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Novartis' Kisqali Scores Big Win In Competitive CDK4/6 Space

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Novartis AG's Kisqali (ribociclib) is the first CDK4/6 inhibitor to show a significant overall survival advantage in HR+/HER2- advanced breast cancer, bolstering its position in the competitive market, where it has struggled to make substantial headway against Pfizer Inc.'s first-in-class Ibrance (palbociclib).

The positive overall survival data from the MONALEESA-7 trial were featured in a press briefing at the American Society of Clinical Oncology meeting in Chicago on 1 June and will be presented at the conference on 4 June, along with a corresponding publication in the *New England Journal of Medicine*.

"Overall survival is the gold standard of [how] we measure treatment in oncology," chief medical officer John Tsai said in an ASCO preview call with the press. "It's a very high mark for us to actually cross this boundary and show significance on this endpoint."

The trial, MONALEESA-7, was conducted in pre- and perimenopausal women, where Kisqali is already approved in the first-line setting, a unique indication for the drug versus two other marketed CDK4/6 rivals, Pfizer's Ibrance and Eli Lilly & Co.'s Verzenio (abemaciclib). Novartis secured US FDA approval for the expanded indication in pre- and perimenopausal women last year, based on progression-free survival data from MONALEESA-7. It was originally approved by the FDA in March 2017 in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women. *(Also see "Novartis Sets 'Flexible Pricing' For Kisqali To Compete Against Pfizer's Ibrance" - Scrip, 14 Mar, 2017.)*

The overall survival data show that of 672 women in the intent-to-treat population, 70.2% were still alive at 42 months versus 46% of those on endocrine therapy alone. The trial was stopped early for efficacy after a pre-specified interim analysis following 192 deaths.

With a median follow-up of 34.6 months, 35% of ribociclib patients were continuing treatment compared with 17% still on treatment in the placebo arm. At the end of the trial, median progression-free survival was 23.8 months for ribociclib versus 13 months for placebo.

Despite lots of advances in breast cancer, five-year survival rates in metastatic breast cancer have only improved by less than 5% over the last 20 years, and advanced breast cancer is the leading cause of cancer death in women age 20-59, according to Novartis. At least two-thirds of breast cancer is hormone receptor-positive. "There's also significant unmet need in the pre- or perimenopausal women population because we know the disease in this population of patients is more aggressive than the standard breast cancer patients," Tsai said.

NOTCHING A WIN WHERE IBRANCE DID NOT

Kisqali is the first of the three marketed CDK4/6 inhibitors to show a survival advantage in any advanced HR+, HER2- breast cancer population. Last year, Ibrance failed to show an overall survival benefit in combination with fulvestrant compared to fulvestrant alone in women with HR+, HER2- metastatic breast cancer whose disease had progressed after prior endocrine therapy in the PALOMA-3 trial.

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from the editor

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Our reporters have been scouring the data and presentations and quizzing experts at the American Society of Clinical Oncology's annual meeting in Chicago this week, and the first half of our issue this week is dedicated to ASCO. Highlights have included strong overall survival data for Novartis' Kisqali in pre- and perimenopausal women with advanced HR+/HER2- breast cancer (see cover story); promising progression-free survival data for Merck & Co's/AstraZeneca's Lynparza in the difficult indication of metastatic pancreatic cancer (p4), and positive data in multiple myeloma for Sanofi's isatuximab and Johnson & Johnson's Darzalex (p9).

Also of interest given the number of cancer drugs that are granted accelerated approval was a session on what went wrong with Lartruvo, the Eli Lilly soft tissue sarcoma drug that won accelerated approval in the US and conditional approval in the EU in 2016 before being withdrawn this year after failing a post-marketing efficacy study (p7).

Oncology aside, we report from the Drug Information Association's annual meeting in China (p16). China has been an important source of revenue growth for many big pharma companies so far this year, and the country's increased interest in innovative therapies is proving attractive. But it's not all rosy, with the US/China trade dispute continuing and China's new competitive bidding scheme looming. Nevertheless, Pfizer is bullish about its new Upjohn global HQ in Shanghai (p17).

Looking to the future, we bring you a round-up of key drugs expected to be launched over the next 12-18 months, based on analysis done by our colleagues at Biomedtracker (p15).

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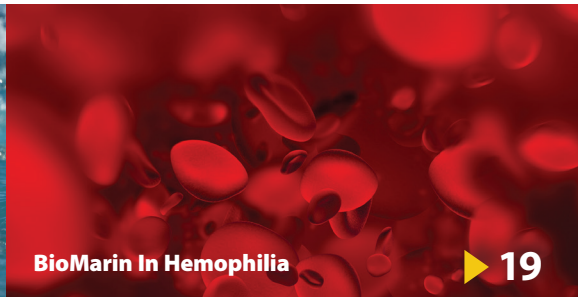

exclusive online content

OptumRx WatchList Includes Rare Disease Drugs, Potential Price Disruptors

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UnitedHealth Group Co. pharmacy benefit manager OptumRx Inc. spotlights five prescription drugs expected to have a big impact on payers in the coming months in a new report released 28 May.

The first in a recurring series of reports, the Drug Pipeline Insights Report outlines issues around adoption, effectiveness and expected cost for the drugs and offers some insight into how the PBM will approach coverage policies and price negotiations for them. The report covers drugs that have been recently approved or are expected to be approved in the coming months. Most are treatments for rare diseases but a couple are aimed at crowded categories.

"For consumers, these drugs represent new options for certain niches within that condition," the report explains. "The introduction of several of these drugs gives consumers much-needed access to alternatives when first line treatments may have been ineffective." However, "prior authorization requirements are likely in order to ensure appropriate use."

In addition, "some of these drugs have outstanding questions about efficacy (magnitude and/or duration of benefit) or whether they are better than the treatments we already have today," OptumRx said. "This raises questions about how much value they bring to the table and if they are worth a premium price relative to existing options."

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The results showed a trend toward improving survival, but were not statistically significant. The trial was powered for PFS, not overall survival, which was a secondary endpoint.

"It's important to note that it's very difficult in metastatic breast cancer to show a significant impact in overall survival because patients can receive other treatments after coming off the trial," MONALEESA-7 investigator Sara Hurvitz, UCLA, told the ASCO press briefing. Novartis researchers believe Kisqali's higher potency against CDK4 over CDK6 could differentiate the drug from its rivals, pointing out that CDK4 is likely the dominant CDK driver of disease progression in breast cancer.

Novartis and Lilly have been looking to carve out niches in the CDK4/6 space to gain ground against Pfizer's Ibrance, which has grown into a mega-blockbuster. But while Ibrance generated more than $1bn in sales in the first quarter of 2019, Kisqali and Verzenio generated $91m and $109.4m, respectively, in the first quarter.

The commercial market is big because HR+/HER2- breast cancer is the most common form of breast cancer, accounting for about 70% of all cases. HER2- breast cancer tends to be less aggressive than HER2+ breast cancer, where Roche's Herceptin (trastuzumab) is the standard of care.

Each of the three CDK4/6 inhibitors are approved for slightly different indications, which could further differentiate them, though they are largely viewed on efficacy and safety as being similar.

Ibrance had a two-year head start in the market, with an accelerated approval from the FDA in February 2015. It's approved in combination with an aromatase inhibitor as initial endocrine therapy in postmenopausal women or men; or with fulvestrant in women with disease progression following endocrine therapy. Verzenio, approved in September 2017, is the only CDK4/6 inhibitor approved with a continuous dosing schedule.

In a recent interview, Novartis Oncology CEO Susanne Schaffert said the company learned some lessons from the early and challenging launch of Kisqali, but that it had begun to better differentiate the product with expanded approvals in the pre-menopausal population and in combination with fulvestrant.

During the ASCO press briefing on MONALEESA-7, Hal Burstein, Dana Farber Cancer Institute, commented on how the survival benefit should help with payers. "In an era where we are thinking about value in oncology care, the demonstration of robust survival difference I think substantially adds to a value proposition for products like ribociclib that are discussed here," he said. "Hopefully these data will enable access to this product to more women around the world, particularly in health care systems which assess value rigorously as part of their decisions for national access to drugs."

Novartis is also expanding in breast cancer with the launch of a new potential blockbuster, Piqray (alpelisib). The PI3K inhibitor cleared the FDA on 24 May for HR+, HER2- breast cancer with PIK3CA mutations. About 40% of those patients have PIK3CA mutations and are currently being treated with a CDK4/6 inhibitor.

Novartis was the first to secure approval for a PI3K inhibitor, based on positive PFS data, despite some other failed attempts.

Additional reporting from ASCO by Mary Jo Laffler (maryjo.laffler@informa.com).

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AZ/Merck & Co's Lynparza POLO Study 'Practice Changing'

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AstraZeneca PLC/Merck & Co. Inc.'s PARP inhibitor Lynparza nearly doubled progression-free survival in patients with germline *BRCA*-mutated (g*BRCA*m) metastatic pancreatic cancer, according to the full results of the Phase III POLO study. The data were hailed by experts as "practice changing" at the American Society of Clinical Oncology meeting in Chicago, where they were presented in a plenary session on 2 June.

"Metastatic pancreatic cancer is a dismal disease," POLO principal investigator Hedy Kindler, University of Chicago, said during the late-breaking abstract presentation. "Even with modern chemotherapy regimens, patients generally live less than a year. Historically most do not receive second-line treatment."

AstraZeneca and Merck & Co announced in February that the POLO trial had met its primary endpoint of improving progression-free survival (PFS) in g*BRCA*m pancreatic cancer patients whose disease had not progressed on first-line platinum-based chemotherapy, but the extent of the benefit was previously unknown.

The updated results, which have also been published in the *New England Journal of Medicine*, show Lynparza maintenance therapy reduced the risk of disease progression or death by 47%. The median PFS for Lynparza patients was 7.4 months compared with 3.8 months for those on placebo, with more than twice as many patients remaining progression free at both one year (34% vs. 15%) and two years (22% vs. 10%).

POLO randomized 154 patients with g*BRCA*m metastatic pancreatic cancer whose disease had not progressed on first-line platinum-based chemotherapy to Lynparza (300mg twice daily) as maintenance monotherapy or placebo until disease progression. Eligible patients must have received at least 16 weeks of first-line platinum-based chemotherapy without progression (there was no maximum limit to the duration of chemotherapy).

Median duration of follow-up for progression was 9.1 months (range, 0 to 39.6) and 3.8 months (range, 0 to 29.8) in the olaparib and placebo arms, respectively, and analysis of the primary endpoint was performed at 68% data maturity.

While overall survival data are yet to mature, the PFS improvement seen is regarded as clinically meaningful and a significant advance given that the median survival of metastatic pancreatic cancer is currently under 12 months. "Roughly one in five patients responded to olaparib for a median of two years, which is truly remarkable for metastatic pancreatic cancer. For patients with *BRCA*-driven metastatic pancreatic cancer, we may be seeing a change in patients' disease trajectory," Kindler said.

But so far there is no difference between the arms in overall survival (OS). An interim OS analysis at 46% data maturity showed a median OS of 18.9 months for olaparib and 18.1 months for placebo (HR 0.91, CI, 0.56 to 1.46, p=0.68). The final OS analysis is due later this year, when the data reach 69% maturity.

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Summary Of PFS Data

	LYNPARZA (N=92)	PLACEBO (N=62)
Number of patients with event (%)	60 (65)	44 (71)
Median (in months)	7.4	3.8
Hazard ratio (95% CI)	0.53 (0.35-0.82)	-
P-value	p=0.004	-

Source: ASCO

The adverse event and quality of life data – important for a maintenance therapy – were also acceptable with the PARP inhibitor, Kindler said. Olaparib's adverse event profile was similar to that seen in other tumors, with serious side effects (grade 3, 4, or 5) occurring in 40% of olaparib patients compared with 23% of those taking a placebo. Treatment discontinuations due to toxicity occurred in 5.5% of olaparib patients and 1.7% of placebo patients. Health-related quality of life was preserved with olaparib treatment and showed no difference between arms.

"Our results are the first from a Phase III trial to validate a targeted treatment in a biomarker selected population of pancreatic cancer patients, highlighting the importance of germline *BRCA* mutation testing in this setting," said Kindler. "We conclude that a strategic approach of first-line platinum-based therapy followed by maintenance olaparib treatment should become a new standard of care for patients with metastatic pancreatic cancer who have a germline *BRCA* mutation."

Suzanne Cole of UT Southwestern Medical Center, commenting on the results during the ASCO press briefing, said that POLO represented a huge step forward for metastatic pancreatic cancer. "This is the first time that a targeted medication has been successful in stopping the growth of metastatic pancreatic cancer in people who carry the *BRCA* mutation," she said.

"Now that we have a targeted medication that can benefit patients who have the *BRCA* mutation when they present with metastatic prostate cancer, it is our duty to search for this gene mutation in all patients with metastatic prostate cancer so we can identify those people who have the *BRCA* mutation and can benefit from being treated with an oral agent that can extend their life."

Discussing the results during the plenary, however, Wells Messersmith of the University of Colorado Cancer Center was more measured in his response, although he agreed molecular tumor testing should be standard for advanced pancreatic cancer patients. While the PFS seen in POLO was "considerable," especially in the pancreatic cancer setting, he noted that in this context it was "humbling" that no OS benefit was yet apparent despite the modest rates of subsequent PARP inhibitor use in the placebo arm. Overall, he thinks the chances of a POLO producing a positive OS benefit are slim.

Messersmith told the meeting that maintenance olaparib "should be an option for gBRCAm patients. It is unclear how this approach compared to continuation of FOLFIRINOX or other platinum-based therapies" in terms of efficacy, total costs and quality of life. It would be "very reasonable" to continue platinum-based therapy in these patients, he said.

"Most oncologists continue first-line therapy indefinitely and platinums are very active in these patients," Messersmith added. Moreover, he noted that the cost of 7.4 months of olaparib therapy at 300mg (2x150mg tablets) twice daily at an AWP of $140/tablet would be in the region of $124,540. "Dropping one of these [tablets] down the sink is like losing your phone."

HOW MUCH MARKET POTENTIAL?

With POLO, Lynparza may become the first targeted therapy approved for pancreatic cancer in a biomarker-selected population, but this particular population is small: only between 4% and 7% of pancreatic cancer patients harbor the germline *BRCA* mutation. And not all of these will be suitable for Lynparza therapy – of the patients initially enrolled in POLO, 38% did not progress into the study arms as they had disease progression, were ineligible or declined randomization after chemo.

Even so, AZ and Merck, if they gain regulatory approval, would have this field to themselves for some appreciable time. Two rival PARP inhibitors, Pfizer Inc.'s Talzenna (talazoparib) and Clovis Oncology Inc.'s Rubraca (rucaparib), are still in Phase II for pancreatic cancer, while GlaxoSmithKline PLC/Tesaro Inc..'s Zejula (niraparib) does not appear to be in clinical development for this indication.

A filing to the US Food and Drug Administration based on POLO is expected in the second half of the year, with submissions in the EU and Japan slated for 2020.

AstraZeneca reported Lynparza sales of $647m in 2018, representing year-over-year growth of 118% (116% at CER), driven by expanded use in ovarian cancer and the its first breast cancer approvals. Its recent approval as a first-line treatment of patients with *BRCA*m ovarian cancer in the US, which was received earlier than expected, should support further expanded use.

The pancreatic population is dwarfed by Lynparza's current indications, but by swooping into an unserved population with little competition on the horizon, Lynparza would be emulating the performance of AZ's immune checkpoint inhibitor Imfinzi (durvalumab) in Stage III non-small cell lung cancer – an indication not held by the other PD-1/L1 inhibitors.

This would also be in keeping with AstraZeneca's ambition to follow the science and make step-change improvements in outcomes, EVP and president of oncology David Fredrickson told *Scrip*. He added that while AZ's current oncology portfolio for breast and lung cancers was quite robust, it was more lacking in "the GI realm," where its candidates for colorectal, pancreatic and gastric cancers were earlier stage.

"As a family of cancers, GI cancers are important and I think this is exciting in that though this represents a small portion of patients in a relatively small cancer type, it begins to set a foothold into the GI cancer space which is a critically important area."

But in terms of market potential for olaparib in pancreatic cancer, the key element will be finding the eligible patients for Lynparza therapy. The good news is that genetic testing is already recommended by NCCN for pancreatic tumors, analysts at Credit Suisse pointed out.

"We would expect a rapid FDA approval and meaningful adoption of Lynparza in this subset. But the limited duration of responses (7.4 months) and the relatively small subset of patients (5-8% of pancreatic), combined with the shared economics on Lynparza mean it will not move the dial materially for AstraZeneca," they said in a 2 June note. *Published online 3 June 2019*

Merck & Co's Keytruda Gets Foot In The Door For First-Line Gastric Cancer

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Keytruda's favorable side effect profile and hints of a benefit in a subpopulation are keeping hopes aloft that the checkpoint inhibitor will have a place in the treatment of newly diagnosed patients with gastric and gastro-esophageal junction (GEJ) cancer following the presentation of the full results from Merck & Co. Inc.'s KEYNOTE-062 study.

The results of the first Phase III trial testing an anti-PD-1 therapy as a front-line treatment for this patient population were mixed, but suggest that Keytruda (pembrolizumab), already approved for third-line use, should be brought in earlier in the treatment paradigm as it is better tolerated than standard chemotherapy and may extend survival in some patients. But the drug will need positive results from other Phase III studies ongoing in the first-line gastric cancer setting to secure an expanded label. Keytruda may be the only checkpoint inhibitor in the US currently with a gastric cancer indication, but Bristol-Myers Squibb Co.'s Opdivo (nivolumab, which does have a gastric cancer indication in Japan) is on its tail.

Keytruda received accelerated approval from the US Food and Drug Administration in September 2017 for patients with recurrent, locally advanced or metastatic gastric or GEJ cancer with tumors that express PD-L1 with a combined positive score (CPS, calculated based on the number of PD-L1 positive cells derived from biopsied tissue and the number of viable tumor cells) on the basis of the Phase II KEYNOTE-059 trial. The 763-patient KEYNOTE-062 was a confirmatory Phase III study for that initial approval and was also originally designed to support a label expansion into the first line setting.

Merck released the top-line results from the three-arm study in April, saying Keytruda monotherapy was non-inferior to chemotherapy in terms of overall survival in PD-L1-positive, HER2-negative advanced patients, meeting that endpoint, but that the combination of Keytruda plus chemotherapy was also no better than standard chemotherapy in these patients, missing the endpoint for superiority.

All roads lead to Chicago and ASCO for oncologists

The full data, which were featured in a press briefing at the American Society of Clinical Oncology meeting in Chicago on 1 June and presented at the conference on 2 June, reveal just how close the results were. In the overall population, mean OS was non-inferior with pembrolizumab at 10.6 months compared with 11.1 months with chemotherapy (hazard ratio 0.91). OS for the pembrolizumab plus chemo arm was 12.5 months.

But subpopulation data reveal some differences in OS benefit. In the 281 patients (37%) with high levels of PD-L1 expression (*i.e.*, PD-L1 CPS of 10 or more), there was a "clinically meaningful" mean OS of 17.4 months compared with 10.8 months (hazard ratio 0.69). At two years, 39% of patients who had PD-L1 CPS≥10 and received pembrolizumab alone were alive, compared with 22% of people who received standard chemotherapy.

Moreover, the rates of serious side effects in the study were lowest when the checkpoint inhibitor was used by itself. Grade 3 or higher toxic treatment-related adverse events were seen in 17% of people receiving pembrolizumab, 73% of people receiving pembrolizumab and chemotherapy, and 69% receiving only chemotherapy. Pembrolizumab's safety profile was consistent with previous use and the most common adverse events were nausea and fatigue.

KEYNOTE-062's lead researcher Josep Tabernero, of the Institute of Oncology, Barcelona, Spain, told the ASCO press conference that the study showed that front-line pembrolizumab is effective and "could provide a new opportunity for people newly diagnosed with advanced gastric or gastroesophageal junction cancers."

The lack of other therapeutic options could help it sell. ASCO's senior vice president and chief medical officer Richard Schilsky commented at the press briefing that gastric cancer was "a tough disease to treat; the patients are often older, often frail, often malnourished. Until just recently there wasn't much available apart from chemotherapy, which is difficult to tolerate … so this is a disease in desperate need for new treatment approaches."

There had been a "glimmer of hope," he said, when it was found that about 15% of patients were amenable to Herceptin

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(trastuzumab) therapy, and this product is now approved in this subset, but that is a minority of patients.

Schilsky added that it was reasonable to conclude, as the KEYNOTE-062 investigators did, that pembrolizumab is not inferior to chemotherapy. "It certainly met the prespecified definition of not being worse and together with [the] substantially improved safety profile I think it would be pretty clear to me that this would be a preferred treatment for this patient population," he commented.

He was also persuaded by the potential CPS biomarker. "It's not so clear that it met the traditional definition of statistically significance, but [it is] certainly clinically quite clear that the pembrolizumab is superior to chemotherapy in the higher biomarker positive population CSP>10," Schilsky said.

"What I take away from this study is that in patients with advanced gastric and GEJ pembrolizumab should really in many cases replace chemotherapy as a first-line treatment. It's certainly not worse; it may well be better." Questions remain though as to why there was no additive benefit by combining pembrolizumab and chemotherapy, and investigations into this are ongoing.

OTHER TRIALS KEY

Keytruda's two ongoing late-stage trials in the first-line setting include both HER-2 positive and negative patients. KEYNOTE-811 is adding Keytruda to the standard of care in HER-2 positive gastric cancer, Herceptin and chemotherapy, and KEYNOTE-859 is combining Keytruda with chemotherapy in HER-2 negative patients.

However, BMS's Opdivo is in Phase III in combination with ipilimumab in the CHECKMATE-649 study with top-line results due by the end of this year. Analysts at Biomedtracker note that Opdivo seems to have the advantage in terms of timing. CHECKMATE-649 was initiated in late 2016, while the Keytruda first-line studies began last year. "It's a CTLA-4 and PD-1 versus chemo so it needs to be without chemo and that's a big hurdle," they said. "It would also have to get its first approval essentially in the US for that first-line setting, so that's also a bit of a roadblock as well."

While lung cancer remains the major battleground for the checkpoint inhibitors, Merck and BMS are increasingly focused on other tumor types.

Gastric cancer has proved a tricky indication for the checkpoint inhibitors. Keytruda had already disappointed in the Phase III KEYNOTE-061 in second-line advanced gastric cancer in late 2017, missing both OS and PFS endpoints. Fortunately for Merck, that failure did not lead to any change in the product's labeling despite it coming after the accelerated US approval in third-line PD-L1-positive advanced/metastatic gastric cancer. *(Also see "Commercial Fallout From Merck's Failed Keytruda Gastric Cancer Trial May Be Limited" - , 15 Dec, 2017.)*

Rival anti-PD-1 Bavencio (avelumab) from Pfizer Inc./Merck KGaA also failed to significantly improve OS in the Phase III third-line gastric cancer JAVELIN Gastric 300 study in late 2017. *(Also see "Pfizer/Merck KGAA's Bavencio Gastric Cancer Failure Not As Bad As It Seems" - Scrip, 28 Nov, 2017.)*

About 27,510 new gastric cancers and 11,140 deaths are expected to occur in the US in 2019, according to ASCO, and it is the fifth most frequently diagnosed cancer worldwide.

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Lartruvo Could Be A Failure Of The Drug, The Design Or The Disease

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The release of the full results of the ANNOUNCE trial for Eli Lilly & Co.'s soft tissue sarcoma drug *Lartruvo*, now withdrawn from the market, at the American Society of Clinical Oncology (ASCO) annual meeting served as a post-mortem on what went wrong after the early approvals of the product.

The US FDA granted accelerated approval for Lartruvo (olaratumumab) in October 2016 for use in combination with doxorubicin for first-line treatment of soft tissue sarcoma (STS) based on positive Phase Ib/II data, and the European Medicines Agency followed a month later with a matching conditional approval.

But those decisions have drawn scrutiny after the Phase III study failed to confirm the earlier benefit. The ANNOUNCE data were presented by lead investigator William Tap, Memorial Sloan Kettering Cancer Center, at the plenary session of ASCO on 2 June, and were praised for the rigor and diligence in examining the data to figure out what happened.

With a strong, significant survival benefit in the Phase Ib/II study ("an unprecedented 11.8 months improved overall survival favoring the combination of doxorubicin and olaratumumab," Tap noted) and the well-designed confirmatory Phase III trial already fully enrolled, there is little concern that the approvals were granted. FDA officials have also maintained that the accelerated approval program should have some failures – otherwise the agency is being overly conservative.

In this case, the well-designed, fully enrolled Phase III trial was a good bet. "Accelerated approval allowed patients to have access to a potential life-prolonging drug with little added toxicity to conventional therapy. Olaratumumab gained wide usage and acceptance, but not unconditionally," Tap told ASCO, adding that "confounders of the Phase Ib/II trial and cost fueled a continuous debate."

In the wake of the withdrawal, the bigger debate was over the issue of payment for accelerated approval drugs. *(Also see "Lilly's Lartruvo Withdrawal Stirs Questions About Payment For Accelerated Approval Drugs" - Scrip, 25 Apr, 2019.)* And at ASCO, the only real criticism was of the combined cost of the drug, which totaled approximately half a billion dollars for the two-plus years it was on the market. "That seems to be a lot of expenses for a drug without appropriate evidence of efficacy," Jaap Verweij, Erasmus University, commented in responding to the presentation of ANNOUNCE.

But while it may not have been a regulatory failure, things did go wrong somewhere.

PARSING THE DATA & DESIGN

The Phase Ib/II data have been "highly debated and scrutinized," Tap told ASCO. "Extensive subgroup and sensitivity analyses did not reveal any bias or meaningful imbalances that could have explained the results." Also, "there are no noted discrepancies in study conduct and data integrity which could explain these findings or the differences between the two studies," Tap concluded.

ANNOUNCE was planned as a fully randomized, placebo-controlled, double-blind Phase III study. There were no notable demographic differences. Most patients had leiomyosarcoma, as planned, followed by liposarcoma, plus 26 unique histologies. The trial was powered for dual primary endpoints to look at overall survival in the total population and in the leiomyosarcoma subtype.

However, ANNOUNCE showed no difference in overall survival using an intent to treat analysis in either the total population or the leiomyosarcoma population. The doxorubicin arm had slightly higher survival than seen in previous upfront Phase III studies, though Tap explained that survival has been improving in trials over time due to improvements in care. But it was the "highest survival to date in any Phase III sarcoma study and is particularly of interest as ANNOUNCE did not mandate treatment in the first line," Tap said.

There was no significant difference in overall response rate, though there was a statistically significant improvement in progression-free survival in the leiomyosarcoma subgroup. The disease control rate (complete response plus partial response plus stable disease) also reached significance in the leiomyosarcoma group.

There were differential outcomes in subtypes based on albumin levels. Tap also noted that PDGFR alpha positive tumors tended to do worse. "These analyses are very exploratory and it is uncertain as to the prognostic or predictive significance of these findings. Additional biomarker analyses are ongoing," he said.

A higher dose than typical was used for doxorubicin (up to 600mg/m^2 cumulative), and there were discrepancies in use of cardioprotectants, which were left to investigator discretion. But despite this, "the onset of identified cardiac dysfunction was low and balanced across the two arms," Tap reported.

> "The reasons for the erroneous predictions of Phase II studies may be hidden in the combination of small numbers coupled with major heterogeneity in STS subtypes." – Jaap Verweij

Adverse events were well-balanced between the two arms. "Almost all patients had an adverse event," Tap noted, "but few patients discontinued due to toxicity." There was little difference between the two arms in treatment-emergent AEs, including in neutropenia and musculoskeletal pain, which were identified as AEs of interest after Phase II.

WHAT NOW?

The investigation of the ANNOUNCE data is not complete. "A large and concerted effort is going on to understand the ANNOUNCE results alone and in context with the Phase Ib/II study," Tap said.

"It is possible that olaratumumab has no activity in soft tissue sarcomas and that the Phase Ib/II results were due to, among other things, the small sample size, numerous represented histologies with disparate clinical behavior, the effect of subtype-specific treatments given subsequently or even by chance," Tap concluded.

"It is also possible that olaratumumab has some activity in STS with outcomes being affected by the heterogeneity of study populations, differences in trial design, and the performance of the control arm."

Verweij is hopeful "the ANNOUNCE study will stimulate change in the course of clinical research in STS," moving away from "lumped" trials in favor of subtype-specific, biomarker-driven studies.

IS THE PROBLEM THE DISEASE ITSELF?

One of the possible explanations lies in the collection of subtypes in the olaratumumab trials. Soft tissue sarcoma is rare, comprising only 1% of all cancers, and it is a heterogenous collection of malignancies originating from mesenchymal precursors.

There is both inter- and intra-subtype heterogeneity, Tap noted, and there are variable response patterns. The outcome measures are poorly defined and validated and historical data and practice patterns are also variable. Thus, while it is a significant unmet need, it presents significant challenges as well.

"Being rare and heterogenous creates a double challenge in performing clinical trials in these diseases," Verweij agreed. "The different histological subtypes basically behave like different diseases."

There has been better success targeting specific subtypes. Imatinib (Novartis AG's *Gleevec* and generics) is clearly effective in gastrointestinal stromal tumors (GIST), plus Bayer AG's *Nexavar* (sorafenib) has had positive results in desmoid tumors and AstraZeneca PLC's cediranib is being studied in alveolar soft part sarcoma.

Those have been much smaller trials, "but there's no doubt as to the activity of the drugs," Verweij said.

There were close to 30 different histological subtypes in the olaratumumab studies – and in the Phase II trial, the arms were 66 and 67 patients. "There may have been hidden differences there," he added.

The small number of patients is a critical issue in Phase II studies, certainly in diseases as heterogeneous as sarcoma, Verweij noted, so even a few tumors with slow growth in their natural history can make a big difference. He suggested that trials require documentation of progression in the weeks prior to enrollment, to screen out indolent tumor types.

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Another problem with Phase II trials in this space is that there are poor predictive factors for survival, possibly due to the differences in the subtypes.

ISSUES WITH PHASE II, TRIAL DESIGN?

Verweij cited a review of cooperative group trials showing "response to first line treatment and overall survival are not predicted by the same factors." His conclusion is that "response should not be the only endpoint for evaluation of new agents and combinations."

"Whatever the reason," he said, "just like in other diseases, OS is related to multiple factors and therefore it will be a confounded and complex endpoint for Phase III trials … even more so in the lumped group of heterogenous soft tissue sarcomas."

Progression-free survival also has issues. "It is striking to note that without exception … in the preceding Phase II trials, including the Phase II trials that were randomized," he said, PFS "consistently overestimated and wrongly predicted the outcome of the subsequent Phase III study." And, "the results of the ANNOUNCE study are no exception."

"The reasons for the erroneous predictions of Phase II studies may well be hidden in the combination of small numbers coupled with major heterogeneity in soft tissue sarcoma subtypes, likely leading to type 1 error in Phase II."

Verweij believes Phase II trials in lumped STS should be viewed as a screening tool that does not have a high probability of truth. "The results may be misleading and they obviously always need to be confirmed in subsequent Phase III studies," he added, "even if Phase II activity data are compelling."

TRY TO AVOID LUMPS

Verweij suggested avoiding adding drugs to doxorubicin in the first-line setting, but his strongest recommendation was to avoid "lumping" different subtypes of STS as a group – even though the numbers are small. "We should favor subtype specific, biomarker-driven studies whenever possible." Phase II studies in second-line therapy in lumped STS, and in specific subtypes, have been better able to predict the outcome of subsequent Phase III studies, he noted.

"Since we are dealing with rare diseases, innovative trial methodologies should be explored," such as novel statistical design and clustered hierarchical design, Verweij said. "Hopefully big data and data repositories such as CancerLinq will lead to new trial methodologies that will support rare disease research."

Another possibility raised by Tap was looking at platelet derived growth factor (PDGFR) as a target.

Overexpression and mutations of PDGFR have been reported in STS and play a role in interstitial tissue pressure in the tumor, Verweij agreed, "so trying to explore the role in STS makes sense." He noted that imatinib has been clearly effective in PDFGR mutant tumors, but other subtype studies haven't looked at PDGFR status.

"If a drug seems to work in the absence of its target, I would question and push the results before embarking on a large trial," Verweij noted.

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Sanofi Myeloma Drug Isatuximab Shines But Darzalex Dominates Still

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Data on Sanofi's multiple myeloma (MM) candidate isatuximab have gone down well at the American Society of Clinical Oncology meeting in Chicago but it remains to be seen whether it can compete with Johnson & Johnson's blockbuster and fellow anti-CD38 antibody Darzalex.

Having presented positive topline results from the Phase III ICARIA-MM trial in February, the French firm has unveiled the full data set at ASCO. Isatuximab combined with the standard of care – Celgene Corp.'s Pomalyst (pomalidomide) and the corticosteroid dexamethasone – showed statistically significant improvements compared with pom-dex alone in patients with relapsed/refractory MM. Specifically, treatment with the triple combo led to a 40% improvement in progression-free survival (11.53 months versus 6.47 months) compared with pom-dex, an outcome described as noteworthy by Paul Richardson of the Dana-Farber Cancer Institute and principal investigator, "because this trial included a particularly difficult-to-treat,

Sanofi has some distance to make up in the multiple myeloma space

relapsed and refractory patient population that was, in my view, highly reflective of real-world practice."

Sanofi also highlighted that the isatuximab combination therapy demonstrated a significantly greater overall response rate compared with pom-dex alone (60% versus 35%) consistently across multiple subgroups, including patients 75 years and older, patients with renal insufficiency, and patients who were refractory to Celgene's MM blockbuster Revlimid (lenalidomide).

The isatuximab/pom-dex combo was filed with the European Medicines Agency and the US Food and Drug Administration earlier this year and approval is widely expected. However, it will be up against J&J's big-selling Darzalex (daratumumab) and more positive data presented on the Genmab AS-partnered drug at ASCO emphasized the size of the challenge awaiting Sanofi.

Results from the Phase III CASSIOPEIA study showed that the addition of Darzalex to J&J/Takeda Pharmaceutical Co. Ltd.'s Velcade (bortezomib), thalidomide and dexamethasone (VTD) before and after autologous stem cell transplantation resulted in deeper responses and longer PFS compared with VTD alone in patients with newly diagnosed multiple myeloma who are transplant eligible.

Results from the first part of CASSIOPEIA, presented for the first time as part of an oral session at ASCO, showed a stringent complete response rate in the Darzalex/VTD arm of 28.9% compared with 20.3% for VTD, which is the standard of care in the US for induction therapy. A couple of days before the ASCO presentation, the FDA granted a priority review to Darzalex/VTD for frontline MM, setting an action date of 26 September. *(Also see "Darzalex Excites As Potential Grows In Multiple Myeloma" - Scrip, 30 Oct, 2018.)*

More good news for J&J came with the confirmation in the Phase III COLUMBA trial of the non-inferiority of subcutaneous (SC) versus intravenous (IV) Darzalex. Overall response rates were 41% SC vs. 37% IV, with median PFS and overall survival comparable, plus a significantly lower rate of infusion-related reactions (13% SC vs 35% IV). On top of that, the results confirmed the drastically shorter time of injection (five minutes) compared with seven hours for the first IV infusion.

Responding to the ASCO news, analysts at Deutsche Bank wrote in an investor note that the Phase III data for isatuximab were "compelling on a stand-alone basis [and] well received as it provides physicians and patients with a further treatment option." However, they believe isatuximab "is likely to play only a niche role and seems unlikely to threaten the dominance" of Darzalex, sales of which they expect to reach $7.2bn in 2023.

The broker argued that the 40% reduction in PFS falls short of the 60% or so benefit demonstrated with the addition of Darzalex to standard treatment regimens in the relapsed/refractory setting, "albeit in less refractory patients." Although isatuximab benefits from a shorter infusion time (three hours vs four-seven with Darzalex), "this now looks likely to be redundant given compelling data for SC-delivered Darzalex."

Deutsche Bank pointed out that speakers at ASCO suggested a possible role in patients with asthma and/or chronic obstructive pulmonary disease "given isatuximab's lower complement activation" but the analysts agreed with consensus forecasts that the drug's sales in 2023 will be in region of €360m.

Analysts at Jefferies noted that both the Darzalex and isatuximab data were positively received at ASCO, "further cementing the role of anti-CD38s in MM." They added that "whilst feedback suggests we cannot yet say if one is superior to the other, or how/if they could be cycled, we feel that Darzalex's entrenched position is unlikely to be threatened on data to date," particularly given that the SC formulation of the latter could be approved next year.

Even without the SC approval, Jefferies concluded that by 2020, "Darzalex is likely to be entrenched as a backbone of first/second line treatment, where duration on drug is years not months, hence the competitive impact [from isatuximab] is probably minimal."

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So Far, Still So Good For Seattle Genetics/Astellas' Bladder Cancer ADC

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Updated data from the first cohort of the Phase II EV-201 study of Seattle Genetics Inc./Astellas Pharma Inc.'s antibody-drug conjugate enfortumab vedotin continue to impress, with a confirmed 44% objective response rate and a median survival time of 11.7 months in a heavily pre-treated advanced urothelial cancer population.

Principal investigator Daniel Petrylak at Yale Cancer Center, who presented at the American Society of Clinical Oncology meeting in Chicago on 3 June, said enfortumab vedotin (EV) was the first novel product to show clinical activity in patients who have progressed after platinum chemotherapy and a PD-1/L1 inhibitor, the current standard of care. The response to therapy was swift and 12% of EV patients experienced a complete response.

Similar responses to therapy were seen across all patient subgroups in the 125-patient cohort, irrespective of response to prior PD-1/L1 inhibitor or the presence of liver metastases, and the safety profile was manageable. The Phase II data mirror those seen in the product's Phase I EV-101 trial in the same population and together they "support submission to the FDA for accelerated approval," Petrylak claimed. "EV may have the potential to become a new standard of care in patients who have progressed after platinum and PD-1/L1 inhibitors."

The US Food and Drug Administration has already granted the product a breakthrough therapy designation for people with locally advanced or metastatic urothelial cancer that has progressed during

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or following checkpoint inhibitor therapy based on that Phase I trial.

However, data are still awaited from the second cohort of the study in patients who have not received a platinum-containing chemotherapy and who are ineligible for cisplatin – enrolment is continuing so no timeframe has been given.

Seattle Genetics is due to submit the product – which consists of an anti-Nectin-4 monoclonal antibody attached to a microtubule-disrupting agent monomethyl auristatin E (MMAE) using a proprietary linker technology – for accelerated approval in the second half. Meanwhile, a global, randomized Phase III confirmatory clinical trial (EV-301) is ongoing and is intended to support global registration submissions next year.

COHORT 1 DATA

The full results to date from the first cohort of the EV-201 study were as follows:

ENDPOINT	RESULTS FOR EV
Objective Response Rate (ORR) per blinded independent central review (BICR) (Primary endpoint)	44% (55/125; 95% CI: 35.1-53.2)
Complete Response (CR)	12% (15/125)
Median Duration Of Response (DoR) (Secondary endpoint)	7.6 months (95% CI: 6.34 - not yet reached).
Median Overall Survival (OS) (Secondary endpoint)	11.7 months (95% CI:9.1-not reached)
Median Progression-Free Survival (PFS) (Secondary endpoint)	5.8 months (95% CI:4.9-7.5)

Most responses occurred within the first cycle of treatment, and were similar in the subgroups of patients analyzed, including those who had the worst prognosis, such as patients who had three or more previous lines of therapy, patients with liver metastases, and those who had not responded to a PD-1/L1 inhibitor:

PRE-SPECIFIED PATIENT SUBGROUP	ORR WITH EV
Three or more prior therapies	41% (26/63)
Non-responders to PD-1/L1 inhibitors	41% (41/100)
Liver metastases	38% (19/50)

There was a relatively quick median time to response of 1.8 months, which Biomedtracker analyst Michael Ramirez said was consistent with the cytotoxic payload of EV and was a positive feature for patients who have already relapsed on multiple lines of therapy.

Treatment-related adverse events that occurred in 40% or more of patients were fatigue (50%), alopecia (49%), rash, decreased appetite (44%), taste distortion and peripheral neuropathy. Only 12% of patients discontinued because of these, with peripheral neuropathy being the most common reason (6%).

ASCO expert Robert Dreicer of the UVA Cancer Center agreed that the data were "compelling", particularly given the lack of other treatment options in this setting, and said he "would support" accelerated approval. "For decades front-line chemotherapy was all that we had. The approval of the checkpoint inhibitors was important but response rate [to them] is basically one out of every four or five people."

The FDA recently approved Janssen's Balversa (erdafitinib) for patients with locally advanced or metastatic urothelial carcinoma with susceptible *FGFR3* or *FGFR2* genetic alterations that has progressed during or following platinum-containing chemotherapy, but Dreicer pointed out that this "only impacts about one out of five patients who have a particular mutation so new therapies are badly needed."

He was also impressed with the activity in the "harder-to-reach disease sites like the liver – the median survival of these patients approaches a year and albeit it's a Phase II study, the reality is front-line chemotherapy is the best we have and here the median is 13 months."

Dreicer added, "When urothelial cancer metastasizes to the liver it's ultimate badness and when you start to see metastasis activity is maintained in those sites you know that there is something going on."

The study discussant, Andrea Necchi of Fondazione IRCCS Istituto Nazionale dei Tumori in Milan, Italy, said the data were "very promising pending Phase III studies" but wondered whether the efficacy would be reproducible with other ADCs, eg Immunomedics' sacituzumab govitecan; this has recently gone into a registrational study in bladder cancer.

GOOD LAUNCHING POSITION FOR OTHER SETTINGS

Seattle Genetics president and CEO Clay Siegall told *Scrip* that "as a single agent [EV] arguably is one of the most active, or the most active, single agent for metastatic urothelial cancer that I have seen and that gives us opportunities to go past just treating the patients that have had prior therapies."

The company is investigating EV in earlier lines of treatment for patients with locally advanced or metastatic urothelial cancer. The EV-103 study is underway to evaluate EV in combination with pembrolizumab (Merck & Co's Keytruda) and/or platinum chemotherapy in newly diagnosed patients as well as patients who have progressed from earlier-stage disease.

Metastatic disease affects about 20,000 of the 80,000 patients diagnosed with urothelial cancer in the US each year, he noted. "We are going be taking EV and putting it into early stage – that way we can address all 80,000 patients."

Siegall added that the scientific rationale for combining EV with a checkpoint inhibitor was sound. "We think that antibody-drug conjugates are a preferred partner with checkpoints." The company has already proved this in one setting, with its marketed ADC product Adcetris (brentuximab vedotin), which targets CD-30 in Hodgkin's lymphoma, he said, and it is also testing the hypothesis with its other investigational ADCs in cervical cancer and triple-negative breast cancer.

"I'm excited about trying to see, could we have a chemo-free regimen and use EV plus a checkpoint inhibitor," Siegall said.

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Amgen's KRAS Inhibitor AMG 510 Leans Toward Tumor-Dependent, Not Agnostic, Approach

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KRAS inhibition maybe suitable for a tumor-agnostic drug development approach, but Amgen Inc. hasn't decided yet if that's the path it will take with AMG 510 based on the initial set of Phase I data for the company's first-in-class drug, which targets G12C mutations of the elusive KRAS oncogene.

Phase I data for AMG 510 were presented on 3 June at the American Society of Clinical Oncology (ASCO) meeting in Chicago. Amgen senior vice president of global development Elliott Levy told *Scrip* that the dose escalation stage of the study has been completed and the highest dose tested – 960mg taken once daily – has moved into dose expansion. So far, he said, lung cancer results support a tumor-dependent approach, at the very least, but noted it's too early to tell if AMG 510 will work in patients with KRAS G12C mutations regardless of tumor type or if its activity will vary greatly in different cancers.

"In looking at these data, it was an open question of whether this drug would behave more like a tumor-agnostic targeted therapy or a tumor-dependent targeted therapy," Levy explained. "It appears, from the early data we have, that it's behaving more like a tumor-dependent therapy. The data are sparse, so I would interpret them cautiously, but we do appear to see a more marked response in lung cancer than in colorectal cancer."

Amgen is the first company to take a KRAS inhibitor targeting G12C mutations into the clinic, but it has multiple competitors following close behind.

Levy said the 50% response rate with one complete response observed in 10 evaluable patients with non-small cell lung cancer (NSCLC) was "very encouraging," but noted that while 13 out of 18 evaluable patients with colorectal cancer (CRC) achieved stable disease (72%), none had had a clinical response. The dose escalation portion of the Phase I study enrolled 35 patients with locally advanced or metastatic cancers – 14 with NSCLC, 19 with CRC and two with appendiceal cancer.

While AMG 510 appears to have shown less efficacy in colorectal cancer, Levy pointed out that only one CRC patient was treated with the 960mg dose of AMG 510, which is more than five times the lowest dose tested; the other three doses were 180mg, 360mg and 720mg. Also, he said, it's possible that responses will continue to improve in both lung and colorectal cancer over time.

A 3 June Biomedtracker analysis of the data also noted that, "3/5 NSCLC responders were treated with the highest dose. As intra-subject dose escalations are allowed in this trial, it is possible that CRC patients could show improved response at the highest dose."

RESPONSES MAY IMPROVE OVER TIME

Response rates have improved in the NSCLC cohort over time. There initially were two partial responses among six patients for a response rate of 33%, according to an ASCO abstract that was released on 15 May. Now with five out of 10 responders in the updated data presented at ASCO, bringing the response rate up to 50%, and another four who achieved stable disease, the disease control rate for the evaluable lung cancer patients is 90%.

In colorectal cancer, "the majority of patients were treated at the first two dose levels, suggesting further room for improvement at the higher dose in the dose expansion phase or more likely combination therapy will be needed here," Jefferies analyst Michael Yee wrote in a 3 June note.

Nine patients have discontinued treatment in the dose expansion portion of Amgen's Phase I study because of disease progression, but 26 remain in the trial.

Treatment-related adverse events (AEs) were observed in 68% of the study's first 35 patients, most of which were grade 1, and there were no dose-limiting toxicities. There were two grade 3 treatment-related AEs – anemia and diarrhea – but no grade 4 treatment-relate AEs and no serious treatment-related AEs were reported.

The dose expansion portion of the Phase I trial is testing the 960mg dose in a larger number of patients to confirm that this is the dose that will be studied in the next planned clinical trial, which is intended to support regulatory applications for approval. "Once the dose expansion phase is complete, then we would move rapidly to a registrational phase of the program," Levy said.

Amgen's stock rose on 3 June as analysts noted that the 50% response rate in lung cancer was better than expected and as they reiterated prior blockbuster sales forecasts for AMG 510 based on the early results presented at ASCO, with the share price closing 3.4% higher at $172.36. "We think Amgen could quickly move forward here and we'll see if the expansion could end up being a pivotal-type study and [AMG 510] could be on the market much sooner than expected," Yee said. Credit Suisse analyst Evan Seigerman said in a same-day note that Amgen may be able to seek approval for AMG 510 based on a single-arm trial.

"If '510 can show a deep and durable response, the drug could provide significant upside," Seigerman wrote. "However, we do not include '510 in our [Amgen] valuation given the relative immaturity of the data. Positive, full Phase I data would help raise our conviction on the asset further (although we are very encouraged with the data set today), and we see upside for Amgen shares if the company can articulate a path to approval."

FOLLOWERS CHASE AMGEN IN KRAS RACE

Amgen is the first company to take a KRAS inhibitor targeting G12C mutations into the clinic, and could be the first to commercialize a KRAS inhibitor, but it has multiple competitors following close behind.

Mirati Therapeutics Inc. is expected to report initial Phase I results for its KRAS G12C inhibitor MRTX849 in the second half of 2019, while Johnson & Johnson and its partner **Wellspring Biosciences Inc.** recently received investigational new drug (IND) application approval from the US Food and Drug

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The number of patients with lung cancer who will be candidates for this therapy is considerably higher than the number with colorectal cancer.

Administration to take their G12C-targeting KRAS inhibitor ARS-3248 into a Phase I trial.

Other preclinical programs include mRNA-5671, a cancer vaccine that targets the four most common mutations of KRAS, from messenger RNA (mRNA)-based drug developer Moderna Inc. and partner Merck & Co. Inc.

Also, **Oblique Therapeutics AB** is developing aKRAS, a selective antibody targeting mutated KRAS; Cotinga Pharmaceuticals Inc. has a small molecule inhibitor of mutant KRAS called COTI-219; Mirati is developing a KRAS G12D inhibitor; and Revolution Medicines Inc. acquired a preclinical KRAS G12C inhibitor from Warp Drive Bio Inc.

CRACKING THE KRAS CODE WITH AMG 510

KRAS has been studied for more than 30 years as a powerful driver of cancer across tumor types – sort of a master switch for cancer, Amgen vice president of oncology development Greg Friberg explained. As a master switch, drug makers have tried for decades to target the oncogene, but have been unsuccessful in finding a molecule that can attach to the smooth surface of mutated KRAS.

"We have come up with a covalent binder that binds with a specific groove that locks the enzyme into its inactive form," Friberg said. AMG 510 was specifically engineered to bind to cysteine 12 on mutated KRAS so that it's highly selective for the oncogene, which may explain the initial efficacy and the lack of severe AEs observed to date in Phase I.

Levy noted that while AMG 510 is a targeted drug, it has the potential to treat a fairly large number of cancer patients. KRAS G12C mutations are found in about 13% of NSCLC – one of the most common cancers in the world – as well as in about 3%-5% of CRC and about 1%-2% of other cancers. About 30,000 patients in the US alone are diagnosed with cancers driven by KRAS G12C mutations each year with no approved drugs to specifically target that mutation.

"The number of patients with lung cancer who will be candidates for this therapy is considerably higher than the number with colorectal cancer," Levy said. "Our estimates are that probably five to 10 times as many patients with lung cancer have the G12C mutation compared to those with colorectal cancer. There are more colorectal cancer patients in the trial, but I believe that reflects the fact there are few therapeutic options available for them today."

MORE DATA NEEDED FOR POSSIBLE TUMOR-AGNOSTIC APPROACH

Credit Suisse's Seigerman noted that AMG 510 still may be an important therapy in CRC given the lack of effective therapies for those patients. It may turn out that AMG 510, while it's more active in lung than in colorectal cancer, still is an improvement versus current standards of care.

"Commentators [at the ASCO data presentation] suggested that AMG 510's pattern of response in CRC might eventually resemble the pattern of response to BRAF inhibitors in CRC patients with BRAF mutations, where the responses are neither as deep nor as durable as they are in BRAF-mutated melanoma, but are still clinically valuable," the analyst wrote.

A tumor-agnostic approach still is in play at Amgen, with caveats. Levy pointed to "targeted therapies for cancer that appear to work equally well in patients with a defined genetic abnormality regardless of the tumor type," but acknowledged that "there are many other examples of targeted therapies that work well in certain cancer types with a defined genetic abnormality and less well in others – BRAF inhibitors are an excellent example of that."

However, the US FDA has shown a willingness to consider tumor-agnostic approaches. Merck's Keytruda (pembrolizumab) won the first tumor-agnostic indication in the US in 2017 when the FDA approved the PD-1 inhibitor to treat solid tumors that are microsatellite instability (MSI)-high or are mismatch repair deficient (dMMR) regardless of tissue type.

Keytruda's MSI-high/dMMR indication was followed into the tumor-agnostic realm by Bayer AG's NTRK inhibitor Vitrakvi (larotrectinib), developed under a partnership with Eli Lilly Japan-acquired Loxo Oncology Inc., in November.

"I think it's too early to tell" if Amgen will take a tumor-agnostic approach going forward, Levy said. "We've only treated one colorectal cancer patient with the 960mg dose and there are a number of colorectal cancer patients who have reductions in tumor mass that is approaching the threshold for response. I believe we have to be a bit patient here."

COMBOS COULD PUSH RESPONSES HIGHER

Amgen intends to move AMG 510 forward as both a monotherapy and in combination with various other mechanisms of action, which could improve responses and move treatment to earlier lines of therapy. Patients who received AMG 510 monotherapy in the dose escalation portion of the Phase I study were required to have undergone at least two prior stand-of-care lines of therapy and many had been through at least three prior treatment regimens.

Amgen already opened a cohort in the dose expansion stage of its Phase I study to evaluate AMG 510 in combination with Keytruda. Levy noted that AMG 510 combined with a PD-1 inhibitor was "highly active" in nonclinical *in vivo* studies.

"In lung cancer, of course, immunotherapy layered onto chemotherapy is the front-line therapy of choice where they are seeing at least a third of patients, or a quarter of patients, are long-term survivors," Friberg noted. "It would be reasonable to try and improve on that by adding a new therapy in the front line."

Levy said a variety of other agents will be assessed in combination with AMG 510, including drugs that inhibit pathways that are regulated by KRAS. "We have a high interest in pursuing combinations with these agents as well and would anticipate opening cohorts to explore their activity in the very near future," he said.

One of the challenges of combination therapies is that the combined toxicity of two or more agents can limit dosing, treatment durations or both. "The very attractive safety and tolerability profile, so far, of 510 suggests that it would combine well," Levy noted.

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Product Launches To Plan For In 2020

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Informa's drug development database Biomedtracker believes that more than 50 candidate medicines, across 15 broad therapeutic categories and involving more than 60 companies, may come to market over the next 12 to 18 months, according to its new report.

The products include MacroGenics' margetuximab, Genfit's elafibranor, Allergan's ubrogepant, Merck & Co's ebola vaccine and GlaxoSmithKline's antibody-drug conjugate GSK2857916.

Active thyroid eye disease could gain its first pharmaceutical therapeutic with Horizon Pharma USA Inc.'s teprotumumab, with peak sales estimated at $750m.

The productivity of the pharmaceutical and biotech industries is evident from the report, *Key Potential Drug Launches in 2020*, which highlights some of the diseases and conditions that could benefit from new therapies during the year, including liver fibrosis, sickle cell anemia, prostate cancer, multiple myeloma, ebola and dengue fever.

The report builds on the quarterly reports already issued by the pharma pipeline analysts and may give clues to what may be changes to standards of care in the years to come, the market opportunity for new products, and how new drug classes may improve patient outcomes.

PARP INHIBITORS FOR PROSTATE CANCER

Of the four PARP inhibitors currently in Phase III studies for prostate cancer, GlaxoSmithKline PLC's Zejula (niraparib) and Clovis Oncology Inc.'s Rubraca (rucaparib) appear likely to gain the new indication first, the report notes. Rubraca's Phase III TRITON3 study is still ongoing but top-line results were positive and Clovis may file for accelerated approval in the near future. Likewise, Zejula's Phase II GALAHAD study has seen positive top-line data, and partner Janssen Pharmaceutical Cos. could file for approval this year.

PARP inhibitors are likely to be of benefit in castration-resistant prostate cancer patients with BRCA1/2 mutations who have few treatment options after failing therapy on next-generation androgen receptor targeted therapies or chemotherapy, so the commercial potential of the newer agents could be high, the report remarks.

HER2-POSITIVE BREAST CANCER

MacroGenics Inc.'s Fc domain-engineered Mab, margetuximab, has been shown to improve progression-free survival (PFS) in top-line data from the Phase III SOPHIA study, and the company expects to file for approval by the end of 2019.

There are currently no approved medicines for metastatic HER2-positive breast cancer who have received Herceptin (trastuzumab), Perjeta (pertuzumab) and Kadcyla (trastuzumab emtansine), and margetuximab could become a valuable treatment option for third- or fourth-line patients, according to the Biomedtracker report.

SICKLE CELL ANEMIA, BETA-THALASSEMIA

Starting in 2020, a new wave of products for sickle cell anemia and transfusion-dependent beta-thalassemia could reach the market, the report notes. These newer agents include Global Blood Therapeutics Inc.'s voxelotor, which increases hemoglobin's affinity for oxygen, thereby reducing the sickling of erythrocytes.

Others include Novartis AG's crizanlizumab and Pfizer Inc.'s rivipansel, which are selectin inhibitors currently being evaluated for reducing the rate or extent of vaso-occlusive crises in sickle cell. Gene therapy companies are also making progress in hematology, with bluebird bio Inc.'s Zynteglo just approved in the EU and possibly being approved for transfusion-dependent beta-thalassemia in the US in 2020. Acceleron Pharma Inc.'s ligand trap luspatercept, is likely to be approved for marketing in 2020, the report says.

Already approved in China, the potential anemia therapy, roxadustat, could gain additional approvals in 2020 for three companies involved in its global development, AstraZeneca PLC, FibroGen Inc. and Astellas Pharma Inc..

MERCK'S EBOLA VACCINE

Merck & Co. Inc.'s ebola vaccine, V920, which is administered in a single-dose schedule and addresses a major unmet medical need, particularly in West Africa, has been submitted for approval in the US and Europe, and the company hopes it will gain prequalification status from the WHO, allowing the vaccine to be bought and distributed by healthcare bodies such as UNICEF and GAVI.

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Available data from its use in front-line healthcare workers suggests V920 is effective, although the presence of medical teams in the locality where the candidate vaccine was administered may have induced behavioral changes in the population.

TAKEDA'S DENGUE VACCINE

Dengue fever appears to be spreading around the world, and Takeda Pharmaceutical Co. Ltd. is developing a new tetravalent live-attenuated vaccine, TAK-003, to prevent the viral infection, which could gain approval in the US and in selected dengue-endemic Latin American and Asia-Pacific markets starting in late 2020.

TAK-003 is likely to have a more convenient dosing schedule than Sanofi's marketed vaccine, and a better efficacy in seronegative children, the report suggests. The candidate vaccine has the potential to have superior efficacy and safety in young children, and initial studies in children have not raised any safety concerns.

GSK AND BLUEBIRD BIO IN MULTIPLE MYELOMA

GlaxoSmithKline's antibody-drug conjugate, GSK2857916 is directed toward the B-cell maturation antigen, BCMA, expressed on the cells of a high proportion of multiple myeloma patients, a novel mode of action, and promising results have been reported so far in initial clinical studies. These could become the basis of initial filings.

Bluebird bio Inc.'s idecabtagene vicluecel (bb2121) is a CAR-T therapy targeting BCMA, that has also shown promise in initial studies in multiple myeloma patients, and top-line results from a registration-enabling Phase II KarMMa trial are expected in the second half of 2019. Bluebird is collaborating with Celgene Corp., which is currently merging with Bristol-Myers Squibb Co., on the development of bb2121. The Celgene/BMS transaction is expected to close in the third quarter of 2019.

VIIV'S LONG-ACTING ANTI-HIV INJECTABLE

The first long-acting injectable (LAI) to enter the HIV market is expected to be ViiV Healthcare /Johnson & Johnson's cabotegravir/rilpivirine. The product could become a blockbuster if patients prefer it to once-daily oral tablets, Biomedtracker points out.

ViiV filed for US approval in April 2019 and an EU filing is expected shortly, based on positive data from the FLAIR and ATLAS studies.

ALLERGAN'S ORAL MIGRAINE THERAPY

Allergan PLC's ubrogepant is in the driving seat to become the first oral, calcitonin gene-related peptide (CGRP) receptor antagonist approved for the acute treatment of migraine in the US, with a PDUFA date of December 2019.

The approval of ubrogepant is expected to be closely followed by Biohaven Pharmaceutical Holding Co. Ltd.'s oral CGRP antagonist, remegepant, although based on pivotal clinical trials, ubrogepant appears slightly superior to rimegepant with regards to efficacy, the report says.

INTERCEPT & GENFIT'S NASH THERAPIES

Intercept Pharmaceuticals Inc.'s Ocaliva (obeticholic acid) and Genfit SA's elafibranor could be the first products to be marketed for non-alcoholic steatohepatitis (NASH).

Ocaliva is the first drug to show it reduces fibrosis without worsening NASH in a Phase III study in non-cirrhotic NASH and liver fibrosis, the report says. The compound has the potential advantage of already being familiar to physicians as it is already approved for primary biliary cholangitis. However, it has been associated with increases in LDL-cholesterol and pruritus.

The Phase III RESOLVE-IT study of elafibranor in patients with NASH and fibrosis is due to read out at the end of 2019, possibly with a diagnostic which could help expand the NASH patient population, the report says.

LUSPATERCEPT IN MDS

Acceleron Pharma's and Celgene's luspatercept is involved in the later stages of erythropoiesis, while erythropoietin is involved in earlier stages. It is nearing the market for use in patients with myelodysplastic syndrome-associated anemia and beta-thalassemia-associated anemia.

In the MEDALIST Phase III study, 33.3% of MDS patients achieved transfusion independence for 12 weeks or more during the first 48 weeks of luspatercept treatment, compared with 11.8% of placebo-treated patients. Transfusion requirements were also reduced by the candidate therapy. Approval submissions have already been made in the US this year.

HORIZON PHARMA'S TEPROTUMUMAB

Active thyroid eye disease, also known as Graves' ophthalmopathy, could gain its first pharmaceutical therapeutic with Horizon Pharma USA Inc.'s teprotumumab, which has reduced proptosis (eye bulging) in a high proportion of patients studied in the Phase III OPTIC trial, notes Biomedtracker.

An approval filing is planned for 2019 and because the product has US orphan drug, breakthrough therapy and fast-track designations, it could gain an approval early in 2020, with peak sales estimated at more than $750m.

TRIPLETS IN CF, ASTHMA

Vertex Pharmaceuticals Inc.'s triplet combination regimen involving a new next-generation corrector for cystic fibrosis, either VX-445 or VX-659, is nearing the market. Approval of the combination, which will include tezacaftor and ivacaftor, has been effective in patients with a wider range of genotypes, including those with difficult-to-treat CF.

The approval should be straightforward, but market access barriers may hold back the product's commercial potential, Biomedtracker reckons. That said, the triple combination is expected to do well in large markets, like the US.

Another triple therapy in the works is the use of GlaxoSmithKline's triple combination, Trelegy Ellipta, in the additional indication, severe asthma. Trelegy Ellipta contains an inhaled corticosteroid, long-acting beta2-agonist and long-acting muscarinic antagonist (fluticasone, umeclidinium and vilanterol), and is expected to be used in patients with exacerbations despite use of a dual combination of a steroid and a beta-agonist.

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Value Assessment Vexes Pharma As China Costs Soar, Prices Fall

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Jiangsu Hengrui Medicine Co. Ltd. is widely considered a national champion for the pharma industry in China, having not only licensed an anticancer asset to US firm Incyte Corp. in a $900m deal, but also developed its own oncology drugs that have gained several approvals in China.

In the first quarter, Hengrui reported its revenues jumped by 29% to CNY4.97bn ($719m), driven by new launches including anticancer drug Iruini (pyrotinib), and another oncology product, apatinib, that was launched earlier.

On the other hand, the Lianyungang-based company also reported that R&D expenses grew even faster than sales, up 57% compared with the same period in 2018; its quarterly R&D costs reached CNY662m.

This relative level of R&D spending (equivalent to around 13% of sales) puts Hengrui in the same league as its overseas peers, the only issue being that it can't command the same price premiums for novel new drugs as these companies, noted Jianjun Zou, a vice-president at the company.

"Our R&D expenses are on a par with large drug makers but the product price in China, for instance, is like CNY200 [$30] compared to $1,000 in the US," Zou told attendees at the Drug Information Association's China annual meeting, held 22-24 May in Beijing.

Zou's reference to the large price gap reflects a widening view that China's price control policies, including steep price reductions in exchange for reimbursement coverage, could potentially deter innovation in the sector.

Assessing a novel drug's proper valuation is thus seen as key in pricing policy and negotiations, especially during this time when China is building up to including many additional new drugs in its National Drug Reimbursement List (NDRL), a process that started this April and will be complete in September. Any products that have been approved in the country prior to 1 January are eligible for the coverage.

The process is divided into two stages, one for low-priced drugs that will be added without pricing negotiations and another for high-priced products, for which many are expected to go through multiple rounds of pricing negotiations.

Out of 17 anticancer drugs that were covered using a similar mechanism in the past, the average price reduction was 55%.

R&D COST CONSIDERATION

Entering May, China is kicking into high gear for the NDRL update and drug companies are busy persuading medical experts about the value of their products.

Doing so needs a large amount of epidemiology data which needs to be assessed with a holistic view, Kun Zhao, director of Health Technology Assessment (HTA) at the China National Health Development Research Center, told the DIA meeting.

Real world evidence, and not only data from clinical trials, is playing a growing role in determining product value, noted Zhao, while citing uncertainties in these studies. "Is it an iceberg or just the tip?" he asked.

Furthermore, a clear mechanism and transparent process are needed, so guidelines and methodology should be publicized to convince the public, stressed the expert. For drug makers like Hengrui, experts should take R&D costs into consideration in order to provide a fair assessment, Hengrui's Zou said.

MARKET ACCESS ISSUES

Aside from such assessments, market access also poses a major challenge for high-priced drugs in China, including the world's best-selling biologics. AbbVie Inc.'s Humira (adalimumab) may have $20bn in worldwide sales but just $20m - 0.1% of this figure - in China, noted Ning Li, CEO of Junshi Pharmaceutical Group.

"There is more that can be done besides quantifying a product's value using HTA analysis, especially when it comes to drug pricing," Li proposed during a panel discussion at the annual gathering. Such options include patient assistance programs (PAPs) and local provincial reimbursement schemes.

Li's company is one of four makers of immuno-oncology products that have been launched in China, where its Tuoyi (toripalimab) became the first domestic IO agent to be approved. However, it is priced at CNY7,200 per 240mg vial, less than half the level of Merck & Co. Inc.'s Keytruda (pembrolizumab), which costs CNY17,918 per 100mg in China. This in turn is already nearly 50% lower than the drug's US price.

BETTER POSITIONING

Pricing aside, both domestic and foreign drug firms routinely provide PAPs to qualified patients in China, with Merck and Junshi having such schemes in place that award free drugs after a certain amount of purchases.

Pricing, PAP and private insurance are known as the "three Ps" for both multinational and innovative domestic companies wanting to expand product access in China.

Despite the national reimbursement scheme offering potentially large volume uptake, companies are also now actively looking to get local coverage that will help new drugs get to patients faster. Both Keytruda and Tuoyi, for example, were recently added to Zhuhai city's coverage scheme for cancer treatments. This means a patient can get 90% of the cost covered for the purchase of listed anticancer drugs priced in a range of CNY10,000 to CNY300,000.

The combination of pricing strategy, local scheme coverage and PAPs will hopefully provide buffers for pharma companies to feel better positioned entering negotiations for NDRL coverage, or some might even forgo the process altogether.

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Pfizer Unveils Upjohn Global HQ In China Amid Unprecedented Pricing Pressures

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Getting closer to customers and responding to local needs fast is what executives had in mind as they decided last year to locate the global headquarters of Pfizer Inc.'s established products unit, Upjohn, in Shanghai, the hub of the pharma industry in China.

With a fast-aging population and rising incidence of chronic diseases, success in the country is critical to a suite of 20 mature Pfizer products, ranging from the antihypertensive Norvasc (amlodipine) and cholesterol drug Lipitor (atorvastatin) to pain treatments Celebrex (celecoxib) and Lyrica (pregabalin).

The move is a bold one. Out of a total of 12,000 Upjohn employees, 5,000 will be based in China, including at the new Shanghai base, a formulation and manufacturing plant in the northeast city of Dalian and at sales and marketing networks across the country.

But there are also some ominous signs around the timing. While Pfizer made the decision to choose China's commercial megacity as its global anchor last July, nearly one year later the US drug maker is facing a very different environment in China, both commercially and policy-wise.

First, the country late last year initiated the massive "4+7" centralized bidding mechanism in major cities for dozens of widely prescribed off-patent drugs, including multiple statins and other cardiovasculars against which Pfizer Upjohn products are currently competing.

Then the trade dispute between China and the US, which started around a year ago, has now escalated significantly, with trade negotiations breaking down and no immediate end in sight.

Does China still offer attractiveness for such a large-scale corporate move? Executives think so. "China is critical for us," noted Michael Goettler, group president of Pfizer Upjohn, during an opening ceremony in the brand new Shanghai headquarters on 30 May.

Calling Shanghai a strategic location, the CEO said the China decision would allow the company to respond to local needs fast and to attract talent in an increasingly competitive market.

EMBRACING THE STORM

To combat the impact of the 4+7 bidding mechanism, Pfizer Upjohn has cut prices for some of its best-selling drugs in China and is adding more resources to explore the so-called broad market in smaller cities.

The price of Lipitor has been reduced by 30% but the drug still lost out in the bidding process to domestic maker Jialin Pharma, a subsidiary of Luye Pharma, which slashed its atorvastatin price by 83%.

Pfizer hopes the price cut will still be able to attract more self-pay patients, offsetting the negative impact. "We didn't win the bid in the 11 cities process," noted Goettler, adding "the volume is expected to decrease."

Lipitor is the top-selling product in China, growing by 16% in 2018, according to IQVIA data collected from hospitals with over 100 beds. Combined with a similarly strong showing for Norvasc, it has propelled Pfizer to the ranks of top multinational pharma firms in China. *(Also see "Calm Before The Storm: Pharma Opens 2019 With A Bang In China" - Scrip, 9 May, 2019.)*

> "We believe we can be part of the growth in treating cardiovascular disease going forward." – Michael Goettler

In other provinces such as Hubei, where the 4+7 process has not yet started, Pfizer is also reportedly lowering prices of 15 products, with reductions ranging from 3.4% to 10.2%. Going forward, the company said it can't predict further cuts.

DEEPENING 'IN CHINA, FOR CHINA' APPROACH

The ongoing US-China trade dispute, which has had only limited impact so far on the health products sector, has prompted more US companies to adopt an "In China, For China" strategy, noted a recent business survey.

As many as 35% of American companies in the country are adopting localized manufacturing and sourcing to mainly serve the China market, noted the American Chamber of Commerce (AmCham) in China in a survey released 22 May. "Such strategy constitutes a rational choice for many companies to insulate themselves from the effects of tariffs while maintaining their ability to pursue domestic market opportunities," it noted.

Despite pharma being less impacted by the raising of tariffs, the lingering trade war could eventually disrupt the business, noted Goettler.

Roughly one quarter of surveyed businesses said the increases so far in US and Chinese tariffs were having no impact, but 43% of AmCham members supported a return to the status quo, showing that members want a trade deal and a return to the pre-tariff predictability and stability in the US-China trade relationship.

GOING BEYOND THE PILL

Despite the focus on price-cutting and volumes, Pfizer Upjohn executives emphasized at the opening increasing efforts to go beyond the pill. "Price is not the first concern," stressed Goettler, who added that improving patient awareness and

deepening the In China, For China strategy form part of the larger picture.

Despite years of uncovering patient needs, demand in China for cardiovascular treatments remains large. One signature program run by the company is "Bending the Curve", a multi-year partnership started seven years ago between Pfizer China and China's health ministry. This is designed to raise awareness, patient education and early screening for cardiovascular conditions including hypertension and strokes.

In a bid to sharply cut rising mortality rates from cardiovascular diseases, the program includes large-scale screening of populations with high-risk factors. While incidence and mortality have turned downward in the US, these keep rising in China and the multi-year initiative aims to turn the tide.

The goal is to reach out to millions with conditions that have not been diagnosed and treated, and in the meantime to expand the reach of therapies from large cities to lower-tier cities, the so-called broad market that has yet to be fully tapped.

There is unmet need "not only in rural areas but also in big cities..we believe we can be part of the growth going forward," Goettler told reporters during a press round table at the opening. To that end, the company is adding 600 staff in 2019 to further explore China's broad market segment.

With annual cardiovascular patient numbers exceeding 270 million in China – meaning one in five adults suffer from such disorders – and roughly 3 million associated deaths, the need for early diagnosis and preventative care seems huge.

Despite the company having previously partnered with Sinopharm to reach out to lower-tier cities and counties, "We are big in big cities but small in small cities," conceded Tianxiang Miao, Pfizer China's general manager. To change that, he said the company would combine digital tools with additional on the ground sales people.

Predicting "turbulence in the short term," Miao said closely aligning with the central government's Health China 2030 strategic plan would be key to success in China's fast-changing environment. Pfizer's strategy is "synchronized with the government," he said.

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Legal Challenge To First Japan Rituxan Biosimilar Dismissed

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A lower court in Japan has dismissed an effort by originators to halt biosimilar competition to a big-selling hematological cancer drug, meaning the product will continue to face such lower-priced competition, at least for the time being.

In the first ruling in a case concerning Rituxan (rituximab), originally brought by Roche affiliate Genentech Inc. at the end of 2017, the Tokyo District Court dismissed the plaintiff's patent infringement claims.

Assisted by Japan co-distributor Chugai Pharmaceutical Co. Ltd., the US firm had been seeking an injunction against continued sales of the first-to-market biosimilar version, Rituximab BS, launched by Kyowa Hakko Kirin Co. Ltd. in January 2018.

The central claim was infringement of three use patents owned by rituximab originator Biogen Inc., which are licensed exclusively to Genentech.

But the court dismissed the claim, in the process allowing the biosimilar to remain on the market. Chugai in Tokyo told *Scrip* that it was not currently in a position to comment on whether the ruling would be appealed, noting that Genentech would make this decision.

FALLING SALES

Rituxan, a chimeric monoclonal antibody targeting the CD20 protein, is an important contributor to sales at Chugai, also majority-owned by Roche. The company distributes Rituxan in Japan along with Zenyaku Kogyo Co. Ltd., the main local distribution rights holder.

It was Chugai's third-largest product domestically in calendar 2018 with sales of JPY21.3bn ($194m), but hit in addition by the general April 2018 price revision, these slumped by 36% from the previous year.

By contrast, KHK reported a strong start for its biosimilar, which logged sales of JPY4.3bn in the same period, and is forecasting these will almost double to JPY8.4bn this year.

In the first quarter, the product "achieved market penetration and sales growth as planned," the company noted in its results for the period. Under Japan's pricing rules, biosimilars are normally reimbursed at 70% of the original's current national insurance price.

KHK's biosimilar version was licensed exclusively in January 2018 from Sandoz International GMBH, the generics arm of Roche's Swiss peer Novartis AG, for distribution and promotion in Japan in return for undisclosed upfront, milestone and royalty payments. Sandoz holds the Japanese marketing authorization and is the manufacturer, while KHK conducts sales, marketing and promotional activities.

Both the original and biosimilar are marketed for the same indications - indolent, CD20-positive B-cell non-Hodgkin's lymphoma (NHL) and lymphoma of this same type in immunosuppressed patients, plus Wegener's granulomatosis and microscopic polyangiitis.

GENERAL BIOSIMILAR PRESSURE

In common with parent Roche, Chugai is facing broad pressure from biosimilars for its mainstay oncology biologics portfolio, which is all licensed from the Swiss giant.

Japanese sales of HER2-targeting breast cancer drug Herceptin (trastuzumab) also fell last year, by 16% to JPY28.1bn, hit mainly by the price cut, and Daiichi Sankyo Co. Ltd.'s biosimilar version (its first such product, licensed from Amgen Inc.) was launched in late November. First quarter Herceptin sales fell by around 9%.

Chugai has also been involved in legal action against this product, filing a lawsuit as a co-plaintiff last October with the Tokyo District Court seeking suspension of manufacturing and distribution, citing infringement of a Genentech patent.

Chugai's top seller by far, Avastin (bevacizumab), remained strong last year, growing by 3% to JPY95.6bn, but is expected to face its first local biosimilar competition from around November, bringing a new threat to these revenues.

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BioMarin Says It's Got The Hemophilia Therapy Data For Approval And Value

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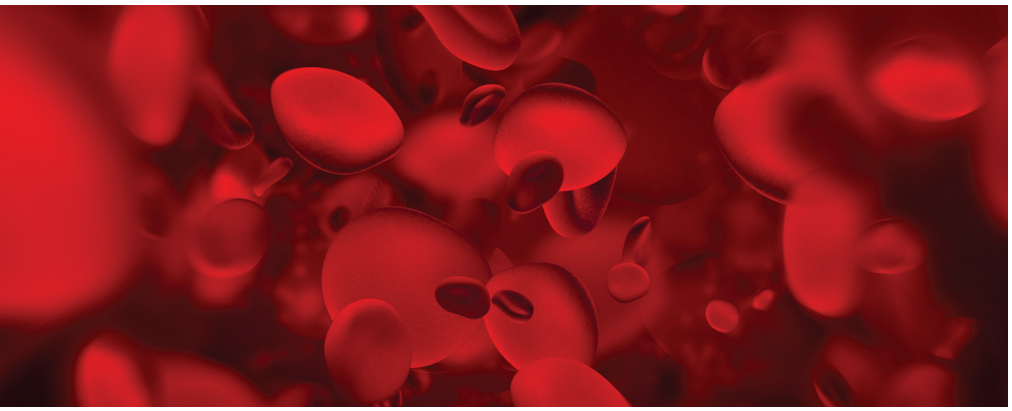
BioMarin Pharmaceutical Inc. will begin regulatory discussions in the US and Europe for its gene therapy for severe hemophilia A based on interim data from an ongoing Phase III trial and updated three-year data from an ongoing Phase I/II trial.



The latest data for BioMarin's gene therapy for severe hemophilia A raise some questions about its long-term durability, but BioMarin management believes it has the data it needs to secure regulatory approval of valoctocogene roxaparvovec, or valrox, and also demonstrate the treatment's value to payers.

Durability is a particularly important measure when it comes to determining the commercial value of expensive gene therapies that are expected to carry seven-figure price tags, like Novartis' newly approved Zolgensma for spinal muscular atrophy, which carries a $2.1m price. *(Also see "It's Official: Novartis SMA Gene Therapy Zolgensma Is World's Most Expensive Drug" - Scrip, 24 May, 2019.)*

Drug makers are generally positioning gene therapy as potential one-time cures that will generate major savings to healthcare systems over the life of a patient and should therefore command ultra-premium price tags. At the same time, the durability of the first generation of gene therapies has not yet been proven.

That is particularly the case for valrox because levels of Factor VIII – the protein that helps clot blood – have steadily declined in patients treated with the therapy and because a few patients have not responded to therapy.

BioMarin released top-line results from two trials on 28 May, with the full data scheduled to be presented at the International Society on Thrombosis and Haemostasis meeting in Australia in July. The company provided updated data out to three years from a Phase I/II study and interim results from an ongoing Phase III study, GENEr8-1, testing a high dose of valrox in which eight of 20 patients achieved Factor VIII levels of 40 international units per deciliter (IU/dL) or more at 23-26 weeks, meeting the prespecified criteria for Factor VIII activity levels.

The company said the interim Phase III data were strong enough to begin regulatory filing discussions with the US Food and Drug Administration and the European Medicines Agency. BioMarin is pushing for accelerated reviews and eyeing a potential launch in late 2020. Management said it would update investors on the timeline for the review in the third quarter following those regulatory discussions.

"We believe we have all the elements coming together to hold those pre-submission meetings and it's really an i-dotting and t-crossing exercise," worldwide president R&D Henry Fuchs said during a same-day conference call.

The big takeaway from the two data updates is that valrox helped control bleeding in hemophilia A patients and substantially reduced the median Annual Bleed Rate (ABR) while patients also significantly reduced their median annualized Factor VIII usage, an expensive and burdensome treatment regimen.

People with hemophilia A lack enough of the Factor VIII protein to clot blood and are at risk for painful and life-threatening bleeds. The 43% of patients with severe hemophilia A are treated with a prophylactic regimen of Factor VIII infusions administered two to three times per week, though many patients continue to experience bleeds.

In the Phase III study, of the 16 patients who reached week 26 by the April 30 cutoff following administration of the gene therapy, the estimated median ABR was zero and the estimated mean ABR was 1.5, representing a reduction of 85% from baseline levels, where all patients were on standard of care prophylaxis.

FACTOR VIII LEVELS CONTINUE TO DECLINE

The concern around durability centers on the fact that Factor VIII levels have steadily declined in patients following treatment. But the three-year data from the Phase I/II study showed that the higher dose of the gene therapy maintained bleeding control out to three years with a median ABR of 0 and a mean ABR of 0.7. In addition, BioMarin said Factor VIII levels appear to be approaching a plateau in year three.

Factor VIII levels measured with the chromogenic substrate (CS) assay at the end of year three were mean and median of 32.7 IU/dL and 19.9 IU/dL, respectively, compared with mean and median of 36.4 IU/dL and 26.2 IU/dL, respectively at the end of year two.

Additionally, in the Phase III interim results, three of the 20 patients never achieved Factor VIII expression levels greater than 5 IU/dL through 26 weeks. One of the patients is bleeding and receiving prophylactic therapy, while the other two have not received prophylactic therapy, BioMarin reported.

Nonetheless, Fuchs insisted BioMarin had achieved what it set out to do. "You've got to remember when we started this program, our target criteria was getting 80% of the patients over 5 IU/dL," he said. "That was everybody's wildest dream in the gene therapy space. I think we really maintain activity data way in excess of people's expectations for the program."

The Phase III program includes two studies with valrox, one testing a 6e13 vg/kg dose (GENEr8-1) and one studying a 4e13 vg/kg dose (GENEr8-2). GENEr8-1 is enrolling approximately 130 patients.

WILL PAYERS AGREE?

BioMarin CEO Jean-Jacques Bienaimé said he was confident payers would understand the value in the treatment based on reductions in prophylactic treatment. "This is what costs them money. They are not equipped to track Factor VIII levels."

Putting the three-year Phase I/II data into context, he pointed out patients saved around 450 infusions of Factor VIII over three years.

"Assuming standard of care [of] around $600,000 in the US, we've saved $1.8m over three years of the payers' year," Bienamé said. "This is how we're going to look at it, not Factor VIII level."

The company expects to have accumulated even more durability data on valrox by the time it reaches the market so that it can make the case for five years of durability, Bienamé said. Convincing payers to consider a gene therapy's value beyond five years would be a hard case to make regardless, he indicated.

"Zolgensma was recently approved and [Novartis] basically priced on a five-year basis. I don't know if we're setting the stage for pricing in the gene therapy field, but I would say, even if we have eight to 10 years of documented efficacy … it might be difficult to get payers to agree to pay for much more than five years of cost of current standard of care," he said.

Analysts were mixed on their reaction to interpreting the two data updates. SVB Leerink analyst Joseph Schwartz said the three-year update from the Phase I/II study was better than expected, while the interim data from the Phase III trial raised new questions about the overall response, which, with eight of 20 patients responding to the prespecified Factor VIII level of at least 40 IU/dL, was slightly lower than in the Phase I/II study.

"While this information is new and could introduce some incremental regulatory risk, as the company begins discussions with FDA/EMA how to handle the remaining 96 patients in the study, we believe it is likely a manageable issue that will be clarified in the near term when BioMarin provides a regulatory submission update in 3Q," he said.

Morgan Stanley analyst Matthew Harrison was optimistic, noting, "updated three-year data support slowing of factor level declines and interim Phase III data support an accelerated filing. We see today's news as an upside surprise."

The company's stock price declined about 5% on the news to close 28 May at $84.50.

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J&J Leverages Novel Mechanisms In Neuropsychiatry And Neurodegeneration

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Johnson & Johnson is planning on significant expansion in the neuroscience field, both through additional indications for its marketed products and first approvals for new potential blockbuster drugs in neuropsychiatry and neurodegeneration. Janssen Neuroscience therapeutic area head Husseini Manji spoke with *Scrip* about near- and long-term milestones following a recent R&D day.

Manji said during J&J's 15 May investor event detailing its pharmaceutical research and development pipeline that neuroscience indications of interest to the company generated $39bn in sales across the pharma industry in 2018, with a 3% compound annual growth rate (CAGR) projected for those segments between 2018 and 2023. During that time, J&J plans to add indications to 14 approved products and submit 10 new therapies for approval, including four drugs and five indications in the neuroscience portfolio.

Those five supplemental or new filings include a suicidal ideation indication for newly approved depression drug Spravato (esketamine) in 2019, a first filing for the multiple sclerosis drug ponesimod in 2019, a six-month injection that will expand the company's antipsychotic paliperidone franchise in 2020, and submissions for the orexin-2 antagonist seltorexant to treat depression in 2020 and insomnia in 2023.

MULTIPLE MECHANISMS IN DEPRESSION

The US FDA cleared the selective NMDA receptor modulator Spravato, the first FDA-approved version of ketamine, in March for individuals with treatment-resistant depression (TRD) – patients with major depressive disorder (MDD) who have had a lack of response to at least two antidepressants. *(Also see "J&J Foresees Broad Insurance Coverage For Groundbreaking Spravato Nasal Spray" - Scrip, 6 Mar, 2019.)*

Manji told *Scrip* that feedback on Spravato has been overwhelmingly positive, because of the drug's novel mechanism and rapid efficacy. The inhaled medication must be administered in certified treatment centers because of its potential side effects, but he noted that more than 800 centers have been certified to administer the drug.

As with TRD, Spravato has a breakthrough therapy designation from the FDA for its next indication in MDD with suicidal ideation. "Unfortunately, we have 47,000 deaths from suicide in the US ev-

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ery year and, unfortunately, many of these people do have suicidal ideation, but that wasn't in the first indication," Manji said.

Immediate reduction of suicidal symptoms is difficult to achieve with existing antidepressants, which can take several weeks to provide relief, so rapid response to Spravato – usually observed within 24 hours of treatment – may help prevent some of these deaths, he noted. Phase III trials in this indication are nearly complete and a supplemental new drug application (sNDA) is anticipated in the fourth quarter of this year.

J&J expects to seek approval for its next depression drug within the next three years, but the company and its partner Minerva Neurosciences Inc. first must finish Phase II studies before moving seltorexant into Phase III. A Phase Ib and a Phase II study have been completed, but the design of a Phase III program will be determined after the partners review data from two additional Phase II studies.

Janssen discovered the orexin 2 antagonist and entered into an agreement with Minerva in 2014 to co-develop the drug for neuropsychiatric disorders and insomnia – an indication where orexin antagonists are known to be effective. *(Also see "J&J Innovation Centers report 12 new partners, investments" - Scrip, 19 Jun, 2014.)* Merck & Co. Inc.'s Belsomra (suvorexant), which binds to the orexin-1 and orexin-2 receptors, was approved to treat insomnia in 2014. *(Also see "Merck sleep aid Belsomra OK'd by FDA" - Scrip, 14 Aug, 2014.)*

"What we recognized was that the orexin system and the circuitry it affects really should be well-placed to regulate what is seen in many patients with depression, which is a limbic system hypothalamic hyperactivation," Manji said. "Many patients, when you do imaging studies, you can show that they have this hyperactivation of the system and they have a depression that's characterized often by what some people call hyperarousal, where they have agitation, rumination – thoughts that just go on and on in their head – [and] insomnia, so we have predicted something that would be a selective orexin 2 antagonist not only would help sleep, but it would help these core symptoms of depression."

> Feedback on Spravato has been overwhelmingly positive, because of the drug's novel mechanism and rapid efficacy.

Seltorexant showed antidepressant effects in a Phase Ib study when items pertaining to sleep were removed from a depression scale. In a Phase II study, Manji noted, significant effects were seen in the overall depression population with an even bigger effect in patients with hyperarousal.

J&J has not disclosed the timing for its Phase III studies of seltorexant in depression, but the company believes it will have data in time for an NDA filing in 2022.

A DIFFERENTIATED S1P1 RECEPTOR MODULATOR IN MS?

In multiple sclerosis, a new indication for J&J, the company's ponesimod – acquired in the $30bn purchase of Actelion Pharmaceuticals Ltd. in 2017 – is likely to be the fourth sphingosine 1-phoshate receptor 1 (S1P1) modulator on the market following its expected NDA submission later this year and potential approval in 2020. *(Also see "J&J's $30bn For Actelion Buys Immediate And Longer-Term Value" - Scrip, 26 Jan, 2017.)*

Celgene Corp.'s ozanimod was resubmitted for FDA approval during the first quarter of this year, while Novartis AG has two S1P-targeting drugs on the market – Gilenya (fingolimod) and the newly approved Mayzent (siponimod).

"We have very good Phase II data where we show about an 80% reduction in the MRI signal for new MS lesions and we also show markedly reduced relapsed rates," Manji said.

Ponesimod is being evaluated now in a 1,100-patient, head-to-head superiority trial against Sanofi's immunomodulator Aubagio (teriflunomide), but data are expected this year to support an NDA filing before the end of 2019.

Manji said the drug has a number of differentiating factors, including a rapid pharmacodynamic effect that requires shorter first-dose monitoring than competing therapies. Ponesimod also has a shorter patented up-titration regimen, rapid restoration of immune system function when patients stop taking the drug – important in a disease that primarily affects women of childbearing age – and no need for pre-treatment genotyping.

PALIPERIDONE'S CONTINUING POTENTIAL

In schizophrenia, an important neuropsychiatry disease area for J&J for many years, the paliperidone franchise generated nearly $3bn in 2018 sales and grew 17% in the first quarter of 2019. That gain was driven by the rapidly increasing use of long-acting injectables – a market that totaled $6.8bn in 2018 and has a projected CAGR of 7% between 2018 and 2023, with sales expected to total $8bn by 2023.

J&J's paliperidone products include the oral (now generic) drug Invega, the once-monthly injection Invega Sustenna (Xeplion in Europe) and Invega Trinza (Trevicta in Europe), which is injected every three months. Paliperidone injections dosed every six months are in Phase III with data expected in time for a filing with the FDA in 2020.

"What we've found from going from oral to one months to three months was that once we had stabilized people for a long time, the longer that they were stable, the longer that they remained stable even after discontinuing the medication," Manji said.

That's important, he noted, because schizophrenia patients often go off their medications and have psychotic episodes when the drug effects wane, which can lead to hospitalization and incarceration.

"What we've found is as we've introduced the newer, longer-lasting medications we get more people going onto these medicines, so we're very confident that once we launch the six-month [injection], it could bring more people onto long-acting medication," Manji said.

In fact, he pointed out, the American Psychiatric Association and other medical bodies are working on treatment guidelines that may recommend the use of long-acting therapies much earlier in schizophrenia treatment, because data suggest that these types of drugs are most effective in preventing relapse.

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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, 24–30 MAY 2019

PHASE III

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Updated Results	Alkermes plc	ALKS 3831 (olanazapine/samidorphan)	Schizophrenia	ENLIGHTEN-2; Weight Gain Reduced	0	57
Phase III Top-Line Results	BioMarin Pharmaceutical Inc.	valoctocogene roxaparvovec	Hemophilia A	GENEr8-1 (6E13 vg/kg); Positive Data	1	66
Phase III Top-Line Results	Cara Therapeutics, Inc.	Korsuva (CR845/difelikefalin)	Pruritus In Hemodialysis Patients	KALM-1; Positive Results	4	70
Phase III Top-Line Results	Novartis/Merck & Co	QMF149 (indacaterol/mometasone)	Asthma, Inadequately Controlled	QUARTZ (vs. MF Twisthaler); Met Primary And Secondary Endpoints	0	0
Phase III Trial Initiation	Ansun BioPharma, Inc.	Fludase (DAS181)	Influenza	STOP PIV; In Hospitalized Patients	34	61
Phase III Trial Initiation	Reata Pharmaceuticals, Inc.	Bardoxolone Methyl	Polycystic Kidney Disease	FALCON; Double-Blind Study	38	63
Phase IIb/III Trial Initiation	NeuroRx, Inc.	NRX-101 (D-cycloserine/lurasidone)	Bipolar Disorder	Encouraging Results	0	51

PHASE II

Event Stage	Lead Company/Partner	Drug Name	Indication	Comments	Change To LOA (%)	LOA (%)
Phase II Updated Results	Windtree Therapeutics, Inc.	istaroxime	Acute Decompensated Heart Failure	Improved Cardiac Function	0	0
Phase II Updated Results	The Medicines Company/Alnylam	inclisiran	Dyslipidemia	ORION-2; Reduced LDL-C	0	57
Phase II Updated Results	Axsome Therapeutics, Inc.	AXS-05	Major Depressive Disorder	ASCEND; Rapid Symptom Reduction	0	57
Phase II Updated Results	MimiVax, LLC	SurVaxM	Brain Cancer, Survivin-Positive	Encouraging Results	0	10

Source: Biomedtracker | Informa, 2019

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Beyond its near-term regulatory submissions, J&J has several novel mechanisms of action in preclinical and clinical development, including multiple assets that work within the glutamate system for the treatment of numerous neuropsychiatric conditions. The lead program in that area is JNJ-0284, which selectively modulates the AMPA receptor via the AMPA gamma-8 accessory protein.

That protein, Manji explained, is present almost exclusively in the limbic regions of the brain, allowing J&J's drug to dampen the receptor rather than shutting it down completely. "That's in clinical testing and it may have utility in a number of conditions that are characterized by limbic hyperexcitability," he said.

Less selective AMPA-targeting drugs have been tested in epilepsy, depression, Alzheimer's disease and a variety of other indications with little success, with the exception of Eisai Co. Ltd.'s Fycompa (perampanel), approved in the US for adjunctive treatment of partial-onset seizures in 2012. *(Also see "Eisai's Fycompa approved in US with boxed warning, awaits DEA scheduling" - Scrip, 23 Oct, 2012.)*

In neuroimmune interaction, J&J is working on drugs that target microglia – immune cells in the brain – that may be involved in neurodegenerative disorders, including Alzheimer's disease, and certain neuropsychiatric disorders, such as depression or prodromal schizophrenia. The company's P2X7 antagonist JNJ-5446, in Phase I development, is designed to regulate microglial function.

TARGETING TAU FOR ALZHEIMER'S DISEASE

Also in Alzheimer's, J&J has a three-pronged approach to targeting the tau protein that continually drives the disease rather than targeting amyloid, which is more involved in initiating the disease. The company has given up on multiple amyloid-targeting therapies, most recently the BACE inhibitor atabecestat, which was discontinued in Phase IIb/III a year ago.

"There's some question about do you want to target all of tau or do you want to target specific aspects of tau," Manji said. He noted that J&J has focused on the mid region of the tau molecule present in tau seeds, which seems to propagate Alzheimer's disease. The monoclonal antibody JNJ-3657 targeting tau seeds has completed Phase I studies and will move into Phase II soon.

"There are some competitors that are already in Phase II, but their monoclonal antibodies seem to be targeting the n-terminal domain of tau," Manji said. "We've done extensive Phase I studies, where we've seen robust lowering of tau in spinal fluid, and now we're going to be embarking on a Phase II study." J&J also has a tau vaccine in early clinical studies under a collaboration with AC Immune. *(Also see "Janssen picks up AC Immune's Alzheimer's vaccine" - Scrip, 12 Jan, 2015.)*

"That's kind of a similar mechanism, where you're administering a vaccine for the individuals to generate their own antibody and the antibody would presumably tie up extracellular tau that is propagating and spreading the disease," Manji said.

In addition, J&J has a small molecule approach that targets intracellular tau in preclinical development.

Regarding the breadth of the Janssen neuroscience R&D pipeline, Manji said, "there's such unmet need and these are devastating illnesses. And while they are undoubtedly very complex – nothing's more complex than the brain – I really do think we're making a lot of progress."

Published online 29 May 2019

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Pascal Touchon	Atara Biotherapeutics Inc	Chief Executive Officer and President	Novartis Oncology	Global Head, Cell and Gene	24-Jun-19
Edward Conner	Audentes Therapeutics Inc	Chief Medical Officer and Senior Vice President	Sangamo Therapeutics	Chief Medical Officer and Senior Vice President	15-Jul-19
Paul McKenzie	CSL Behring	Chief Operating Officer	Biogen	Executive Vice President, Pharmaceutical Operations and Technology	3-Jun-19
Johanna Mercier	Gilead Sciences Inc	Chief Commercial Officer	Bristol-Myers Squibb	President and Head, Large Markets	1-Jul-19
Laura Sepp-Lorenzino	Intellia Therapeutics Inc	Chief Scientific Officer and Executive Vice President	Vertex Pharmaceuticals	Vice President, Head, Nucleic Acid Therapies, Research Leadership, and member of the External Innovation Team	28-May-19
Dietmar Berger	Sanofi	Head, Development	Atara Biotherapeutics Inc	Global Head, Research and Development	30-May-19

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