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Hudson To Succeed Brandicourt As Sanofi CEO

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Sanofi's search for a new CEO to replace Olivier Brandicourt, who has decided to retire, has ended with the appointment of Paul Hudson, head of pharma at Novartis AG, to its top post.

The announcement is something of a coup for Sanofi as Hudson, who is 51 years old, comes with a wealth of experience in the sector, most recently as head of pharmaceuticals for AstraZeneca PLC in North America before he moved to Novartis in 2016. In the three years he has been at the Swiss major, Hudson has built up an impressive track record when it comes to successful launches of key products, notably Cosentyx (secukinumab) for psoriasis, psoriatic arthritis and ankylosing spondylitis, which has become Novartis's best-selling product. One of his last major projects at Novartis was the acquisition of dry eye drug Xiidra (lifitegrast) from Takeda. SC125196

Hudson has built up an impressive track record when it comes to successful launches of key products.

Serge Weinberg, Sanofi's chairman, said that Hudson's skills and experience "give him all the assets he needs to accelerate growth and lead the group's adaptation to new strategic challenges, particularly in the areas of R&D and digital." He went on to say that the "human values" of Hudson, a British citizen and avid supporter of Manchester United, will "enable him to mobilize all the energies and increase the agility, that a group such as Sanofi needs, to face the new challenges of our industry and the changes in healthcare systems around the world."

It was no secret that Brandicourt, who joined from Bayer AG in 2015, was looking to retire and Sanofi began the search for his successor earlier this year. Nevertheless, observers were surprised that the search produced a candidate so quickly to replace the Frenchman, who Weinberg thanked "for the energy with which he has steered the group through a complex period and for his decisive contribution to the company's return to growth."

TSCHUDIN NEW PHARMA HEAD FOR NOVARTIS

Hudson's replacement will be Marie-France Tschudin, currently president of Advanced Accelerator Applications SA, the French nuclear medicine specialist that Novartis acquired last year, gaining access to its approved peptide receptor radionuclide therapy Lutathera (lutetium Lu 177 dotatate). A Swiss citizen who speaks six languages, she joined Novartis in January 2017 and became head of pharma for Europe. Before joining Novartis, Tschudin spent 10 years at Celgene Corp. in a variety of leadership positions.

Tschudin said she was "excited to be given the opportunity to lead and further develop one of the greatest businesses in our industry. I would like to thank Paul for his leadership and his focus on people and I wish him continued success going forward." *Published online 7 June 2019*

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from the editor

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Paul Hudson has his work cut out to deal with the ongoing challenges faced by Sanofi following the retirement of Olivier Brandicourt. He will need to act decisively to provide Sanofi with clear direction for the future, while at the same time treading carefully and winning the confidence of the board: Brandicourt's predecessor Chris Viehbacher's radical actions were not warmly welcomed by the French company's directors and he was fired in 2014. Chairman Serge Weinberg remains.

The market was encouraged by Hudson's appointment: Sanofi's share price on the Paris bourse rose by 4.4% on the day of the announcement, adding more than €4bn to the company's market capitalization. This contrasts with the negative reception for Viehbacher's sacking in October 2014, which prompted a 4.5% sell-off, and with the news of Brandicourt's appointment in February 2015, which was met by a 1% decline. For more on the challenges facing Hudson at Sanofi, see p4.

Novartis is also feeding into the new Bristol-Myers Squibb management: following the latter's merger with Celgene, Samit Hirawat, Novartis's head of oncology development, will join to lead drug development across the business. More details of the changes at BMS, including planned departures of the CSO and CFO, can be found on p5.

For those of you looking for a career move yourselves, have you considered CBER? As our reporters at BIO found out, the FDA's biologics evaluation center is keen to get new people on board and in training to deal with the growing cell and gene therapy workload (see p8-9).

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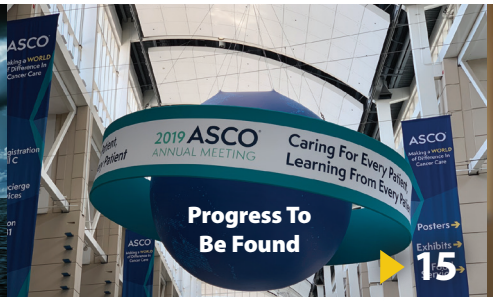

exclusive online content

Sanofi Pasteur Head: Global Flu Vaccination Rates 'Dangerously Low'

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The chief of Sanofi's vaccines arm is on a mission to convince governments around world to increase their overall flu vaccination rates, especially in China, which is dangerously low at around 2%.

David Loew believes such action would prevent thousands of deaths and help reduce use of antibiotics and fight antimicrobial resistance.

While flu vaccination rates in the US, UK, Canada and Australia "are fairly healthy" the rest of the world needs to raise their levels to better protect their populations and reduce healthcare costs, Loew said in an interview.

"Clearly Germany, France, Switzerland and others need to make stronger efforts. The World Health Organization has recommended that countries achieve a 75% flu vaccination rate for their overall populations. Nobody is there at that level yet," Loew told *Scrip* when in London this week for meetings with British government officials.

He added though that the UK has done better than most other countries on that score.

"The UK's flu vaccination rate is around 65% overall. That's because the country recognized the importance of flu vaccinations very early on as a preventative measure and has done a stellar job by being very systematic, resulting in very high vaccination rates."

Published online 5 June 2019

To read the rest of this story go to: https://bit.ly/2IwZKoB

inside:

The Challenges Facing Paul Hudson At the Helm of Sanofi

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Expectations will be high when Paul Hudson takes over as Sanofi CEO from Olivier Brandicourt on 1 September. Analysts are already weighing up the challenges that will face the former head of pharma at Novartis AG in his new job.

He leaves the Swiss major with praise ringing in his ears from former boss Vas Narasimhan, who spoke of Hudson's "exceptional leadership in positioning our pharmaceuticals business for strong future growth. He also established a new culture of commercial excellence, integrity and nurtured a strong, diverse talent pool." *(Also see "Hudson To Succeed Brandicourt As Sanofi CEO" - Scrip, 7 Jun, 2019.)*

Narasimhan later tweeted, "I will always be personally grateful for his support as I took on the role of CEO." Now it is Hudson's turn for a top job and the 51-year-old Briton is not lacking in experience; before joining Novartis in 2016, he was head of pharmaceuticals for AstraZeneca PLC in North America.

Serge Weinberg, Sanofi's chairman, said that Hudson's skills and experience "give him all the assets he needs to accelerate growth and lead the group's adaptation to new strategic challenges, particularly in the areas of R&D and digital." Tellingly, he added that the new man has the "human values" that will "enable him to mobilize all the energies and increase the agility, that a group such as Sanofi needs, to face the new challenges of our industry and the changes in healthcare systems around the world."

In the three years he has been at the Swiss major, Hudson has an impressive track record when it comes to successful launches of key products, notably Cosentyx (secukinumab) for psoriasis, psoriatic arthritis and ankylosing spondylitis, which has become Novartis's best-selling product. Under his stewardship, after a slow start the heart failure drug Entresto (sacubitril/valsartan) has become a blockbuster and he has been instrumental in planning the commercial strategy for Novartis's just approved spinal muscular atrophy gene therapy Zolgensma (onasemnogene abeparvovec). *(Also see "It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug" - Scrip, 24 May, 2019.)*

Analysts have greeted the appointment of Hudson with enthusiasm. Deutsche Bank in a 7 June note said, "This will be positively perceived by investors as it shows that the board of Sanofi is ready to appoint a non-French speaking CEO, which is positive for the culture in terms of internationalization."

Four years ago, Frenchman Brandicourt replaced Canadian-German national Chris Viehbacher, who was pushed out of Sanofi at the end of 2014, amid speculation at the time that his exit was linked to a decision to relocate to Boston. Sanofi has repeatedly said that nationality is irrelevant and the appointment of Hudson (who Sanofi stressed will move to Paris) follows the hiring of US citizen John Reed as R&D chief last year from Roche *(Also see "More Than French Flavor To Sanofi CEO Search, Chairman Says" - Pink Sheet, 24 Nov, 2014.) (Also see "Zerhouni Retires, Sanofi's New R&D Chief John Reed Brings Early Research Experience From Roche" - Scrip, 24 Apr, 2018.)*

> "I will always be personally grateful for his support as I took on the role of CEO."
> – Vas Narasimhan

Bryan Garnier analyst Jean-Jacques Le Fur wrote in a 7 June note to investors that the move was good news for Sanofi given that "Hudson has considerable experience and expertise." He noted that the Paris-headquartered firm, like Novartis, had been engaged in a reorganization in the past couple of years, and "we have the feeling the changes are being conducted at a slower pace [and] although talented top executives have joined, we have some difficulties to see significant organisational changes and qualify Sanofi as a lean organisation."

Le Fur expects Hudson to form "a very dynamic and productive tandem" with Sanofi's new chief financial officer Jean Baptiste Chasseloup de Chatillon (who joined from Peugeot in September 2018) "that will convince the investment community about its strategy and present a new roadmap, hopefully by the end of the year."

The analyst added that Hudson's arrival represents a cultural change for Sanofi as he brings "an Anglo-Saxon mindset associated with deep experience of a lean company - AstraZeneca, then Novartis." Le Fur argued that this new culture may well fit with the changes de Chatillon, coming from the automotive industry, is already implementing.

STRATEGIC DECISIONS LIKELY

From a strategic standpoint, he noted that the established medicines segment of Sanofi's portfolio is "a larger piece of the total than in any other company" and Hudson may conduct "an AstraZeneca-like type of policy" to refocus the portfolio and divest older products. Le Fur concluded by saying that "the other obvious question refers to the consumer health division since all other players in this field have decided to exit – and GlaxoSmithKline PLC and Pfizer Inc. to combine – while Sanofi has so far decided to stay. The new management team may have a new fresh eye on the topic."

Under Brandicourt, who has decided to retire aged 63, Sanofi has been in a transitional period as it continues to cope with

patent losses, particularly on its blockbuster diabetes treatment Lantus (insulin glargine). There have been successes, notably the performance of anti-inflammatory Dupixent (dupilumab), which is partnered with Regeneron Pharmaceuticals Inc. and is selling well for atopic dermatitis and asthma, while Brandicourt hit the acquisition trail last year to buy Bioverativ Inc., a developer of hemophilia therapies, and Ablynx NV.

Hudson will also have noticed that in February, the French drug maker unveiled an R&D pipeline overhaul, saying it could potentially submit nine new medicines and 25 additional indications to regulatory authorities from 2019 to 2022. At the time, Sanofi said it was fast-tracking 17 programs, including eight in oncology, while 13 development and 25 research projects were being discontinued.

However, Hudson will have his hands full trying to turn around Sanofi's cholesterol therapy Praluent (alirocumab). First-quarter sales were up 10.2% to $56m but down 26.9% in the US, lower than consensus forecasts as higher US rebates continued to impact sales of the injectable PCSK9 inhibitor. *(Also see "Dupixent And Vaccines Dominate As Sanofi Profits Rise" - Scrip, 26 Apr, 2019.)*

Sanofi is scheduled to hold a 'meet the management' day on 26 June, but it is unlikely that Hudson will attend if it goes ahead, given that the new job does not start until the autumn.

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Bristol-Myers Squibb Unveils Post-Celgene Leadership Team, With Big R&D Changes

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Bristol-Myers Squibb Co. will make some big changes to its research and development leadership after it merges with Celgene Corp.. The company announced its new post-merger research and commercial leadership teams on 5 June, with an outsider taking over the top R&D spot.

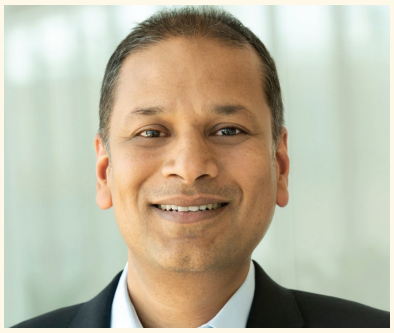
Novartis AG's head of oncology development Samit Hirawat will join the company as chief medical officer-global drug development, leading drug development across therapeutic areas. He will be responsible for overseeing the pipeline from proof-of-concept through commercialization. A leader from Celgene, Rupert Vessey, who heads early research there, will oversee early research at the combined company as president of research and early development.

Both Hirawat and Vessey will report to CEO Giovanni Caforio and serve on the executive leadership team. BMS's current chief scientific officer Tom Lynch will leave the company in October, Bristol announced.

BMS said the changes play to each company's strengths, with Vessey being responsible for drug discovery and working with business development to tap outside sources of innovation, an area in which Celgene has a reputation for being proactive. Bristol's Paul Biondi will continue to lead business development.

Hirawat brings extensive experience in oncology, notably in areas that fall outside of BMS's core strength in immunotherapy drugs with the PD-1/L1 inhibitor Opdivo (nivolumab) and Yervoy (ipilimumab), which targets CTLA-4.

Rupert Vessey



Samit Hirawat

Novartis largely sat out the first wave of the PD-1/L1 development craze, focusing its immuno-oncology efforts instead on chimeric antigen receptor T-cell (CAR-T) therapies, where Celgene brings a presence. Novartis has been focused on a diversified approach to oncology drug development, emphasizing targeted therapies and radiopharmaceuticals in addition to immuno-oncology. *(Also see "Novartis' New Oncology CEO Schaffert Has A Potential Blockbuster Launch On Her Hands " - Scrip, 23 May, 2019.)*

Hirawat oversaw the development of drugs like the CDK4/6 inhibitor Kisqali (ribociclib) and the first-in-class PI3K inhibitor Piqray (alpelisib), recently approved for HR+/HER2-negative breast cancer. The company said it was looking for a successor.

BMS's pending $74bn acquisition of Celgene, announced in January, is expected to close in the third quarter. *(Also see "Bristol Values Celgene's Hematology, Immunology Portfolio At $74bn, But Does It Price In Risk?" - Scrip, 3 Jan, 2019.)*The new leadership team will become effective upon completion of the merger. Shareholders overwhelmingly approved the deal in April. *(Also see "As Expected: Shareholders Back Bristol's $74bn Celgene Buy" - Scrip, 12 Apr, 2019.)*

BOERNER TO OVERSEE COMMERCIAL

BMS also announced its commercial leadership team, which will oversee nine blockbuster marketed products and six near-term launch opportunities in four areas: oncology, hematology, immunology and cardiovascular.

The company's current chief commercialization officer Chris Boerner will continue in that role, responsible for commercial strategy for the portfolio across all geographies. Following the closing of the Celgene transaction, he will assume an expanded role, the firm said, to oversee the oncology, immunology and cardiovascular businesses; worldwide value, access and pricing; and worldwide commercial operations.

Meanwhile Celgene's current president, global hematology & oncology Nadim Ahmed will serve as president, hematology – a nod to Celgene's expertise in the field, where it is a leader with the multiple myeloma drug Revlimid (lenalidomide). Ahmed also will oversee cell therapy.

BMS has two near-term potential launches on the horizon in cell therapy, both coming from Celgene. The first is CAR-T therapy lisocabtagene maraleucel (liso-cel; JCAR017), acquired with Juno Therapeutics Inc., with an initial indication of diffuse large B-cell lymphoma (DLBCL). The other is bb2121, a CAR-T therapy targeting B-cell maturation antigen (BCMA) and developed with bluebird bio for multiple myeloma. Both products are on track for regulatory filings in 2019.

The chief financial officer will also change over, with Celgene's CFO David Elkins stepping in as BMS's Charles Bancroft plans to retire in 2020 after 35 years at the company. In the meantime, Bancroft will oversee the integration of the two companies' operations.

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Aceto Claims Aurobindo Caused Its Collapse

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US Aceto Corporation has accused the Indian company Aurobindo Pharma Ltd. of deploying a calculated and systematic scheme to destroy Aceto's generic pharmaceutical business run through its subsidiary Rising Pharmaceuticals, forcing it out of the US generic market. The Indian group's actions also allegedly contributed "substantially" to Aceto's bankruptcy filing.

The case essentially revolves around Aceto's 2016 acquisition of rights owned by Citron Pharma LLC and its affiliate Lucid Pharma LLC to products manufactured by Aurobindo for $270m in cash, plus other considerations. The US group claimed that Aurobindo actually had no intention of partnering with Rising Pharmaceuticals or supplying its requirements once the deal between Aceto and Citron/Lucid closed and that PV Ramprasad Reddy, a founder of Aurobindo, made representations that were "unequivocally false and misleading".

Reddy's wife in the US wife apparently held a substantial portion of Citron's and Lucid's equity. Once Citron had sold the assets to Aceto, Mrs Reddy is said to have divested her economic interest in the business.

Aceto and US subsidiaries, which filed for relief earlier this year under Chapter 11 of the US bankruptcy code, have made a range of serious allegations against the Indian group claiming that Aurobindo began by deliberately failing to supply products, which caused "massive failure-to-supply liability" to Rising Pharmaceuticals that "drained" Aceto's cash flow and made it difficult for the company to service its debt. *(Also see "Aceto Files For Bankruptcy As It Offloads Rising And Chemicals Businesses" - Generics Bulletin, 22 Feb, 2019.)*

Aceto claimed that the Indian company then went on to implement "arbitrary and capricious caps" on the volume of product which Rising Pharmaceuticals could buy from it.

> "Aurobindo vigorously denies the allegations in the complaint and looks forward to addressing the matter in due course."

"And then, once Aurobindo had succeeded in critically wounding Rising Pharmaceuticals, Aurobindo struck the death blow: it began stealing critical customers from Rising Pharmaceuticals," Aceto said in its case filing in the US Bankruptcy Court, District of New Jersey.

Aurobindo has, however, strongly rebutted Aceto's charges. "Aurobindo vigorously denies the allegations in the complaint and looks forward to addressing the matter in due course," the Hyderabad-based company told *Scrip*, but provided no further specifics. Meanwhile, in a statement to the Bombay Stock Exchange, Aurobindo said it has yet to receive a copy of the litigation proceeding. "On preliminary examination of the compliant, the company has been advised by its legal advisors that the case appears to be devoid of merits and consists of baseless allegations against the company, Aurolife [a step-down subsidiary in the US] and Ramprasad Reddy alleging fraud, negligent misrepresentation and the failure of the company and Aurolife to fulfill their obligations, inter-alia, under a supply contract entered into with the company," a statement from Aurobindo said 7 June.

Aceto, which has been effecting divestments under bankruptcy proceedings, completed in April the sale of the assets of Rising Pharmaceuticals and its subsidiaries to Shore Suven Pharma, Inc; the chemicals business assets were sold to an affiliate of New Mountain Capital. With the disposition of its operating assets, Aceto has also ended the services of its president and CEO William Kennally, effective 31 May. Kennally, though, will continue to serve as a director on the company's board.

"CALCULATED EFFORTS" TO SABOTAGE SUPPLY CHAIN?

Aceto's case filings against Aurobindo provide specifics around how the Indian firm allegedly precipitated the collapse of its business.

Among a string of claims, Aceto said that between 2017 and 2018, Rising Pharmaceuticals incurred at least $13m in failure-to-supply liability triggered by Aurobindo's "calculated efforts to sabotage Rising's supply chain". Products that the Indian firm allegedly failed to supply included duloxetine, mirtazapine, tamsulosin, atomoxetine, clarithromycin and valacyclovir.

Aceto claimed that Aurobindo did not honor the orders because it chose to favor production for its own account over Rising's requirements and allocated production capacity to products that Aurobindo sold directly to customers in competition with Rising.

"Aurobindo thereby also sought to damage Rising's position as a competitor in marketing the same drugs," Aceto claimed in the court filing dated 31 May. Aceto essentially focuses on the marketing, sale and distribution of human health products, pharmaceutical and performance chemicals.

DAMAGE TO CASH FLOW?

Another charge revolved around how Aurobindo apparently "stole" the rosuvastatin business of Rising's largest customer, Walgreens, after wrongfully withholding the active pharmaceutical ingredient (API). This supply chain disruption hurt Rising's relationship with Walgreens, which eventually awarded the contract to Aurobindo.

Besides, due in part to Aurobindo's tactics, Aceto said it was forced to write off substantial goodwill associated with the products acquired from Citron/Lucid – over $250m – accounting for almost the entire purchase price.

"And the damage to its cash flow caused by Aurobindo's misconduct substantially contributed to Aceto's insolvency," it added.

Aceto and its subsidiaries, have among other relief, now sought damages against the Indian group caused by their alleged fraud and multiple, material breaches of the supply agreements.

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BIO 2019 Notebook: Sharpless On Pricing, Takeda M&A Strategy, FDA Cell And Gene Therapy Staffing

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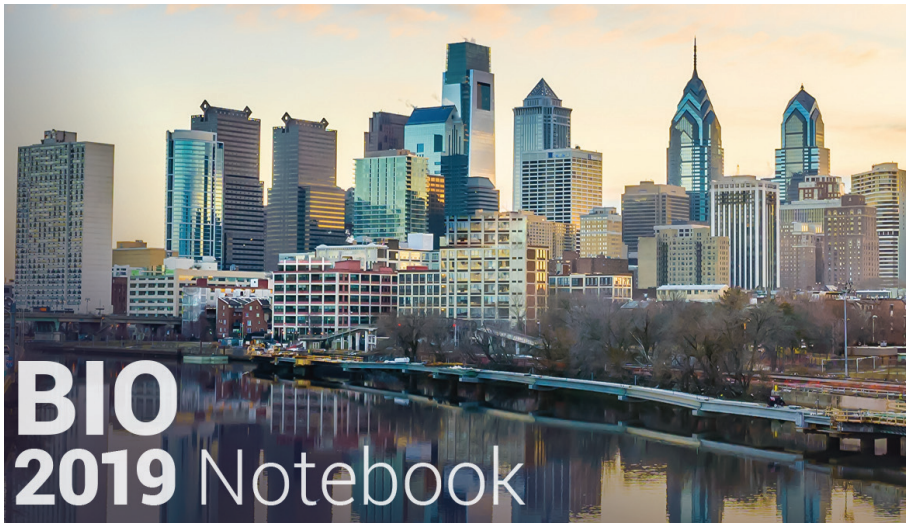

During his first two months on the job, US Food and Drug Administration acting commissioner Ned Sharpless generally has come across as unflappable in his public appearances. However, press coverage of the approval of Novartis AG's gene therapy Zolgensma (onasemnogene abeparvovec-xioi) for spinal muscular atrophy (SMA) has got him riled up.

Following the agency's 24 May approval, many of the headlines focused on the therapeutic's $2.1m price tag, as well as Novartis' annuity-like payment model, under which the therapy would cost $425,000 annually for five years. *(Also see "It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug" - Scrip, 24 May, 2019.)*

All this focus on price is missing the point, Sharpless said during a fireside chat at the BIO International Convention in Philadelphia on 4 June.

SMA is a "devasting pediatric neurologic syndrome," Sharpless said. "I was a little disappointed in the coverage of that, that the focus was on the $2.1m price tag.

"This is a completely novel, like almost magical medical miracle that ends a devastating disease for lots of little kids, and the thing you care most about is the price? I mean, really," he continued. "If you're so cynical you can't see how wonderful and great that is and what an advance that is, then you need to sort of re-wear your happy hat."

Although prices of novel technologies such as CAR-T therapies and gene therapies are "shockingly expensive" right now, they should come down with manufacturing process improvements, Sharpless said, providing a little historical context.

"When we first made penicillin, it was so expensive to make they would filter the urine of the people who had taken it and crystallize it," he said. "We got better at making penicillin eventually. It's not so hard to make anymore."

Later in the conversation, Sharpless once again grew animated on the subject of Zolgensma pricing when the mother of an eight-year-old SMA patient whose

medical costs likely already have exceeded $3m asked why the focus has been more about the gene therapy's price and not the clinical benefits. "What this does [is] it affords these babies to achieve average childhoods and over the long term save money, but that's not being conveyed," she said. "Where do you see the chance of economic impacts in the future to make that point?"

"You can sense my frustration on this topic," Sharpless responded. "I'm with you. I think the messaging got lost."

He then drew upon a biblical analogy to make his point.

It's "probably like at that wedding that Jesus was at where he turned water into wine. There was probably somebody saying, 'Hey you know, I wanted chardonnay. This is red wine,'" Sharpless said to peals of laughter in the room. "I almost feel like it's that reaction."

He added, "I've been working my whole career to see these kinds of medical miracles take place, and to have it just sort of be discounted, that bothered me."

Although the FDA does not make approval decisions based on cost, the attention to drug pricing may take some getting used to for Sharpless, who previously was director of the National Cancer Institute at the National Institutes of Health.

"At the NIH, we didn't really worry about the concept of value for the patient or value for the consumer," he said. "Whereas at the FDA that is an issue, so the FDA can do things like incentivize generic drug approvals to control drug costs."

TAKEDA'S ARIAD BUYOUT SHOWS ITS DIFFERENTIATED M&A PHILOSOPHY

During a session on M&A valuation strategies at the BIO International Convention on 4 June, Takeda Pharmaceutical Co. Ltd.'s Evan Lippman said his company's internal view of the value of its $5.2bn acquisition of Ariad Pharmaceuticals Inc. in 2017 probably differs from the way other biopharma companies and industry analysts see it.

When the deal was unveiled in January 2017, some questioned the wisdom of paying an 89% premium ($24 per share) for the Cambridge, MA-based oncology firm, whose lone commercial product, leukemia drug Iclusig (ponatinib), had produced sluggish sales to that point. *(Also see "Takeda Acquires Ariad In $5.2bn Deal – US Infrastructure A Key Component?" - Scrip, 9 Jan, 2017.)*

Two years later, Takeda has more than doubled the product's worldwide sales take and has a second drug from Ariad's pipeline approved, in anaplastic lymphoma kinase (ALK) inhibitor Alunbrig (brigatinib) as a targeted therapy for a subset of non-small cell lung cancer patients. *(Also see "Can Takeda's Alunbrig Take On Roche's Alecensa In First-Line ALK-Positive Lung Cancer? " - Scrip, 26 Sep, 2018.)*

Takeda's first priority in M&A is therapeutic fit, said Lippman, Takeda's head of corporate development and business development finance. Beyond the transformational merger with Shire PLC, Takeda looks for partnerships and bolt-on acquisitions in its core therapeutic areas of oncology, neuroscience, gastrointestinal disease and rare diseases, he said. That's part of why Ariad made sense for Takeda in a way that was not immediately apparent to many outsiders.

"With the platform that we bring to the table, we will look at a structure, whether it's tax-oriented, business-oriented or from an upside – take Ariad as an example," Lippman told the session. "I think we had a certain set of expertise we brought to the table. We believed in those pipeline products as well as the ones that are about to launch on the market and we thought we could do very well there, in what I'd say was an outsized expectation relative to the market. And I think we've proven that.

"And so, the valuation in our eyes was very reasonable and it's turned out to be an exceptional transaction for us and an exception transaction for the counter-party from the premium we paid," he continued.

This philosophy also shows up in how Takeda's partnership in gene therapy with TiGenix NV ultimately evolved into an acquisition, Lippman said. *(Also see "Takeda Secures TiGenix But Investor Shire Concerns Bubble Up " - Scrip, 8 Jun, 2018.)*

"We're more than willing from an early stage all the way until late stage to be investing, working with companies in order to fund the ecosystem, give them access to our individuals to make their programs better and then go off and let them be great," he explained. "And then, if that program continues to proceed, we both share in the upside potential of that. If at the right time, like we did with TiGenix, that program looks to be opportunistic for us to bring in house, we can go an M&A route to do so."

Lippman added that the $62bn combination with Shire was a departure for Takeda in more ways than one. *(Also see "Takeda Grabs Shire At Last After Long Pursuit" - Scrip, 8 May, 2018.)* Not only was it a transformational M&A transaction for a company more comfortable with smaller, bolt-on deals, but it required significant financial creativity to be finalized, he said.

"It's probably lost on some people, but Shire, that's the first time a Japanese company issued shares to acquire a company ever," the exec noted. "It's the first time that a UK company received US dollar denominated interest in currency instead of British pounds for shares. We worked a particular type of exchange mechanism to make that transaction happen."

CBER'S PDUFA VII FOCUS: CELL AND GENE THERAPY STAFFING

The US FDA's staffing need to deal with the influx of cell and gene therapies will be a topic for discussion in the next round of prescription drug user fee negotiations, Center for Biologics Evaluation and Research Director Peter Marks told BIO.

CBER's cell and gene therapy workload is growing very quickly, Marks said during a 4 June FDA Town Hall. "I think as we move towards the next set of user fee agreements, we're going to be trying to think creatively about how you have to think in real time about staffing up when you're on a very steep part of the growth curve."

The current iteration of the prescription drug user fee program (PDUFA VI) runs through September 2022.

A year ago, Marks predicted CBER would soon face a growth spurt to deal with the burgeoning product area. *(Also see "US FDA's Biologics Center Director Expects It Soon Will See 'Growth Spurt'" - Pink Sheet, 2 Jul, 2018.)* In January, the agency announced plans for the biologics center to add up to 50 new reviewers in the coming years. *(Also see "Shutdown Bite Tightens At US FDA, But Gene Therapy To Get 50 More Reviewers" - Pink Sheet, 15 Jan, 2019.)*

The FDA received more than 200 investigational new drug (IND) applications in 2018 for cell and gene therapies, almost double

"I could easily see needing to staff up by 50% in the next two years over our current levels because of the growth." – Peter Marks

the number from 2017. Marks said the 2019 tally is likely to grow as well, perhaps by as much as 50%.

He compared CBER's current workload in the emerging area to the early phase of bacterial growth, "when the shaker flask is still clear but you know the bacteria are still growing, and then in about an hour later it turns really cloudy. We're at the point where we kind of know that within one-to-two years it's going to be really cloudy in the shaker flask, and so we have to figure out a way to get people on board."

Proactively hiring ahead of the deluge is important to ensure adequate time to get new staff up and running, Marks said.

It takes one-to-two years to train new employees so that they can handle a meeting with a sponsor seeking development advice, Marks pointed out. "We want the people meeting with you to be giving you good advice and tell you the right answers," he said. "It takes a little while to train them to get there. That means we're going to have to figure out a way to start bringing people on board, and it may mean that initially we might seem a little overstaffed."

In addition to the increasing IND load, it's only a matter of time before some of those INDs start turning into biologics license applications, "which are large review issues because then we're reviewing the chemistry, manufacturing and controls portions of these files," Marks said.

"We're going to be having to really bulk up there, so it will be a challenge," he said. "I think we'll have to think proactively. I could easily see needing to staff up by 50% in the next two years over our current levels because of the growth."

Marks made a pitch for people currently working in industry to considering joining the FDA staff.

"We value the people we get from academics, from graduate programs," he told the audience. "It's just that it takes us longer to get those people up to speed. Industry people tend, I'd say in this area, to come up to speed a little bit faster."

THE AEROBIC BENEFITS OF BIO 2019 CONTINUE

In our day one Notebook, we noted that the layout of the Pennsylvania Convention Center, which crosses over and includes meeting rooms on both sides of 13th Street, created some confusion for delegates and caused some delays in getting to scheduled appointments and meetings. *(Also see "BIO 2019 Notebook: Merck; Out-Licensing Deals; RMAT" - Scrip, 3 Jun, 2019.)*

We suppose there is another way to look at it, however. Attendees confirmed during day two of the meeting on 4 June that they were getting an excellent workout from walking from session to session – one delegate who normally works from home even enthused that she had met her daily steps goal on her Fitbit during the first day of BIO 2019.

Published online 10 June 2019

Click here for more coverage of the BIO meeting:
https://bit.ly/2WtiFFN
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Motif Plunges As FDA Demands New Iclaprim Study

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Motif Bio PLC has been dealt a serious blow from the US Food and Drug Administration which has told the cash-strapped UK biotech it needs to carry out an additional trial for iclaprim if it wants any hope of getting approval for the antibiotic.


Storm clouds over Motif Bio

The company has been on unsteady ground ever since February when the FDA issued a complete response letter for iclaprim, a next-generation diaminopyrimidine antibiotic for the treatment of acute bacterial skin and skin structure infections (ABSSSI). The agency indicated that additional data were needed to further evaluate the risk for liver toxicity for the drug. *(Also see "Keeping Track: Rebuff Of Iclaprim Creates Early Pileup Of CRLs For Novel Drugs" - Pink Sheet, 18 Feb, 2019.)*

A crunch type A meeting with the FDA was held on 3 May to discuss the to discuss the points raised in the complete response letter and Motif has received the official minutes of the discussion. They indicate that an additional clinical trial will be required prior to granting marketing approval "to address the agency's continued concerns about potential liver toxicity."

Motif was remarkably upbeat, saying it "has been encouraged by the FDA to put forth a proposal for a future study and to submit it for review." CEO Graham Lumsden said, "We now have confirmation of what will be required for a path forward for iclaprim. We intend to meet with the agency to agree on the specific require-

ments of the trial, which will enable us to estimate its size and scope and, therefore, the costs and funding requirements."

He went on to note that in parallel, Motif expected to continue discussions "with potential commercial partners and will determine the best options for funding the trial once we have clarity from the FDA." Financing is a serious problem for Motif; as of May 31 this year, it had a cash balance of $2.3m and $7.1m of outstanding debt drawn down from a loan facility from Hercules Capital. *(Also see "Money Too Tight To Mention At Motif After Iclaprim 'No' From FDA" - Scrip, 19 Feb, 2019.)*

Motif believes it has enough money to continue funding operations into September 2019 "with diligent cash management" but will clearly have to raise additional capital, "either through equity financing and/or from non-dilutive sources."

On a conference call, Lumsden said it was too early to give any definitive timelines, noting that "what we have to do is put together the proposal to send back to the FDA" about the new study which he suspected would require a comparator arm and not be limited to evaluating liver toxicity. He stressed that the FDA "is encouraging us to set up a meeting" but when that will be depends on how busy the agency's anti-infectives division is; the 3 May meeting took longer to set up than Motif had hoped for due to a backlog at the agency.

Lumsden insisted that "we continue to believe that iclaprim has the potential to be an important new treatment option for hospitalized patients with ABSSSI and potentially also in patients with hospital-acquired bacterial pneumonia, including ventilator-associated bacterial pneumonia." He added that Motif was exploring the use of iclaprim in other disease areas, citing pacts inked last month.

The first was with Lamellar Biomedical Ltd. evaluating the drug as part of a combination for *Staphylococcus aureus* lung infections in patients with cystic fibrosis. The second alliance is with the Otto-von-Guericke University in Germany where the partners will conduct a study evaluating iclaprim for toxoplasma chorioretinitis, a parasitic disease that may result in severe life-threatening infections and/or blindness.

Lumsden pointed out that those two collaborations are built around orphan indications "which we think are particularly attractive." He added that the company was also looking at additional partnerships, as "we have shown that we can do late stage clinical trials [and] many of the companies that we talked to, they have expertise confined to the preclinical space."

The CEO concluded by saying that he could not be more specific at the moment but "we are confident that there are some pretty exciting opportunities out there where we can utilize our three assets; management team, late-stage clinical development skills and access to the public markets." Motif is listed on the AIM exchange in London and on the Nasdaq.

Investors are less enthusiastic however, and Motif's shares sank 51% to just £0.04 each at the end of trading on 6 June.

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Bayer Pays Arvinas $50m To Form Protein Degrader R&D Pact

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Bayer AG is moving into the development of protein degraders through a deal with Arvinas Inc. worth $50m upfront.

The potential for bifunctional small molecules to use cellular machinery to eliminate disease-causing proteins has attracted considerable interest, in large part because it offers a potential way to drug the estimated 80% of proteins that are beyond the reach of existing small molecules. While conventional small molecules block the activity of proteins, targeted protein degraders order their destruction.

This new class of drugs works by tethering target proteins to enzymes that mark them for destruction by the proteasome. The proteasome destroys the protein, turning it into amino acids and releasing the molecules that orchestrated its demise so that the process can start again. In theory, this could lead to the rapid removal of disease-causing proteins.

Bayer has bought into the idea, in part because it thinks "it may be possible to retool previously ineffective inhibitor molecules" as protein degraders and will work with Arvinas on protein-degrading drugs against cardiovascular, oncological and gynecological diseases. The Leverkusen-based firm will pick the targets, subject to some exclusions, and have Arvinas apply its proteolysis-targeting chimera (PROTAC) technology to them.

A Bayer spokesperson told *Scrip*, "PROTACs can allow us to address a novel target space, namely targets that have not been addressable by classical small molecular approaches. Examples can be targets without enzymatic activity or signaling molecules with scaffolding functions. Also, acquired resistance may be an interesting application area for PROTACs." The spokesperson added "We consider interesting targets in all our indication areas beyond oncology and as we are focusing on cardiovascular disease and gynecological therapies in our research activities and can provide expertise in these areas, they are of particular interest."

Arvinas, which raised $120m in an IPO last year, broke the financials of the deal down in a US Securities and Exchange Commission filing. Bayer is paying $17.5m upfront and buying $32.5m of Arvinas stock at a 20% premium over the biotech's closing price the day before news of the deal broke (4 June). Arvinas' stock rose 10% following news of the deal.

Bayer could pay Arvinas considerably more as assets discovered through the collaboration advance. The deal features $12m to support four years of research at Arvinas, plus $197.5m tied to the achievement of developmental milestones. Post-approval, Arvinas could receive up to $490m in sales-based milestones and up to low-double-digit royalties on net sales of the targeted protein degraders.

The figures are in line with the numbers disclosed with Arvinas' previously inked deals with Roche's Genentech Inc. unit and Pfizer Inc. Genentech paid $11m to start working with Arvinas in 2015 and added $34.5m in upfront and expansion target payments to expand the agreement in 2017. The development milestones in the Genentech deal stand at $44m per target. *(Also see "Deal Watch: Genentech Expands Upon Arvinas PROTAC Collaboration" - , 15 Nov, 2017.)*

ARVINAS DEALS

Pfizer struck its deal with Arvinas late in 2017. Over the following six months, Arvinas received $28m in upfront payments and other fees from the US behemoth and if the collaboration hits all its milestones, the alliance could be worth $830m to Arvinas.

Arvinas has carried out these business development activities while advancing wholly-owned assets. The firm's lead candidate, the oral androgen receptor-targeted protein degrader ARV-110, entered the clinic in metastatic castration-resistant prostate cancer earlier this year.

That milestone made ARV-110 the first targeted protein degrader to be tested in humans. Rival protein degradation biotechs such as C4 Therapeutics Inc. and Kymera Therapeutics Inc. aim to follow ARV-110 into the clinic, as do larger companies including Novartis AG and Vertex Pharmaceuticals Inc. that have in-house and partnered programs. *(Also see "Vertex Targeting Protein Degradation In $1bn Kymera Deal" - Scrip, 16 May, 2019.)*

Another strand of Bayer's deal with Arvinas could further expand the use of protein degraders into other areas. The partners are setting up a joint venture, supported by $56m from Bayer, that will explore the use of Arvinas' PROTAC technology in agriculture.

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Time For AI To Deliver In Drug Discovery, Says Atomwise CEO

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Eli Lilly & Co. is the latest big pharma to unveil a major artificial intelligence (AI) drug discovery collaboration after signing an agreement with one of the pioneers in the field, San Francisco-based Atomwise Inc..

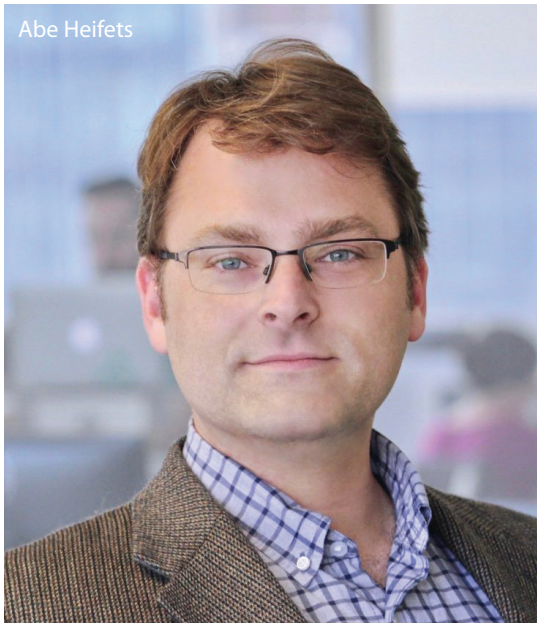
The companies will collaborate on up to 10 drug targets selected by Lilly, with the goal of accelerating the time it takes to identify and develop potential new medicines. Atomwise could receive up to $1m per target in discovery milestones and will be eligible for up to $550m in development and commercialization payments.

In an interview with *Scrip*, Atomwise CEO Abe Heifets acknowledged that "there's a ton of excitement about AI which is a very broad space in the same way that pharma is broad. We're seeing many different applications, everything from patient diagnosis to basic biology, but we focus on the chemistry side. There are applications throughout the process which is part of the reason why you see such interest."

There are a lot of AI companies targeting the pharma industry, which is looking for ways to lift its traditionally low success rates for bringing drugs from discovery through clinical development and onto the market. The hope is that new technologies can improve those success rates, but Heifets noted that it is not easy.

"Nobody can take a look at an algorithm and say, yes of course, for this particular problem, this particular algorithm will be the best. I don't think anybody can just do it from the underlying math," he said. "Like so much drug discovery, it's an empirical science and you have to just go and demonstrate success after success after success. You have to show where it works, where it doesn't, you have to convince people through data, and I think the burden is on us, the AI practitioner, to provide that evidence – and that's what we've done."

Atomwise said that it can analyze a very large chemical space involving billions and billions of compounds to identify a small subset with high specificity for synthesis and testing. The company, which was founded in 2012 and invented the first deep learning AI technology for structure-based small molecule drug discovery, added that processes – that traditionally take years can be compressed with Atomwise's technology to a matter of weeks.


Abe Heifets

Heifets said that the projects the company is already running showed that "our approach is working." He cited an alliance with the Drugs for Neglected Diseases initiative (DNDi), whose scientists selected three "verified but challenging" therapeutic protein targets that would inhibit the action of the parasite that causes Chagas disease. For each disease protein, Atomwise screened millions of compounds to predict those that bind and potentially inhibit protein function. In April the partners announced that the research had delivered drug-like compounds that would go on to further optimization and then potential development.

A partnership with the University of Connecticut has seen the discovery of inhibitors of the protein that becomes overactivated during ischemic strokes, Heifets noted, pointing out that as well as the

Lilly pact, which is focused on developing drugs for novel target proteins that "are often challenging and less well studied," Atomwise is also working alongside other big pharma players, notably Merck & Co. Inc., AbbVie Inc. and Bayer AG, "and we're showing that in a wide range of disease areas that it works."

The company also linked up with the contract research organization Charles River Laboratories International Inc. in January with the aim of making "historically intractable targets become new therapeutic opportunities." The total potential value of the royalties to Atomwise with success in all projects could exceed $2.4bn.

The Lilly deal, which gives Atomwise the option to develop compounds that Lilly chooses not to advance into clinical testing, is a welcome boost financially for a company which has raised $51m so far, $45m of which came in a series A financing in March 2018. Heifets said that the new partnership "really underscores our belief that AI is the industry standard but as I said, it's not easy and the true mark of success is going to be the eventual development of new therapies and new options."

In a recent interview with *Scrip* following the signing of a deal with the UK's BenevolentAI, Mene Pangalos, head of R&D biopharmaceuticals at AstraZeneca PLC, noted that "there is a lot of hype about machine learning" and while he is optimistic about how AI could indeed transform drug discovery and development, "right now it's a hypothesis. I'm not going to say it will be very useful until I have got some evidence that it has actually generated something that we wouldn't have otherwise done on our own." *(Also see "AZ Inks Machine Learning Deal With BenevolentAI" - Scrip, 30 Apr, 2019.)*

Heifets thinks that is a fair point, saying this is "both a nice and challenging thing and we've got to raise the table stakes, go out for a couple of dozen projects where nobody knew what the right answer was, find the right answer and show it was the right answer. In AI, there is a lot of predicting yesterday's stock price but it is much more interesting if you can predict tomorrow's."

He concluded by saying that "scientists are willing to be persuaded by data, so you have to show them data and then they're willing to believe." Atomwise has run over 200 projects and "we have had successes in over 60% of them, a significantly higher rate than with other technologies."

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Disorderly Brexit May Necessitate Drug Airlifts, Sanofi UK Head Warns

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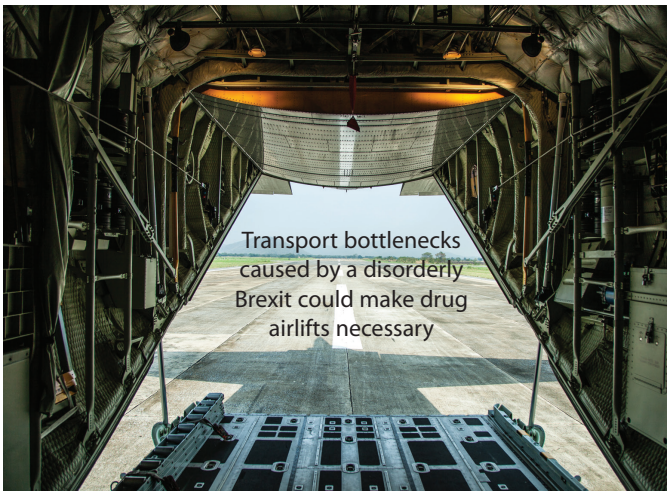

Transport bottlenecks caused by a disorderly Brexit could make drug airlifts necessary

The possible need to airlift drugs into the UK has become part of Sanofi's contingency Brexit planning, along with the stockpiling of APIs and finished drugs, the France-based drug maker's UK managing director told *Scrip*.

The pharmaceuticals industry has been stashing away drugs in the UK in preparation for the country's eventual departure from the European Union, in accordance with the June 2016 referendum result, just in case a no-deal Brexit meant that cross-border trade seized up.

It's an expensive, time-consuming exercise. Its extent was underscored by the UK first-quarter GDP figures.

The Office for National Statistics in May said the pharmaceuticals sector's production output increased by 9.4% in the first quarter, mainly driven by growth in exports of pharmaceutical products, "some of which was likely in anticipation of the UK's original exit date from the European Union at the end of March 2019."

In April, that Brexit deadline was shifted back, to 31 October 2019 after the European Council decided that the UK should have an extension beyond the original Brexit date, amid continued political paralysis over the issue in the UK.

Further uncertainly has been injected by the coming change in the ruling Conservative Party's leadership. Theresa May stands down as leader of the Conservative Party on Friday, 7 June, but she will remain prime minister until a successor is named at the end of July.

'KEEP CALM, CARRY ON' PLANNING

The pharmaceutical sector therefore remains in a high state of readiness, as a no-deal scenario remains a possibility.

But the severity of the situation as the clock runs down is clearly causing pharma executives to plan for the worst-case scenario. Most big drug makers say they have built up three months' supply within the country's borders.

"The stockpiling sits on our balance sheet. We're a big global company. We can keep it up for a certain amount of time. But it still weighs on you," said Hugo Fry, managing director for Sanofi UK & Ireland. The new Brexit date of the end of October is particu-

larly worrying for Sanofi's vaccines arm, Sanofi Pasteur, because that occurs during the seasonal influenza period.

"We're worried, because in that scenario maybe the ports and [administrative] costings [processes] will get clogged up … In that case we might need to enable some of our more robust contingency plans to get flu vaccines into the country, and that could include air lifts, if transport queues make that necessary," Fry said in an interview.

"We've got alternative routes here, which we never used to have before. If they're blocked, then we would look at air lifts, and we have taken options out on that, just in case."

FLU VACCINE WORRIES

"This approach applies to any product. But it's specifically flu vaccines because you cannot stockpile it; you make it and then ship it. And the window is thus very small," Fry said.

The looming prospect of a disorderly Brexit at the end of October is increasingly scaring those in the pharmaceuticals sector and life sciences industry, where the development of drugs and other products depends heavily on the political and regulatory conditions of a country and often require planning years in advance, while the provision of drugs to patients often requires tight timetables. *(Also see "EMA Chief Says Brexit Has Impaired Ability To Support R&D " - Pink Sheet, 8 May, 2019.)*

But the worsening political uncertainty in the country has forced the sector's players to keep their stiff upper lipped reserve, at least publicly, while hoping for the best.

"Companies are doing everything they can to protect the supply of medicines whatever the Brexit outcome. As part of this they have increased stocks of medicines in line with government guidance, Mike Thompson, chief executive of the Association of the British Pharmaceutical Industry (ABPI), recently said.

"With the extension of Article 50, we will work with government to consider how best to prepare and review whether current plans for a 'no deal' Brexit are still appropriate."

Spokespeople for the ABPI and the BioIndustry Association said no new advisories were currently planned by their organizations regarding Brexit.

Industry observers believe sector players will have more to say once a new Conservative leader – and hence prime minister – is chosen next month.

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With New Leadership, Roche Goes Back To Basics At ASCO

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In the absence of a major new molecule coming forward or franchise expansion, Roche's analyst event at the American Society for Clinical Oncology annual meeting fell back on perennial themes, emphasizing the depth and breadth of its oncology business during its portfolio review – with no shortage of superlatives.

The back-to-basics focus on franchise management may reflect Roche's current time of transition. Chief executive officer Bill Anderson took the helm at Roche Pharmaceuticals only six months ago, on 1 January. Anderson, who had been CEO of Roche subsidiary Genentech Inc., succeeded Daniel O'Day, who left to take over as CEO and chairman of Gilead Sciences Inc. *(Also see "Gilead Lures Roche Pharma CEO O'Day As CEO; Genentech's CEO Will Replace Him " - Scrip, 10 Dec, 2018.)*

Roche has restructured its oncology business to organize around disease areas, rather than molecule-based franchises, Alan Sandler told *Scrip* during an interview at ASCO. Sandler is the new co-head of product development, along with Nancy Valente – though he noted they might split up hematology and solid tumors.

"It's now a disease-based organization, the franchises are diseases," he said. As to where immuno-oncology fits in, "we're still working on the best way to do that. Should it have its own area in some fashion, should it be melded across all of the franchises? It's clearly very important to all the franchises, and now that it's begun to mature a bit, does every franchise have enough expertise, if you will, to incorporate it within the franchise and take it on, as opposed to when it's new and novel it's separate, right?"

Roche's cancer immunotherapy group is also in transition. Dan Chen, who had been global head of Roche's cancer immunotherapy franchise, now leads clinical development at private biotech IGM Biosciences. *(Also see "Lessons Learned In Immuno-Oncology From Former Roche Exec Dan Chen " - Scrip, 5 Mar, 2019.)*

Without O'Day and Chen, the 2019 ASCO event was also missing some of the venerable themes of recent years, notably discussion of the tumor immunophenotype model that has guided Roche's cancer immunotherapy efforts. The model grew from a seminal publication by Chen and Genentech VP-cancer immunology Ira Mellman. The 2019 ASCO event also saw less talk about the transformational potential of comprehensive diagnostics and data analytics.

NIMBLE BEHEMOTH

The Roche executives presenting at the ASCO event repeatedly emphasized the sheer size of the company's oncology business. "The scale of the Roche effort in cancer is almost overwhelming," Anderson declared.

The portfolio includes 16 medicines, the CEO said, adding that "it should be 18 medicines by the end of this summer." (Antibody-drug conjugate polatuzumab vedotin has a 19 August user fee goal in DLBCL, and kinase inhibitor entrectinib has an 18 August goal for two indications, one tumor agnostic and the other in ROS1-positive NSCLC.) "We expect to add another five to eight over the next few years," Anderson predicted.

The clinical studies supporting the oncology portfolio are vast in number, "but there is tremendous power in this," Anderson

stated. The company is adept at managing the network of studies, he said, and can "move very rapidly because of the scope that we have."

Combination studies benefit from the large portfolio, he said, reiterating a long-time Roche theme. "We have 72 ongoing studies in cancer immunotherapy right now," he reported as one example. "Of the 72, 64 of them are combinations."

Product development co-head Nancy Valente echoed the theme when presenting the hematology portfolio. "We have one of the largest portfolios in hematology in the entire industry," she said, which "also gives us a great opportunity that's unique to Roche to combine our therapies within our portfolio."

Roche hematology has seven products in late-stage development or marketed, she noted. "We also have five different mechanisms of actions that these products, that these therapies comprise, as well as four different platforms and that includes small molecules, antibodies, anybody-drug conjugates and T-cell engaging bispecific antibodies." Roche hematology products have been awarded seven breakthrough therapy designations and one PRIME designation, she observed.

Sandler added perspective from key solid tumor spaces, highlighting the "very exhaustive number of agents" in Roche's breast cancer portfolio, a market position that has "not only has been years but literally decades in the making with our HER2 franchise." He also pointed to "what we believe to be the most comprehensive lung cancer program in the industry."

"We have the ability to offer patients and physicians a solution in almost every form of lung cancer," Anderson said. This "will be increasingly powerful as we move forward with health systems demanding simpler solutions and more comprehensive solutions for their patients."

EFFICIENCIES OF SCALE

Like any large organization, Roche wrestles with bureaucracy. Anderson cited a reorganization that is paying dividends in shorter filing timelines.

Roche is "simplifying our team structure, but putting a lot more decision-making power directly with the teams so that they can see opportunities and pursue them without having to navigate a lot of governance committees and things like that," he said. "We're seeing big payoffs on this, and things like faster filing."

Across the portfolio, Roche shaved five weeks off the average filing timeline last year, and it had 25 major filings, Anderson reported. "That's an extraordinary number."

"To be able to take off five weeks has a huge impact for patients and for our business, and we're not even beginning to be done with that," he continued. "This is something that we're going to put a lot more energy into."

LANDMARK ANALYSES

Throughout the meeting, Roche emphasized the value of long-term data on established cancer medicines. Roche was not alone in proclaiming the value of landmark data from patients with long follow up. Merck & Co, for example, presented an analysis of five-year survival data from the KEYNOTE-001 trial of Keytruda (pembrolizumab) in non-small cell lung cancer. *(Also see "ASCO Review: Progress Is Where You Find It" - Pink Sheet, 5 Jun, 2019.)*

Sandler pointed to a landmark analysis of patients in the CLEOPATRA trial, a Phase III trial in first-line HER2-positive metastatic breast cancer that evaluated Perjeta (pertuzumab) plus Herceptin (trastuzumab) and docetaxel vs Herceptin and docetaxel. "This is a study that's been around for a while," he commented. The first interim analysis was reported in May 2011, followed by a second interim look in May 2012 and the final overall survival analysis in February 2014. At this year's ASCO, Roche presented data through November 2018.

"What I want to point out here is the landmark analysis at eight years," he told the analysts: overall survival was 23% in the Herceptin/chemo arm and 37% in the patients who received Perjeta as well. Median OS was 57.1 months in the Perjeta arm, which Roche called "unprecedented," and 40.8 months on the comparator. "I just want to hearken back to where we were before Herceptin and Perjeta, where a median survival for women with this diagnosis would have been less than one year," Sandler said. "Now you're looking at landmark analysis of nearly 40% of patients alive at eight years, other patients even beyond that mark and hint at least of a bit of a plateau in this highly difficult disease."

And importantly, no additional safety issues have been seen, he reported.

Roche also updated analysts on the maturing data from the Phase III IMpassion 130 trial of Tecentriq (atezolizumab) in first-line triple-negative breast cancer. The US FDA granted accelerated approval to Tecentriq plus Celgene's Abraxane (nab-paclitaxel) for use in previously untreated advanced TNBC patients with PD-L1 expression on ≥1% of tumor-infiltrating immune cells on 8 March. The Tecentriq regimen is "the first therapy to cross the two-year landmark OS benefit in PD-L1+ mTNBC," according to company slides.

At two years, 42% of Tecentriq and 39% of control arm patients survived. In the PD-L1+ population, the two-year OS was 51% for Tecentriq and 37% for control. "Although not formally testable due to the pre-specified statistical analysis plan, updated median OS improvement from 18 to 25 months was observed in the PD-L1+ population."

Sandler also pointed out that Tecentriq + nab-paclitaxel was "well tolerated, with no cumulative toxicities and no new or late-onset safety signals."

LOOKING FOR DEEP AND DURABLE RESPONSES

With market and clinical experience, Roche is also pushing therapy into earlier-stage disease – a research strategy Roche is employing across malignancies, looking at earlier intervention where there's more possibility for a cure, Sandler noted.

"At the core of our strategy has always been that the patients should obtain a deep response and with this deep response comes a translation to a long remission," Valente stated. "I think the story here is how we're able to go deeper and offer bigger patient benefits in some of the diseases where we've been strong," Anderson commented.

"We've been able to show that relationship across multiple different disease states," Valente said. "When you achieve a minimal residual disease state, so a really deep response, we've been able to show in CLL and follicular lymphoma and in AML that translates into prolonged or extended progression-free and sometimes

even overall survival," she said, referencing data on approved uses of Venclexta (venetoclax) in chronic lymphocytic leukemia and in the pending BLA for polatuzumab vedotin for diffuse large B-cell lymphoma (DLBCL). Gazyva (obinutuzumab) is accepted as the standard of care for first-line indolent non-Hodgkin's lymphoma "with estimated three years longer mPFS than Rituxan."

"We've been able to do that again in the new CLL14 study," she declared. The trial supported approval of the combination of a chemotherapy-free, fixed-duration regimen of Venclexta plus Gazyva in previously untreated CLL or small lymphocytic leukemia on 15 May, just over two months after sNDA submission, thanks to the FDA's Real-Time Oncology Review (RTOR) pilot program. *(Also see "US FDA's Real-Time Oncology Review Times Coming Into Focus" - Pink Sheet, 19 May, 2019.)*

"Many of the therapies that are given to patients with CLL are used until progression," she commented, so the fact that this is a 12-month treatment course "is really unique." She called the Kaplan-Meier curve for CLL14 "really stunning," showing 89% of patients are progression-free at two years. "The hazard ratio of 0.33 translates to benefit with a 60% chance of the reduction in the disease worsening or death of 67%," she said.

"Importantly, there's really deep MRD data here," Valente continued. "The rate of MRD negativity is much higher here in the Venclexta plus Gazyva arm than the control arm both in the blood and bone marrow. And this is at the end of treatment, about three months after treatment."

Roche chief medical officer Sandra Horning commented on CLL14 from the floor. "I think one thing to think about the Gazyva-Venclexta combination is the potency," she said. "The potency in achieving minimal residual disease even to less than one in a million cells, and what that translates then into is long progression-free survival, and that translates into the opportunity with a fixed duration regimen for patients to be both off treatment and without active disease."

"I think that's where the real magic is," Horning said. "It's in achieving those very deep remissions."

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BeiGene, Hengrui Among China Firms Flexing New Oncology Muscle At ASCO

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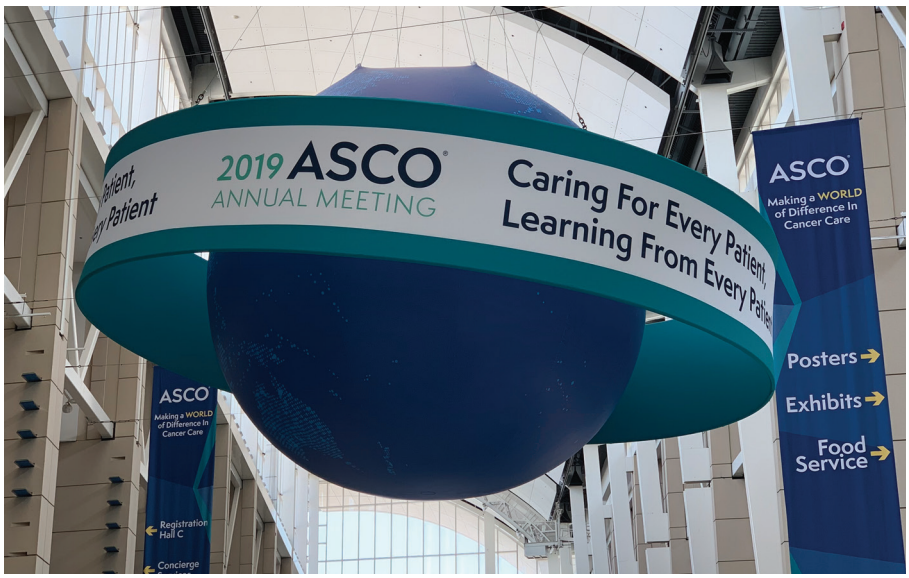
Days after China's regulators cleared the country's fifth PD-1 checkpoint inhibitor for marketing, both excitement and anxiety is emerging over the increasingly overcrowded oncology research area in the country.



China is already the largest market in Asia for oncology drugs, as it has the largest patient population for several forms of cancer including lung, breast and liver. Its drive to facilitate the development and commercialization of more and newer cancer therapies has also been bearing fruit, some of which was on show at the recent American Society of Clinical Oncology (ASCO) meeting in Chicago.

Heeding a series of policy and regulatory changes, more international companies are also eyeing the Chinese market, and there are now more PD-1-targeting drugs in Phase III development in China than the US. Similarly, the figure for CAR-T studies for hematological malignancies has also overtaken the US.

GOVERNMENT SUPPORT

Antibody therapy is one of several sectors singled out recently by the Chinese government as a core healthcare area for concentrated development. A new proposal released on 8 April by the National Reform and Development Commission also called for support for vaccines, gene and cell therapies and recombinant proteins, as well as nucleotide drugs.

> Despite all the new data. in comparison Chinese companies' deal-making at this year's ASCO was muted.

Supported by government policy and positive regulatory reforms, the investment has been flowing in and the speed to catch up with the rest of the world has been stunning.

As one example, five years ago when the director of regulatory affairs of a then little-known biotech startup called BeiGene Ltd. flew to Washington, DC for an IND meeting with FDA, she had to fly economy despite having a fever. Unlike the multinationals she had been with for years in the same capacity, the cash-

crunched biotech simply couldn't afford the luxury of business class.

Fast forward and BeiGene is now much different, being duel-listed on Nasdaq and in Hong Kong, with multiple oncology agents under late-stage development or pending approval in both China and the US.

Riding the wave of faster reviews and approvals coming out of China's regulatory reforms, companies like BeiGene and Jiangsu Hengrui Medicine Co. Ltd. are now rapidly emerging to dominate new treatments for some of the most prevalent cancer types in China, such as lung, breast, liver, gastric, gastroesophageal and nose and throat cancer.

ASCO PRESENCE

Hengrui presented positive Phase I/II data for pyrotinib at ASCO. The small-molecule pan-ErbB inhibitor was combined with capecitabine to treat HER2-positive breast cancer patients previously treated with *Herceptin* (trastuzumab) and taxanes, and showed statistically significant better progression-free survival than placebo plus capecitabine.

Pyrotinib was launched last year in China for HER2-positive gastric cancer.

During the world's largest annual gathering for oncologists, BeiGene also presented Phase III in-progress data for its anti-PD-1 antibody tislelizumab in patients with locally advanced or metastatic gastric and gastric-esophageal junction cancer.

China has the one of the highest incidence rates worldwide for nasopharyngeal cancer, particularly in Southern China, and BeiGene presented at ASCO preliminary Phase II results for tislelizumab in this setting, showing a confirmed objective response rate of 43%.

China recently cleared its fifth PD-1 checkpoint inhibitor, Jiangsu Hengrui Medicine Co. Ltd.'s *Iruito* (camrelizumab), and tislelizumab is pending approval for typical Hodgkin's lymphoma, set to become the sixth PD-1 agent to be commercialized in China. *(Also see "Fifth PD-1, Zavicefta, Novel Psoriasis Ointment Among Latest China Approvals" - Pink Sheet, 4 Jun, 2019.)*

Meanwhile, other developers including CStone Pharmaceuticals Co. Ltd., Junshi and Innovent Biologics Inc. also brought their latest PD-1 antibodies to the ASCO gathering. Innovent's xinlitimab is being studied for non-small cell lung cancer, Junshi's topalizumab for bladder, gastric and nasopharyngeal cancer and CStone's CS1001 for solid and blood malignancies. Ascentage Pharma Group Corp. Ltd. presented data for APG-115 and APG-1387 for solid cancers.

MUTED DEAL-MAKING?

Despite all the new data. in comparison Chinese companies' deal-making at this year's ASCO was muted, one attendee told *Scrip*.

Amid the trade war stand-off between China and the US and attractive pipeline assets being increasingly harder to scope, investors and deal makers seem to have become more cautious.

However, some disagreed. "There is a lot of money in China that is available for investment," which makes partnering in China attractive, noted analysts from Credit Suisse, noting a potential change in deal flow.

While people are "used to seeing Chinese companies as in-licensing international assets, [they are] now seeing Chinese companies that want to out-license to the US," the investment bank noted.

Published online 7 June 2019

ASCO Review: Progress Is Where You Find It

MARY JO LAFFLER maryjo.laffler@informa.com

Without a definitive new drug ready to change practice, many observers rejected this year's American Society of Clinical Oncology as slow.

But coming out of the meeting, the trends highlighted show a remarkable amount of progress and the tremendous efforts underway to realize the full potential of genomic research to identify new therapies, find the best treatment settings and combinations and match them to the right patients.

True, none of the plenary abstracts featured a new molecular entity (and one was on a drug already withdrawn for lack of effect). But that allowed ASCO to put a spotlight on other areas of progress.

As Credit Suisse analysts put it going into the 31 May-4 June conference in Chicago, "the intense scrutiny on detailed data points from numerous pivotal trials from our large-cap companies (most notably Merck and Bristol-Myers) has been replaced by what we expect to be some still-important data presentations, but also with a focus now on bigger picture themes as we think about the emerging oncology landscape," including "how patients/physicians are managing the costs/side effects related to various therapies, as well as how our healthcare system may need to evolve to accommodate the large number of novel but expensive therapies that have shown impressive clinical results in recent years."

SIGNATURE ACHIEVEMENTS

That's not to say there weren't signature achievements. The POLO study showed a dramatic effect in a subset of patients with a notoriously difficult cancer – in pancreatic cancer patients with germline *BRCA* mutations, AstraZeneca PLC/Merck & Co. Inc.'s PARP inhibitor *Lynparza* (olaparib) yielded median progression-free survival (PFS) of 7.4 months compared with 3.8 months for placebo, with more than twice as many patients remaining progression-free at both one year (34% vs. 15%) and two years (22% vs. 10%).

Astellas Pharma Inc./Pfizer Inc. got confirmation that enzalutamide has a role when added to testosterone in first-line treatment of hormone-sensitive prostate cancer from ENZAMET, with longer overall survival but also some increased toxicity.

But progress doesn't always come with great leaps forward; sometimes it's a matter of incremental advance. Going fast can miss things – the checkpoint inhibitors rightly made a big splash and have come to dominate many cancers (and billboards around the city of Chicago).

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But the first few years were filled with questions about how to identify the right patients, better information on dosing and appreciating differences between the PD-x drugs (remember when it was thought *Keytruda* (pembrolizumab) and *Opdivo* (nivolumab) might be interchangeable?) – the sort of thing that isn't fleshed out when moving on a fast track.

In recent years, there's been a lot of filling in around the edges as more information rolled in. Researchers have clarified differences between the drugs in terms of efficacy and tolerability, better dosing regimens have been established in some cases, and the utility of the PD-L1 biomarker has been debated. This year there was a notable focus on emerging biomarkers for IO as well as understanding resistance patterns.

And Merck presented five-year survival data from the KEYNOTE-001 study with Keytruda in non-small cell lung cancer – a landmark analysis that codifies the impact IO is having on the cancer landscape.

Whereas traditionally lung cancer has had a five-year survival rate of 5% or less, Merck Research Labs' chief medical officer Roy Baynes noted, the five-year overall survival (OS) rate was 23.2% in treatment-naïve patients and 15.5% in previously treated patients. In patients with high levels of PD-L1, five-year OS was 29.6% in treatment-naïve patients and 25.0% in previously treated patients.

The trial also supports longer-term use. In patients who had been on therapy for two or more years, the five-year OS rate was 78.6% in treatment-naïve patients and 15.5% in previously treated patients. "The data also bodes well for Merck's ability to gain traction with payers, including those outside of the US who may look for more longer-term data to fully support a product," Credit Suisse analyst Vamil Divan said in a 2 June note.

Landmark data were also presented for Roche/Genentech Inc.'s *Perjeta* (pertuzumab) in combination with *Herceptin* (trastuzumab) and docetaxel in patients with previously untreated HER2-positive metastatic breast cancer, with an "unprecedented" effects seen at an end-of-study analysis.

After eight years of follow up, patients on the Roche regimen had a 16.3 month improvement in survival over patients on the comparator – a statistically significant 31% reduction in the risk of death.

PRICING REMAINS A PAIN POINT

Long-term use does raise financial issues, however, and cost concerns came up again and again in scientific presentations, especially regarding combination therapy. ASCO 2019 featured more than a handful of talks on value assessment, including a town hall on drug pricing and a specific session on oncology reimbursement reform that reviewed lessons learned from the oncology care model.

In addition, health services/quality of care research took prominence with the presentation of research in the plenary session showing how Medicaid expansion under the Affordable Care Act almost eradicated racial disparity in cancer care compared to states that did not expand Medicaid.

> "Analysts and physicians alike are keenly tracking the emergence of new checkpoint inhibitors beyond the PD-1/L1 family, and ASCO featured early data on a few hotly watched targets.

It was one of several abstracts showing almost 10 years into Obamacare that access to care and better insurance are connected to better survival. *(Also see "US Affordable Care Act Impact On Cancer Care Quantified At ASCO" - Pink Sheet, 2 Jun, 2019.)*

FINDING A WAY WITH BIG DATA

There was a dedicated education session on big data, and the role of artificial intelligence and data analytics to process vast amounts of information – and the potential to better harness real-world evidence – came up in multiple tracks. The exhibit hall also reflected a shift toward more incorporation of a wide spectrum of technology into drug development and clinical practice, with splashy booths for sequencing and AI companies. And the plenary abstract on racial disparities was conducted using Flatiron Health claims data. Read the full article here

Big pharma continues to explore ways to exploit data analytics. Roche has fully embraced it, making it a centerpiece of its oncology strategy with its early alliances (and later acquisitions) of Flatiron Health and Foundation Medicine. *(Also see "Next-Generation Roche: How Data Analytics Will Keep It In The Lead In Oncology" - Scrip, 8 Jun, 2018.)*

Lilly announced a deal with AI specialist Atomwise during ASCO. *(Also see "Time For AI To Deliver In Drug Discovery, Says Atomwise CEO" - Scrip, 4 Jun, 2019.)*

While using non-traditional data sources like electronic health records and claims databases "are not designed with clinical evidence generation in mind, and analyses of these databases are retrospective rather than prospective, they can yield important insights into real-world practice and include many more patients than is typical for an oncology trial," Informa Pharma Intelligence analyst Dan Chancellor told *Scrip*. "This is particularly useful for studying niche populations, such as those with rare tumors or unique molecular/genetic signatures."

Data analytics companies are eager to expand the role of real world evidence (RWE). Private AI play ConcertoHealthAI, which had a fairly large booth in the exhibit hall, has come up with a model for prospective research and is working with Pfizer, Bristol-Myers Squibb Co., Astellas and other undisclosed partners, including payers.

President Jeff Elton talked about how encouraging the US FDA has been in embracing RWE and modernizing data collection and analysis in an interview at ASCO. "FDA has been spectacular leadership in this," he said. "They are ready for innovation and want to see protocols."

Big data is generating big buzz, Merck's Baynes agreed, as companies look to systematize datasets for pattern recognition and clues – but it's early days yet.

"You're only as good as the algorithms you employ," he commented. "There's tremendous enthusiasm around [data analytics] and it's important to pursue, but at the end of the day you need to recognize that the findings are hypothesis-generating."

CHECKING IN ON NEW CHECKPOINTS

Analysts and physicians alike are keenly tracking the emergence of new checkpoint inhibitors beyond the PD-1/L1 family, and ASCO featured early data on a few hotly watched targets.

The data on Aduro Biotech Inc./Novartis AG's ADU-S100, a stimulator of interferon genes (STING) activator, were from a dose escalation study, but they showed an encouraging 100% disease control rate among the eight patients with triple-negative breast cancer evaluable for response, "strengthening the value of STING activation as a novel immunotherapy approach for solid tumors. There is now preliminary efficacy across TNBC, melanoma, adding to previous data for Merck's MK-1454 in head and neck cancer and thyroid carcinoma," according to Biomedtracker analysts.

Both ADU-S100 and MK-1454 are delivered intra-tumorally. Merck's Baynes noted that there was "no question of local effect" for STING and that Merck is in the process of expanding its trials. Aduro noted that enrollment in a study of ADU-S100 and ipilimumab in relapsed/refractory melanoma is ongoing and it anticipates initiating a trial with pembrolizumab in first-line head and neck cancer in the second half of 2019.

There were also early data on LAG-3, another next wave checkpoint inhibitor. But no monotherapy patients responded to Regeneron Pharmaceuticals Inc./Sanofi's REGN3767 and only 5% of patients receiving it with the anti-PD-1 cemiplimab achieved a partial response. Patients who converted to PD-1 monotherapy after receiving the LAG-3 drug did the best.

"It suggests that LAG-3 may be best used as a sequential agent and it does sensitize tumors to PD-1 inhibition, but the effect in this trial was weak (16% PR). This was a dose escalation study and not designed to determine efficacy, but you can't ignore the low overall response rates," Chancellor told *Scrip*.

WHAT CAN WE LEARN FROM FAILURE?

ASCO threw the interesting twist of highlighting a trial failure for one of the four plenary spots, which served as a post-mortem on the accelerated approval and subsequent withdrawal of Eli Lilly & Co.'s Lartruvo (olaratumab) and an examination of what it was about soft tissue sarcoma (STS) that contributed to the failure.

It played out like a mystery – here was a drug that had a significant survival benefit in a large randomized Phase II trial, but then missed the survival endpoint in the Phase III study.

The principal investigator William Tap, Memorial Sloan Kettering Cancer Center, walked through the Phase II evidence, the sound decision for accelerated approval and the rigor and quality of the Phase III study. Both he and the discussant on the trial, Erasmus University's Jaap Verweij, identified issues about the heterogeneity of the STS classification and the likelihood of differential responses in subgroups. Read the full article here

The public debate of the findings seem to put to rest any concerns about the accelerated/conditional approval mechanisms – this is an example of a "successful failure" and a confirmation that these programs that push for new advances on early evidence must necessarily have some that don't work out.

Failure is of course an all too common part of the drug development process. Focusing on the olaratumab experience showed how much can be learned out of failure, and how it can inform future development.

When Merck comes up with a failed trial, it rallies a team to pull it apart – look at the setting, the degree that it missed the endpoint, if there were crossover effects or there might be a subgroup that is responding, Baynes explained in an interview at ASCO.

Even a positive trial is picked apart to glean intelligence about subgroups and response patterns, Baynes said, "but if a study fails, we spend a lot of time trying to [understand what happened]."

Failed trials are tremendous learning opportunities. As Genentech oncology product development leader Alan Sandler told *Scrip*, "the only mistake in clinical development is if you think you know more than you do."

NOT ACTUALLY SO QUIET?

It may have been a year that investors and analysts found quiet – although according to Baynes, ASCO was "anything but quiet." Of course Merck now has the leading IO franchise in Keytruda and the leading PARP inhibitor in Lynparza, and presented some of the biggest results of the conference.

But the different areas of focus at ASCO 2019 drive home the changing landscape in oncology, as IO falls into place as an established pillar of oncology, political and commercial pressure tightens on reimbursement and pricing, and new technologies raise new possibilities for R&D.

It sets the stage for what to look out for in 2020.

Published online 6 June 2019

Novartis's Drug Discovery Head Jay Bradner On What NIBR Is Investing In

JESSICA MERRILL jessica.merrill@informa.com

As the president of Novartis AG's Institute for Biomedical Research, James (Jay) Bradner oversees drug discovery and early development at the big pharma, committing resources to going after "high-hanging fruit" in some cases. He built his reputation in part from pioneering work on targeted protein degradation studying targets that are considered undruggable, and he has been an outspoken critic of industry at times for a tendency to chase after the same targets.

As Bradner said in a recent interview at NIBR's Cambridge, MA, headquarters, "I loathe fast-follower innovation."

Bradner has been working to infuse a highly innovative and entrepreneurial spirit into Novartis' drug discovery research engine since taking over the leadership of NIBR in 2016. He has quietly reshaped the early research unit over three years, emphasizing collaboration and externalization. Brader talked to *Scrip* on 22 May about those changes, the science he's excited about right now, and some of the ways NIBR is investing its $2.6bn budget.

His ambition for NIBR when it comes to pouncing on new innovation is "to be faster than a venture capitalist." That's a high bar in today's cash-rich startup environment, but one Bradner knows a thing or two about. His background is a mix of academic star power and entrepreneurial acumen.

He was recruited to Novartis from academia and medicine, having previously worked as a researcher at Harvard Medical School and as an attending physician in stem cell transplantation within the Department of Medical Oncology at the Dana-Farber Cancer Institute. He has co-developed several biotech companies, including C4 Therapeutics Inc., built out of research on targeted protein degradation, and Tensha Therapeutics Inc., focused on disrupting BET proteins for cancer and acquired by Roche in 2016.

At NIBR, he oversees drug development from discovery through proof-of-concept, after which drug development is led by chief medical officer John Tsai, who is also relatively new to Novartis. Tsai was recruited from Amgen Inc. last year, succeeding his current boss, Vas Narasimhan, who took over as CEO about 18 months ago.

Jay Bradner

All three top executives – Narasimhan, Tsai and Bradner – say they are committed to changing the culture at Novartis. Narasimhan and Bradner have obviously worked closely together in R&D now for several years, and Bradner said they are close friends with a shared vision.

REDUCING NIBR'S SCOPE TO BALANCE EXTERNAL RESOURCES

"We have quietly reduced the size of NIBR," Bradner said. "We've evolved the portfolio to be more focused and better resourced." The refinements were partly fueled by necessity following the patent expiration of the mega-blockbuster Gleevec (imatinib) in 2016, but they were also driven by a strategic decision to better balance internal and external research.

Today, NIBR has 6,000 scientists and 340 drug discovery programs spanning eight therapeutic areas.

"I believe we are right-sized for the opportunity in disease biology where we work today, for the innovation of new science in therapeutics and for partnering with the outside world," Bradner said.

Of NIBR's $2.6bn budget, about $2bn is dedicated to internal research while the rest is put toward external collaborations, with the flexibility to tap other funding mechanisms for bigger deals, he said. He's agnostic about the balance of internal/external drugs in the portfolio.

"The truth is I just don't care where it comes from," he said. "I do want the best and right medicines to have access to Novartis because I think it's such a powerful vehicle for access worldwide, one of our truly unique strengths."

One funding mechanism Novartis relies on for partnering is called the NIBR External Research Fund (NERF), which he has expanded over the last three years to pave the way for more nimble, rapid-fire investments.

"Members of our leadership can show up to an academic lab, learn about a new technology, and have their checkbook open, to start working right away, to not be bureaucratic," Bradner explained. NERF supports year-on-year investments in committed partnerships like Novartis' ongoing work with the University of Pennsylvania on CAR-T therapies and with the University of California, Berkeley on chemistry and proteasome research. But NIBR can also tap into other funding

mechanisms within Novartis for more expensive deals, like the company's recent acquisition of IFM Tre, which Bradner said would have depleted the NERF fund. Novartis announced the acquisition of the Boston-based startup for $310m up front and potentially up to $1.58bn in April, gaining a pipeline of anti-inflammatory drugs targeting the NLRP3 pathway, which plays a role in the body's innate immune system.

GOING IN BIG ON THE INFLAMMASOME

NLRP3 is an emerging area Bradner has been keeping a close eye on for some time, inspired partly by Novartis' internal research on the monoclonal anti-IL-1β antibody canakinumab, marketed as Ilaris. NLRP3 inhibition works upstream of IL-1β, and when activated triggers an inflammatory response through the assembly of a multi-protein complex called the inflammasome.

Ilaris, a mature drug marketed for several rare disease including cryopyrin-associated periodic syndromes (CAPS) and Muckle-Wells Syndrome, has been intriguing in other areas, including cardiovascular disease prevention and cancer prevention.

Though the FDA ultimately declined to approve canakinumab for cardiovascular risk reduction in patients with a previous myocardial infarction in 2018, based on the results of the 10,000-patient CANTOS trial, requesting more information instead, Novartis has been mining the data. CANTOS has yielded loads of information about inflammation inhibition, including notably a potential benefit on lung cancer prevention. Novartis is now running a broad Phase III program called CANOPY in non-small cell lung cancer, with the first potential filing in second-line metastatic NSCLC targeted for 2021.

"I've been really inspired by the canakinumab data in cancer prevention, and I've learned so much in coming to NIBR about the interleukin-1β pathway, the role of myeloid cells in cancer and inflammasome signaling in microglial cells," Bradner said. "And Novartis has learned a lot from having canakinumab for so many years about white spaces to explore with drug development."

"We see three or four clarified paths forward for inflammasome pathway inhibitors, and therefore, we wanted to be first-in-class, first into the clinic," he added. The IFM Tre programs complement ongoing work internally at NIBR on IL-1β and NLRP3.

"We wanted two programs, a CNS program which we thought we would be in the best position to innovate, and a non-CNS program, which we might access through one of these partners, and in the end, IFM Tre emerged as having the first into human molecule with what we thought were some differentiating properties."

IFM Tre's first drug candidate, IFM-2427, only just started Phase I and is being explored for a wide array of chronic inflammatory disorders, including gout, atherosclerosis and non-alcoholic steatohepatitis (NASH). Bradner said the first step will be exploring tolerability in humans, noting "there's a lot a mouse, a dog and a rat can't tell you."

"That's the first mission, is this a thin therapeutic index that requires us to think about serious diseases such as cancer or end-stage nerve generation or is this a well-tolerated medicine with little immune compromise at which point we can think about gouty arthritis, NASH, cancer prevention, giving a medicine like this to well people?" he questioned.

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Scrip's weekly **Pipeline Watch** tabulates the most recently reported late-stage clinical trial and regulatory developments from the more than 10,000 drug candidates currently under active research worldwide.

Click here for the entire pipeline with added commentary: http://bit.ly/2mx4jY3

PIPELINE WATCH, 31 MAY – 6 JUNE 2019

Event Stage	Lead Company/Partner	DrugName	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Final Results	Novartis	Arzerra	Chronic Lymphocytic Leukemia (CLL)	COMPLEMENT 1	0	100
Phase III Final Results	AbbVie Inc./ J&J	Imbruvica	Chronic Lymphocytic Leukemia (CLL)	RESONATE	0	100
Phase III Final Results	Roche Holding AG	Kadcyla	Breast Cancer	KRISTINE	0	100
Phase III Final Results	Merck & Co., Inc.	Keytruda	Head and Neck Cancer	KEYNOTE-048	0	100
Phase III Initiation	Eyenovia, Inc.	MicroPine	Myopic Macular Degeneration/Pathological Myopia	CHAPERONE	51	51
Phase III Initiation	Aeglea BioTherapeutics, Inc.	Pegzilarginase	Urea Cycle Disorders and Derangements	PEACE	38	64
Phase III Initiation	Novan Therapeutics	SB206	Antiviral - Other Treatments	B-SIMPLE1, B-SIMPLE2	34	64
Phase III Initiation	Roivant Sciences, Inc.	Tapinarof	Psoriasis	PSOARING 1, PSOARING 2	39	60
Phase III Published Results	Foamix Pharmaceuticals Ltd.	FMX101	Acne	FX2017-22	0	97
Phase III Published Results	Daiichi Sankyo Co., Ltd.	Quizartinib	Acute Myelogenous Leukemia (AML)	QUANTUM-R vs. Chemotherapy	0	81
Phase III Suspension	Takeda Pharmaceutical Company Ltd	Ninlaro	Amyloid light-chain (AL) Amyloidosis	TOURMALINE-AL1	-62	0
Phase IIIb Top-Line Results	Helsinn Healthcare	Akynzeo	Chemotherapy Induced Nausea and Vomiting (CINV)	Breast Cancer	0	100
Phase III Top-Line Results	AstraZeneca PLC	Calquence	Chronic Lymphocytic Leukemia (CLL)	ELEVATE-TN (vs. Obinutuzumab) (First-Line)	1	43
Phase III Top-Line Results	Roche / Shionogi	Xofluza	Influenza (excluding vaccines)	BLOCKSTONE	0	100
Phase III Top-Line Results	Roche/Novartis	Xolair	Nasal Polyposis	POLYP 1 and 2	5	67

Source: Biomedtracker | Informa, 2019

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CHARTING A PATH IN GENE THERAPY

Deal-making has also propelled Novartis's gene therapy development, on the commercial front but also within the pipeline at NIBR. Novartis's acquisition of gene therapy developer AveXis Inc. for $8.7bn in 2018 put the company at the forefront of the emerging field. Zolgensma (onasemnogene abeparvovec-xioi), developed by AveXis, was approved by the FDA on 24 May as a gene therapy for spinal muscular atrophy.

But Bradner insisted the acquisition was pivotal to progressing Novartis' broader ambitions in gene therapy. "It just charted a path through a very dense forest," he said.

"When I joined Novartis, we had three gene therapy programs, one of which was ready for human clinical investigation," he said. It was CPK850 in development for retinitis pigmentosa, a group of rare genetic eye disorders.

"Of our more than 60 global manufacturing sites, not one could make adeno-associated virus," he added. "We worked with contract manufacturers and it took us four years to get enough clinical supply of this material to bring to these patients."

AveXis has solved some of those manufacturing challenges and Novartis now has 10 gene therapy programs in development, including CPK850 and two AveXis candidates, one for Rett Syndrome and another for amyotrophic lateral sclerosis (ALS). Two undisclosed neuroscience programs from NIBR are moving over to AveXis for manufacturing, Bradner said. For now, Novartis is focusing on AAV as the vector for delivering gene therapies, and largely neuroscience and ophthalmology.

EXPANDING IN LIVER AND KIDNEY DISEASE

While most of NIBR's budget is reserved for research in core therapeutic areas like cancer, cardiovascular disease, ophthalmology and pulmonary disease, 20% of the investment is reserved for exploring outside those boundaries with the goal of expanding in new directions. Out of this effort, for example, has emerged an FXR agonist tropifexor, or LJN452, in Phase II development for NASH.

"Novartis doesn't have a history in hepatology, but we emerged with what we think – and honestly what some of our peers think – is the best-looking molecule in the space, and it could be a platform to develop other medicines for NASH, so that brought us into the liver domain," Bradner said.

In a similar way, Novartis is moving into kidney disease. "We saw it as an open water to swim in," Bradner said.

The company repositioned a complement factor B inhibitor LMP023 to study complement-mediated kidney disease and stitched together some other programs, including a first-in-class anti-CD40 medicine to prevent kidney transplant rejection and improve kidney function. Novartis now has five early clinical programs in development for kidney disease.

While NIBR plans to continue to invest in kidney disease, Bradner cautioned that despite advancements in kidney biology, it remains challenging biology and developing new treatments won't be easy.

Published online 5 June 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Rob Ciappenelli	Dicerna Pharmaceuticals Inc	Chief Commercial Officer	Momenta Pharmaceuticals	Global Head, Commercial	4-Jun-19
Tracey Lodie	Gamida Cell Ltd	Chief Scientific Officer	BlueRock Therapeutics	Senior Vice President, Translational Immunology	5-Jun-19
Robert Iannone	Jazz Pharmaceuticals Plc	Executive Vice President, Research and Development	Immunomedics	Chief Medical Officer and Head, Research and Development	29-May-19
Edwina Baskin-Bey	Nanobiotix	Chief Medical Officer	Innocrin Pharmaceuticals	Chief Medical Officer	4-Jun-19
Jeff Settleman	Pfizer Inc	Senior Vice President, Group Head, Oncology Research and Development	Calico Life Sciences	Head, Oncology Research	1-Jul-19
Stephen Prescott	ProBiotix Health Ltd	Chief Executive Officer	Probi AB	Vice President, Marketing and Applications	28-May-19
Glenn Reicin	Sigilon Therapeutics Inc	Chief Financial Officer	Greyrock Biomedical Advisors	President and Founder	3-Jun-19
Andrew Hindman	Theravance Biopharma U.S Inc	Chief Financial Officer and Senior Vice President	Acorda Therapeutics	Chief Business Officer	4-Jun-19

Click here for all appointments: https://bit.ly/2oHWRYn

Source: Medtrack | Informa, 2019

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