances of getting there in the first place. Bulls argue that TG's issues with its cancer ambitions are separate from its work in MS, but the risk of complete disaster can never be ruled out.

Digging into biopharma's big buyout areas

BY AMY BROWN AND EDWIN ELMHIRST

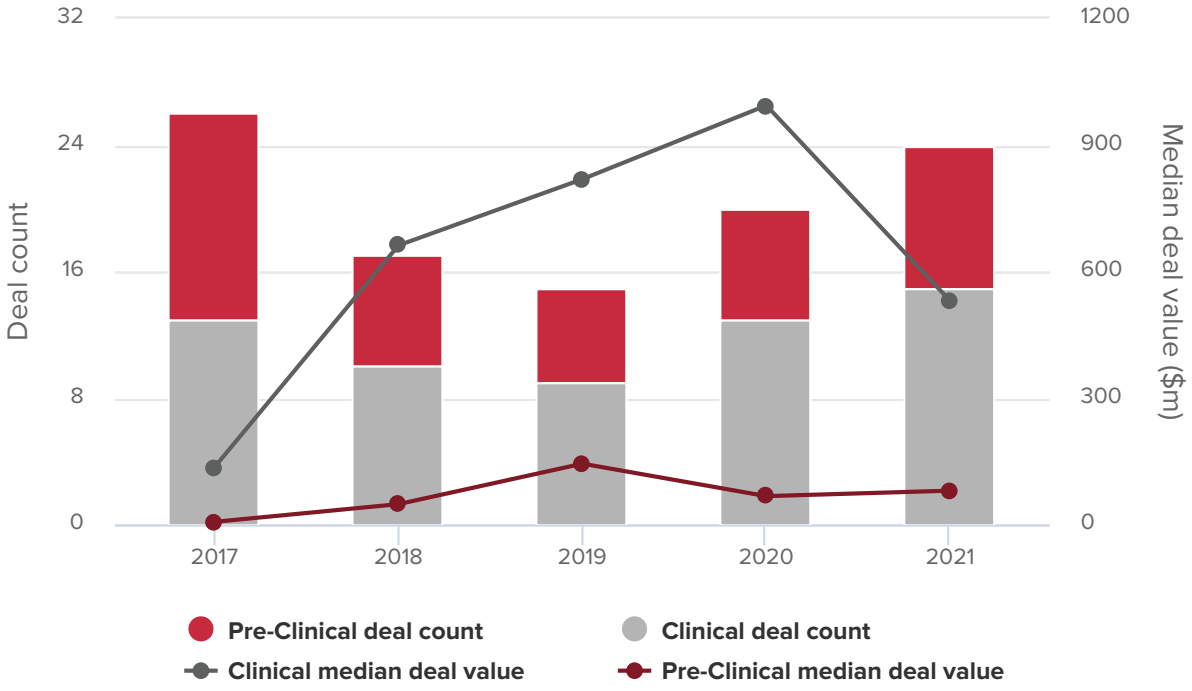
Cancer, rare diseases and neurology targets account for a big chunk of biopharma's buyouts, with interest showing no sign of waning.

Developers working in oncology, conditions of the CNS and rare diseases have been the target of more than half of the biopharma sector's buyouts in the last five years, and half the sums spent.

Beyond these therapy areas the volume of deals happening each year makes spotting more trends harder, but a closer look at cancer and rare diseases throws up some interesting insights.

For this deep dive into Evaluate Pharma's M&A data, Evaluate Vantage grouped the last five years of buyout targets by their main therapy area focus of the deal target. Companies can be very hard to pigeonhole, however, which speaks to a major caveat of this analysis: many developers work in multiple disease areas. Targets were only excluded if no clear, dominant focus could be identified.

Oncology - deal count and median deal values



Source: Evaluate Pharma.

Oncology represents by far the largest area of deal-making for biopharma, accounting for more than a quarter of the transactions and sums spent, over the past five years. As the chart above shows, there was an uptick in acquisitions last year, after a quieter period.

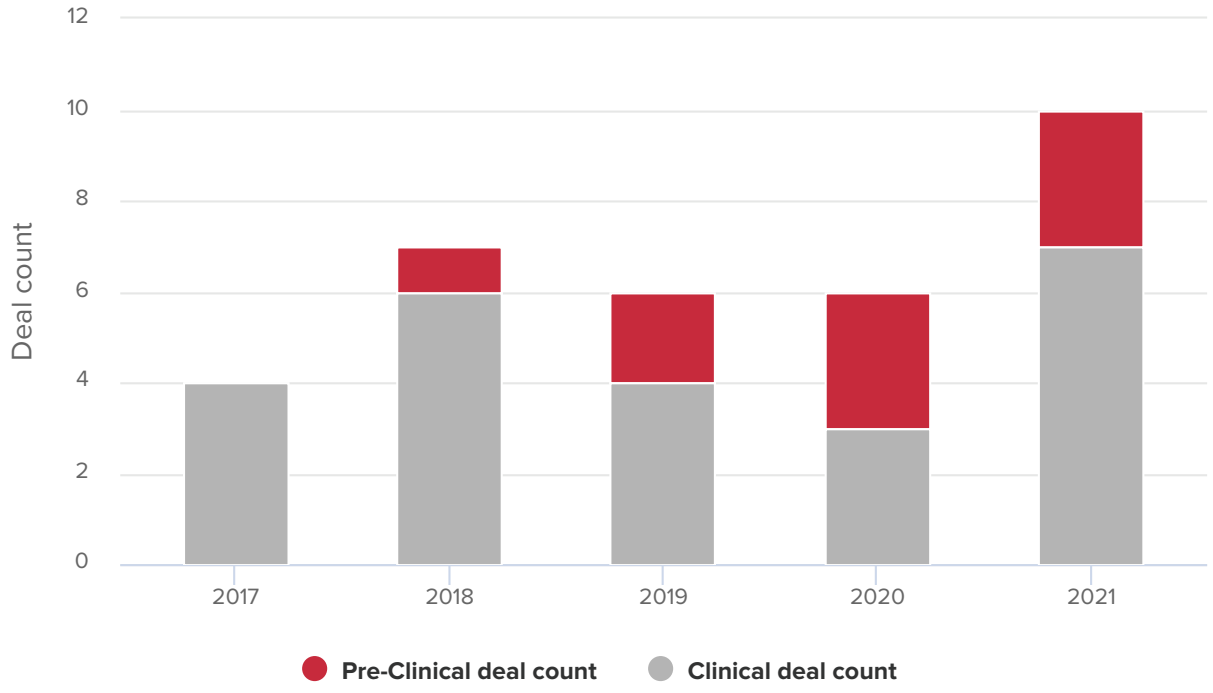
The sums deployed tells a different story, however, namely that these transactions were mostly very small. Only $11bn was spent on cancer companies in 2021, the lowest amount for five years and a third of the sums deployed in 2021 and 2020.

Lower spending in the cancer field must have been a major factor behind last year's disappointing M&A stats.

Interest in rare diseases shows no signs of waning, meanwhile. And as the chart below suggests, buyers are increasingly prepared to bring in these assets at the preclinical stage. This could well be a result of heightened competition pushing up valuations, forcing those with less firepower to take earlier-stage risks.

The deal count in the two charts includes all transactions, whether terms are disclosed or not, but in reality only half of these deals revealed this data. These figures are required to calculate mean and median acquisition values, but for the rare disease category the volume of buyouts each year falls too low for this sort of analysis to throw out anything meaningful.

Rare diseases - Deal counts



Source: Evaluate Pharma.

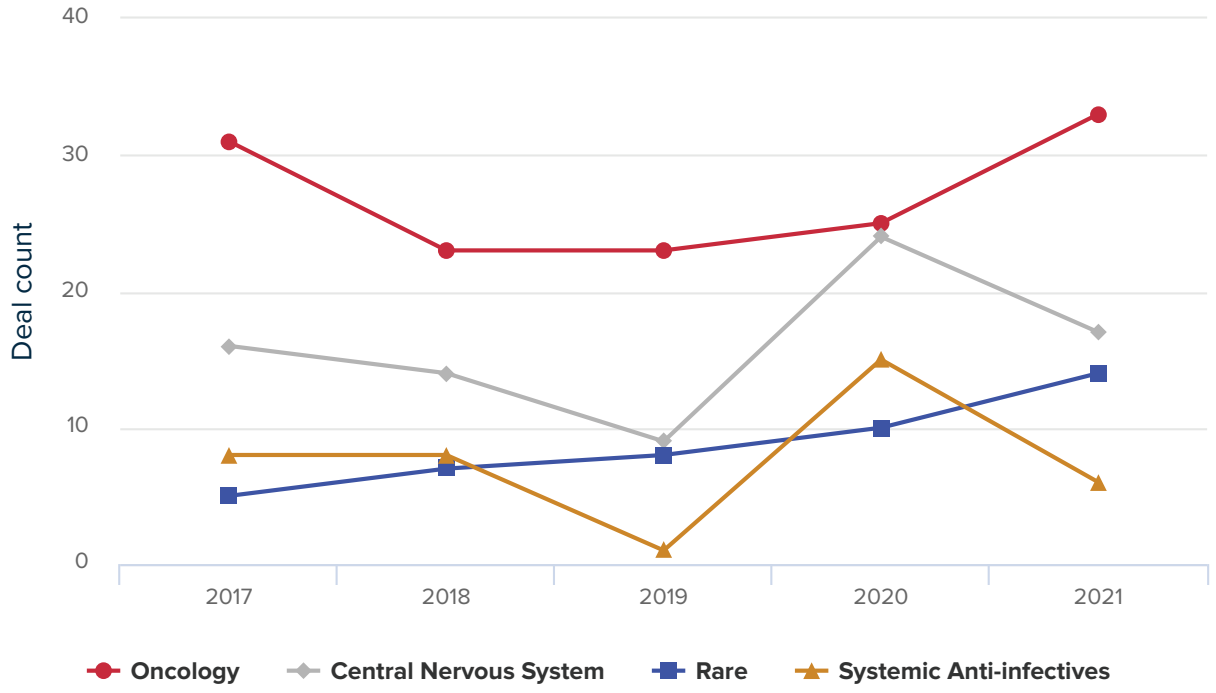
Finally, developers working on CNS-related diseases represent the second biggest area of deal making for biopharma, and here there has been something of a pick-up in activity on both the volume of deals and sums spent. This latter measure reached at least a five year high in 2021, with $8.5bn spent on CNS-focused buyouts.

This was boosted by Jazz's $7.2bn acquisition of GW Pharmaceuticals for its epilepsy product Epidiolex, a transaction that strays into the rare disease space and demonstrates the problems encountered when trying to categorise buyouts by therapy area.

It is also worth noting that for this analysis, only the up-front portion of a deal has been considered. The methodology is explained in more detail in a previous article in this series (Rare disease and neurology takeouts tick higher, March 2, 2022)

Outside of these most active therapy areas, it is almost impossible to reliably identify M&A trends because very few buyouts happen each year. What does stand out, however, is the pick-up in anti-infective transactions that coincided with the pandemic. That particular motivation might have expired, but many are hoping that a deployment of Covid-generated cash will trigger the next peak in biopharma M&A.

Annual deal count by therapy area



Source: Evaluate Pharma.

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