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ASCO 2018: Optimism As Industry Resets And Looks To What Is Next

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Overwhelming was one common way to describe the American Society of Clinical Oncology (ASCO) annual meeting this year, but optimistic was another. ASCO's tagline for the meeting, held June 1-5 in Chicago, was "delivering discoveries: expanding the reach of precision medicine," but data presented over the five days highlight the reality of overcoming ever-increasing complexities before accomplishing the mission, even as impressive progress has been made.

ASCO didn't disappoint this year. There were plenty of promising data – some of it potentially paradigm shifting – with all of the boisterous debate attendees have come to expect over how key data sets may translate to clinical practice.

It wasn't a ground-breaking year, not like the first peeks at the immune checkpoint inhibitors, shedding light on a new class of PD-1/L1 drugs that have become the blockbusters *Opdivo* and *Keytruda*.

"Scientifically, to me, here this isn't like a big aha immunotherapy moment," said Jill O'Donnell-Tormey, the CEO of the nonprofit Cancer Research Institute.

It was more a year of refinement as industry digests the big advances that have been made in the last five years and pivots toward where to go next.

"Right now, we are refining our knowledge, filling in gaps. We are learning about how to use these new medicines," **Pfizer Inc.** Chief Medical Officer Mace Rothenberg said in an interview. "That's been the sense of this ASCO, the amazing pace of advances but also understanding and getting more confidence in the way we use these drugs."

As Penn Medicine Abramson Cancer Center's Angela DeMichele put it in a discussion of new breast cancer data, "I think it's a really good time to take stock of what we know, what we don't know and what the future holds."

THE BREAKOUT DATA SETS

Merck & Co. Inc. scored the biggest headlines with data on *Keytruda* (pembrolizumab) as a monotherapy versus chemotherapy in lung cancer from the KEYNOTE-042 trial, presented June 3 (see story on p5). The data solidify Merck as the dominant leader in immuno-oncology, though there are still questions about how the results will play out in the real-world in patients with PD-L1 expression of less than 50%.

Rival **Bristol-Myers Squibb Co.** and partner **Nektar Therapeutics** presented notable data on the combination of the PD-1 inhibitor *Opdivo* (nivolumab) in combination with the IL-2 agent NKTR-214 showing the combination could turn immunologically "cold" tumors "hot." O'Donnell-Tormey pointed to the data on the IL-2 combo as one of the highlights of the meeting (see story on p7).

Other data impressed in early and in niche patient populations. **Loxo Oncology Inc.** got attention with Phase I data testing the RET inhibitor LOXO-292 in RET-mutant cancers as a potential tissue-agonistic treatment in a rare subset of patients, a year after impressing the conference with its TRK inhibitor larotrectinib, another tissue-agnostic

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BROUGHT TO YOU BY THE EDITORS OF **PHARMASIA NEWS**, **START-UP** AND **SCRIP INTELLIGENCE**

from the editor

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If last week's issue was all about the early curtain-raisers and strategy updates from companies preparing for their annual trip to the American Society of Clinical Oncology meeting, this week it's all about what happened when they got there.

Our reporters on the ground were Jessica Merrill and Emily Hayes; in our cover story Jessica sums the meeting up (as far as that is possible for such a hive of R&D variety that is positively buzzing with minute dissection of detail). It felt like a meeting where people focused on taking stock of the major leaps that we've seen in oncology in recent years, and drilling down into that detail, unlike previous years when it was all about the fanfare around the big new breakthroughs.

That's not to say there weren't market-moving presentations and stocks that flourished under the lights of ASCO exposure. Merck & Co went into the meeting at $59.52 per share and came out at $61.39, up 3.1%. Bluebird bio went in at $179.05 and rose to $189.65 by the time it was time to leave Chicago, up 5.9%. But these are not hold-the-front-page increases, and on the whole, this year's meeting felt less like an opportunity for investors to win big than other recent ASCOs, not least because figuring out the finer details and analysing nuance can be hard to follow – and bet on.

Over in Boston, BIO has now got under way, and there's a plea for other disease areas to get as much attention as oncology (see p10).

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Darzalex Solid Tumor And PD-(L)1 Combo Future Dashed
https://bit.ly/2LqRwOG

Hopes for Genmab/Janssen's myeloma drug daratumumab in solid tumors have faded after the CALLISTO trial in combination with Roche's Tecentriq in NSCLC was halted for lack of benefit and increased mortality. The future is dim for Darzalex in combination with PD-(L)1 therapies in general.

Madrigal May Shake Up NASH Race With Phase II Resolution Data
https://bit.ly/2kQ6yIF

Madrigal reports data showing that MGL-3196 resolved non-alcoholic steatohepatitis and improved key secondary measures, data that suggest a better effect than other NASH candidates.

Filgotinib Shaping Up To Be Success Story For Gilead and Galapagos
https://bit.ly/2JALcHb

Impressive Phase II data for Gilead and Galapagos' filgotinib in psoriatic arthritis and progress into Phase III for ulcerative colitis suggest that the investigational JAK inhibitor could potentially become a market leader in the class for these and other inflammatory indications.

We Are Family: Why Recent Deals Show China And US Won't Part Long
https://bit.ly/2szYbz0

Recent deals linking Chinese and foreign firms indicate new and bolder views on China's prospects for cutting-edge oncology and rare disease treatments, helped by recent regulatory changes, but a mix of factors is still at play, veteran executives say.

Deal Watch: Takeda Continues Shire Merger Prep With Out-License Of Relugolix Rights
https://bit.ly/2M0exsG

As it narrows focus to core therapeutic areas ahead of acquiring Shire, Takeda sends uterine fibroid and endometriosis rights to compatriot firm ASKA. Zai Lab and Crescendo team up on antibody candidate for inflammatory indications.

Finance Watch: Six More IPO Filings As Three More Biopharmas Go Public In The US
https://bit.ly/2sJniOX

Public Company Edition: Kiniksa, Scholar Rock and Iterum launch the most recent US IPOs and at least five more drug developers join the queue. Also, Polyphor go public in Switzerland, Valeant and Ligand sell notes, and MyoKardia led recent follow-on offerings.

inside:

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approach (see story on p8). The company said it is hoping to engage with regulators on the results of the single arm Phase I data for '292. But even as drug developers hope to move toward treating cancer on the molecular basis of disease rather than location of the tumor, ever more questions pop up about the importance of tumor tissue of origin.

AstraZeneca PLC presented striking Phase III data on its first-in-class anti-CD22 immunotoxin moxetumomab versus standard chemotherapy in patients with hairy cell leukemia, a disease with no current therapy. Treatment resulted in a 75% objective response rate and 41% complete response rate in the 80-patient trial, and 82% of treated patients achieved negative minimal residual disease (MRD). Moxetumumab is under priority review at the US FDA.

Updates on next-generation CAR-T therapies from **bluebird bio Inc.** and **Celgene Corp.** were largely incremental (see story on p6).

ABSORBING THE PROGRESS

There was a deluge of data at ASCO around refining patient populations, exploring resistance mechanisms and evaluating drug combinations across a wide range of tumor types and mechanisms of action, from immunotherapy to targeted therapy, and opening a seemingly endless number of new questions.

Wall Street struggled to absorb the data, and investors weren't overwhelmingly impressed by what they saw. Several drug stocks in the headlines over the weekend opened up modestly higher or flat June 4. Nektar took a big hit, opening down 31% at $62.27 and ending the day down 41.8% at $52.57. Bristol took a more modest blow, ending the day down 3% at $51.45

Investors are understandably squeamish after having heard for several years that IO/IO drug combinations are the path forward, only to see data on those combinations fall flat. But for drug industry attendees at ASCO, the meeting felt more like a renewal, an opportunity to refocus on what is next after digesting several big clinical trial disappointments. The big one came when PD-1/L1s failed to show a benefit in combination with IDO inhibitors, which last year had been hailed as the next big thing. Several drug makers have scrapped development of programs in this class.

Data from the ECHO-301 Phase III trial testing Keytruda in combination with **Incyte Corp.**'s IDO inhibitor epadcadostat in metastatic melanoma were presented at ASCO, sparking dialogue about how the industry might have avoided the multimillion-dollar misstep and if drug makers should have moved slower and conducted more early research before moving into large Phase III trials.

WHAT COMES NEXT

Industry didn't want to dwell on the IDO mess up at ASCO, however, and drug manufacturers said the disappointments have all been part of the learning process.

"I think there was an expectation that when we found checkpoint inhibitors that everything else was going to be easier," **Novartis AG** Oncology CEO Liz Barrett said. "If you think about how long it took us to get to the checkpoint inhibitors, I think we thought we were over it and everything else would just be easier, and what we are finding out is that it's not."

One of the challenges is measuring large quantities of fast-evolving science against an increasingly competitive commercial market for new drugs. The rush to win can lead to fumbles.

"The differentiator is going to be who can move most quickly, incorporate the greatest insights into that strategy and really drive that to completed trial as quickly as possible – and recognize when those things align," Pfizer's Rothenberg said. "If you pull the trigger too early, you are going to increase the risk for failure. If you wait too long, the competition is going to go right by you."

AstraZeneca PLC Oncology Business Unit Global Head David Frederickson acknowledged the company might not have had the best approach for studying IO combinations early on, pointing to the development strategy for its PD-L1 inhibitor *Imfinzi* (durvalumab) in combination with its investigational CTLA-4 inhibitor tremelimumab. Two studies in lung cancer failed to show a progression-free survival benefit for the combination, and Imfinzi showed more benefit as monotherapy in the ARCTIC study. The Phase III MYSTIC trial studying Imfinzi with tremelimumab versus chemotherapy in Stage IV first-line NSCLC is continuing, with a final analysis expected in the second half of the year, though expectations are not high.

Now AstraZeneca is focused on improving the way combinations are evaluated early on to make better choices about which ones to move forward, Frederickson said. "I would say that was not the approach we took with CTLA-4," he said. "Instead of picking one combination and moving forward with it, [the strategy] is how do we get multiple different ones and then pick the best ones."

Despite some setbacks, conquering cancer is going to require combinations, and pharma is pushing hard to test combinations of all sorts. "It is not going to necessarily be IO/IO combinations, but it is going to be IO/targeted therapy combinations. It is going to be IO/radiotherapy combinations. It could be CAR-T therapy in combinations with targeted therapies," Barrett said. "That's really going to be the future here."

No one meeting or a handful of high-profile data sets out of the thousands presented at ASCO really represents the progress that has been made in just the last few years. The feeling of optimism comes from the sense that despite detours, potholes and a lot of flat tires, industry has at least reached a vantage point from which it can imagine a future with long-lasting cancer cures.

Perhaps the most remarkable moment at ASCO was when National Cancer Institute Director Norman Sharpless gave oncologists permission to use the word cure when talking to patients about their cancer diagnosis. Drug makers and physicians generally are reticent to use cure to describe oncology treatment, aware of dangling false hope in front of patients. But in an address during the opening plenary session at ASCO, Sharpless said the time to talk about cures is now.

"I think we have become scared to tell our patients that we actually hope to cure them. It may be time to reexamine how we communicate our efforts in this area," he said. "Curing cancer, that is making it go away and never come back, is really hard and the word here should not be thrown around lightly." But, he said, "We are curing patients now, more than ever, even some people with really bad cancer."

It's far too early to claim victory, but every incremental improvement lights the path forward. The disappointments help to point the way too. And both were heralded at ASCO 2018.

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Merck's Keytruda Monotherapy May Get Stuck With Small Role In First-line Lung Cancer

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Merck & Co. Inc.'s PD-1 inhibitor *Keytruda* (pembrolizumab) as a monotherapy is likely to get a more modest slice of the first-line lung cancer pie than some hoped for, following the release of detailed data from the first-line KEYNOTE-042 study on June 3 at the American Society of Clinical Oncology meeting.

The KEYNOTE-042 study tested Keytruda as a monotherapy against combination chemotherapy in 1,274 patients with first-line non-small cell lung cancer (NSCLC), including squamous and non-squamous types, with expression of the PD-L1 biomarker greater than 1% and no EGFR or ALK mutations. Investigators reported significantly better survival in those with more than 1% of PD-L1 expression.

Results from a pooled analysis of three studies evaluating Keytruda as a monotherapy previously showed that of 4,784 patients whose tumors were evaluable for PD-L1 expression, 33% had a PD-L1 tumor proportion score (TPS) of less than 1%, 38% had a TPS of 1%-49% and 28% had a TPS greater than 50%.

Investigators reported data during a plenary presentation at the ASCO meeting, held June 1 to 4 in Chicago, that showed there was a significant benefit for those in the overall population of patients with at least 1% PD-L1 expression, but only modest activity for the monotherapy versus the chemotherapy combination for those with PD-L1 ranging from 1% to 49%.

It appears that the overall positive result was driven by patients with high PD-L1 expression, that is over 50%, commented discussant Leena Gandhi, director of thoracic medical oncology at the Perlmutter Cancer Center at NYU Langone Health, during the June 3 plenary session.

Gandhi's discussion suggests that the patient population should be segmented for treatment based on a range of factors, including the degree of PD-L1 expression, and that a more selective approach was appropriate, as opposed to treating a larger population with greater than 1% PD-L1 expression with Keytruda monotherapy.

Keytruda was cleared by the US FDA in October 2016 as a monotherapy in first-line NSCLC for patients with high levels of PD-L1 expression (more than 50%), based on results from the single arm KEYNOTE-024 study.

The combination of Keytruda with **Eli Lilly & Co.**'s *Alimta* (pemetrexed) was approved for first-line NSCLC in May 2017 based on mid-stage data. Then Merck reported positive results at the American Association for Cancer Research annual meeting in April, including an overall survival benefit for this combination versus chemo alone in the Phase III KEYNOTE-189 of first-line non-squamous NSCLC, solidifying its leading position in this indication.

The many positive data points across the board for the Keytruda/chemo combo in KEYNOTE-189 included an overall survival (OS) benefit with a very strong hazard ratio of 0.49, which was better than expected.

The KEYNOTE-042 study has held promise for expanding the eligible population for Keytruda monotherapy to those with at least 1% expression of the PD-L1 biomarker, a less toxic mode of therapy that would hold appeal with prescribers if the benefit was good enough in those with lower levels of PD-L1 expression.

The primary endpoint was OS by PD-L1 expression over 50%, 20% and 1%, evaluated sequentially. The company said on April 9 that significant benefits were reported for these three PD-L1 cutoff points, but details were not provided.

This spurred speculation about whether the results in the patients with high expression were driving the overall positive outcome; full data released at the ASCO plenary session on June 3 suggest that this indeed was the case.

The KEYNOTE-042 study randomized first-line NSCLC patients to Keytruda monotherapy or chemotherapy – paclitaxel/carboplatin or pemetrexed with carboplatin.

Those with PD-L1 expression of at least 50% lived for 20 months with Keytruda versus 12.2 months for chemotherapy. Among patients with greater than 20% expression, the Keytruda group lived for 17.7 months versus 13 months in the chemotherapy group. For PD-L1 expression over 1%, patients lived for 16.7 months with Keytruda versus 12.1 months for those treated with chemotherapy.

Lead investigator Gilberto Lopes said during a June 3 press briefing that there were not large differences in response rates for Keytruda versus chemotherapy, but the responses were much more durable for Keytruda monotherapy. For example, in those with PD-L1 expression of at least 1%, the response rate was 27.3% for Keytruda versus 26.5% for chemotherapy, but the duration of response was 20.2 months versus 8.3 months.

Across groups of PD-L1 expression, the median duration of response for Keytruda monotherapy was 20.2 months versus a range of 8.3 months to 10.8 months for chemo.

The hazard ratios for the overall survival improvement in the patients on Keytruda monotherapy versus chemotherapy were 0.69, 0.77 and 0.81 for the cohorts with PD-L1 expression of 50%, 20% and 1%, respectively.

More importantly, the patients had fewer adverse events, said Lopes, a medical oncologist at the Sylvester Comprehensive Care Center at the **University of Miami** Health System in Florida, during the press briefing.

Keytruda was much better-tolerated. In all patients treated, the rate of treatment-related adverse events was 62.7% versus 89.9% for chemotherapy. The rate of Grade 3-5 adverse events was 17.8% for Keytruda, including one death due to pneumonitis, and 41% for chemotherapy.

ASCO lung cancer expert John Heymach noted during the press briefing that the data represent a double win for patients, because the benefits come without the cost of significant added toxicities. Patients in the study were living longer, but also getting substantially less of the toxicity associated with chemo, which includes myelosuppression, nausea, hair loss and numbness of fingers and toes.

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"This really impacts the day-to-day life of these patients," said Heymach, chair of thoracic and head and neck medical oncology at the **University of TexasMD Anderson Cancer Center** in Houston.

However, the results in general, including for the high expressers, don't compare well in cross-trial comparisons against KEYNOTE-189, which established combination therapy with Keytruda and chemo as the standard of care in first-line non-squamous NSCLC.

And soon after the KEYNOTE-042 data were reported, some lung cancer specialists suggested on Twitter that the benefit for the patients with at least 50% lung cancer expression had driven the result in the trial and that Keytruda monotherapy was not appropriate for those with less than 50% PD-L1 expression.

Trial investigators reported that in an exploratory analysis, the hazard ratio in those with PD-L1 expression ranging from 1-49% PD-L1 expression was 0.92 (the confidence interval was 0.77 to 1.11).

In addition to KEYNOTE-042, Merck reported detailed results from the positive KEYNOTE-407 study of Keytruda and chemotherapy versus chemotherapy in 560 patients with metastatic squamous NSCLC – a hard-to-treat subset of the disease, accounting for about one-third of cases – at the ASCO meeting on June 3. This followed a submission to the FDA for early approval based on response rate data and an announcement that the combination demonstrated overall survival and progression-free survival benefits in the study.

Investigators reported that a survival benefit was seen across PD-L1 groups and that overall the data suggest that pembrolizumab and chemotherapy should become a new standard of care for first-line treatment of metastatic squamous NSCLC across all levels of PD-L1 expression.

Discussing results at the meeting, Charles Drake, director of genitourinary oncology at the **New York-Presbyterian Hospital /Columbia University**, said that the trial "was clearly a win."

Roche's combination of the PD-L1 inhibitor *Tecentriq* (atezolizumab) demonstrated a progression-free survival benefit – but not an overall survival benefit as yet – in the pivotal IMpower131 study, which is slated to be presented at the meeting on June 4.

Roy Baynes, head of global clinical development at **Merck Research Laboratories**, said during an interview at the meeting that the Keytruda/chemotherapy combination defines the standard of care in first-line treatment of both squamous and non-squamous NSCLC.

As for Keytruda monotherapy, this could be an option for those who cannot tolerate the chemotherapy combination and/or who have a malignancy that is "relatively well-behaved," Baynes said.

"At the end of the day, it's a practice-of-medicine decision," and physicians in consultation with patients are going to have to decide what the goals of therapy are, he said.

Heymach commented in an interview that he expects no first-line NSCLC patients should be getting chemotherapy alone, though there are exceptions, for example those with an autoimmune disease that prevents them from getting immunotherapy as part of their treatment regimen.

Heymach also said that whether first-line NSCLC patients with over 1% PD-L1 expression get chemotherapy with Keytruda or Keytruda alone is going to be up for interpretation by physicians. Starting with Keytruda and moving on to Keytruda with chemotherapy may make sense as they could potentially avoid taking chemotherapy for years, Heymach said. However data supporting this strategy are currently lacking.

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Bluebird's BCMA CAR-T: How Will It Fly In Early Myeloma?

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The headliner on the opening day of the American Society of Clinical Oncology annual meeting June 1 was **bluebird bio Inc.**'s updated data on the second-generation chimeric antigen receptor T-cell (CAR-T) therapy bb2121, targeting B-cell maturation antigen (BCMA) in patients with relapsed/refractory multiple myeloma.

The updated data, including the first progression-free survival data in patients with multiple myeloma, eased investors as bb2121 showed notable safety and efficacy. Nonetheless, the data didn't overwhelm and left plenty of questions about how CAR-T therapy could best be used to treat multiple myeloma.

The spacious meeting room at Chicago's McCormick Center was standing room only to hear the results, reported by Noopur Raje, Harvard Medical School. The updated results from the CRB-401 open-label Phase I trial included data from 43 heavily pretreated patients (a median of seven previous lines of therapy).

The median PFS for patients in the dose-escalation phase treated with CAR-T cells 150x10 or greater was 11.8 months, while patients receiving the low 50x10 CAR-T cells had a median PFS of 2.7 months.

In the dose escalation and expansion phase of the study, all patient who responded and were evaluable for minimal residual disease (MRD), 16 patients, were MRD negative at one or more time points. The median PFS in MRD negative responders was 17.7 months.

Those results were in line with what investors had been hoping to see, though they didn't surpass expectations. The data raise questions too because even patients who are MRD negative relapse.

Discussion leader Parameswaran Hari, professor of hematology at Medical College of Wisconsin, said the MRD results were disappointing because bb2121 does not appear to be a cure. "I'm perplexed by MRD negative," he said. Nonetheless, he called the results the "most exciting" of the multiple myeloma data presented at the session, and noted his patients are "demanding" treatment with CAR-T.

Bluebird insisted the data support moving into earlier lines of multiple myeloma treatment. CEO Nick Leschly said during a same-day conference call that the company and its partner Celgene are committed to studying bb2121 in earlier multiple myeloma, including possibly the first-line setting.

The pivotal Phase II study KarMMa is recruiting in North America and Europe in relapsed and refractory multiple myeloma patients and should support the first regulatory filing in MM in 2019.

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A Plea For Patience For BMS/Nektar's Opdivo/NKTR-214

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The combination of **Bristol-Myers Squibb Co.**'s PD-1 inhibitor *Opdivo* with **Nektar Therapeutics**'s IL-2 agent NKTR-214 yielded deepening responses over time and demonstrated signs of being able to turn immunologically "cold" tumors "hot" – making them susceptible to immuno-oncology approaches, specialists reported at the American Society of Clinical Oncology (ASCO) annual meeting June 2.

Bristol and Nektar have been partnered since February on NKTR-214's development in nine tumor types and 20 indications, under a massive development deal signed in February worth $1.85bn.

NKTR-214 is a CD-122 agonist, meaning it binds with and activates CD-122, one of three components of IL-2 receptors found on the surface of T-cells. Nektar's pegylated product adds polyethylene glycol to human recombinant IL-2, which has the effect of delaying breakdown, allowing more convenient dosing and hopefully a better safety profile.

At the time the agreement was announced, the companies said they planned to move rapidly with development, starting pivotal trials in melanoma and renal cell carcinoma and intending to begin all registration-enabling studies within 14 months.

Nektar reported very impressive data for the drug in the dose escalation stage of the Phase I/II PIVOT study of immunotherapy-naïve cancer patients at the Society for Immunotherapy and Cancer (SITC) meeting in November 2017, with response rates in the 60% range, though the dataset was small – just 38 patients. In March, the company reported that the data from the dose-escalation phase looked even better. For example, in first-line metastatic renal cell carcinoma (RCC), the objective response rate (ORR) improved to 71% from the time data was reported at SITC.

RESULTS IMPROVE OVER TIME

The PIVOT study is set to enroll more than 400 patients with melanoma, urothelial, non-small cell lung cancer and triple-negative breast cancer.

According to updated data presented at ASCO by Adi Diab, **University of TexasMD Anderson Cancer Center**, responses in the dose-escalation phase continued to deepen over time, as of a data cut-off on May 29.

In first-line metastatic melanoma, for example, 11 out of 13 had a partial response or complete response, an objective response rate of 85%.

Diab reported increased lymphocyte proliferation in blood and CD8 T-cells in tumors. Investigators also noted that some patients who were PD-L1 negative at the study start converted to PD-L1 positive after treatment.

If a certain level of efficacy was shown relative to historical controls with monotherapy in a particular tumor type, the study advanced to the next phase, where additional patients were evaluated. For this stage, Bristol and Nektar reported data for 94 evaluable patients: 37 with melanoma, 47 with RCC and 10 with urothelial cancer.

Relative to the initial dose escalation phase, the objective response rates were lower. Out of 28 patients with melanoma, for example, 14 responded (ORR 50%). Importantly, the combination was very effective in 25 patients with known PD-L1 status; the ORR was 42% (five of 12) in those who had been negative and 62% in those who were positive (eight of 13).

In metastatic renal cell carcinoma, the response rate was 46% (12 of 26). The ORR in those who had been PD-L1 negative was 53% (nine of 17) and 29% in those positive for PD-L1.

In advanced urothelial cancer, six of 10 had a response (60%). The ORR in the PD-L1 negative patients was 60% (3/5) and 60% in those who were positive (3/5).

With safety data for 283 patients, the most common treatment-related adverse events for the combination were Grade 1/2 flu-like symptoms (58.7%), rash (44.5%), fatigue (42%) and pruritus (31.4%). The rate of treatment related Grade 3+ adverse events was 14.1% and the dropout rate was 2.1%. The rate of Grade 3 or higher immune-mediated adverse events was 3.5%, including one death due to pneumonitis.

While acknowledging the hazards of cross-trial comparisons, ASCO discussant Heather McArthur said that the 50% ORR for advanced melanoma patients in the second phase of the study compared well to monotherapy data in this indication. Opdivo (nivolumab) as a monotherapy demonstrated an ORR of 44% and 40%, respectively, in the CheckMate 067 studies and CheckMate 066 studies in melanoma, she noted. A small improvement in response rate for immunotherapies can translate into an overall survival benefit, said McArthur, who is medical director of breast oncology at the Cedars-Sinai Medical Center in Los Angeles.

McArthur also noted that it is remarkable to see that the drug works in PD-L1 positive and negative tumors, with some converting from negative to positive status after treatment. Those who were PD-L1 positive at the start or who had converted from PD-L1 negative to positive status were more likely to derive benefit from clinical treatment, McArthur said, adding that "you have to be patient as responses happen over time."

This shows the potential of the combination for turning "cold" tumors "hot" – meaning they become primed for IO treatment – and raises the question of whether conventional biomarkers still matter, McArthur said. McArthur also noted that the toxicity compares well to IL-2 historically, including lower rates of immune-related adverse events.

The pegylation of NKTR-214 helps with tolerability. The PEG chains slowly and irreversibly dissociate from NKTR-214 to gradually reveal biological activity, according to Nektar. This slow release of PEG chains in the blood allows less frequent dosing, stops over-activation of the immune system and overcomes traditional IL-2 toxicity such as capillary leak syndrome, the company explains.

With NKTR-214, regulatory T-cells are still generated in the periphery, where they can play a positive role without interfering with the drug's activity.

Data for the NKTR-214/Opdivo combination reported in an ASCO abstract ahead of the conference disappointed investors, as the response rates were lower in the second phase of the trial.

Citeline analyst Maria Berezina commented, however, that the deepening of responses from the dose escalation phase at the time of SITC to ASCO strongly suggests that the latest data will also improve.

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Loxo '292 And Cancer Drug Development Today: So Much Promise, So Many Questions

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Loxo Oncology Inc.'s highly selective RET inhibitor LOXO-292 stood out at the American Society of Clinical Oncology annual meeting as one example of where cancer drug development is going – toward cancer treatment based on the molecular underpinnings of disease rather than tissue of origin. But while Loxo presented encouraging data as a tissue agnostic approach for select patients, the importance of tissue of origin can't be ignored. Data presented on a different drug, **Roche**'s PI3K inhibitor taselisib, from a basket trial funded by the National Cancer Institute, disappointed, highlighting the persistent challenges.

The drug industry is increasingly moving the precision medicine goalpost forward, from chimeric antigen receptor T-cell (CAR-T) therapy to next-generation sequencing that can rapidly characterize the genetic mutations marking a patient's cancer – and matching treatment to those genetic markers. LOXO-292 – along with Loxo's lead drug, larotrectinib, now pending at the FDA – showcases how far the industry has come from the early targeted therapies like HER2 and EFGR.

The US FDA approved the first molecularly-defined cancer indication last year, clearing **Merck & Co. Inc.**'s PD-1 inhibitor *Keytruda* (pembrolizumab) for microsatellite instability-high or mismatch repair deficient solid tumors. *(Also see "Loxo Edges Closer To Commercial Market With Larotrectinib, But Diagnostic Challenge Persists" - Scrip, 29 May, 2018.)* The approval was based on retrospective data, whereas Loxo's TRK inhibitor larotrectinib could be the first drug prospectively developed and approved for a tissue-agnostic claim. The TRK inhibitor, which **Bayer AG** partnered on after the data presented at ASCO last year, has a Nov. 26 user fee date. *(Also see "Loxo Edges Closer To Commercial Market With Larotrectinib, But Diagnostic Challenge Persists" - Scrip, 29 May, 2018.)*

"There are clearly examples where tumor-agnostic and tissue of origin-agonistic therapies can apply," Vanderbilt University's Christine Lovely said. "There are also clear examples where tissue of origin is important."

Loxo released Phase I data from LIBRETTO-001 at ASCO June 2, testing '292 in a range of tumors altered by RET. The trial has enrolled 82 patients with a range of tumors, including non-small cell lung cancer, thyroid cancer, pancreatic cancer and medullary thyroid cancer (MTC). The overall response rate among the 53 patients evaluated across all tumor types was 77%, including for NSCLC, but the overall response rate for MTC was 45%. Four patients enrolled without a known RET alternation did not respond to treatment. Toxicity was minimal with most treatment-emergent adverse events being Grade 1 in severity.

The data put Loxo squarely in the early lead versus rival **Blueprint Medicines Corp.**, which is also developing a RET inhibitor, BLU-667, for patients with RET altered solid tumors. But early data from the Phase I ARROW trial presented by Blueprint at the American Association for Cancer Research in April showed overall response rates of 50% in NSCLC and 40% in MTC.

The LOXO-292 data impressed so much so that investors immediately turned their attention to when '292 could be filed with regulatory authorities, notable given that the data are from a Phase I study intended to determine the best dose. The company's stock jumped 5% to $186.69, and its market cap stands at $5.6bn. After the ASCO abstracts were released after the market close May 16, Loxo opened at $160.50, up 15% from $139.50 at closing May 16.

DIFFERENT FILING TIMELINES

"We plan to start engaging with global regulators in the various populations," Chief Business Officer Jacob Van Naarden said during a same-day investor briefing. He said the company will provide an update on the timeline after it gets input from the FDA.

The agency under Commissioner Scott Gottlieb has certainly shown an inclination to get effective medicines to patients faster. Gottlieb addressed ASCO attendees during the opening session the same day and announced two new pilot programs intended to speed the drug review process for cancer drugs. He also made a point to highlight the FDA's willingness to approve drugs based on limited data sets, pointing to the approval of Keytruda for microsatellite instability-high or mismatch repair deficient solid tumors. However, straightaway Loxo told investors that the conversations with FDA would be different for RET fusion-positive cancer and RET-mutant MTC patients, where the response rate was lower and some currently marketed kinase inhibitors are already used. RET fusions and RET mutations are two different mechanisms in cancer, and an expedited review appears more likely for RET fusion cancer, including NSCLC.

"With respect to single-arm [trial] paths to approval, I think we are likely to be restricted to a population that is refractory or intolerant to those first-line drugs," Van Naarden said. "That would most assuredly require a randomized study."

Beyond FDA approval, there are other challenges, like finding the few patients with RET fusion mutations to treat, only about 2% of patients with NSCLC and 10%-20% of patients with papillary and other thyroid cancers, for example. The company signed a partnership with **Illumina Inc.** in April to develop a multi-gene panel for broad tumor profiling that can be used as a companion diagnostic for larotrectinib and '292, but the company has acknowledged the test won't be approved on the same timeline as larotrectinib at least. And, the data are early. The durability of the response remains a big unknown

RET inhibition is not a new drug target. It was first identified as a potential drug target in 1985. Other multi-kinase inhibitors that have been developed can also inhibit RET but less selectively and with less potency, which is where the work Loxo has done stands apart.

"I think this is part and parcel to the profound excitement around the LOXO-292 data," said Christine Lovely, Vanderbilt University, leading a discussion of the data at ASCO. "The first generation of RET inhibitors, all of these RET inhibitors, were multi-kinase inhibitors. They were not designed to have

activity against RET." Multi-kinase inhibitors like those that work against VEGF have had modest efficacy and higher toxicity.

She pointed to LOXO-292 and BLU-667 as next-generation drugs that raise the bar for precision medicines. But they also raise outstanding questions, like why the response rate is higher in RET-fusion NSCLC versus RET-mutated MTC. The experience was similar with BLU-667.

"Why is that the case," Lovely asked "How does the site of origin play into the underlying response?"

Loxo has its own thoughts on that question, with CEO Joshua Bilenker noting it is "interesting to hypothesize." One possibility is that MTC patients are more heavily pre-treated with prior multi-kinase inhibitors, he said.

Lovely pointed out that tumor origin can't be ignored. "There are clearly examples where tumor agnostic and tissue of origin-agonistic therapies can apply," she said. "There are also clear examples where tissue of origin is important." She pointed to BRAF mutations in colon cancer as an example; Roche's VE-BASKET trial of its BRAF inhibitor *Zelboraf* (vemurafenib) in patients with any type of nonmelanoma cancer who had BRAF V600 mutations suggested that tumor type mattered. Puma's SUMMIT trial also showed that neratinib worked in some types of cancer with HER2-activating mutations but not others. *(Also see "Puma's Neratinib SUMMIT Study Shows Potential & Pitfalls Of Precision Medicine" - Pink Sheet, 2 Apr, 2017.)*

PI3K INHIBITION UNDERWHELMS

Alongside the promising data around LOXO-292, disappointing data was reported on another emerging targeted pathway: PIK3CA mutations in breast cancers and other cancers. Data was presented from the NCI's 14-arm MATCH trial, a basket study intended to treat patients based on the results of genomic sequencing. Patients with solid tumors (excluding breast cancer) with a PIK3CA mutation treated with Roche's PI3K inhibitor taselisib as monotherapy did not experience confirmed objective responses, though there was limited activity.

"It's possible that PIK3CA mutations may not be the major driver in these particular tumors that we looked at, and other mutations act as bypass around the PI3K inhibition," Dana-Farber's Ian Krop said in presenting the data at ASCO.

Roche has been investigating taselisib as a late line of therapy for advanced HR+/HER2- breast cancer, but the company said it would not pursue a regulatory approval in breast cancer after Phase III data showed only a modest two-month improvement in PFS. The results of the Phase III SANDPIPER trial were also presented at ASCO. Roche said it will continue to evaluate the pathway, however.

As the discussant for the taselisb data, Fabrice Andre of the Institute Gustave Roussy pointed out that PIK3CA mutations can occur late in disease progression and may be correlated with the evolution of the disease.

He also speculated that industry has reached a threshold when it comes to single-targeted drugs. "My interpretation is that we are starting to reach a plateau with this strategy," he said. "We need to reach a second generation, where we do comprehensive molecular portraits."

As more data becomes available, it showcases the challenges the industry faces, and that more needs to be known about particular mutations, tissue of origin and the role each plays in driving cancer or blocking treatment.

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Loxo Edges Closer To Commercial Market With Larotrectinib: **https://bit.ly/2J8iD4a**

Sotio's Dendritic Cell Vaccines Promise

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Cancer vaccine research has had its fair share of disappointing clinical trial results, but a central European company, **Sotio AS**, owned by the international finance group, PPF Group, presented positive Phase II results with two DCVAC vaccines, for potential use in ovarian and lung cancer, at the ASCO meeting on June 3, backing the promise of this emerging therapeutic category.

The use of DCVAC/OvCa in patients with ovarian cancer, and DCVAC/LuCa in patients with lung cancer, significantly decreased the risk of disease progression or death, researchers reported, and Sotio is planning further clinical studies including a global Phase III study of DCVAC/OvCa. The Prague, Czech-based biotech already has a prostate cancer product candidate, DCVAC/PCa, in Phase III clinical studies.

In Sotio's autologous cell manufacturing process, monocytes are harvested from patients and differentiated into dendritic cells, during which the cells are also exposed to a tumor cell line that has been killed by a proprietary process involving high hydrostatic pressure. When immature dendritic cells are cultured in the presence of the tumor antigens, the antigens are taken up and displayed on the surface of the dendritic cells, the company explained. When these cells are transfused back into patients, as DCVAC, they are believed to initiate an immune response against the tumor.

In interim results presented at ASCO by Lukas Rob, of the University Hospital Karlovske Vinohrady in Prague, Czech Republic, 92 patients with ovarian cancer were treated with chemotherapy and either concomitant DCVAC/OvCa (arm A of the study), maintenance DCVAC/OvCa (arm B), or placebo (arm C), for up to eight doses of DCVAC/OvCa, in the randomized open-label SOVO1 study.

Those patients treated with maintenance DCVAC/OvCa as first-line therapy showed a gain of around six months in median PFS, from 18.6 months to 24.3 months, and a 57% reduction in risk of progression or death, Rob reported. Current data on overall survival "are trending in the same direction as PFS," and DCVAC/OvCa was well tolerated, he added.

In a second Phase II study, SOVO2, DCVAC/OvCa has been associated with prolonged survival in patients with ovarian cancer after first recurrence, compared with patients treated with chemotherapy alone, in a preliminary view of the data.

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Other Therapeutic Areas Left Behind As Deal-Making, Financing Focus On Oncology, Rare Diseases

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Boston – While investment capital and deal-making interest remain plentiful for cancer and are increasing for rare disease programs, other prevalent disease areas such as cardiovascular, respiratory and psychiatry are being overlooked, David Thomas, BIO's managing director of industry research and policy analysis, notes.

Thomas said while giving an overview of the *Emerging Therapeutic Company Investment and Deal Trends* report issued on June 4 – the opening day of the 2018 BIO International Convention – that the organization is studying the investment and business development trends in these underserved therapeutic areas. BIO already has issued reports on the depression, pain and addiction therapy spaces, and plans to release a report on diabetes and obesity in the fall with others on Alzheimer's and Parkinson's diseases expected in early 2019.

"Overall, across both investments and deal-making, there continues to be an emphasis on oncology and rare diseases over high prevalence disease areas, such as cardiovascular and psychiatry," the report states. "For example, venture investment into novel drug R&D has declined for companies focused on psychiatry, cardiovascular, endocrine, respiratory [and] gastrointestinal diseases."

In reviewing research-and-development stage licensing deals completed during 2016 and 2017, Thomas found 53 such deals for cancer assets in 2016 and 47 in 2017, dwarfing not just other therapeutic areas, but combined deal-making in some areas. In 2016, there were 33 deals for R&D-stage assets in the neurology, endocrine, infectious disease, metabolic, ophthalmology, cardiovascular, gastrointestinal, respiratory and psychiatric sectors combined. However, in 2017 the aggregate total of deals in those sectors increased to 55, outstripping cancer.

The therapeutic area with the second most deal activity over the two years was neurology, with 11 deals in 2016 and 12 in 2017.

The trend toward oncology carries through in start-up investment as well. Of 132 Series A financings recorded in 2016, 54 were for oncology plays. In 2017, cancer accounted for 49 of the 146 Series A rounds. Aggregate dollar amounts for Series A financings followed the trend – $778m out of $1.98bn recorded in 2016, and $957m out of $2.92bn in 2017.

DISADVANTAGES FOR CANADIAN BIOTECHS

US-based biotechs not focused on cancer, however, still might consider themselves fortunate in comparison to their counterparts in Canada, **Trillium Therapeutics Inc.** CEO Niclas Stiernholm told *Scrip* on June 4. His Missisauga, Ontario-based firm is one of five biotechs in the clinic with CD47-targeted immuno-oncology therapies, but Trillium's financial capacity for R&D falls short of not only the big biotech **Celgene Corp.**, but smaller competitors such as **Alexo Therapeutics Ltd.** and **Surface Oncology Inc.**

Now comes word that as of June 1, following a well-received presentation at the American Society of Clinical Oncology meeting, **Forty Seven Inc.** has filed plans with the SEC to seek up to $115m in an initial public offering. Trillium hopes to have Phase I data for intravenous and intratumoral formulations of lead candidate TTI-621 in cutaneous and peripheral T-cell lymphoma later this year, but currently has a market cap of roughly $78m.

Besides valuation, Trillium faces a further disadvantage, because there isn't enough of a biotech community presently in Canada to provide needed expertise or venture capital backing, Stiernholm said. The government-funded MARS (Medical And Related Sciences) incubator in Toronto is a start, he added, but homegrown investors just aren't accustomed yet to the realities biotech investors face, including slow development compared to the natural resource industries like mining and logging that are more prevalent in Canada.

"There's a disadvantage in that there is a valuation disconnect [for Canadian biotechs]," Stiernholm said. "I think most people would agree that if Trillium was based in Boston or San Francisco, we wouldn't have the low market cap that we have. I think that's a given. But I'll get over that."

More challenging is the fact that Trillium and other clinical-stage companies in Canada need to go to the US for talent. "There are certain positions that are more difficult to fill in Canada, because our sector is not even close to being as mature as the US biotechnology sector," the exec continued. "We don't have individuals with 20 years of drug development experience in the immuno-oncology field. In some instances, particularly when it comes to senior clinical leadership, it is almost inevitable to have to go to the US and hire – and that presents problems with relocation."

Some Canadian biopharma companies have addressed this issue by establishing outposts in Boston, Stiernholm said, a route Trillium hasn't taken yet, but won't rule out.

The establishment of MARS, he added, was triggered in part by Canadian biotech execs seeing the Broad Institute in Cambridge, Mass., and the hub of biotech activity around Kendall Square and saying "we need something like that."

"It's coming along, it's taking quite a bit of time," Stiernholm concluded. "I think the Canadian issue goes deeper than that. Never have we had a success story like **Genentech Inc.** or **Amgen Inc.** – there is no Canadian Genentech. When something gets close, it gets bought."

ENTREPRENEURSHIP AT NIBR

After leaving **Harvard Medical School** and **Dana-Farber Cancer Institute** to become president of the **Novartis Institutes for BioMedical Research Inc.** (NIBR) in 2016, Jay Bradner was surprised and pleased to see how similar the mindset was at the institute compared to the academic setting he was used to. Bradner shared this and other observations during a "fireside chat" at the BIO convention on June 4.

One NIBR effort he is especially excited about – which largely has been kept under wraps to date, he said – is the NIBR Schol-

ars program. Bradner called it a "social experiment" in which great innovators were "badged up" and set loose in the NIBR complex with the resources available within a big pharma setting.

"We're two years into this grand experiment at two of our sites and it's wonderful," he said. "Nobody has developed an acute hypersensitivity reaction, no ideas were tweeted …. But moreover, we've seen new pipeline projects come through from these collaborations. … We've seen teams rally around new ideas."

"We imagine large chemical libraries emerging that we can share," Bradner continued. "It's early days, it's definitely too early to be very congratulatory, but if NIBR is to be a platform of drug discovery for the [biotech] ecosystem, then people have to know that they can give us a call."

Asked about the risks of an excited scientist in this setting tweeting about an otherwise unreported finding, Bradner said the **Novartis AG** early drug discovery arm doesn't have a set policy as of now on when to publish a novel finding. In a general sense, Bradner thinks such a decision should be based on three criteria – whether the science has led to demonstrably learning something, what the status of the intellectual property is, and whether there is economic value in the discovery that occurred.

"Interestingly enough, most of the time there isn't," he said. "In academic publishing, often you patent because you don't actually know where the science is headed or you're trying to create an estate of patents that you can present to an investor. We're already fully invested, so we'd rather publish early and patent late with a definitive molecule, and I think that leads to a strong biomedical ecosystem."

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Allergan May Sell Women's Infectious Disease Units

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The result of **Allergan PLC**'s board-directed strategic review is a plan to divest its women's health and infectious disease units – narrowing the company's focus to four primary therapeutic areas – but it isn't time yet to consider splitting off aesthetics into a separate business, CEO Brent Saunders said May 30.

Saunders stressed that Allergan does not need to sell off any business segments and is not undertaking a fire sale – despite recent investor sentiment to "do something" to improve the Dublin-headquartered firm's market value – in remarks during the Bernstein Strategic Decisions CEO Conference. The executive said during Allergan's first quarter earnings call April 30 that an ongoing strategic review would consider five options: staying the current course, divestitures, a corporate split, aggressive share buybacks or mergers and acquisitions.

Allergan's stock price leveled out during the trading day May 30 after an initial negative take on the decision. It closed at $151.49 per share, up 0.3% for the day, after falling slightly during and immediately after Saunders' comments. Activist investors have at least partially driven the talk of splitting Allergan into two companies, but Saunders noted May 30 that doing so would be quite complex, as top-seller *Botox* delivers significant sales both for aesthetic and therapeutic uses.

Evercore ISI analyst Umer Raffat largely dismissed Saunders' announcement as nothing groundbreaking, since during the Bernstein presentation, new Allergan Chief Financial Officer Matt Walsh conceded that women's health and infectious diseases are "relatively modest-sized parts of the company" bringing in top-line revenue of roughly $1bn and $200m, respectively, on an annual basis.

"I didn't hear anything on the 'strategic update' that was groundbreaking," Raffat wrote in a same-day note. "Women's health plus anti-infective divestiture: not a biggie in my view. The only way it matters is if Allergan doesn't get a reasonable price for them and the divestiture is dilutive at some level."

Saunders said both units have new products in their research and development pipelines, and offer potential growth, so Allergan is not desperate to move on from them, despite a decision going forward to focus R&D and business development resources on the four core areas of medical aesthetics, central nervous system, ophthalmology and gastrointestinal health.

"With respect to infectious disease and women's health, it always takes another party to actually consummate a deal," the CEO pointed out. "We will not sell those businesses unless we get the intrinsic value we believe they are worth."

ESMYA ISSUES

The value of the larger women's health unit may be tough to agree on with a potential buyer, however, because of the cloudy forecast for one of Allergan's top late-stage pipeline candidates, uterine fibroid candidate *Esmya* (ulipristal). Cited in 2017 as one of Allergan's "six stars" that would help ameliorate the impact of five of the company's drugs facing potential generic competition in 2018, Esmya suffered a setback in February when the US FDA pushed its user fee date back three months to August 2018.

The agency mentioned liver safety concerns flagged by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) when it revised the action date for Esmya.

Morningstar analyst Michael Waterhouse said in a May 30 note that "recent restrictions on uterine fibroid drug Esmya in Europe over liver concerns diminish one of the larger opportunities for the company's women's health franchise, which has likely advanced management's interest in parting with this business."

Still, Morningstar thinks Allergan could obtain a combined price tag of $4bn.

However, Morgan Stanley analyst David Risinger wrote May 30 that it's not possible to assess the valuation of either unit since Allergan does not disclose net revenues for women's health or infectious disease products, but cited a third-party estimate that the women's health business could attract a price higher than $5bn.

Risinger added that women's health brought in total product sales of $1.04bn in 2017, about 6.5% of Allergan's overall revenue, while infectious diseases yielded $257m, about 2% of the overall enterprise.

Should Allergan manage to sell off either unit or both, Saunders said the proceeds would be used both to reduce debt and buy back additional outstanding shares. The process to find buyers for the two businesses has been initiated, he added.

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ICER Says Amgen/Novartis' Aimovig Is Cost Effective

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The price for **Amgen Inc.**'s and **Novartis AG**'s first-in-class calcitonin gene-related peptide (CGRP) inhibitor *Aimovig* (erenumab-aooe), approved recently in the US for migraine headaches, won an endorsement from the Institute for Clinical and Economic Review (ICER) – at least in patients with chronic migraines who haven't been helped by older preventative therapies.

ICER released a revised assessment of CGRP inhibitor costs on May 31 based on Aimovig's list price of $575 per month, or $6,900 annually. The independent nonprofit evaluator of cost effectiveness estimated the biologic's net cost at $5,000 per year after rebates and discounts negotiated with payers, and said that was reasonable for the prophylactic treatment of patients who suffer from chronic migraine headaches and have not benefitted with other, mostly generic, drugs.

The FDA approved Aimovig on May 17 for migraine prevention in adults with a broad label, not restricting use based on whether patients experienced chronic migraines – 15 or more headaches per month – or episodic migraines, which is defined as 14 headaches or less per month.

ICER's revised analysis is not much changed from the first draft of its CGRP inhibitor analysis unveiled in April, which also said Aimovig and the competing candidate fremanezumab, from **Teva Pharmaceutical Industries Ltd.**, would be most cost effective for chronic migraine patients who have failed earlier lines of treatment.

However, the institute said on May 31, "following the announcement of erenumab's list price of $6,900 annually, ICER updated these analyses. Assuming a 27% discount reflective of typical rebates and discounts to reach a net price of $5,000, cost-effectiveness findings became substantially more favorable than in the draft report."

ICER maintained its position that the relative lack of clinical data for **Eli Lilly & Co.**'s galcanezumab makes it difficult to determine whether that CGRP inhibitor is a cost-effective migraine prophylaxis option. Both fremanezumab and galcanezumab are under FDA review with user fee dates later this year, though a manufacturing delay could give Lilly's product a slight lead over Teva's.

Evercore ISI analyst Umer Raffat said in a May 23 note that according to a conversation he had with Teva CEO Kare Schultz, a September approval decision now seems likely for fremanezumab, which is right around the time a decision is expected for Lilly's galcanezumab.

PRICE SET FOR SUCCESS?

Raffat also noted that Amgen's pricing strategy for Aimovig "has been very mature and is aimed at maximizing access. This is a good setup for the class."

The analyst was encouraged by the 255 prescriptions for Aimovig that IQVIA recorded during the product's first week on the market, he said in a June 1 note. Raffat said he got additional color from Amgen on negotiations with payers, which "are currently under way to ensure minimal utilization management criteria."

Specifically, he noted, most payers are expected to require patients to fail one to two prior therapies and to have tried a triptan, but they may not have to fail treatment with **Allergan PLC**'s neurotoxin *Botox* (onabotulinumtoxinA), which is approved for chronic migraine prevention.

Triptans are for acute treatment as on-demand therapy to reduce symptoms when a migraine strikes. In addition to Botox, ICER noted that three classes of generic medicines are frequently used off-label for migraine prevention: antidepressants, such as amitriptyline and venlafaxine; anti-seizure drugs, including divalproex, valproate and topiramate; and beta-blockers, including propranolol and metoprolol.

Amgen estimates that millions of patients have already failed these therapies and are eager to try something new. Mizuho Securities analyst Salim Syed said in a June 1 report about his recent interaction with Novartis that the US market for migraine prevention includes 3m patients on treatment and 2m-4m who have discontinued therapy. "Management noted that it is not looking to displace Botox and that the opportunity is not in taking away share from Botox, but to expand the migraine market as a whole," Sayed wrote.

The Coalition for Headache and Migraine Patients (CHAMP) issued a statement on May 31 welcoming the ICER endorsement and calling on "all stakeholders in health care to work together to ensure that the millions of Americans who endure the pain and disabling effects of migraine disease have full and unrestricted access to these life-changing medicines."

One issue to watch as Amgen negotiates with payers is whether any of its value-based or outcomes-based agreements will be tied to a reduction in the number of headache days patients experience each month or whether patients are able to cut the number of their headache days by 50% or more.

Key opinion leaders have suggested that the primary endpoint used in the CGRP inhibitor clinical trials – a reduction in the median number of headache days per month versus placebo – will be less important to patients and prescribers than the drugs' ability to cut headache days in half.

The median reduction in headache days per month versus placebo was one to three days across the CGRP inhibitor studies, but a significant number of migraine patients treated with the biologics saw their headache days cut by 50% and some reported a 75% reduction. That's important for a group of patients who experience frequent and severe disability when a migraine hits and have several of these headaches – each one lasting several hours to a few days – each month.

For a chronic migraine patient, cutting headache days from 15 monthly to seven or eight per month would be significant for the individual, their families and caretakers, and their employers, doctors have said. Aimovig cut headache days by 50% or more for 40% of episodic migraine patients treated with the drug in the Phase III ARISE trial.

"CGRP inhibitors appear to offer modest improvements in outcomes for patients with chronic migraine and frequent episodic migraine. For individuals for whom prior preventive therapies have not been effective or tolerated, the price of erenumab after expected discounts seems to align with those added benefits for patients," ICER Chief Medical Officer David Rind said.

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Novartis To Ape Aimovig's US Market Strategy In The EU As CHMP Gives Market Go-Ahead: https://bit.ly/2kNFP9e

Lilly Prices Olumiant For JAK Battle

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Eli Lilly & Co.'s *Olumiant* (baricitinib) faces a tough battle for market share in the US based on its FDA-approved label in rheumatoid arthritis, but the company priced its janus kinase (JAK) inhibitor at $25,000 per year in hopes of gaining sufficient traction among patients with few treatment options.

A 2 mg daily dose of the oral JAK1/2 inhibitor Olumiant was approved in the US on June 1 to treat adults with moderate to severe rheumatoid arthritis (RA) who have had an inadequate response to at least one tumor necrosis factor (TNF) inhibitor. Lilly's 4 mg dose was not approved, in line wirh the recommendation of FDA's advisory committee, which had concerns about the safety of the higher dose, including thrombosis – one of multiple risks flagged in a boxed warning on Olumiant's label. Read the full article here

Olumiant, which Lilly developed in partnership with **Incyte Corp.**, already is approved in about 40 ex-US markets and is available in those countries at both the 2 mg and 4 mg doses. It was the first JAK inhibitor approved in the EU.

Lilly Biomedicines President Christi Shaw confirmed to *Scrip* that the FDA approval for the 2 mg dose came ahead of the user fee date for Lilly's resubmitted new drug application (NDA); the original filing was met with a complete response letter in April 2017. She also said the company is talking to the FDA about a path to approval for the 4 mg dose.

Shaw noted that Olumiant's list price of $25,000 per year is 60% lower than the $60,000 cost – before rebates and discounts – for market-leading anti-TNF therapy *Humira* (adalimumab) from **AbbVie Inc.** It's also half the $50,000 list price for the first JAK inhibitor on the US market – **Pfizer Inc.**'s blockbuster *Xeljanz* (tofacitinib), which the FDA approved for RA six years ago.

"When we look at our pricing, most of it has to do with how do we make sure patients can access the innovative medicine," she said. "As we look at the United States of America, the immunology market is very unique compared to other therapeutic areas and in terms of different countries in how patients access new and innovative treatments."

"We're hoping to change the dynamic that exists today, by actually – as we talk to payers – collaborating with them," Shaw continued. "They've said this kind of list price reduction would actually warrant them to make it available to patients in the second line post-TNF just as it's indicated for."

That's important for the post-TNF patient population in RA, because they've run out of options, she noted, saying that "we don't want to have to make them jump through hoops to get Olumiant."

The executive referred to results from the Phase III RA-BEACON clinical trial showing that significant numbers of these severe RA patients, who were intolerant of or inadequate responders to TNF inhibitors, achieved at least a 20% reduction in RA symptoms, with some patients feeling the drug's effects on pain and function within the first week of treatment.

"Rather than approving Olumiant for methotrexate failures, FDA approved it as a later-line therapy for TNF failures. That being said, we expect minimal commercial impact, because we had assumed payers would restrict Olumiant access to TNF failures anyway," Morgan Stanley analyst David Risinger wrote on June 1. However, analysts said the drug's labeled indication and safety warnings could affect sales of Olumiant in the US as it attempts to go head-to-head with Pfizer's entrenched JAK inhibitor Xeljanz, which does not have a requirement that patients fail treatment with a TNF inhibitor.

Risinger pointed out that "Xeljanz's label states it is approved for patients with 'inadequate response or intolerance to methotrexate. It may be used as monotherapy or in combination with methotrexate or other non-biologic disease-modifying anti-rheumatic drugs' [(DMARDs)]."

Olumiant can be prescribed as a monotherapy or in combination with methotrexate and other non-biologic DMARDs, but it is not recommended for use in combination with other JAK inhibitors, biologic DMARDs or "potent immunosuppressants," such as azathioprine and cyclosporine.

Like Xeljanz, Olumiant labeling carries a boxed warning about the risk of serious infections and malignancies, but it does not have a warning about thrombosis. Serious infections leading to hospitalization or death have included tuberculosis and bacterial, invasive fungal, viral and other opportunistic infections; lymphoma and other malignancies also have been observed in Olumiant-treated patients. Deep venous thrombosis, pulmonary embolism and arterial thrombosis also have been reported in Lilly's trials, including some fatal thrombosis events.

Warnings also include the risk of gastrointestinal perforations, laboratory abnormalities, including neutropenia, lymphopenia, anemia, liver enzyme elevations and lipid elevations. Prescribers also are cautioned not to administer live vaccines to patients taking Olumiant. Upper respiratory tract infections, nausea, herpes simplex and herpes zoster were among the most common adverse events in Lilly's studies of the 2 mg and 4 mg doses.

Lilly and Incyte have agreed to conduct a randomized, controlled clinical trial to evaluate the long-term safety of Olumiant in RA.

"Xeljanz ... now has six years of post-market safety data, which is likely to prove more compelling to physicians than the newer Olumiant." Leerink analyst Geoffrey Porges wrote on June 1, adding that "the approval of only the 2 mg dose, which has inferior efficacy to the 4 mg dose, also eliminates the efficacy advantage over Xeljanz"

SAFETY IS IMPORTANT COMPETITIVE FACTOR

Safety will be a big factor for JAK inhibitors going up against the safety and efficacy experience that doctors have with Xeljanz, including Olumiant, AbbVie's upadacitinib and filgotinib, for which partners **Gilead Sciences Inc.** and **Galapagos NV** recently reported positive Phase II results in psoriatic arthritis.

"Of the JAK class, we expect Xeljanz to continue to increase share in first-line (pre-TNF), and anticipate AbbVie and Gilead's JAK1 inhibitors upadacitinib and filgotinib to corner the second-line market based on superior efficacy in that setting, but only if their higher doses are approved without similar thrombotic safety limitations," Leerink's Porges said. "Ultimately, this label means that Olumiant is likely to be restricted to salvage therapy only, and expect forecasts for the product to decline even further (Lilly consensus remains >$1bn)."

Morgan Stanley's Risinger projected $500m in Olumiant sales in 2023, including the current RA and future atopic dermatitis indications.

Shaw said Lilly will make Olumiant available in the US as soon as possible.

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Pfizer's Xeljanz Pushed By New Tailwind From Approval In Ulcerative Colitis

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Pfizer Inc. has secured fertile new commercial ground for its blockbuster rheumatoid arthritis drug *Xeljanz* (tofactinib) with an expanded US FDA approval in patients with moderately to severely active ulcerative colitis.

The FDA approved the janus kinase (JAK) inhibitor Xeljanz for the indication May 30 as expected, following an unanimously positive recommendation from the agency's Gastrointestinal Advisory Committee in March.

Xeljanz will be the first oral option on the market to treat moderate and severe forms of the chronic inflammatory bowel disease, which affects more than 900,000 patients in the US. Pfizer has described ulcerative colitis as a $5bn opportunity in the seven major global markets. Oral dosing could give Xeljanz an important point of differentiation in a crowded market for ulcerative colitis therapies.

The mainstay treatments for moderate to severe ulcerative colitis are the anti-TNF biologics, including *Humira* (adalimumab), *Remicade* (infliximab) and *Simponi* (golimumab). **Takeda Pharmaceutical Co. Ltd.**'s *Entyvio* (vedolizumab) was approved in 2014 for ulcerative colitis patients who are intolerant or have inadequate response to or relapse after taking a TNF-targeting therapy or immunomodulator, or who have inadequte response to or are intolerant to corticosteroids. It has grown into an important blockbuster for the Japanese pharma.

Adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids:

Oral aminosalicylates, including **Allergan PLC**'s now-generic *Asacol* (mesalamine), also are approved for ulcerative colitis, but only for mild and moderate forms of the disease. However, several more drugs are in the pipeline for moderate to severe ulcerative colitis, including new oral therapies. *(Also see "New Agents To Invade UC Market As Biosimilars Put Pressure On Stalwarts" - Scrip, 7 Sep, 2017.)*

Use of Xeljanz isn't restricted to treatment after TNF inhibitors or to those intolerant them, which could be another benefit for Pfizer's drug. The labeling does include a "Limitations of Use" that says Xeljanz is not recommended in combination with other biological therapies for UC or when potent immunosupressants like azathioprine and cyclosporine are used.

Xeljanz was approved for UC at both the 5 mg dose and the higher 10 mg dose, which also is a win for Pfizer. Labeling recommends dosing at 10 mg twice daily for at least eight weeks, followed by 5 mg or 10 mg twice daily after. "Discontinue after 16 weeks of 10 mg twice daily, if adequate therapeutic benefit is not achieved. Use the lowest effective dose to maintain response," it states.

The FDA's advisory panel had some concerns with the safety of the 10 mg dose, but didn't want to limit the use of the high-dose solely to TNF-failure patients in labeling, citing concerns that payers might take that language as a mandate to require TNF drugs be used first.

THIRD INDICATION FOR XELJANZ

Ulcerative colitis is the third US indication for Xeljanz, originally approved in November 2012 as the first oral, next-generation, disease-modifying drug for the treatment of rheumatoid arthritis. Pfizer gained a second indication for Xeljanz to treat psoriatic arthritis in November 2017.

Sales of Xeljanz were slow initially, with physicians and patients concerned about the safety of the new drug, including the risk of malignancy and serious infections that can lead to death, but physicians have grown more comfortable after years of experience. The launch disappointed investors, but the drug has snowballed into a blockbuster that continues to grow at double-digit rates. Now, Xeljanz represents how pharma companies can build blockbuster brands over time in crowded, challenging commercial markets. *(Also see "Pfizer's Xeljanz: The Slow Road To Blockbuster Status" - Scrip, 4 May, 2017.)*

Sales of Xeljanz totaled $1.35bn in 2017, growth of 47%. Xeljanz only received approval in Europe last year as well, another growth platform for the brand.

The latest approval was based on the results of three Phase III clinical trials, including two eight-week, placebo-controlled trials that demonstrated the 10 mg dose of Xeljanz given twice-daily induces remission in 17% to 18% of patients by week eight. In a trial in patients who achieved a clinical response by week eight, Xeljanz at 10 mg or 5 mg was effective in inducing remission by week 52 in 41% and 34% of patients, respectively.

Pfizer has another tailwind blowing in its favor too when it comes to Xeljanz. **Eli Lilly & Co.** is gearing up to launch its own oral JAK inhibitor in the US for rheumatoid arthritis, baricitinib, but safety risks, including the risk of thrombosis, led an FDA advisory panel to recommend limiting use to later lines of treatment or approving only the lower, less-effective dose. *(Also see "Lilly May Need To Reassess Baricitinib Market After FDA Advisory Committee" - Scrip, 24 Apr, 2018.)*

Following behind both companies, **AbbVie Inc.** plans to submit its Phase III JAK1 inhibitor upadacitinib for FDA approval in rheumatoid arthritis later this year and has Phase II and III studies under way in several other indications, including ulcerative colitis.

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All Over For AZ's Fasenra In COPD

AstraZeneca PLC's slim hopes that its asthma drug *Fasenra* (benralizumab) could have a future as a treatment for chronic obstructive pulmonary disease have been dashed with the failure of a second Phase III trial in the space of just three weeks.

The company has announced top-line results from the TERRANOVA trial which reveal that Fasenra did not meet the primary endpoint of a statistically significant reduction of exacerbations in patients with moderate to very severe COPD. The study is part of VOYAGER, which AstraZeneca had touted as the largest COPD biologics development program in the world with close to 4,000 patients.

The news follows the failure, reported May 11, of a similar trial, GALATHEA, which also missed the same primary endpoint. Both trials were evaluating the interleukin-5 inhibitor as an add-on to dual or triple inhaled therapy compared with placebo in patients with a history of exacerbations across a range of baseline blood eosinophils.

Although AstraZeneca has not definitively pulled the plug on Fasenra for COPD, and a full evaluation of the data from the two studies is ongoing, the company said it did not currently intend to make a regulatory submission.

Chief medical officer Sean Bohen acknowledged in a statement that the results were "disappointing because uncontrolled COPD patients already on dual or triple inhaled therapy need new treatment options." AstraZeneca noted that about 30-40% of moderate to severe COPD patients on triple inhaled therapy remain uncontrolled and continue to experience exacerbations.

Expectations for TERRANOVA were fairly low following the disappointment of GALATHEA. However, Eric Le Berrigaud at Bryan Garnier issued an investor note on May 30 saying that the failures were "surprising" because **GlaxoSmithKline PLC**'s rival severe asthma drug *Nucala* (mepolizumab), an IL-5 antagonist, had shown some benefit in COPD.

kevin.grogan@informa.com, 30 May 2018

Big Launch Year Coming Up In US For Sun But Spends High Too

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It's going to be a relatively big launch year for **Sun Pharmaceutical Industries Ltd.**, with expenses also moving upwards in tandem as India's top-ranked drug firm gets set to introduce three specialty products – *Ilumya* (tildrakizumab), *Yonsa* (abiraterone acetate), and *OTX-101* (cyclosporine A, ophthalmic solution 0.09%) – on the US market.

Management commentary around Ilumya and Yonsa was encouraging, but specifics around strategy or pricing outlook were minimal.

"FY19 will mark the crossing of some important milestones in our specialty journey. We plan to commercialize Ilumya, OTX-101 and Yonsa in the US market in FY19 and hence will have to incur significant expenses for these important launches," Dilip Shanghvi, Sun's founder and managing director, said on an earnings call May 25, post market hours.

The Sun boss also referred to plans for additional clinical trials for a new indication of Ilumya, an IL-23p19 inhibitor. Ilumya is expected to directly take on **Johnson & Johnson**'s first-in-class IL-23 blocker, *Tremfya* (guselkumab), in a rather crowded psoriasis market.

Yonsa, a novel formulation in combination with methylprednisolone, for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) is expected to be commercialized in the current quarter in the US, while launch preparations for Ilumya have commenced and Sun expects to introduce the product in Q2 FY19. OTX-101 will be commercialized in FY19.

YONSA, ILUMYA OUTLOOK

Shanghvi said that Yonsa could be "an interesting product" and that it was a step towards building the company's specialty business in oncology. Sun also expects to continue to "evaluate opportunities" in the specialty segment to further enhance this business, though it's unclear if this specifically entails any near-term acquisition of assets in the space.

Sun Pharma had acquired Yonsa from Churchill Pharmaceuticals, which is entitled to upfront and sales-linked milestone payments, and royalties on sales from Sun for the product.

The Sun management was, however, sparing in sharing its outlook on Yonsa vis-à-vis Johnson & Johnson's *Zytiga* (abiraterone) except for referring to a comparative study between Yonsa and Zytiga. Sun said the label that "finally came" had yet to be "completely" studied by it and that it needed to be clear on "patent and legal matters" before sharing comparative specifics. *(Also see "The Most Successful Oncology Launches Of A Decade" - Scrip, 28 Feb, 2018.)*

On Ilumya, Sun's CEO (North America) Abhay Gandhi said that he expects IL-23 as a class to continue to gain share.

"Every patient would like to be clear of psoriasis and sustainably at that; doctors are accepting the use of IL-23 as part of the treatment modality. I think that class will continue to grow," Gandhi said. *(Also see "Sun Builds On Psoriasis Data But Can It Hold In Crowded Space?" - Scrip, 3 Apr, 2017.)*

KOL response too appears to be encouraging to the IL-23 class.

"When I speak to the KOLs, what I understand from them that where they see a clinic difference is, I think the quality of the response, and with the side effects being much lower than what they see with the other class of drugs," Gandhi added in response to an analyst's query on the benefits of IL-23 in general over IL-17 inhibitors.

Prominent IL-17 inhibitors that Ilumya goes up against include **Novartis AG**'*Cosentyx* (secukinumab) and **Eli Lilly & Co.**'s *Taltz* (ixekizumab), though anti-TNFs like **AbbVie Inc.**'s *Humira* (adalimumab), J&J's *Remicade* (infliximab) and **Amgen Inc.**'s *Enbrel* (entanercept) have long been around.

HDFC Securities said that although the top line guidance for FY19 "looks achievable", there are several headwinds for margin improvement including declining profits of Taro (an arm of Sun), the higher R&D (8-9% of sales) and increased marketing spend for specialty products like Ilumya and Yonsa, among others.

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Real-World Data Helping To Drive Rise Of Novartis' Heart Failure Drug Entresto

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After getting off to an extremely slow start, sales of **Novartis AG**'s heart failure drug *Entresto* (sacubitril/valsartan) are rocketing and the Swiss major has presented more real-world data that it hopes will convince physicians and payers even more about the benefits of the therapy.

Interim findings from the CHAMP-HF registry have been unveiled at the European Society of Cardiology Heart Failure congress in Vienna, in a study that is assessing short-term, health status benefits in chronic heart failure patients with reduced ejection fraction (HFrEF) of Entresto in real world US clinical practice. The analysis showed statistically significant improvement in health status as measured by the 12-item Kansas City Cardiomyopathy Questionnaire.

The questionnaire is a self-administered tool for patients with heart failure which looks at four domains: physical limitation (showering/bathing, walking one block on level ground, hurrying or jogging), symptom frequency (shortness of breath, fatigue and swelling of the feet, ankles and legs), social limitation (hobbies/recreational activities, working/doing household chores, visiting family/friends out of the home) and quality of life (impact on lifestyle and satisfaction of spending rest of life with current HF status). Read the full article here

Patients on Entresto scored numerically higher on all domains, notably in symptom frequency and quality of life, and the proportion of patients with a large improvement in overall score (defined as a greater than 20-point improvement from baseline) was 21.4% (78 out of 365 patients) for those on Entresto vs. 12.5% (91 out of 730 patients) for those not taking the drug.

Shreeram Aradhye, chief medical officer for Novartis Pharmaceuticals, told *Scrip* the fact that the interim analysis from CHAMP-HF was accepted as a late-breaker at the congress in Vienna "is an indirect indicator of what the heart failure community thinks of the importance of this real-world data." The drug was first approved in the US in July 2015 to much fanfare on the back of stellar results from the landmark PARADIGM-HF study and "having delivered an amazing drug" that in clinical trials showed a reduction in risk of cardiovascular death and heart failure hospitalization in HFrEF patients, he said that "we are now filling in the colors with additional data showing quality of life benefits in clinical practice."

Taking the real world route is a key approach that has been adopted by Novartis following the lackluster launch of Entresto. Sales for its first full year on the market – 2016 – were $170m, $30m shy of the company's own forecast. *(Also see "Novartis' Late Bloomer Entresto Leads Take-Off Of Heart Failure Market" - Scrip, 29 Jan, 2018.)*

However, the turnaround in Entresto's fortunes has been eye-catching, after Novartis spent very heavily to build up its sales and marketing effort in the US. Revenues soared 138% year-on-year to $200m in the first quarter, due to increased adoption by physicians both in the US, where new-to-brand prescriptions (NBRx) reached an all-time high in the quarter, and the rest of the world.

Aradhye told *Scrip* that getting new drugs into practice was usually a long drawn out process, with some observers arguing that it can take up to 15 years for new innovations to become standards of care. It would appear to be particularly challenging to change prescribing habits in chronic heart failure, given that physicians have been treating patients with cheap angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for many years. *(Also see "Entresto Facing Pressure From Diabetes Drugs" - Scrip, 15 May, 2017.)*

Although physicians "love the data from PARADIGM," he said, they wanted to see "a flow of evidence to inform clinical practice," which is where real-world data comes in to help them with their decision making in treating people who are living with a chronic condition.

The CMO noted that Novartis had established FortiHFy, the largest global clinical program in the heart failure disease area across the pharma industry to date. It comprises over 40 active or planned studies and as for CHAMP-HF, the registry has enrolled approximately 5,000 patients from 150 US sites.

PAY-FOR-PERFORMANCE PACTS'

Entresto is now meeting expectations and the Basel-based company's confidence in the angiotensin receptor blocker/neutral endopeptidase (ARB/NEP) inhibitor is highlighted by the multiple outcomes-based contracts signed for Entresto in the US. These pay-for-performance agreements with big insurance companies such as Aetna, Cigna, Humana and Harvard Pilgrim, tie the cost of Entresto to a measurable resource utilization endpoint of reduction in hospitalization, which was used as a primary endpoint in the PARADIGM trial.

In Europe, Datamonitor Healthcare analyst Louisa Joseph noted in a recent report that Entresto's initial prescription had been restricted to specialist hospital physicians in Germany, Italy, the UK, and in certain regions in Spain. She added that this was "likely due to the drug's high cost in comparison to generic ACE inhibitors, the complicated titration process, and expected tolerability issues within the first few months of treatment."

These restrictions are likely to considerably reduce the uptake of Entresto, as many stable HF patients are frequently treated in the primary care setting, Joseph wrote. However, payers surveyed by Datamonitor Healthcare value Entresto's demonstrated ability to reduce time to first heart failure hospitalization in PARADIGM, she claimed, and real-world evidence showing this as well as improvements in quality of life will lead to continued uptake.

However, in order to get to Novartis's target peak sales figure of $5bn, much rides on other indications than HFrEF. This is why analysts are keeping a close eye on the PARAGON-HF study, which is examining the efficacy of Entresto in patients with preserved ejection fraction.

The market opportunity for the latter is similar to HFrEF and Aradhye told *Scrip* that PARAGON was on schedule for a 2019 data read-out.

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Novo's Oral Semaglutide Passes PIONEER 2, But Weight Loss Result A Bit Disappointing

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Novo Nordisk AS's once-daily, oral version of the GLP-1 agonist semaglutide demonstrated superior blood sugar lowering in the Phase III PIONEER 2 study, which tested the drug against **Eli Lilly & Co./Boehringer Ingelheim GMBH**'s SGLT-2 inhibitor *Jardiance* (empagliflozin), while falling a bit short on weight loss and carrying nausea as a common side effect.

The Phase III PIONEER program includes 10 studies in type 2 diabetes and Novo plans to report results from all of them this year, potentially paving the way for an oral semaglutide filing in 2019 and launch in 2020 (*see graphic*). The company announced positive results from the PIONEER 2 study, the second pivotal trial, on May 29, following a positive release for PIONEER 1 in February. *(Also see "Novo Nordisk's Oral Semaglutide Succeeds In First Phase III, But Prompts Questions" - Scrip, 22 Feb, 2018.)* Novo launched *Ozempic*, the subcutaneous injectable formulation of semaglutide, in the first quarter and has reported good initial uptake, with 50% access in the US. *(Also see "Novo Nordisk: Switch To Weekly Ozempic Has Begun, Biopharma M&A Sought" - Scrip, 2 May, 2018.)*

The company is positioning its oral semaglutide as a competitor to oral classes – DPP-4 and SGLT-2 inhibitors in particular – for patients at an earlier stage of diabetes. To compete, it must offer enough of an improvement in blood sugar lowering compared with more established oral classes in terms of weight loss, a strength for SGLT-2 inhibitors, and tolerability.

SUPERIOR BLOOD-SUGAR LOWERING

All three doses of oral semaglutide tested in the earlier PIONEER 1 study showed superior blood sugar lowering versus placebo, but only the highest dose showed significant and superior weight loss versus placebo in an intent-to-treat (ITT) analysis. The ITT group included all participants in the study, not just those who completed treatment, which is the evaluation typically favored by the US FDA.

PIONEER 2 is an open-label study that tested the safety of a 14 mg daily dose of oral semaglutide versus 25 mg of Jardiance in 816 patients with type 2 diabetes inadequately controlled by metformin.

The primary endpoint was blood sugar lowering after 26 weeks of treatment and results were analyzed in two ways – using an ITT approach as the primary statistical analysis as well as an evaluation of those who completed treatment and did not need rescue medication.

WEIGHT LOSS DIFFERENCE NOT SIGNIFICANT AT 26 WEEKS

Novo Nordisk released more information for the patients who completed treatment than for the ITT group and Credit Suisse analyst Rebekah Harper observed in a May 29 note that the completer analysis is directly comparable to competing products.

In the primary, intent-to-treat analysis, the drug demonstrated superior lowering of hemoglobin A1c (HbA1c) versus empagliflozin. However, the difference in weight loss at that point was not statistically significant.

In the analysis of those who completed the study, there was a reduction in HbA1c of 1.4% at 26 weeks and 1.3% at 52 weeks versus 0.9% and 0.8%, respectively, for Jardiance, Novo reported.

For the completer analysis, 72% on oral semaglutide reached targets established by the American Diabetes Association versus 47% for Jardiance after 52 weeks of treatment.

Also in the completer analysis, patients on oral semaglutide lost 4.2 kg and 4.7 kg at 26 and 52 weeks, respectively, versus 3.8 kg at both 26 and 52 weeks for Jardiance. This was a significant difference at 52 weeks, but not 26 weeks.

Bernstein Research analyst Wimal Kapadia said in a May 29 note that given FDA's guidelines require use of the primary statistical evaluation at 26 weeks, to account for patients who dropped off the study and moved on to other treatment, the weight loss superiority is unlikely to be on the product label.

"We still struggle with the primary methodology from FDA. If patients on the Jardiance arm moved to injectable GLP-1s and patients in the oral [semaglutide] arm moved to insulin, data will be skewed negatively. The EU label will be more flexible and closer to the secondary analysis methodology," Kapadia said.

ISI Evercore analyst Umer Raffat observed on May 29 that empagliflozin's weight loss effect was bigger than expected though it plateaued at week 26, whereas it continued with oral semaglutide. Empagliflozin's performance could be due to the trial protocols around fasting, the analyst suggested.

Novo Nordisk also reported that oral semaglutide was "well-tolerated and with a profile consistent with GLP-1-based therapy."

The most common adverse event for oral semaglutide was mild-to-moderate nausea, which was reported in 20% of patients on oral semaglutide. The treatment-related dropout rate was 11% for semaglutide versus 4% for Jardiance.

In PIONEER 1, the rate of nausea in the highest dose tested – 14 mg – was 16%. The dropout rate for the treatment arms ranged from 2% to 7% for oral semaglutide versus 2% for placebo.

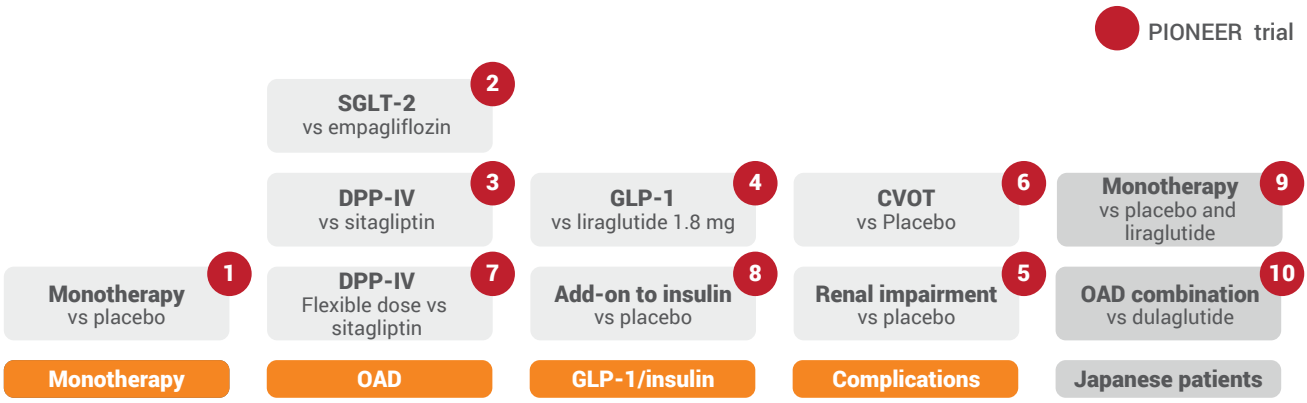
MORE PIONEER STUDIES AROUND THE CORNER

Overall, the pivotal PIONEER program includes 8,845 patients and multiple readouts this year.

The PIONEER 3 and PIONEER 4 studies test oral semaglutide against **Merck & Co. Inc.**'s DPP-4 inhibitor *Januvia* (sitagliptin) and Novo's daily injectable GLP-1 *Victoza* (liraglutide), and results from those comparative studies are expected in the second quarter. The PIONEER 7 flexible dose escalation study is also due to report in that time frame.

ISI Evercore analyst Raffat said that the real question ultimately is how well oral semaglutide performs in the "all important" PIONEER 4 study against Victoza. Based on Phase II data it doesn't appear to be 100%

PIONEER program for oral semaglutide investigates the entire treatment cascade



SGLT-2: Sodium-glucose co-transporter-2; DPP-IV: Dipeptidyl peptidase-4; OAD: Oral anti-diabetic; CVOT: Cardiovascular outcomes trial

locked in that the weight loss profile will be comparable to Victoza, Raffat said.

NAUSEA, TIME TO SIGNIFICANT WEIGHT LOSS ARE CONCERNS

Credit Suisse's Harper said that while the overall results from PIONEER 2 are solid, questions around nausea and discontinuation rates, as well as the fact that it took 52 weeks for oral semaglutide to separate from Jardiance on weight loss "may limit some enthusiasm for the data" and come as a relief to Lilly investors concerned about the competitive risk.

Harper also noted that the somewhat higher rate of nausea in PIONEER 2 versus PIONEER 1 was a "slight concern."

It also will be important to monitor the discontinuation rates in future PIONEER trials, because if they are higher than the second study reported, "there could be a commercial/payer risk, in our view," Harper wrote.

Bernstein's Kapadia, however, said the side effect profile is in line with or superior to injectable GLP-1s and shows that the dose titration schedule for the drug is working.

The difference in weight loss at week 52 was modest and it would be useful to have more details on the results to make sure nausea did not contribute substantially to this result or to the A1c reduction, Pharma Intelligence analysts from Biomedtracker and Datamonitor said in a May 29 report about the PIONEER 2 data.

"More details are needed on rates of vomiting in the trial, and it will be important to see once the drug is approved that physicians in the real world do not find a higher rate of nausea or feel tolerability issues are too much of an issue to use the drug earlier in the treatment paradigm," the Pharma Intelligence analysts wrote.

Overall, Pharma Intelligence analysts see the PIONEER 2 data as strong and supportive of potential uptake of oral semaglutide, but they also noted that the drug needs to be taken while fasting in order to be orally absorbed. It's possible, they noted, that efficacy may not be as strong in clinical practice, although the half-life is long, so Novo does not believe lapses in fasting would have a big effect.

Convenience of dosing – including when patients must take their pills – is important, since established injectable GLP-1 inhibitors are more effective than DPP-4 and SGLT-2 inhibitors, but are viewed to have less convenient administration than oral therapy.

Evercore ISI analyst Raffat has previously noted the challenges in making an oral version of semaglutide, observing that Novo's studies for the pill form of its GLP-1 agonist have strict criteria for use, including the amount of water intake needed with the drug and instructions on fasting. Oral semaglutide must be taken in the morning 30 minutes prior to eating, which is not necessarily convenient for a chronic therapy.

> 'It will be important to see once the drug is approved that physicians in the real world do not find a higher rate of nausea or feel tolerability issues are too much of an issue'

Semaglutide requires a large amount of protein to be delivered through the gut, so tolerability and adherence have been under scrutiny. The company is developing a next-generation oral version of the drug that would be easier to manufacture. *(Also see "Novo Nordisk Already Plans A 'Next Generation' Oral Semaglutide - CEO" - Scrip, 8 Mar, 2018.)*

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Almirall CEO Guenter Plots 'Play To Win' Future

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Peter Guenter has just finalized his five-year plan for **Almirall SA** after taking time to understand the company in his first seven months as CEO. In his first exclusive interview since joining the company, he tells *Scrip* about his vision for the dermatology-focused, family-controlled Spanish company.

When Guenter's appointment was announced, Almirall was reeling from damaging developments in its US business which had dragged down its sales and earnings and forced it to lower its financial guidance for 2017. Not only had generic competition struck the antibacterial *Acticlate* (doxycycline hyclate), an important product in the US, but its Aqua Pharmaceuticals business there (now renamed Almirall US and under new management) was hit by inventory destocking and wrongful use of its patient assistance programs by some pharmacies, and the ThermiGen aesthetics business, acquired in 2016, was also under-performing. *(Also see "Almirall Knocked Back By US Woes, Could Affect Other Companies Too" - Scrip, 10 Jul, 2017.)*

The former president of **Sanofi**'s diabetes and cardiovascular business unit took the helm at Almirall in October 2017. By mid-November 2017, when the company announced a delay in the expected European approval of its psoriasis drug tildrakizumab, the firm's share price had sunk to €7.56, down from €16.60 only six months earlier, before the US revelations broke. Since then, however, Guenter has overseen a gradual but important recovery, with the share closing at €11.55 on May 21, 2018, a few days after Almirall unveiled first-quarter results that beat analyst expectations.

Guenter's plan for Almirall's recovery sees the US business put on the backburner for the time being, even if he recognizes the importance of the US market for the future. Instead, the focus is on building a strong franchise in dermatology in Europe and having a more robust attitude to the competition.

"I come with a vision of thinking bigger," he told *Scrip*. "I want to change the culture in the company to be bolder, to instill a confidence in the teams. We have good assets and we should not be shy."

Peter Guenter

'I want to go from 'play to play' to 'play to win''

High on his list of priorities is to "beef up some capabilities," being bolder and more ambitious, and smooth the transition and collaboration between the commercial and R&D teams at Almirall. "People are well organized in terms of interaction," he noted, "but sometimes lacking in ambition and thinking big. Great assets drive great franchises. I want us to go from 'play to play' to 'play to win'."

He went on: "I'm also in the final phase of looking very deeply at a strategic refresh. We need to be bolder on the level of innovation, both in R&D and commercially." This will involve developing more new chemical entities, and potentially repositioning molecules from other therapeutic areas. But incremental change like tweaking concentrations and reformulating existing products for the same disease will be an increasingly "challenging" strategy for companies, he warned.

Like many executives who move from big pharma to smaller firms, Guenter appreciates the ability to make decisions faster in his new role. He is also appreciative of Almirall's ownership structure, which sees around two-thirds of its shares controlled by the Gallardo family who founded the firm in 1943. "The current chairman [and former CEO Jorge Gallardo Ballart] is totally involved and committed to the company," he pointed out.

Aside from its size and family ownership, what makes Almirall "unique", Guenter said, is that it comes with "a fully-fledged portfolio and a commitment to dermatology."

PSORIASIS RANGE

In particular, Almirall is building out a range of products for psoriasis, adding to its established topical treatment offering typically used in first-line treatment (for example, the vitamin D analog *Curatoderm* (tacalcitol)) with potentially more lucrative products for moderate to severe disease: first with the oral systemic treatment *Skilarence* (dimethyl fumarate) and ultimately with the injectable biologic interleukin-23 inhibitor tildrakizumab, which Guenter expects will beat class rival risankizumab (from **Boehringer Ingelheim GMBH** and **AbbVie Inc.**) to become the second anti-IL-23 approved in Europe after Janssen's *Tremfya* (guselkumab). He anticipates approval by late 2018 or early 2019.

Skilarence is performing strongly in its roll-out in initial European markets following EU approval in June 2017. The first oral fumaric acid ester product to be licensed by the European Medicines Agency, Almirall says it has now taken 50% of the sales by volume of **Biogen Inc.**'s *Fumaderm* (fixed dose dimethyl fumarate and other fumaric acid esters) in Germany, the only country where such a treatment is currently registered for moderate to severe plaque psoriasis. The product is also performing well in the UK, with the Netherlands coming soon. Later this year it will be rolled out to Southern European territories including Spain and Italy, where unlike in Northern Europe there is no previous experience of using fumaric esters to treat the condition, which means the uptake is likely to be more gradual. *(Also see "Almirall To Position Oral DMF For Psoriasis Ahead Of EU Biologics Use" - Scrip, 24 Apr, 2017.)*

"It's priced very responsibly, and significantly below [**Celgene Corp.**'s] oral treatment *Otezla* [apremilast], so all over Europe we will have market access possibilities versus Otezla," said Guenter. On its IL-23 inhibitor, noting that treatments cannot be

compared outside of head-to-head studies, Guenter nonetheless highlights that tildrakizumab is dosed every three months versus Tremfya's two-monthly schedule. The product will also be up against **Novartis AG**'s strongly performing anti-IL-17 product *Cosentyx* (secukinumab) and **Eli Lilly & Co.**'s rival IL-17 inhibitor *Taltz* (ixekizumab). "You could say that IL-17s show faster onset of action, but psoriasis is a lifelong condition and durability, ease of use and long-term safety is more important," he said. "At the American Association of Dermatology meeting we published two-year safety data for tildrakizumab, and we will have longer data by launch."

Data aside, Guenter believes Almirall has an advantage because of its focused commitment to dermatology, a therapeutic area in which selling products relies heavily on establishing good connections with physicians.

"We are an outlier in the market in that we have a portfolio of products. Some of our competition comes to psoriasis from immunology, whereas we're rooted in dermatology, which is a very relationship-driven community. Our R&D engine is entirely dermatological, and that is important: it demonstrates that we are here to stay, and we are focused." Guenter believes that Almirall is in a position to build a strong relationship with dermatologists based on this total dedication to their area.

As the company prepares for the hoped-for approval of tildrakizumab, Guenter admitted the pricing landscape in Europe for novel antipsoriatic biologicals was "a moving target", with Tremfya only recently launched and Eli Lilly having recently adapted its pricing of Taltz in Germany. He said he was still working on the pricing strategy, but underlined that "Almirall has a reputation of pricing responsibly and competitively."

FUTURE PRODUCTS

Guenter has worked with Almirall's head of R&D Bhushan Hardas – who joined in May 2017 after previously heading **Allergan PLC**'s dermatology and aesthetics R&D – to review the company's pipeline portfolio. That resulted in a Phase III program (P3073) in nail psoriasis "which did not meet our criteria for continued development" being stopped and the company's P3058 Phase III onychomycosis program being focused "only on Europe because of the changing market environment," with US trials halted. Guenter acknowledged the now pruned pipeline was "looking a little bit empty" and that the company therefore "needs to get serious about late-stage in-licensing, as well as focus on its own R&D in preclinical and be more ambitious with the level of innovation we want to achieve.

> 'Our R&D engine is entirely dermatological, and that is important: it demonstrates that we are here to stay, and we are focused'

"We are agnostic on invented here or not invented here," he explained, citing the December 2017 addition of the actinic keratosis candidate KX2-391 from **Athenex Inc.** for which Phase III results are expected in the third quarter of 2018 as an example of an externally sourced future growth driver (with peak sales potential of at least €250m). "This is a potential game changer for a condition in which current treatments are limited either by local skin reactions which can lead to discontinuation, or otherwise low efficacy."

DEALS AHEAD?

"Further in-licensing of late stage assets is a very high priority," he said, and M&A is also on the cards.

"The good news is that the company has virtually no debt post the **AstraZeneca PLC** transaction [when the latter acquired Almirall's respiratory franchise for $900m plus up to $1.22 billion related to development, launch, and sales-related milestones milestones of $1.22 billion and royalties (not disclosed)]." *(Also see "Flush with AZ cash, Almirall seeks dermatology assets" - Scrip, 30 Jul, 2014.)*

"We have the firm intention to do a deal if the right opportunity arises, if it is immediately accretive and increases our critical mass in the big five European countries and the US," Guenter declared. "But we need the right opportunity in dermatology, and the right price." He revealed that he has been screening "lots of opportunities" but noted "even with the right appetite we will be disciplined."

On a separate front, the company has a "second leg" in its home country: it sells a wider range of products in Spain where its footprint is more significant, particularly in cardiovascular and diabetes. One recent addition that immediately added to its top and bottom lines was AstraZeneca's statin *Crestor* (rosuvastatin), and the firm has capacity for more such deals "which we can integrate at marginal cost."

Further afield, Almirall's business in emerging markets, where it operates through distributors, are performing well, growing at more than 15% in the most recent quarter.

In the longer term, the US should play a role again: the key milestone there will be the launch of the actinic keratosis product, slated for 2021 should all go to plan. "That is our bridge to the future for a more differentiated product platform in the US. But for us in the US right now, the name of the game is to keep our foot in the door. We want to increase critical mass there, but for now the real growth driver will be Europe."

Guenter concludes: "We've just finalized our five-year plan. As a standalone company, we have what it takes for good growth rates. But M&A would accelerate this growth even more. I'm confident, when we look back in five years' time from now, that we'll have brought Almirall to the next level."

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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

Selected clinical trial developments for the week 25–31 May 2018

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
PHASE III RESULTS PUBLISHED			
Bristol-Myers Squibb Co.	*Opdivo* (nivolumab) plus ipilimumab	non-small cell lung cancer (NSCLC)	CheckMate-227; the *NEJM*, May 31, 2018.
Gilead Sciences Inc.	*Vosevi* (sofosbuvir, velpatasvir, voxilaprevir)	hepatitis C	POLARIS-1; *The Lancet Gastroenterology & Hepatology*, May 30, 2018.
Northwest Biotherapeutics Inc.	*DCVax* (autologous dendritic cell vaccine)	glioblastoma	Interim survival data; *Journal of Translational Medicine*, May 29, 2018.
PHASE III INTERIM/TOP-LINE RESULTS			
Novo Nordisk AS	semaglutide, oral	diabetes, type 2	PIONEER 2; improved HbA1c, showed weight loss.
Roche	*Tecentriq* (atezolizumab) with chemo	NSCLC, non-squamous	IMpower 130; met overall survival and PFS endpoints.
Shenzhen Chipscreen Biosciences Ltd.	*Epidaza* (chidamide)	breast cancer, advanced	Met primary PFS endpoint.
AstraZeneca PLC	*Fasenra* (benralizumab)	chronic obstructive pulmonary disease	TERRANOVA; missed primary endpoint.
Johnson & Johnson	esketamine, nasal spray	depression, treatment-resistant	SUSTAIN-1, 2; well tolerated, delayed relapse in two long-term safety studies.
Kissei Pharmaceutical Co. Ltd.	KPS-0373	spinocerebellar ataxia	Negative efficacy results.
Astellas Pharma Inc./ FibroGen Inc.	roxadustat	hemodialysis dependent chronic kidney disease	Met primary endpoint, fourth Japan Phase III study.
UPDATED PHASE III RESULTS			
Advicenne SA	ADV7103	distal renal tubular acidosis	Effective and well tolerated.
AstraZeneca PLC	*Imfinzi* (durvalumab)	NSCLC, stage III	PACIFIC; improved overall survival.
DBV Technologies SA	*Viaskin Peanut*	peanut allergy	PEPITES, OLFUS-VIPES; desensitization observed.
Aimmune Therapeutics Inc.	AR101	peanut allergy	PALISADE; efficacy across ages.
ImmuPharma PLC	Lupuzor (rigerimod)	systemic lupus erythematosus	Subgroup analyses.
PHASE III INITIATED			
Kyowa Hakko Kirin Co. Ltd./ Reata Pharmaceuticals Inc.	bardoxolone methyl	diabetic nephropathy	AYAME; taking place in Japan.
PHASE III ANNOUNCED			
Glycomimetics Inc.	GMI-1271	acute myeloid leukemia	In older adults.
Orphazyme AS	arimoclomol	amyotrophic lateral sclerosis	An 18-month study.
PHASE II INTERIM/TOP-LINE RESULTS			
Reata Pharmaceuticals Inc.	bardoxolone methyl	polycystic kidney disease	PHOENIX; improved renal function.
ARCA biopharma Inc.	*Gencaro* (bucindolol)	atrial fibrillation/ flutter in heart failure	GENETIC-AF; signs of efficacy.
DBV Technologies SA	*Viaskin Milk*	milk allergy in children	Symptoms improved, well tolerated.
Achillion Pharmaceuticals Inc.	ACH-4471	C3 glomerulopathy	Alternative pathway hyperactivity reversed.
Clearside Biomedical Inc.	*Zuprata* (triamcinolone acetonide), supra- choroidal	diabetic macular edema	TYBEE; improved visual acuity.
Gilead Sciences Inc./ Galapagos NV	filgotinib	psoriatic arthritis	EQUATOR; well tolerated, symptoms improved.

Source: Biomedtracker

J&J Muscles Into CAR-T Field: Initiates Myeloma Studies

JOHN DAVIS john.davis@informa.com

Janssen Pharmaceutical Cos. (**Johnson & Johnson**) has announced plans to start its Phase Ib/II clinical development program for the CAR-T therapy, JNJ-68284528, in multiple myeloma, in which it will add its expertise in treating the condition to the evolving treatment modality currently led in other disease sectors by **Novartis AG**'s *Kymriah* (tisagenlecleucel) and **Gilead Sciences Inc.**'s *Yescarta* (axicabtagene ciloleucel).

Janssen's CAR-T program, which is being advanced under a collaboration with development partner **Legend Biotech Corp.**, is set to begin patient enrolment in the second half of 2018, following clearance of the IND by the US FDA, the collaborators announced on May 30.

The move might alleviate a little of the disappointment felt earlier this month when Janssen announced that it had halted a clinical study aimed at extending the use of its marketed multiple myeloma drug, *Darzalex* (daratumumab), to include use in combination with an in-house PD-1 checkpoint inhibitor in the disease.

At the same time, it halted a Phase Ib/II study of daratumumab in combination with **Roche**'s checkpoint inhibitor, *Tecentriq* (atezolizumab) in non-small cell lung cancer. However, daratumumab should continue to be a blockbuster product for Janssen; in the first quarter of 2018, Darzalex had net sales of $342m. Janssen licensed the drug from **Genmab AS** in 2012.

JNJ68284528 is based on Legend Biotech's LCAR-B38M, a chimeric antigen receptor T-cell (CAR-T) therapy directed against B cell maturation antigen (BCMA) found on the surface of mature B lymphocytes and malignant plasma cells. It is an autologous product, that will be evaluated in patients with relapsed or refractory multiple myeloma, with the primary endpoint in the Phase II portion of the study being overall response rate (partial response or better) as defined by the International Myeloma Working Group response criteria.

Multiple myeloma is a target of interest for CAR-T therapies: **bluebird bio Inc.**'s bb2121, partnered with **Celgene Corp.**, also targets BCMA and will be reporting early-stage clinical data at the forthcoming ASCO meeting. And **Poseida Therapeutics Inc.** is also active in the field.

Janssen entered a worldwide collaboration and license agreement with Legend Biotech USA Inc and Legend Biotech Ireland Ltd in Dec. 2017 to jointly develop and commercialize LCAR-B38M in multiple myeloma.

The agreement included a $350m upfront and additional milestone payments paid by Janssen to Legend. If approved, Janssen will record worldwide net trade sales, except for sales made in Greater China. The companies will also have a 50/50 cost-sharing/profit-split arrangement, except in Greater China where profits and costs will be split 30/70 in favor of Legend.

In March 2018, an IND to conduct clinical studies of Nanjing Legend's LCAR-B38M in multiple myeloma patients in China was cleared by the China Food and Drug Administration, and the company said it would start clinical trials of autologous infusions in China of LCAR-B38M. Numerous CAR-T therapies are in development in China, and the country has overtaken the US in this regard.

The Legend Biotech and Nanjing Legend companies are subsidiaries of **Genscript Biotech Corp.**, a leading gene and DNA synthesis services provider, founded in New Jersey in 2002 by chairman and CEO Frank Zhang, which is listed on the Hong Kong stock exchange, with operating units in the US, China, Hong Kong, Ireland and other countries.

Published online 31 May 2018

Celgene Corporation has hired ***David V. Elkins*** as executive vice president (EVP), chief financial officer (CFO). He will join Celgene on July 1, and become CFO effective August. Elkins will succeed current CFO ***Peter N. Kellogg***, who will become Celgene's EVP, chief corporate strategy officer until his retirement, planned for mid-2019. Elkins has more than 25 years of finance, strategy, operations, supply chain and business development experience in the US, Europe and emerging markets. He joins Celgene from Johnson & Johnson, where he was worldwide vice president and CFO for consumer products, medical devices and corporate functions. Kellogg joined Celgene as CFO in August 2014.

Henriette Nielsen has been appointed by **Hikma Pharmaceuticals PLC** to the newly created role of chief transformation officer, and will be responsible for leading a number of initiatives across Hikma's global operations to improve operational efficiency. She will join Hikma's executive committee and will report directly to Siggi Olafsson, Hikma's CEO – effective from 4 June 2018. Nielsen joins Hikma from Teva Pharmaceuticals USA, where she was most recently senior vice president, chief transformation officer, global marketing & portfolio.

Ali Mortazavi is stepping down as CEO and as a director of **Silence Therapeutics plc** with immediate effect, having served the company for six years. ***Dr Annalisa Jenkins***, chair of Silence Therapeutics, has assumed the role of executive chair in an interim capacity until a new CEO is appointed.

Andrew Oakley, **Sosei**'s executive vice president and CFO, has resigned. The board has begun a search for a new CFO. ***Chris Cargill***, currently senior vice president of corporate strategy, and head of investor relations and corporate communications, has been appointed interim CFO, while maintaining his current responsibilities with Sosei. Cargill joined Sosei in September 2017 as head of investor relations and corporate communications, and was recently elevated to the role of SVP corporate strategy.

BioNTech AG has appointed ***Dr. Özlem Türeci*** as chief medical officer, effective June 1. Türeci has chaired BioNTech's scientific and clinical advisory board since the company's inception. She has over 25 years' experience in cancer research and immuno-oncology, specifically in the identification of immunotherapeutic drug targets and the development of antibodies, as well as vaccine-based therapies. In 2001, she co-founded Ganymed Pharmaceuticals as chief scientific officer and became its CEO in 2008.

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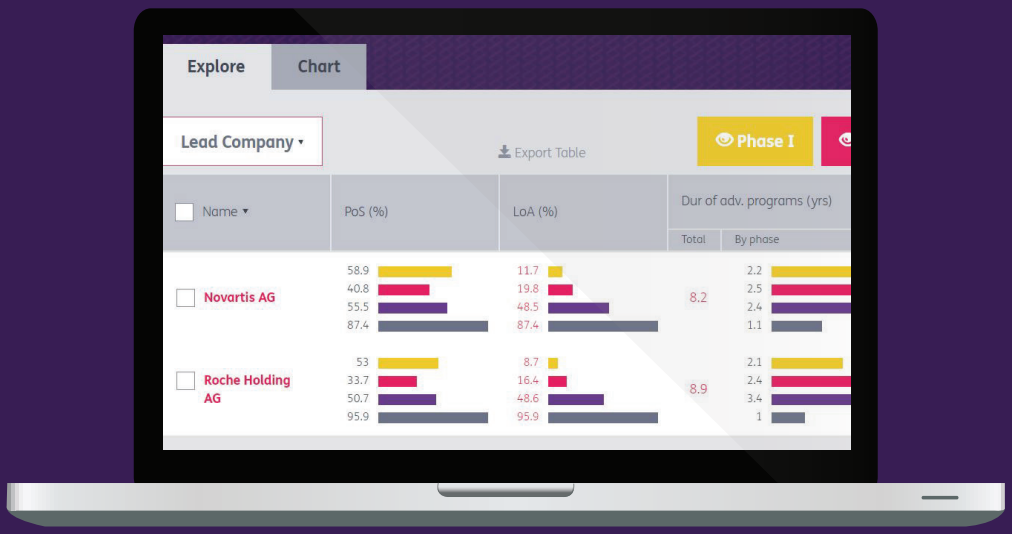

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