Scrip
16 June 2017
No. 3858
scrip.pharmamedtechbi.com
Pharma intelligence | informa


Shutterstock: Lightspring

Roche Pushes The Boundaries Of Cancer Immunotherapy

BRIDGET SILVERMAN bridget.silverman@informa.com

Roche's long-term focus on the biology of the cancer immune cycle may ultimately help the cancer specialist gain an edge in the immuno-oncology field, by allowing the company to move cancer immunotherapy (CIT) into previously unresponsive tumor types.

Although Roche has long held the top spot in the oncology field, it was slower off the blocks than some rivals with CIT, as the early lead went to competitors **Bristol-Myers Squibb Co.** and **Merck & Co. Inc.** in immuno-oncology.

Roche's lead CIT product, the immune checkpoint inhibitor *Tecentriq* (atezolizumab), was the third PD-1/L1 inhibitor to reach the US market. But the firm's extensive clinical trial program has also fed massive amounts of biomarker and outcomes data back into its research engine, allowing Roche and its subsidiary **Genentech Inc.** to investigate why CIT works in some tumors, like melanoma, lung and bladder cancers, but has not been effective in others, like colorectal cancer.

In the past, the company has played up its early research into immuno-oncology – Roche's global head of cancer immunotherapy Dan Chen and Genentech VP-cancer immunotherapy Ira Mellman authored some of the pivotal research on the cancer immunity cycle – and how it is leveraging its diagnostics capabilities to amass and exploit a massive amount of data.

Roche has used this information about immune response, biomarkers and outcomes to refine its tumor immunophenotype model. "This type of categorization then helps us to design our clinical trials," Roche chief medical officer Sandra Horning told a June 5 analyst meeting held in conjunction with the American Society of Clinical Oncology annual meeting. "It helps us with prioritization and rational immunotherapy combinations."

Combinations are where Roche has been planning to shine, taking full advantage of its oncology pipeline to test IO in combination with other IO mechanisms, targeted therapy and chemotherapy. *(Also see "For Roche Immuno-Oncology, It's Steady As She Goes" - Scrip, 24 Jun, 2016.)*

It is the increasing understanding of the immune response that is bearing out the idea that combinations to turn "cold" tumors that wouldn't respond to IO into "hot" tumors that are primed to respond, and that is playing out across the industry. It also may be the area where Roche is best positioned to differentiate itself in the increasingly competitive sector.

PD-1/L1 inhibitors are often described as "releasing the brakes" on the immune system, but Roche has found that anti-tumor immune response can only be accelerated if the tumor already shows some level of immune response. The company is now striving to use combination regimens and new approaches to activate sluggish or potential immune response and to generate de novo immune response.

Roche's ability to design rational combinations that could expand the use of immunotherapy to patients who would not respond to first-generation CIT agents comes from the company's long-term, science-driven strategy. It bet that

CONTINUED ON PAGE 8

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

Biosimilars On The Move

Biosimiliars of Roche's Herceptin prepare for EU approvals (p11)

Bar Raised In Solid Cancers

Developers challenged to strive for new heights with novel ADCs (p12)

ASCO Upsets CDK4/6 Class

Possible demotion to second-line setting with missing survival data (p20)

from the editor

eleanor.malone@informa.com

Did you think we were done with ASCO? Not likely! Our time in Chicago has given us rich pickings for some time to come.

Our cover story looks at the position of Roche in the field of immuno-oncology. For many years the leader in cancer, Roche's pioneer status has been somewhat eclipsed in recent times by the PD-1 trailblazers Bristol-Myers Squibb and Merck & Co. However, it has kept its hand in the game with PD-L1 inhibitor Tecentriq and looks likely to come back strongly in IO's second wave, which will be all about immunotherapy combinations.

The question is, whether Roche will be able to prove that being the first is not the same as being the best. It's something that holds true in many diverse situations: from the London Underground's Circle Line to beating your partner to the end in a musical duet, those that come first are not necessarily those that have the best qualities overall.

Roche's CEO sheds further light on the company's perspective on ASCO in an exclusive interview with Scrip's Sten Stovall on p4-5, while Lucie Ellis reports on the challenge the firm faces in protecting its lucrative Herceptin business (p11).

Meanwhile, we have details of bluebird bio's latest positive results in the CAR-T field (p6), a report on how antibody-drug conjugate developers may need to up their game (p12-13), breast cancer news on p13-14 and p20-21, and more.

ADA has also just concluded: turn to p16-17 for selected reports, and remember – we have lots more content online.

Scrip

LEADERSHIP
Phil Jarvis, Mike Ward

SUBSCRIPTIONS
Daniel Frere

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

EDITORIAL OFFICE
Christchurch Court
10-15 Newgate Street
London, EC1A 7AZ

CUSTOMER SERVICES
Tel: +44 (0)20 7017 5540
or (US) Toll Free: 1 800 997 3892
Email: clientservices@pharmamedtechbi.com

TO SUBSCRIBE, VISIT
scrip.pharmamedtechbi.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

All stock images in this publication courtesy of www.shutterstock.com unless otherwise stated

Scrip is published by Informa UK Limited. ISSN 0143 7690.

exclusive online content

FDA Requests Withdrawal Of Endo's Opana ER
http://bit.ly/2riz7Oq
The US regulatory agency has decided the long-acting opioid's benefits no long outweigh its risks, sparking concern that other strong steps on opioid abuse could be coming.

Big Pharma May 2017: Product Developments Shift Stock
http://bit.ly/2tcDqr9
In a new monthly column, *Scrip* rounds up events on the stock market, noting trends and exceptional performance both good and bad. This month, the focus is on 30 biopharma companies with market caps above $10bn. Between them, these 30 companies account for approximately 75% of the asset value in the pharmaceutical industry.

Starboard-Driven Perrigo Sees CEO Depart After CFO
http://bit.ly/2sUgBcg
Perrigo's CEO John Hendrickson, who was appointed to the post when Joseph Papa left to head Valeant in 2016, is to retire. The company is also looking for a permanent CFO after Judy Brown left in February. The departures follow a board shake-up pushed through by activist investor Starboard Value LP.

Ping An Expands Broad Health Interests With New Fund For Global Tech
http://bit.ly/2skyC6y
China's huge Ping An insurance group is continuing to build its investments in healthcare through a major new Hong Kong-based fund that will seek overseas technologies alongside the company's steadily expanding interests in innovative drugs.

Battle Lines Drawn In New Renal Anemia Market
http://bit.ly/2sklC0H
The treatment landscape in renal anemia is set for major changes over the next few years as a novel class of drugs approaches the market. A new report from Biomedtracker looks at the major players battling it out in the clinic.

inside:

Roche 'Disappointed' By ASCO Focus, Progressing CEA-CD3 Bispecific

STEN STOVALL sten.stovall@informa.com

Roche's Austrian CEO Severin Schwan has a reputation for being mild-mannered, diplomatic and very precise – so when he says he's "disappointed" by ASCO's reception of a key product presentation – namely the Phase III APHINITY trial examining use of *Perjeta* (pertuzumab), *Herceptin* (trastuzumab) and chemotherapy together in the adjuvant treatment of breast cancer – there is a loud message underneath.

"I am disappointed," he told *Scrip* when discussing the group's APHINITY presentation at the just-ended ASCO event in Chicago, during which the Swiss group also made other data presentations.

Analysts before the APHINITY June 5 update – and which followed top-line data released in March – had been hoping for more than a one-percentage-point difference in invasive disease-free survival rates when it came to how much difference Perjeta could make when added to Herceptin and chemo in HER2-positive early breast cancer. Analysts reactions focused on Roche's data presented at ASCO showing that at three years, 94.1% of people treated with the Perjeta-based regimen did not have their breast cancer return compared to 93.2% treated with Herceptin and chemotherapy.

The safety profile of the Perjeta-based regimen was consistent with that seen in previous studies, with a low incidence of cardiac events and no new safety signals.

CEO: ANALYSTS MISSED KEY PERJETA MESSAGE

"This was three-year data. Part of the trial's design is for follow-up data. So, we've followed the patients after four years, five years, and so on. And I regret the fact that everybody is focused on the three-year data whilst from a patient point of view what really counts is the four-year data, which is the latest data," Schwan said in an exclusive interview.

"What we see in APHINITY is that, for the total population we see an improvement that is twice as big, which is 2% and that's the relevant number. And when we have five-year data, that will be the relevant number. It just happens to be that everybody focused on the original numbers [the 3 years' data]."

Roche AG

Severin Schwan "disappointed" by Asco Aphinity reactions

'We are not talking about the prolongation of life, for a certain number of months, we are talking about cure. This is extremely important to keep in mind'

"The key point is that the trajectory curves are further separating, for further follow-up. Meaning the benefit that you see initially doubles after only one year of additional follow-up. I believe this point has been completely overlooked at ASCO, although this is really the important number," Schwan said.

TRIAL HAS CURATIVE SETTING

"We're talking here about a curative setting where the patients have not yet suffered from metastases. In this setting, if you can prevent a relapse then you're talking about cure. So, a small difference in this setting has a huge impact for the respective patients.

We are not talking about the prolongation of life, for a certain number of months, we are talking about cure. This is extremely important to keep in mind. So you need to look at what difference Perjeta makes here. Herceptin is already a fantastic medicine that reduces the risk of relapses so that means roughly 90% of patients don't get a relapse anymore [when given Herceptin and chemo] so that leaves us with ten out of 100 patients who still suffer from a relapse. Now, if you have a 2% improvement, then that [effectively] means two out of ten patients who get cured. So this is 20% of the patients that we are talking about. So while 1% or 2% of the total population sounds like a small relative difference, but what you need to look at is the difference compared with the current standard of care."

SUBGROUPS DISTINCTION

Analysts reacted to the APHINITY update by saying the combo's use is likely to be limited to high-risk, node-positive patients. Schwan acknowledged that there is a difference seen in the study between high-risk

patients – so-called node-positive patients and hormone receptor-negative patients - and low risk patients.

"Node-positive patients represent about 55%, and hormone receptor-negative patients represent about 15% in the trial. If you take those together we're looking at over 65% [of the APHINITY evaluation] are high-risk patients. For those high-risk patients, the effect was even bigger. For low-risk patients at three years we didn't see an effect, actually – but the hope is that the longer follow-up will see an effect in the longer term for the lower risk people but for the time being we don't see that." He stressed that APHINITY is on-going and will read-out over ten years.

WON'T GIVE PERJETA SALES PROJECTIONS

The CEO would not be drawn on what the APHINITY data might imply for Perjeta's eventual indications. "I cannot make any projections or comments on what the label will look like. That's up to the authorities. We will be able to file on this basis and I believe the product will be approved.

"We will have price discussion with authorities and the price is always a reflection of the value we bring to patients. And what we see here is that the value we bring to high-risk patients is bigger than the value we potentially bring to low-risk patients. I'm sure this will be reflected in the pricing discussions," he said.

He said Perjeta would still be a blockbuster but he would not give detailed forecasts, or say whether the therapy could still be as big as big a product for Roche as Herceptin. "I continue to believe that Perjeta will play a very important role in the adjuvant setting. We don't give projected peak sales for Perjeta. What we have guided the market so far is that we believe we can off-set the impact of biosimilars and continue to grow the overall HER2 franchise despite the biosimilars. The adjuvant setting should be a substantial segment given the data we have now," he said.

BUT ALEX IMPRESSED

More positively received at ASCO were impressive data on Roche's ALEX study, in which second-generation ALK inhibitor *Alecensa* (alectinib) showed a significant improvement over **Pfizer Inc.**'s first-generation product *Xalkori* (crizotinib) in progression-free survival when used first-line in advanced ALK-positive non-small cell lung cancer (NSCLC). The current standard of care is crizotinib.

> 'Perjeta will play a very important role in the adjuvant setting. We don't give projected peak sales for Perjeta. What we have guided the market so far is that we believe we can off-set the impact of biosimilars'

"This trial placed Alecensa head-to-head against crizotinib. And it shows an overwhelming difference in terms of efficacy improvement versus the standard of care, and on top of that it also has a more favorable safety and tolerability profile compared with crizotinib," Schwan summarized.

"The risk of progression-free survival was reduced by over 50%. This is massive. We have a median PFS now of around 26 months which compares with ten months with crizotinib, this is more than a year of difference. And Alecensa also very effectively protects against CNS metastases. We have seen unprecedented CNS complete response rates. There, 45% of patients in the Alecensa arm achieved a complete response with the CNS, which is much, much more than the crizotinib arm which had only 9% of patients. So it helps with metastases in the brain which is a particular issue with ALK-positive patients."

So what happens now with Alecensa? "We already have been granted breakthrough therapy designation by the US in first-line setting; it is already on the market in second-line setting. The ALEX Study is the second positive Phase III study for Alecensa, so we will work with regulatory authorities to bring the therapy to the market as soon as possible. I am very confident that the FDA will give a high priority to this medicine given that we already have breakthrough therapy designation and in light of this new data that we presented at ASCO."

ROCHE BISPECIFIC PROGRESS

Moving to earlier-stage assets, Schwan said that he's particularly excited about the preliminary data on the CEA-CD3 bispecific in treatment-refractory colorectal cancer patients which was presented at ASCO. The compound is a novel T-cell bispecific antibody which is being investigated for the treatment of carcinoembryonic antigen (CEA)-expressing solid tumors.

"We have a number of bispecifics. The one highlighted at ASCO uses a very smart mechanism to bring the killer cells to the place where they should act and what is so exciting is that we see in early clinical trials we see very good response rates and we presented data for colon cancer for patients who didn't respond to anything anymore," Schwan explained.

"Specifically, this was a combination of this bispecific with our PD-L1 *Tecentriq* (atezolizumab). We see a dose effect and we see response rates for a number of patients and that is of course exciting because there is no medicine for these kinds of patients. And it is a mechanism which could of course work for earlier lines and improve the standard of care in colon cancer but importantly it could also work for other cancer types. So, it's one of those mechanisms which has a platform. Based on this data we will now bring this into pivotal studies as soon as possible, and we'll go as fast as we can."

ON ASCO RATING: "ROCHE 10, MARKET ZERO"

Asked to rate Roche's ASCO experience this year in Chicago on a scale from 1 to 10, Schwan replied: "It depends how I look at it.

"Seen from a clinical news flow I think ours is really good news for patients – if you look at ALEX, if you look at Perjeta, if you look at the data we showed on Tecentriq, if you look at our early pipeline with the bispecifics in particular, if I put all of this together, I would say ten out of ten for Roche.

"But if I look at how the market reacted – in particular on how it reacted on the APHINITY data, I am disappointed and I would give zero out of ten points," Schwan said with a chuckle.

Published online 7 June 2017

Bluebird Flies On 100% Response Rate For Anti-BCMA CAR-T

JESSICA MERRILL jessica.merrill@informa.com

Investors were energized by **bluebird bio Inc.**'s data on the anti-B-cell maturation antigen (BCMA) chimeric antigen receptor (CAR)-T cell therapy bb2121, presented as a poster at the American Society of Clinical Oncology meeting because the treatment showed a benefit in heavily treated multiple myeloma patients who had for the most part run out of options.

Bluebird's stock jumped 8% to $98.20 on June 6, after the data were presented; the company also held a separate investor briefing the same day.

Despite the limited nature of the trial, which included just 18 evaluable patients, the data were striking because every patient who was treated at what the company determined was a therapeutic dose – a dose level of 150x10 CAR+ T cells or higher – experienced an objective response, including those with high tumor burden; 27% achieved a complete response; and four patients tested for minimal residual disease status were found to be MRD-negative.

None of the patients in the active dose cohorts have had myeloma progression, with a range of follow-up of eight to 54 weeks. While there were some Grade 1 and Grade 2 toxicities, no dose-limiting toxicities were observed.

As CEO Nick Leschly told investors at the briefing, "The data has honestly played out beyond our wildest imagination."

Bluebird is best known as a gene therapy developer working on potential cures for rare diseases like cerebral adrenoleukodystrophy, transfusion-dependent beta-thalassemia and severe sickle cell disease. But the company also has a cancer immunotherapy platform, focused on leveraging its gene transfer technology.

BCMA is a cell-surface protein that is expressed in normal plasma cells and in most multiple myeloma cells, but not in other normal tissue.

Study investigator Jesus Berdeja (Sarah Cannon Research Institute and Tennessee Oncology) said a clinically meaningful response would have to be better than the progression-free survival seen with existing late-line therapies, **Johnson & Johnson**'s *Darzylex* (daratumumab) and **Celgene Corp.**'s *Pomalyst* (pomalidomide), which is four months.

"I will be disappointed if this PFS is four months, but I think if you go beyond six months, and definitely if you go to a year, I think that will be a big wow in this population because that's way beyond what you would expect even for them to live," he said.

Bluebird is partnered on bb2121 with Celgene, which obtained a joint license to the therapy and a broader CAR-T program in 2013 for $75m up front. The partners amended the agreement in 2015, however, when Celgene narrowed the scope of the deal to focus only on BCMA while returning all rights to the broader platform to bluebird. [See Deal] Weeks later, Celgene announced a sweeping, $150m up front deal with CAR-T developer **Juno Therapeutics Inc.** *(Also see "The Bang For Celgene's Buck: Looking Inside The Record-Setting Juno Deal" - Pink Sheet, 13 Jul, 2015.)*

Meanwhile, Celgene and Juno have fallen behind rivals **Novartis AG** and **Kite Pharma Inc.**, the first companies to file a CAR-T therapy with the FDA, because of a safety issue that derailed the lead asset JCAR015. *(Also see "Juno Ends JCAR015 Development In ALL, Cementing Third Place CAR-T Position" - Scrip, 2 Mar, 2017.)* The partners are moving forward with JCAR017 in patients with relapsed and refractory aggressive B cell non-Hodgkin lymphoma and presented data from a Phase I trial, TRANSCEND, at ASCO.

Now, bb2121 could represent an opportunity for Celgene to expand its blockbuster multiple myeloma franchise led by *Revlimid* (lenalidomide).

UP NEXT: MORE STUDIES AND MANUFACTURING

The companies are planning to move forward with an expansion phase of the trial later this year, but management would not talk about longer-term development plans.

"I want to make sure that we translate and finish this study and make sure we understand what the appropriate path is to approval and subsequent to that," Leschly said.

Barclays analyst Geoff Meacham said in a June 5 note, "Although we stress the data are preliminary, we view the data positively, representing a potential win for Celgene as it continues to leverage its partnerships to diversify its portfolio."

One issue with CAR-T therapies is the administration and manufacturing process, because the individualized treatment involves extracting cells from a patient, re-engineering them and reinfusing them back into the patient.

But management from both companies said they are actively working to deliver on the requirements for the commercial setting.

Bluebird and Celgene aren't the only companies pursuing a BCMA cell therapy – or getting attention at ASCO. A relatively unknown Chinese biotech, **Nanjing Legend Ltd**., garnered a lot of media attention at ASCO for its BCMA therapy which also showed encouraging complete response rates in patients with multiple myeloma in an early trial. In that trial, 14 of 19 patients had a complete response, but BMO Capital Markets analyst Matthew Luchini noted in a June 5 research note that the patients were less heavily pre-treated than those in the bluebird trial (a median three lines of therapy versus seven).

"While we expect bb2121 uptake to be rapid given the severity of the population, our estimates leave plenty of room for emerging competition," he said.

Despite the substantial manufacturing challenges around CAR-T and some serious safety setbacks, including deaths, the therapy area continues to push forward. Novartis has recently begun to talk more enthusiastically about the commercial prospects for its CTL019, pending at FDA for pediatric acute lymphoblastic leukemia. *(Also see "Novartis' CAR-T CTL019 Back On The Blockbuster Hit List" - Scrip, 1 Jun, 2017.)*

Published online 6 June 2017

AbbVie May Be Poised For An Oral RA Smack Down

JOSEPH HAAS joseph.haas@informa.com

AbbVie Inc. unveiled promising top-line data from SELECT-NEXT, the first of six Phase III trials of JAK1 inhibitor upadacitinib (ABT-494) in rheumatoid arthritis on June 7. Upadacitinib could have a chance to jump ahead of **Eli Lilly & Co./ Incyte Corp.**'s baricitinib in the race to become the first in a new generation of JAK inhibitors to reach the market.

Analysts covering the data unanimously predicted eventual blockbuster sales for upadacitinib, a selective inhibitor of Janus kinase 1, with Jefferies Equity Research's Jeffrey Holford saying a peak estimate of $3.5bn across several autoimmune indications might be too low. Along with its six-study Phase III program investigating upadacitinib in RA, AbbVie also has initiated a Phase III trial in psoriatic arthritis and is developing the drug for Crohn's disease, ulcerative colitis and atopic dermatitis.

A key plank in AbbVie's strategy to offset expected biosimilar competition to its top-seller *Humira* (adalimumab), upadacitinib is expected to produce data from the Phase III SELECT-BEYOND study in RA during the third quarter.

SELECT-BEYOND and SELECT-NEXT both test upadacitinib in combination with conventional, synthetic disease-modifying antirheumatic drugs (csDMARDs) against placebo, while two upcoming SELECT studies will evaluate upadacitinib monotherapy against methotrexate and two others will examine upadacitinib in combination therapy against comparator regimens – the anti-TNF drug Humira and anti-CD80/86 drug abatacept (**Bristol-Myers Squibb Co.**'s *Orencia*).

In a June 7 note, Credit Suisse analyst Vamil Divan projected that the six studies should read out this year and next, creating a timeline for a US NDA submission during the second half of 2018 and launch in the second half of 2019.

Pfizer Inc.'s *Xeljanz* (tofacitinib), which selectively inhibits JAK1/3 with functional selectivity for JAK2, currently is the only JAK inhibitor approved to treat RA, entering the US market in 2012. Though uptake of the drug was initially slowed by worrisome side effects, it is on track to become a blockbuster this year. Baricitinib, however, sustained a major setback with an FDA complete response letter in April, which some analysts say imposes safety concerns over the entire class. The CRL requests additional data on appropriate dosing of baricitinib, a dual inhibitor of JAK1/2, as well as responses to undisclosed safety concerns.

MEETING THE MARK FOR ACR20

Top-line results from SELECT-NEXT show that two oral, daily doses of upadacitinib (15 mg and 30 mg) given for 12 weeks met statistical significance for the primary endpoint of improvement from baseline on the American College for Rheumatology 20 (ACR20) scale and low disease activity, as well as all secondary endpoints, and also posted a safety profile consistent with results from Phase II studies of the drug. *(See table.)*

Patients enrolled for the study (n=661) were on a stable dose of csDMARD therapy, but responded inadequately to that therapy. For the ACR20 measure, 64% of patients receiving the 15 mg dose and 66% receiving the 30 mg dose achieved that standard, compared to 36% of placebo-arm patients. ACR20 requires at least a 20% improvement in the number of tender and swollen joints, as well as at least 20% improvement in at least three other measures – patient global assessment of disease status, patient's assessment of pain, patient's assessment of function, physician's global assessment of disease status and serum C-reactive protein levels.

For the measure of low disease activity, both treatment arms recorded a 48% response rate, compared to 17% for placebo. On secondary endpoints of ACR50, ACR70 and clinical remission, both doses of study drug achieved statistical significance compared to placebo, as well.

Leerink Partners' analyst Geoffrey Porges asserted in a June 7 note that the ACR50 and ACR70 measures are "the more meaningful endpoints for patients and physicians" even though ACR20 and low disease activity serve as the primary endpoints. He also noted the structural similarity between SELECT-NEXT and the Phase III RA-BUILD study of baricitinib. Both upadacitinib doses outperformed baricitinib on a placebo-adjusted basis when comparing across the two studies for ACR20, ACR50 and ACR70 score, he said.

Noting the difficulty in comparing data across different trials, however, Jefferies' Holford more cautiously declared that upadacitinib "appears to be at least as good as baricitinib based on these two studies." One area of difference between the two studies, he added, is that AbbVie enrolled patients treated with one prior biologic therapy, while the baricitinib patient population was not previously treated with biologic therapy. About 20% of the SELECT-NEXT enrollment had prior treatment with a biologic, "which may imply a slightly more challenging population for ABT-494," he wrote.

AbbVie reported that the top-line safety data were consistent with those seen in Phase II studies of upadacitinib. No new safety signals were detected, and a serious adverse event rate of 4% was recorded in the 15 mg treatment group, 3% in the 30 mg treatment group, and 2% in the placebo arm.

BMO Capital Markets analyst Alex Arfaei said the CRL for baricitinib has created uncertainty for the approval prospects of JAK1-inhibiting drugs, but indicated that AbbVie's overall Phase III program may give it an advantage over the Bristol/Incyte drug. "We believe the FDA may be taking a conservative approach for new treatments in this class because the unmet need is not as great given the number of treatments available," he wrote June 7.

Published online 7 June 2017

Top-line data from SELECT-NEXT study of upadacitinib in RA, by dose and endpoint

DOSE/ENDPOINT	15 MG	30 MG	PLACEBO
ACR20	64%	66%	36%
ACR50	38%	43%	15%
ACR70	21%	27%	6%
Low disease activity	48%	48%	17%
Clinical remission	31%	28%	10%

CONTINUED FROM COVER

increasing knowledge about the cancer immune cycle ultimately would be more valuable than being first to market or achieving early market dominance, a strategy that is starting to play out.

FOLLOW THE IMMUNOPHENOTYPES

The refinement of Roche's immunophenotype model has been rapid, in turn spurring rapid pipeline expansion. As recently as the 2014 ASCO meeting, Mellman described the idea that "tumors defend themselves against T-cell attack by creating an environment that is inherently immunosuppressive" as a "dramatic" and "very, very recent" conceptual advance. *(Also see "Roche Sees Biomarker-Guided Discovery As Key To Unlocking Tumor Microenvironment" - Pink Sheet, 18 Jun, 2014.)*

The company came to the June 2017 meeting, just three years later, with 12 novel cancer immunotherapies in the clinic and one on the market.

Roche quickly homed in on the role of inflammation in the cancer immune cycle, initially characterizing tumors as either inflamed or uninflamed based on the activity of CD8 T-cells. *(Also see "Beyond PD-1: Roche Maps Further Checkpoints On Cancer Immune Cycle" Scrip, 15 Jun, 2015.)* Now, however, "the work that we've done to-date with biomarkers has really led us to think that there are three basic types of immune profile or immune phenotype that exist in tumors," Mellman explained, known as the immune-inflamed, immune-excluded, and immune-desert phenotypes.

Tumors with the inflamed phenotype show infiltration by CD8+ T-cells and "some level of objective immunity," so the goal of immunotherapy is to accelerate or "remove the brakes" on T-cell response, he explained. "Most of the responses that we see to Tecentriq and to similar agents in fact fall within this group," Mellman noted. Melanoma and lung cancers are notably inflamed tumors.

Patients in the immune-excluded group "seem to have T-cell responses, but those T-cells have difficulty actually in entering the tumor and often can be shown to be sequestered in the stroma that often surrounds the tumor," Mellman continued. The goal of therapy for immune-excluded tumors, which include triple-negative breast cancer, is to bring T-cells in contact with cancer cells.

"Finally, there is the immune desert, where one finds patients that are generally devoid of any evidence whatsoever of T-cell immunity coursing into their tumors," Mellman said. "And as a consequence, these are individuals for whom we may have to generate immunity de novo," for instance by increasing the number of antigen-specific T-cells or by increasing antigen presentation.

"The excluded and the desert areas do represent, I think, great opportunities, and also great areas for unmet need," Mellman stated. Such areas include the major market of colorectal cancer, as well as gastric and ovarian cancer.

> 'The cancer types that have not yet responded well to what I would call the checkpoint inhibitors or first-generation cancer immunotherapies are very large'

"The cancer types that have not yet responded well to what I would call the checkpoint inhibitors or first-generation cancer immunotherapies are very large," Roche Pharmaceuticals CEO Daniel O'Day said. "We're talking about more than 70% of the potential out there. You can see colorectal at about 150,000 [patients,] pancreas 57,000, gastric 59,000."

Roche is hardly alone in seeing the market opportunity in patients who fail first-wave immunotherapy, but it may be the company with the most systematic and disciplined campaign. Bristol also has a broad pipeline looking at many of the same new mechanisms to activate immune response in patients who failed or relapsed after existing CIT, but Bristol Head of Early Oncology Development Tim Reilly used words like "daunting" and "haphazard" to describe it in an interview with *Scrip* during ASCO. *(Also see "BMS's Early Oncology Head On Novel IO Approaches & Disruptions" - Scrip, 5 Jun, 2017.)*

Roche is also the most active oncology trial sponsor. A Trialtrove analysis of clinical trials completed in 2016 found that Roche was the sponsor of more oncology trials than any other company by a sizable margin. *(Also see "Clinical Trial Snapshot 2016: Novartis Leads On Volume, But Novo Nordisk Posts Highest Success Rate" - Scrip, 30 May, 2017.)*

CHANGING THE IMMUNE CONTEXT

Roche's Tecentriq combination strategy goes beyond the traditional combination chemotherapy method of bringing different methods of killing cancer together in an anti-tumor package – instead it is trying to use non-CIT drugs to alter the tumor microenvironment so that Tecentriq can work. **AstraZeneca PLC** is similarly testing whether its DNA damage response inhibitors, like the PARP inhibitor *Lynparza*, can prime tumors for treatment with immunotherapy.

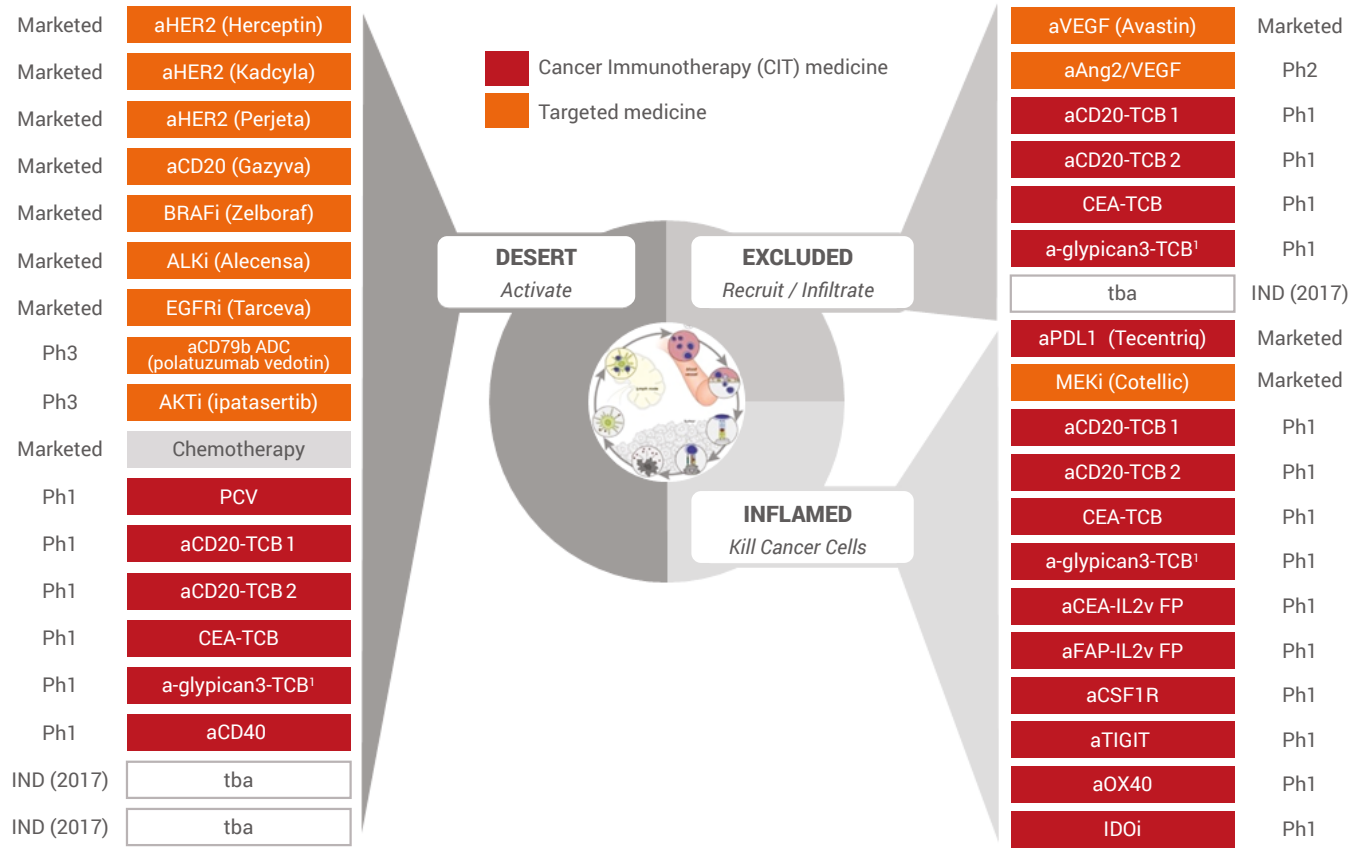
Roche's strategy benefits from its vast oncology pipeline, which provides a wealth of combination options even before dealmaking brings in external candidates. As Mellman said, Roche is "very committed" to understanding "how we can leverage our targeted agent pipeline in conjunction with immunotherapies."

One of the most advanced examples of the targeted therapy/immunotherapy approach is Roche's combination of its MEK inhibitor *Cotellic* (cobimetinib) with Tecentriq, a pairing that is currently being studied in Phase III for first-line metastatic melanoma and third-line treatment of advanced colorectal cancer.

Mellman called Cotellic an "unexpected combo partner" for Tecentriq. "MEK [inhibition] shouldn't have worked, because we all know the T-cells, in order to become primed to recognize their targets, require MAP kinase signaling," he said; in "immune-excluded" and "immune-desert" cancers, which include most CRC patients, single-agent Cotellic has not shown activity.

Nor, as Chen pointed out at last year's ASCO meeting, have anti-PD-1/L1 immunotherapies like Tecentriq. "We think that

Multiple approaches across three tumor phenotypes



Source: Roche presentation to analysts June 5, 2017, during the American Society for Clinical Oncology annual meeting in Chicago

PCV* = personalized cancer vaccine in collaboration with BioNTech; 1= in early development at Chugai; NME = new molecular entity; IND = new investigational drug application; TCB = T-cell bispecific; tba = to be announced

some of the reasons why colon cancer may not respond [to single-agent immunotherapy] is that you get things like down-regulation of MHC class 1 in colon cancer, the molecule that's required to show there's something foreign. If a cancer cell down-regulates that protein, it can become invisible to T cells."

"What was really surprising," Mellman said, and "what we've been now leveraging in the clinic is the fact that MEK also blocks the process of T-cell exhaustion, or at least inhibits it, without really affecting any aspect of other … T-cell biology." The MEK inhibitor Cotellic's direct effects on T-cells and the tumor microenvironment, including reversing the down-regulation of MHC class 1, thus "may help to unlock the full anti-tumor potential of PD-L1 inhibition."

Roche followed up last year's presentation of early-phase Tecentriq/Cotellic data in CRC with data from two Phase Ib studies of the drugs in melanoma. The melanoma studies provided "encouraging" data, including a mean progression-free survival of 15.7 months for the two-agent combo compared with 5.5 months for Tecentriq alone in first-line treatment of metastatic melanoma. Early data from another Phase Ib study that added the BRAF inhibitor *Zelboraf* (vemurafenib) to Tecentriq and Cotellic in first-line BRAF mutation-positive melanoma found an 82% overall response rate.

The Phase Ib studies helped move Tecentriq/Cotellic into a "large" Phase III program in metastatic melanoma, Mellman indicated. The IMspire150 study of the triple regimen with Zelboraf is ongoing in first-line BRAF v600 mutation-positive patients, and the company is planning the IMspire170 trial in first-line BRAF wild-type metastatic melanoma.

COMPREHENSIVE ONCOLOGY STRATEGY

Roche's clinical program was designed to generate massive amounts of data on biomarkers and cancer biology, thanks to trial-design measures like routine, repeated biopsies as well as investment in diagnostic and analytic technology, from assays to the ISIS digital pathology system. As Roche's Chen said in an interview at ASCO 2016, "we believe because we have so much biologic data collected from those studies, it will help us start to understand human immune biology so we can pick the right targets and can pick the right combinations."

Roche spent less time discussing its diagnostic and data platforms at this year's ASCO analyst meeting than at some years past, thanks to a mature and active targeted therapy program. The company highlighted the ALK inhibitor *Alecensa* (alectinib) and the anti-HER combination of *Perjeta* (pertuzumab) and *Herceptin* (trastuzumab) following presentation of Phase III results from the ALEX and APHINITY trials, respectively, at the oncology conference. *(Also see "APHINITY Combo Details Contain No Surprise, Puma's Nerlynx May Benefit"*

CONTINUED ON PAGE 10

CONTINUED FROM PAGE 9

- Scrip, 5 Jun, 2017.) and *(Also see "Roche "Disappointed" By ASCO Focus, Progressing CEA-CD3 Bispecific" - Scrip, 7 Jun, 2017.)*

Nonetheless, O'Day emphasized that "we're clearly being more and more enabled every day by the high-quality availability of data outside of our walls and inside of our walls as it relates to real-world data and better analysis on our randomized clinical trial data and we're growing our expertise on analytics, deep learning that we think is really fundamental."

NGS IN PRACTICE

Roche's presentation of data from the Phase II LOTUS trial of one of its targeted therapy candidates, the AKT inhibitor ipatasertib, provided a look at how the company incorporates diagnostics from both its **Ventana Medical Systems Inc.** diagnostics business, which markets immunohistochemistry (IHC) assays, and its stake in **Foundation Medicine Inc.**'s next-generation sequencing (NGS) platform. NGS can run more tests on a small tissue sample than traditional IHC assays – Roche says the *FoundationOne* NGS platform is designed to detect alterations in more than 300 oncogenes – and O'Day said FoundationOne is "key to identifying relevant patient subpopulations." FoundationOne is under review at FDA.

The Phase II LOTUS trial of ipatasertib plus paclitaxel for first-line therapy of metastatic triple-negative breast cancer (TNBC) had two primary endpoints: progression-free survival (PFS) in all patients and PFS in patients with low levels of phosphate and tensin homology (PTEN). PTEN-low or PTEN-high status was determined by Ventana's IHC assay. As a secondary endpoint, Roche also used FoundationOne NGS to look for another biomarker profile based on PI3K/Akt pathway status – altered PI3KCA/AKT1/PTEN.

The Ventana PTEN assay showed "no projective ability" over the regular intent-to-treat analysis of all patients, Horning said. Roche did, however, see "an improved progression-free survival hazard ratio in those patients that were identified by the FoundationOne NGS assay," she reported. "I think this is a demonstration of our partnership and collaboration that shows that we can streamline the assay in our development program."

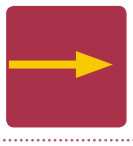
"For triple-negative breast cancer, this is a particularly important diagnostic because of the complex biology, which can include both alterations of the PI3 kinase and AKT, as well as PTEN," Horning said. The FoundationOne NGS data "gives us confidence to move forward with ipatasertib in this [triple-negative breast cancer] setting." Ipatasertib is also being tested with paclitaxel in a Phase II trial in neoadjuvant early-stage TNBC, according to clinicaltrials.gov, and is in Phase III for castration-resistant prostate cancer.

> 'What we've been now leveraging in the clinic is the fact that MEK also blocks the process of T-cell exhaustion, or at least inhibits it, without really affecting any aspect of other ... T-cell biology'

O'Day also highlighted the performance of the NGS assay in the ipatasertib LOTUS trial. "This is again a reason why the comprehensive diagnostic and comprehensive immunodiagnostic paradigm that we're entering into is really going to become more and more important in the years to come," he said.

While NGS is still emerging commercially, uptake is expected to swift, especially as less-invasive "liquid biopsy" technology advances. *(Also see "Companion Diagnostics: The Expanding Reach Of Personalized Medicine" - Scrip, 14 Mar, 2017.)* Roche has made sure it will be well-positioned to take advantage.

Published online 9th June 2017



View Tumor Immunophenotypes Direct Roche R&D Strategy here: **http://bit.ly/2tbNh0n**

Sobi's Platform No Longer For Sale

Swedish Orphan Biovitrum AB (Sobi) has terminated discussions over the sale of the company's Partner Products business. The decision comes just a few weeks after the Swedish firm appointed a new CEO, Guido Oelkers, to replace Geoffrey McDonough.

The Partner Products division offers a distribution platform for niche medicines in Europe, the Middle East, North Africa and Russia. In 2016, the unit had revenues of SEK 820m ($95m). This was up from SEK 771m in 2015.

Sobi revealed in February that it was in discussions with a private equity firm regarding a possible sale of the Partner Products unit. At the time, Sobi was already looking for McDonough's replacement. The company said at the start of 2017 that it wanted a new CEO who would be based in or around the company's headquarters in Stockholm "given the firm's increased demand and focus of our business in Europe," according to Sobi's chair Håkan Björklund.

McDonough, who joined Sobi in 2011, relocated to Boston, Massachusetts in 2015.

Sobi now says its Partner Products business area will remain an integral part of Sobi's business model.

"Our Partner Products portfolio is a valuable rare disease platform in Sobi's business today. We have assessed the options to potentially divest the portfolio, and the conclusion is that going forward this interesting business element will continue to serve as an integral part of Sobi, giving us access to new earnings streams, and supporting both our commercial footprint and attractiveness as a business partner in Europe, the Middle East, North Africa and North America," said CEO Oelkers.

Oelkers joined Sobi from BSN Medical GmbH, where he was CEO.

sukaina.virji@informa.com 6 June 2017

More Herceptin Biosimilars Move In, But Roche Thinks It Can Stand Its Ground

LUCIE ELLIS lucie.ellis@informa.com

Teva Pharmaceutical Industries Ltd./Celltrion Inc. and **Samsung Bioepis Co. Ltd.** reported positive Phase III data at the 2017 American Society for Clinical Oncology annual meeting, held in Chicago June 2-6, for their respective Herceptin biosimilars – piling more pressure onto **Roche**, which reported Phase III results for a new Herceptin combination that didn't live up to expectations.

In a Phase III trial presented at ASCO, Teva/Celltrion's *Herzuma* (also known as CT-P6) demonstrated bioequivalence to Roche's originator biologic *Herceptin* (trastuzumab) when tested as a neoadjuvant treatment for HER2+ early breast cancer.

In the study, a total of 549 patients were randomized at 122 centers in 22 countries, with 271 patients receiving Herzuma and 278 receiving Herceptin. Herzuma demonstrated therapeutic equivalence to Herceptin as determined by pathological complete response in the trial, and the drug was well tolerated with a safety profile similar to the reference product.

Two deaths occurred in the Herzuma treatment arm compared with one death in the comparator arm – however, all fatalities were considered unrelated to the active agents in the study. One death in the Herzuma arm of the study was sudden and the cause is unknown, but investigators deemed it unconnected to the product. Pharmacokinetics and pharmacodynamics were similar between the two treatment groups.

Meanwhile, Samsung Bioepis also reported positive Phase III data for its Herceptin biosimilar, SB3, in early stage HER2+ breast cancer in the neoadjuvant setting. In the trial 875 patients were randomized at 97 sites in 14 countries, with 437 patients receiving SB3 and 438 receiving Herceptin.

Bioequivalence endpoints were met in the study and overall safety was comparable between the two treatment arms in the Phase III comparison trial.

Samsung Bioepis has already filed SB3 in Europe, where a regulatory opinion from the European Medicines Agency's scientific committee, the CHMP, is expected between June and November this year. A US FDA filing for the biosimilar drug is also expected before the end of October 2017.

Teva has already filed Herzuma in Japan and Europe – with a decision expected from the CHMP in Europe between July 2017 and January 2018. A decision from regulators in Japan for the drug is not expected until early- to mid-2018.

Herceptin, the first humanized monoclonal antibody for the treatment of HER2 overexpressing metastatic breast cancer, was approved in the US in 1998; Roche won a label expansion for the drug in 2010 for use in gastric cancer and has expanded to other lines of breast cancer therapy.

Worldwide sales for the drug were $6.9bn in 2016, but the product is expected to lose value steadily over the next 10 years as biosimilar competitors, as well as newer cancer agents such as immunotherapies, reach the market. Revenue from Herceptin is expected to drop to $1.4bn by 2027. Herceptin lost exclusivity in Europe in 2014 and will see its main patents in the US expire in 2019. There are more than 10 other biosimilar Herceptin drugs in development and being considered by regulators in the US and Europe, including copycat options from **Pfizer Inc.**, **Mylan NV** and **Amgen Inc.**

Mylan/Biocon are poised to be first to the US market with biosimilar trastuzumab, which has already launched in some global markets. Their application has a Sept. 3 user fee date and the firms have reached a settlement with Roche. The FDA's Oncologic Drugs Advisory Committee will review the application in July, along with Amgen/**Allergan**'s biosimilar of Roche's *Avastin* (bevacizumab).

Commenting on the trastuzumab biosimilar data presentations at ASCO, Aleix Prat, University of Barcelona, raised a couple practical concerns for physician adoption.

"We probably would like to see some survival outcome data at some point," Prat said, as well as long-term toxicity data.

He also questioned the use of a single Phase III trial to support use in all indications, particularly given the different combinations used in different settings – including with **Novartis AG**'s *Tykerb* (lapatinib) and *Perjeta* (pertuzumab).

CAN APHINITY RELIEVE BIOSIMILAR PRESSURE?

Roche's positive Phase III APHINITY trial, which examined use of Perjeta, Herceptin and chemotherapy together as adjuvant treatment of breast cancer, underwhelmed analysts at this year's ASCO meeting.

APHINITY's aim was to show that adding Perjeta would significantly improve invasive disease-free survival rates in women with early HER2-positive breast cancer. However, analysts believe the combination treatment is likely to be limited to higher risk, node-positive patients only.

Roche's global head of oncology Dietmar Berger told *Scrip* the company is "supportive of biosimilar legislation," when asked about whether APHINITY's results and a potential new treatment setting for Herceptin would help negotiate biosimilar erosion for the drug.

"It's a part of our business, but we need to make sure that biosimilars are safe and effective," he said.

Berger said new formulations of Herceptin, such as a subcutaneous option, will do more to protect Herceptin against biosimilar competitors. Both Herzuma and SB3 are I.V. formulations of trastuzumab.

In an interview with *Scrip*, CEO Severin Schwan stressed that Roche believes "Perjeta will play a very important role in the adjuvant setting," and that "we believe we can off-set the impact of biosimilars and continue to grow the overall HER2 franchise despite the biosimilars. The adjuvant setting should be a substantial segment given the data we have now," he said.

Published online 7 June 2017

The Bar Is Raised At ASCO For ADC Developers

LUCIE ELLIS lucie.ellis@informa.com

Drug developers were challenged to strive for new heights with novel antibody-drug conjugates in solid cancers during a discussion session at the 2017 American Society of Clinical Oncology (ASCO) annual meeting, held on June 2-6 in Chicago.

The session focused on three early-stage clinical data presentations for novel antibody-drug conjugates (ADCs) from **Seattle Genetics Inc.**, **Daiichi Sankyo Co. Ltd.** and **Celldex Therapeutics Inc.**

Anthony Tolcher, director of clinical research at South Texas Accelerated Research Therapeutics (START) – a center that conducts Phase I clinical studies for novel cancer agents – challenged researchers and the drug development industry to "raise their expectations" for ADC clinical study results.

ADCs are a type of targeted cancer medicine that deliver a payload of cytotoxic chemotherapy directly to cancer cells via a linker attached to a monoclonal antibody, which binds to a specific target expressed on cancer cells.

"In patients where we have selected for high tumor target antigen expression, we must now see complete responses to be encouraged," Tolcher said, adding that dose-limiting, off-target toxicities must be substantially less than for a cytotoxic payload alone in new ADCs. "We cannot make this a very expensive delivery system for cytotoxic agents and still have the same toxicities," he said.

Finally, Tolcher noted that drug developers need to make sure that the payloads in their ADC candidates are appropriate for the indication they are targeting. His principle for ADC development is "to match the target to the indication and match the indication to payload," he said.

MIXED PHASE II DATA FOR CELLDEX

Tolcher provided commentary for ADC products in early clinical studies from three pharma companies. First up were mature data from Celldex's Phase II study of glembatumumab vedotin in patients with stage III/IV checkpoint inhibitor-refractory, and, if applicable, BRAF/MEK inhibitor-refractory metastatic melanoma. Glembatumumab vedotin is a fully human monoclonal ADC that targets glycoprotein NMB (gpNMB), a protein overexpressed by multiple tumor types, including metastatic melanoma. However, Tolcher noted that this is still a tumor-associated target rather than tumor-specific.

Tolcher said the safety results were as expected in the study, but he questioned details of a rash seen in patients treated with the ADC therapy and whether this was an on-target or off-target effect. "If it's off-target we have a real problem, because this could become quite dose-limiting," he noted, suggesting further exploration is needed.

Seven of 62 (11%) patients in the Phase II trial experienced a confirmed response, and an additional three patients also experienced single timepoint partial responses. Since data were first reported from this trial in October 2016, one patient has converted from a confirmed partial response to a confirmed complete response, Celldex reported at ASCO.

Median overall survival (OS) for all patients was 9 months, but the company said patients who experienced rash in cycle 1 experienced a more prolonged OS with a median of 15.8 months (p=0.026, HR=0.44) as compared to those who did not experience rash.

"Ten percent is borderline [confirmed response] for any new therapy," Tolcher said, adding that only one complete response is a measure of success from a time when single agent chemotherapy was the only treatment option for patients with melanoma. Having pushed this drug to its maximum dose without strong positive data in the Phase II trial, Tolcher said "you have to assume there is intrinsic resistance in most melanoma patients to an anti-microtubule agent."

Patrick Ott, clinical director of the Dana-Farber Cancer Institute's Melanoma Center and an investigator in the Phase II Celldex study, said: "The single-agent response rate observed in this study, including a complete response, and the duration of the objective responses continue to suggest that glembatumumab vedotin is an active agent in this disease."

Ott also is hopeful that glembatumumab vedotin in combination with checkpoint inhibition will bring benefit to a larger number of patients with melanoma.

Celldex is already investigating combination options in cohorts of the Phase II study for glembatumumab vedotin. In August 2016, Celldex added a second cohort of patients to the Phase II trial, testing glembatumumab vedotin and varlilumab in combination. Varlilumab is Celldex's fully human monoclonal agonist antibody that binds and activates CD27.

DAIICHI DOESN'T BEAT ON SAFETY

Tolcher was more upbeat when discussing preliminary results from the dose-expansion arm of a Phase I study of Daiichi Sankyo's DS-8201. Data from a subgroup analysis of HER2-expressing metastatic breast cancer patients pre-treated with ado-trastuzumab emtansine (T-DM1, **Roche**'s *Kadcyla*) and pertuzumab (Roche's *Perjeta*) in this study revealed a 46.7% overall response rate (14 of 30 patients) and a 100% disease control rate (30 of 30 patients). An ORR of 45.7% (16 of 35 patients) and disease control rate of 100% (35 of 35 patients) was observed in patients pre-treated with only T-DM1.

A total of 134 patients have been treated to date in both the dose escalation (24 patients) and dose expansion (110 patients) parts of the Phase I study. Preliminary results in the overall population of HER-expressing solid tumors demonstrated an overall response rate of 40.2% (39 of 97 patients) with a disease control rate of 91.8%. In the cohort enrolling patients with trastuzumab-treated HER2-positive gastric or gastroesophageal junction adenocarcinoma, a preliminary overall response rate of 44.4% (16 of 36 patients) and a disease control rate of 88.9% (32 of 36 patients) was shown to date with DS-8201.

Antoine Yver, executive vice president and global head of oncology R&D at Daiichi Sankyo, said that "based on these results, we are accelerating the development of DS-8201 and our ADC technology seeking to bring a unique precision medicine to patients and physicians who have exhausted current treatment options."

Daiichi Sankyo told *Scrip* that Phase II clinical studies are currently being planned

to evaluate DS-8201 in HER2-expressing breast cancer globally, while Phase II studies in gastric cancer are being planned in eastern Asia.

Tolcher noted that the Phase I data showed a "very high" response rate in patients who had already received the best standard of care in HER2 metastatic breast cancer. His main qualm despite the mostly positive, early data for DS-8201 was its side effect profile, which Tolcher said was manageable, but not significantly better that cytotoxic therapy alone.

The most common any-grade adverse events observed in the study so far include nausea (66.9%), decreased appetite (57.9%), vomiting (36.8%) and decreased platelet count (34.6%). Grade 4 adverse events included decreased platelet count (3.8%), decreased neutrophil count (3%), anemia (1.5%), and decreased white blood cell count (1.5%).

SEATTLE MOVES AHEAD WITH ENFORTUMAB VEDOTIN

Finally, Tolcher discussed Phase I data for Seattle Genetics and **Astellas**'s enfortumab vedotin as monotherapy treatment for metastatic urothelial cancer (mUC).

Based on the positive data, the companies this year plan to initiate a registrational monotherapy Phase II trial for locally advanced or mUC patients who have been previously treated with checkpoint inhibitor therapy.

Of the 71 patients evaluated for response, 29 patients (41%) had an objective response, including three (4%) complete responses and 26 (37%) partial responses. Disease control was achieved in 51 patients (72%), defined as the sum of patients achieving complete responses, partial responses or stable disease.

A trial evaluating enfortumab vedotin in combination with checkpoint inhibitors is also planned for later this year as part of a broad clinical development program.

Tolcher said the data suggest that enfortumab vedotin is the "single most important single agent in development for urothelial cancer." He added that the early data are comparable "to what we all got excited about a couple of years ago with PD-1." Marketed programmed cell death protein 1 (PD-1/PD-L1) inhibitors include **Merck**'s *Keytruda* (pembrolizumab), **Bristol**'s *Opdivo* (nivolumab) and Roche's *Tecentriq* (atezolizumab).

Tolcher noted that enfortumab vedotin still isn't perfect due to its side effect profile and said better ways of linking the payload still need to be explored in ADC development.

The most common treatment-related adverse events of any grade occurring in 10% or more of patients in the study were nausea (36%), pruritus (31%), fatigue (30%) and diarrhea (28%). The most common Grade 3 or 4 adverse events occurring in 5% or more of patients, regardless of attribution, were urinary tract infections, hypophosphatemia, hyponatremia and anemia.

ENCOURAGING EARLY PIPELINE

Tolcher said all three studies were "incredibly encouraging," but he called for greater diversity around the payloads used in ADC drugs, away from anti-microtubule agents. He said more partial responses still need to become complete responses before industry can begin to combine these drugs with chemotherapy or other immunotherapy agents to get the best results in patients.

AbbVie Inc. also reported Phase I data during ASCO for two ADC therapies in solid tumors: ABBV-399, which targets cMet, and ABBV-221, which targets EGFR. Meanwhile, **Pfizer Inc.** presented data for PF-06647263, an anti-EFNA4 ADC that also is in Phase I for solid tumors.

Published online 5 June 2017

Merck's Keytruda Offers Hope And Risk In Early Breast Cancer

EMILY HAYES emily.hayes@informa.com

Merck & Co. Inc.'s anti-PD-1 *Keytruda* has strong potential in combination with paclitaxel chemotherapy in very early treatment of HER2-negative breast cancer, according to new data, but risks are also emerging in this setting and could have implications for other drugs in the class. Keytruda (pembrolizumab) is currently approved for lung cancer, melanoma, classical Hodgkin lymphoma, head and neck squamous cell cancer, bladder cancer and microsatellite instability-high cancers.

Results from the I-SPY2 study presented at the American Society of Clinical Oncology (ASCO) annual meeting, held from June 2-6 in Chicago, suggest the drug could one day find a role in early treatment of high-risk breast cancer.

Merck presented over 50 abstracts at the meeting, with studies of Keytruda as a monotherapy and in combinations across 16 cancers. The data included longer term survival data in first-line lung cancer and bladder cancer, new data suggesting efficacy as a salvage therapy in gastric cancer, and updated data for Keytruda in combination with **Incyte Corp.**'s selective IDO inhibitor epacadostat in a range of tumor types.

During a June 5 investor event at the meeting, Roger Perlmutter, president of Merck Research Laboratories, stressed the progress made establishing Keytruda as a foundational therapy across a broad range of tumor types and the potential in new claims. "Breast cancer I think is a really important indication. There is a lot of opportunity there for us to do a great deal of good" for patients with few options, such as those with triple-negative disease, Perlmutter said.

THE LATEST GRADUATE

I-SPY2 is a master "umbrella" trial protocol design pioneered with the US National Cancer Institute. With this design, multiple drugs and combinations of drugs from different manufacturers have been tested as neoadjuvant treatment of high-risk breast cancer.

Drugs that show promising pathological complete response (pCR) as a surrogate marker for disease-free survival in the Phase II trial graduate to Phase III studies, typically

CONTINUED ON PAGE 14

CONTINUED FROM PAGE 13

at the sponsor's expense. *(Also see "I-SPY 2 Helping To Normalize Adaptive Trial Designs" - Pink Sheet, 10 Jul, 2016.)*

Puma Biotechnology Inc.'s neratinib and **AbbVie Inc.**'s veliparib both graduated from I-SPY2 for certain types of breast cancer, though they have had mixed results in subsequent trials. *(Also see "Veliparib Phase III Failures Strike Blow To AbbVie's Oncology Strategy" - Scrip, 20 Apr, 2017.)*

At the ASCO meeting, I-SPY researchers noted that Keytruda "graduated" I-SPY2 in three high-risk signatures: triple-negative breast cancer; hormone receptor-positive/HER2-negative breast cancer; and all HER2-negative (including the other segments).

The study randomized early breast cancer patients to paclitaxel chemotherapy (n=180) or paclitaxel with Keytruda (n=69). Patients then had doxorubicin and cyclophosphamide, followed by surgery. Keytruda was given at 200mg every three weeks for four cycles in the trial.

The results reported on June 5 at ASCO by University of Chicago breast oncologist Rita Nanda indicate a tripling in the percent of triple-negative breast cancer (TNBC) patients who achieved pCR, and a near tripling in pCR for patients with hormone receptor-positive/HER2-negative breast cancer and all HER2-negative patients, compared to control (*see table*). Such strong performance on this surrogate suggests a high probability for success in Phase III, according to I-SPY2.

Perlmutter was asked during Merck's investor meeting if, based on probability for success, the data available now were good enough for an early filing. The executive responded that he didn't think so, because there were not enough patients in the study.

"I think we really need to demonstrate that we actually can do a controlled study of [pathological complete response] in a large number of patients," he said.

On the safety front, Grade 3-5 adverse event rates of note in patients on Keytruda included hypothyroidism, hyperthyroidism and adrenal insufficiency, the last of which was reported in five (7.2%) patients on Keytruda vs. 0 for chemotherapy control. The overall rate of key Grade 3-5 adverse events for Keytruda was 12.9% vs. 1% for control.

ADRENAL INSUFFICIENCY

Discussing the results at ASCO, University of Kansas breast oncologist Priyanka Sharma said the rate of adrenal insufficiency was higher than what was seen in other trials of PD-1 inhibitors, and that due to the risk for adrenal insufficiency, researchers recommend serial screening of cortisol levels and ongoing serial thyroid function screening.

> 'It would be wonderful to identify patients who have these extremely sensitive cancers and target immunotherapy for patients with that type of tumor'

Researchers are still learning how checkpoint inhibitors affect the patient's body, commented Erica Mayer, assistant professor of medicine at Harvard Medical School, in an interview after the I-SPY2 session.

It's difficult to know whether adrenal insufficiency is a toxicity exclusive to breast cancer patients or to the particular combination used in the I-SPY2 study or is due to random chance, she said, adding that it shows how important it is to be careful and on the lookout for new types of adverse events, particularly in the curative setting, where expectations for safety are higher.

Mayer said that it's also unclear whether adrenal insufficiency seen in the study is reversible – irreversible cases of this event could present an unattractive safety signal.

Nevertheless, Mayer said that overall she saw the I-SPY2 data for Keytruda in a positive light. "It certainly was encouraging to see the predicted activity in combination with chemotherapy and definitely supports further work in this area," Mayer said.

TRIPLE-NEGATIVE MONOTHERAPY

The ASCO meeting also featured data from the KEYNOTE-086 study of Keytruda as a monotherapy in previously treated and untreated metastatic triple-negative breast cancer. In a cohort of 170 patients who were previously treated, the objective response rate (ORR) was 4.7%. And in a cohort of 52 patients with previously untreated TNBC, the ORR was 23.1%.

Roche reported positive survival results for its PD-L1 inhibitor *Tecentriq* (atezolizumab) in triple-negative breast cancer results at the American Association for Cancer Research annual meeting in April. *(Also see "Roche's Tecentriq Shows Survival In Triple-Negative Breast Cancer, For Some" - Scrip, 3 Apr, 2017.)* Of 112 evaluable patients, including 19 who had Tecentriq as a first-line treatment and 93 who had at least two or more therapies, the overall ORR was 10%.

The 4.3% ORR in the Keytruda study at ASCO disappointed some investors. Mayer noted, however, that those who did respond responded very well.

"It would be wonderful if we could identify patients who have these extremely sensitive cancers and target immunotherapy medications for patients with that type of tumor," Mayer said.

Many questions remain about the use of immuno-oncology drugs in breast cancer, including use as monotherapy versus combination, the right setting for use (preoperative versus adjuvant or metastatic) and biomarkers to guide use, she added.

The answers could come in data releases in the years ahead. Merck is running three Phase III trials in breast cancer:

- KEYNOTE-355: Pembrolizumab plus chemotherapy vs. placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer.
- KEYNOTE-522: Pembrolizumab plus chemotherapy vs. placebo with chemo as neoadjuvant therapy and pembrolizumab vs. placebo as adjuvant therapy in triple-negative breast cancer.
- KEYNOTE-119: Single agent pembrolizumab vs. single agent chemotherapy for metastatic triple-negative breast cancer.

The National Cancer Institute is also running a Phase III study testing Merck's drug as an adjuvant therapy after neoadjuvant chemotherapy in triple-negative breast cancer. The comparator in that trial is observation.

Published online 6 June 2017

View Tables Showing I-SPY 2 Adverse Event Results and Efficacy Data Here: http://bit.ly/2rminkx

APHINITY Combo Details Contain No Surprise, Puma's Nerlynx May Benefit

STEN STOVALL & LUCIE ELLIS

Details of **Roche**'s positive Phase III APHINITY trial examining use of *Perjeta* (pertuzumab), *Herceptin* (trastuzumab) and chemotherapy together in the adjuvant treatment of breast cancer underwhelmed analysts at this year's ASCO meeting in Chicago and prompted many to say the combo's use is likely to be limited to node-positive patients.

APHINITY's aim was to show that adding Perjeta would significantly improve invasive disease-free survival rates in women with early HER2-positive breast cancer. Top-line data from the evaluation – comprising 4,800 patients – were released in March showing it met the primary endpoint, and boosted hopes that Roche's combo would raise prospects the Swiss group can off-set biosimilar threats to its oncology business with new therapies.

But the takeaway from the keenly-awaited abstract – released June 5 at the annual ASCO meeting in Chicago and which contained no immediate upside surprises - showed that adding Perjeta to Herceptin and chemo significantly reduced the risk of breast cancer recurrence or death (invasive disease-free survival, or iDFS) by 19% in people with HER2-positive early breast cancer compared to Herceptin and chemotherapy alone.

Roche said that at three years, 94.1% of people treated with the Perjeta-based regimen did not have their breast cancer return compared to 93.2% treated with Herceptin and chemotherapy. The safety profile of the Perjeta-based regimen was consistent with that seen in previous studies, with a low incidence of cardiac events and no new safety signals.

Datamonitor Healthcare analyst Zachary McLellan said that "while these results are slightly positive in that adding Perjeta to the standard Herceptin and chemotherapy regimen improved iDFS, the benefit was much lower than anticipated. Still, despite only a 0.9% absolute difference between arms of the APHINITY trial, Roche plans to file these data with regulatory bodies as the group will need to rely on expanding the available patient population of Perjeta and Kadcyla to offset the eventual decline in Herceptin's sales in HER2+ breast cancer, mainly due to patent expiry."

He added that one beneficiary of the APHINITY data could be **Puma Biotechnology Inc.**, as it could enhance the value of *Nerlynx* (neratinib) as extended adjuvant therapy for HER2-positive breast cancer. Puma has filed regulatory submissions for Nerlynx in the extended adjuvant setting after the standard adjuvant treatment of Herceptin and chemotherapy. *(Also see "Puma May Face Marketing Hurdles Even If Neratinib Wins Final Approval" - Scrip, 31 May, 2017.)*

"This is good news for Puma Biotechnology's Nerlynx and its targeted indication. If approved, Nerlynx would not be indicated for use in patients that were also treated with Perjeta in the adjuvant setting. Thus, the relatively poor results from APHINITY indicate that Nerlynx may have a place in the treatment paradigm for HER2+ breast cancer," McLellan said.

Analysts at Jefferies in a reaction note said the "APHINITY data are at the bottom end of expectations. The greatest effect was in one of the highest risk groups, with node positive having a Hazard Ratio of 0.77, which accounts for some 34% of patients and where we believe use of the combination will be prioritized." Jefferies project peak sales of $4.5bn for Perjeta in the adjuvant breast cancer setting.

Bernstein analysts agreed, saying that the APHINITY data seems set to limit Perjeta use "to high-risk, [node-positive] patients globally. Furthermore, we worry about what the relevant HR(+) subgroup analysis will show."

Analysts said regulatory bodies will now have a tough task evaluating the magnitude of the benefit against the "financial toxicity" of higher costs for using the potential Perjeta/Herceptin/chemotherapy regimen.

ROCHE TAKES POSITIVE APHINITY VIEW

Roche was sanguine about the APHINITY data, and voiced confidence over its regulatory direction.

Its global head of oncology, hematologist and oncologist Dietmar Berger told *Scrip* in an interview that "APHINITY was positive as designed. It was an all-comers study; everyone was included – low risk and high risk patients – and that's what we will discuss with regulatory authorities, the overall confirmation study."

"The big question in APHINITY was whether you would see benefit with dual targeting in the adjuvant setting. APHINITY is a 4,800-patient study in a curative breast cancer setting so even differences of 2% to 3% are really considered clinically meaningful, because this is 335,000 patients globally, so if you make a difference of 2% to 3% in a curative setting, then it's really clinically meaningful," Berger said

He stressed the APHINITY data released at ASCO was a events driven analysis over 45 months of observation time.

"After four years in the control arm, 90% of patients are disease free, so with Herceptin and chemotherapy that's already good, But what's even more exciting is that, if you add Perjeta to that, you're basically near to 92%. So that makes a real difference for patients."

"If you look at the overall group, there's a risk reduction of 19% - so 19% of women are not seeing progression of their disease…in the higher risk groups those numbers are 23% and 24%, so a Hazard ratio of 0.77 and 0.76, which is clinically meaningful and will change the standard of care," he added.

"We will follow these patients out for ten years and we know that relapses occur so this is still an early analysis, so we will look again after five years and then again after ten years. We know that partially with Herceptin and chemo after ten years there's 25% of patients that have a relapse. So what we're trying to do over that period of time is to improve that benefit."

The drugs used in APHINITY was administered intravenously. Roche is studying whether giving Herceptin and Perjeta in an injection format is feasible. "It doesn't make sense to apply only one subcutaneously and the other as IV, and if you could give both subcutaneously then patients would really benefit from that," Berger said.

Published online 5 June 2017

Third Phase III Success Puts Lexicon/Sanofi's Sotagliflozin On Track For NDA Filing

JOSEPH HAAS joseph.haas@informa.com

Heading into the American Diabetes Association's Scientific Sessions meeting June 9-13, **Lexicon Pharmaceuticals Inc.** reported that sotagliflozin, its oral dual SGLT1/2 inhibitor, met the primary endpoint in a third consecutive Phase III trial, this one apparently intended to provide safety differentiation against other type 1 diabetes drugs in the sodium-glucose cotransporter-2 inhibitor class.

DRUG STUDIED WITHOUT INSULIN OPTIMIZATION

Lexicon recently reported final data showing that sotagliflozin combined with optimized insulin therapy is superior to placebo with the same background therapy in controlling A1c levels in type 1 diabetes. It reported interim data from the pivotal inTandem1 trial this past September, followed by final data May 11 from that study, making sotagliflozin the first oral anti-diabetes drug to succeed in a Phase III study of type 1 diabetes patients with inadequate glycemic control. In December, the firm reported interim data showing that the drug met its primary endpoint in the confirmatory inTandem2 study.

Unlike the first two inTandem studies, inTandem3 did not optimize patients' insulin therapy prior to dosing. Nonetheless, topline data show the study met the primary net-benefit endpoint of superiority to placebo in reducing A1c levels to no higher than 7% with no episodes of severe hypoglycemia or diabetic ketoacidosis (DKA) following randomization.

The trial enrolled 1,402 type 1 diabetes patients receiving infused or daily injectable insulin with A1c levels between 7% and 11%. Study drug was given at 400 mg once-daily over a 24-week treatment period. Lexicon said sotagliflozin posted rates of treatment-emergent serious adverse events, serious adverse events and discontinuations due to SAEs in line with rates seen in the previous two Phase III studies. For hypoglycemia, 2.4% of patients in the treatment arm and 3.0% in the control had an episode, while the rate for DKA was 3.0% in the treatment arm and 0.6% in the placebo arm.

IMPROVING A1C LOWERING EFFECT

The Woodlands, Texas-based Lexicon hopes to file sotagliflozin for FDA approval in 2018, with plans to establish the drug as a novel, oral therapy that can help patients achieve glycemic control that they've been unable to attain on insulin therapy alone. There are more than a million type 1 diabetes patients in the US, the company notes, a majority of whom have not met a goal of lowering serum A1c to 7% or lower.

"Sotagliflozin has the potential to meet several unmet needs in the type 1 diabetes market, and will likely achieve significant commercial success based on its first to market status, if approved," commented Kevin Shannon, an analyst with Datamonitor Healthcare. "The drug's ability to improve glycemic control, potential to reduce insulin dose, and association with weight loss make it very attractive to physicians treating type 1 diabetes. However, concerns over increased risk of DKA remain. Some physicians at ADA 2017 indicated that a 3.0% rate of DKA is too high, considering its serious nature. If the drug is approved, it will likely contain a warning on its label stating the increased risk of DKA. This has the potential to slow the drug's initial growth, although this is expected to be overcome by its several benefits and the lack of non-insulin alternatives in type 1 diabetes."

Speaking at the Bank of America Merrill Lynch Healthcare Conference May 18, Lexicon chief financial officer Jeffrey Wade said the amount of unmet medical need remaining in type 1 diabetes is not widely realized.

"Most type 1 diabetes patients are not achieving their A1c target, about 75% of adult type 1 diabetics in the US are above the ADA target of 7% and more than half are above 8%," he noted. "Part of this is [it's] very challenging to manage this disease with insulin alone, because if you overshoot, you take too much insulin, you can result in severe hypoglycemia. And that's a significant challenge. Weight control is also a significant challenge, and the intraday glucose variability is a challenge for patients with type 1 diabetes. And we believe that sotagliflozin has the potential to target all of these areas of unmet need."

Lexicon's first product – *Xermelo* (telotristat ethyl) – obtained FDA approval in February as the first drug therapy approved for carcinoid syndrome. Sotagliflozin, however, is seen as the bigger value-driver for Lexicon.

Morningstar analyst Karen Andersen, in a May 4 note, said data from inTandem3 – while not a pivotal trial – would be crucial in demonstrating safety differentiation from currently available SGLT2 inhibitors, such as *Invokana* (canagliflozin), *Jardiance* (empagliflozin) and *Farxiga* (dapagliflozin). She predicts sotagliflozin will reach the US market in 2019 with potential for than $1.5bn in sales. Lexicon will realize a sales royalty of between 30%-40% from its partner Sanofi, which signed on to co-develop and commercialize the product for both type 1 and type 2 diabetes in November 2015.

TYPE 1 DIABETES FILING ANTICIPATED

In a June 9 note, WedBush securities analyst Liana Moussatos called the inTandem3 success expected after the positive outcome of the previous two Phase III trials, but said the data would prove important in establishing a safety database for the drug. She added that Lexicon is slated to meet with FDA late in the second quarter to talk about filing sotagliflozin for approval in type 1 diabetes, and that it is anticipated that the agency will give the go-ahead without first asking see Phase III data in type 2 diabetes patients.

Published online 12 June 2017

Novo's Tresiba Significantly Reduces Hypoglycemia Versus Lantus In DEVOTE

KEVIN SHANNON kevin.shannon@informa.com

Novo Nordisk AS's *Tresiba* (insulin degludec) was shown to reduce the risk of severe hypoglycemia in type 1 diabetes by 40% compared to the standard of care, **Sanofi**'s *Lantus* (insulin glargine), in the DEVOTE cardiovascular outcomes trial – a significant achievement given the high prevalence of hypoglycemia and the severe threat it poses to this population.

DEVOTE also showed that Tresiba was non-inferior to Lantus on the primary endpoint of major adverse cardiovascular events (MACE), but it's the hypoglycemia data that are likely to convince many physicians of the benefits of longer-acting insulins, although the effect on formulary positioning remains to be seen. The DEVOTE results were presented on June 12 during the American Diabetes Association (ADA) 77th Scientific Sessions in San Diego, Calif.

Severe hypoglycemia is defined by the ADA as a low blood sugar event requiring intervention by a third party. It can have serious repercussions on a patient's health and is often a scarring experience. One physician at the ADA meeting told the story of a patient who passed out while driving due to a severe hypoglycemic event. After the incident, the patient was so scared of it happening again that they reduced the amount of insulin they injected, allowing their glycated hemoglobin (HbA1c) to rise above target levels. The physician was unable to alleviate the patient's fears and help them regain glycemic control.

This type of reaction is reported to occur in 79% of patients who've experienced a severe hypoglycemic event, according to presenters at the ADA meeting, which makes it nearly impossible for physicians to maintain glycemic control in this patient population. Thus, insulins that have lower risks for hypoglycemia are incredibly attractive to doctors and patient in type 1 diabetes.

Tresiba was shown to lower the risk of hypoglycemia by 40% ($p<0.001$) compared to Lantus in DEVOTE and a sub-analysis showed that this reduction increased to 53% ($p < 0.001$) when looking at nocturnal hypoglycemia, which is considered significantly more dangerous. These results suggest that physicians would have to switch three patients to Tresiba to prevent one severe hypoglycemic event, and only two patients to prevent one nocturnal event.

Shutterstock: Ioannis Pantzi

Reductions in the risk of hypoglycemia give Tresiba a distinct advantage over Sanofi's *Toujeo* (insulin glargine U300), which has failed to consistently show strong reductions in hypoglycemia compared to Lantus. This will aid Novo Nordisk in its attempt to capture a share of the basal insulin market from Sanofi, which held approximately 56% of the market in 2016, according to Datamonitor Healthcare's Type 1 Diabetes Forecast.

Tresiba was also shown to be non-inferior to Lantus in terms of MACE, with a hazard ratio (HR) of 0.91 ($p<0.001$). While this shows a trend towards reducing the risk of cardiovascular events with Tresiba, it did not prove to be significant as the upper confidence interval extended to 1.08. This result, while not surprising, is somewhat odd considering that hypoglycemia is a strong indication of CV risk. However, it has been well established across multiple classes of drugs that reduced risk of hypoglycemia with antidiabetics does not result in a reduction in CV events, though the reason for this is not known.

Physicians seem to be impressed with results from the DEVOTE trial, with several at ADA 2017 stating they would like to prescribe Tresiba in all their type 1 diabetic patients, but the US health care system prevents them from doing so. Currently, patients must fail treatment on the insulin preferred by a patient's insurer – almost always Lantus or an insulin glargine biosimilar – before physicians can prescribe a longer-acting insulin, such as Tresiba.

This has frustrated many physicians who feel it is ridiculous to wait to prescribe a superior product until after the patient has had an adverse event. The sentiment is compounded by the difficulty physicians often face in regaining glycemic control in patients who have experienced a hypoglycemic event. However, insurers must be convinced of the benefit Tresiba provides, and give it preferential formulary placement, before physicians will be able to significantly increase their use of Tresiba as the first line insulin treatment.

DEVOTE marks a major step for Novo Nordisk in its attempt to drive Tresiba to become the market-leading basal insulin. The reduction in the risk of hypoglycemia seems to have impressed physicians who treat type 1 diabetes, convincing many that Tresiba should become the new standard of care. However, before this can happen Novo must convince insurers that the reduced incidence of hypoglycemia experienced by patients when switched to Tresiba provides sufficient benefit for preferential formulary placement.

Kevin Shannon is an analyst at Datamonitor Healthcare and a contributing writer for Scrip.

Published online 13 June 2017

Bristol's New Chief Scientific Officer Lists Oncology Priorities, But Little New

LUCIE ELLIS lucie.ellis@informa.com

During an investor briefing from the 2017 American Society of Clinical Oncology annual meeting, **Bristol-Myers Squibb Co.**'s new executive VP and chief scientific officer Thomas Lynch outlined his top priorities for the firm's cancer drug development strategy – but even as the pressure mounts on the immuno-oncology pioneer, Bristol is sticking to its established strategy.

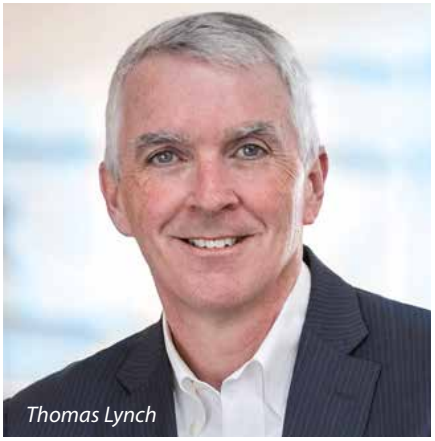
Lynch, who joined the business in March, focused Bristol's June 4 investor update on the company's vast oncology pipeline, particularly its next wave of immuno-oncology agents. With five programmed death inhibitors now on the market, success in the sector is going to be measured by execution of existing strategy and delivering new classes of drugs.

Bristol has promised to move its novel IO candidates, and combinations, swiftly through development.

First, Lynch highlighted that Bristol will continue to invest in the combination of PD-1 inhibitor *Opdivo* (nivolumab) and anti-CLTA-4 drug *Yervoy* (ipilimumab) for use across multiple tumor types. He noted that the company is testing this combination using multiple biomarker sets in cancer patients. "We need to determine the best way to use this regimen, and we believe we have a strategy that's going to get it there," Lynch said.

As the only firm with a CTLA-4 drug on the market, Bristol has been playing up this advantage for years. But **AstraZeneca PLC** is snapping at Bristol's heels with its investigational CTLA-4 inhibitor tremelimumab, and data from the MYSTIC trial on the combination of tremelimumab and AstraZeneca's PD-L1 inhibitor durvalumab in non-small cell lung cancer is expected shortly. These results will come in ahead of Bristol's Opdivo/Yervoy lung data from CheckMate 227, due late 2017/early 2018.

Meanwhile, Bristol is playing catch up to its biggest IO competitor, **Merck & Co. Inc.**, as the fellow US big pharma has already secured US FDA approval of its PD-1 inhibitor *Keytruda* (pembrolizumab) in first-line NSCLC – a setting where Opdivo monotherapy failed in the CheckMate 026 trial – and in combination with chemotherapy in the same setting. Merck also recently added a groundbreaking biomarker-based approval for its PD-1 inhibitor Keytruda for patients with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR).unresectable or metastatic solid tumors.


Thomas Lynch

At ASCO, Bristol reported efficacy and safety data from a mid-stage study, CheckMate-204 – the first data for Opdivo in combination with Yervoy in patients with melanoma that has metastasized in the brain. The combination is already cleared for treatment of metastatic melanoma.

The primary endpoint of intracranial (IC) clinical benefit rate in the study, defined as complete response plus partial response plus stable disease greater than or equal to 6 months, was 60% at the median follow-up of 9.2 months among the 75 evaluated patients. A complete IC response was achieved by 21% (n=16) of patients; 33% (n=25) had partial responses; and 5% (n=4) experienced stable disease.

Despite the positive results, concerns have been raised about the combination therapy because of its harsh side effect profile and the news that three treatment-related deaths were experienced in the trial. These deaths were reported as cardiogenic shock, IC hemorrhage and malignant neoplasm progression.

Vicki Goodman, development lead for melanoma and genitourinary cancers at Bristol, maintained "the CheckMate-204 trial is important because research about therapies for advanced melanoma patients with brain metastases is somewhat limited. Until recently, these patients have been excluded from clinical trials."

Bristol also reported data at ASCO from the Phase II CheckMate-142 trial evaluating Opdivo in combination with Yervoy in patients with previously treated metastatic colorectal cancer, including those with high microsatellite instability (MSI-H). Results from the Opdivo and Yervoy combination cohort of the trial, which also has an Opdivo monotherapy arm, included 84 patients who received their first dose at least 6 months prior to analysis. The primary endpoint of investigator-assessed objective response rate (ORR) was 54.8%. Responses were sustained up to 15.9 months and 85% of responses were ongoing; median duration of response was not yet reached.

IO & RESISTANCE

Beyond expanding Opdivo's uses, Lynch said Bristol will focus on accelerating the delivery of the next wave of assets it has in its oncology pipeline. The firm's oncology pipeline includes 19 ongoing Phase I studies, 13 Phase II trials and 24 Phase III trials (22 of which include Opdivo).

The company's early IO research includes trials for drugs with new mechanisms of action in oncology immunotherapy, such as indoleamine 2,3-dioxygenase (IDO) inhibitors and molecules targeting lymphocyte-activation gene 3 (LAG3).

Bristol and partner **Incyte Corp.** presented updated results at ASCO from the ongoing Phase I/II ECHO-204 trial evaluating the safety and efficacy of epacadostat, Incyte's investigational oral selective IDO inhibitor, in combination with Opdivo in multiple advanced solid tumors. The data revealed that in treatment-naïve advanced melanoma, patients treated with epacadostat (100 mg or 300 mg) plus Opdivo had a combined objective response rate (ORR) of 63% (25/40), including two complete responses and 23 partial responses. Patients in the study also

have a combined disease control rate (DCR) of 88% (35/40).

Furthermore, in previously treated patients with squamous cell carcinoma of the head and neck the combined ORR for epacadostat plus Opdivo was 23% (7/31), including one complete response and six partial responses, and the combined DCR was 61% (19/31). Bristol and Incyte have expanded their partnership and plan to initiate Phase III trials for the combination in first-line non-small cell lung cancer and head and neck cancers.

Bristol also presented Phase I/IIa data that demonstrated "encouraging activity" of anti-LAG-3 (BMS-986016) and Opdivo combination in heavily pretreated advanced melanoma patients who were relapsed or refractory on anti-PD-1/PD-L1 therapy. The company plans to explore this therapy in a number of other cancer types.

In the trial, the addition of BMS-986016 to Opdivo led to partial responses in six of 48 evaluable patients (two unconfirmed responses), and stable disease in another 20 patients.

Lynch also emphasized Bristol will prioritize understanding the biology of resistance in IO. "We learn more from understanding where our drugs don't work than sometimes understanding how our drugs do work," the exec said, adding that the company will be looking both at primary resistance and acquired resistance to immunotherapies.

To reach this goal of tackling resistance in IO, Lynch said the company is investing more in translational science and the concept of data and analytics. "When you look at the complexity of what our pipeline offers, if we can't find a way to develop this pipeline in a more focus and more data-driven fashion, we will never get through the pipeline even by the time that everybody in this room finishes their career," he said during the conference call.

Bristol head of oncology Fouad Namouni told *Scrip* that the pharma is also tapping into innate immunity with its pipeline. "Not a lot of people are looking at the innate immunity but we believe at BMS that it could be a strong ally to the adaptive immune system. So, when you step back we are attacking cancer and the immune system from most if not all the angles," the oncology chief said in an exclusive interview at ASCO. Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body.

From a research standpoint, Lynch noted that Bristol's full oncology pipeline offers the company "unrivaled flexibility" to test various cancer combinations quickly. From a commercial standpoint, he said that if "Bristol has the compounds in-house, we can create products that have an appealing value proposition within the market. And I don't need to tell this room [of analysts and investors] how crucial that will be in drug development over the next decade."

QUICK COMBOS OR BACKUP PLANS?

In line with this promise to quickly progress investigation assets in combination studies, Bristol is advancing its other in-house IDO inhibitor BMS-986205 – which it expects to be competitive with Incyte's epacadostat despite only having very early clinical data in hand. Some analysts have suggested Bristol's decision to advance BMS-986205 to registrational studies shows a lack of conviction in its Opdivo plus Yervoy combo. But Leerink analysts called the move "a prudent strategy to capitalize on an intriguing target, with an eventual triple therapy combination possible," in a June 5 note.

BMS-9286205 is currently in Phase II trials in combination with Opdivo for use in solid tumors.

Lynch also talked about developing new combinations in cancer as another key factor in the company's strategy. He cited the CHOP-R, five-drug chemotherapy regimen used for some lymphoma patients that has been shown to improved outcomes. "What is the approach to pancreas cancer going to be with IO? It may very well be a four- or five-drug regimen," he said, "It's very important to think about how do we develop combinations to move forward."

Finally, Bristol's CSO hinted that the company is on the lookout for business development opportunities, within and outside of the oncology space. "BMS is committed to its non-cancer portfolio just as much and we will continue to accelerate the development of our assets. We will always be looking at business development as a way of augmenting and enhancing our pipeline, both to combine with our current drugs and as a way to bring new agents into our pipeline," Lynch said.

Published online 6 June 2017

ReNeuron Spies SPA and RMAT For SC Therapy

ReNeuron Group PLC hopes to start a pivotal study of its stem cell therapy CTX for stroke disability in early 2018 following an end of Phase II meeting with the US FDA where it was advised to seek an SPA for the trial and apply for Regenerative Medicine Advanced Therapy (RMAT) designation for the product.

The benefits of RMAT designation are similar to those of Breakthrough Therapy designation, and include increased interactions with the FDA during development and eligibility for priority review and accelerated marketing approval.

The meeting was based on the results of its PISCES II trial, which, though it did not quite meet its primary endpoint, was nonetheless considered promising, especially when added to strongly positive results in its other endpoints, and the large unmet medical need.

ReNeuron now plans to submit both the SPA and RMAT designation applications within the broader IND application to begin a Phase III clinical trial with CTX for stroke disability in the US. It expects to make this combined submission in the final quarter of this year, with the study now due to start in early 2018, slightly later than previously planned second half of this year.

ReNeuron CEO Olav Hellebø said the company was greatly encouraged by the feedback it received from the FDA, especially with the SPA recommendation.

Analysts at Edison Investment Research said they expected the trial to focus on measures of disability and daily living such as the Barthel Index and the modified Rankin Scale, as these are particularly favoured by regulators. They also note the product's prospects in Japan, "The Japanese market offers an interesting opportunity as there are regulations that offer the potential for conditional marketing approval at an earlier stage of clinical development."

alex.shimmings@informa.com 6 June 2017

Read full story at: **http://bit.ly/2rgm781**

ASCO Upsets CDK4/6 Class: Strong Data For Lilly's Abemaciclib, But Pfizer's Ibrance Disappoints

EMILY HAYES emily.hayes@informa.com

Phase III progression-free survival data from the MONARCH 2 study presented at the American Society of Clinical Oncology meeting put **Eli Lilly & Co.** in a good position to file the CDK4/6 inhibitor abemaciclib in the second quarter as planned, though a different release by rival **Pfizer Inc.**'s *Ibrance* raised questions about whether the class will be able to show an overall survival benefit.

MONARCH 2 tested abemaciclib with the selective estrogen receptor degrader fulvestrant in 669 hormone-receptor positive (HR+), human epidermal growth factor receptor-2 negative (HER2-) metastatic breast cancer patients who relapsed or progressed after endocrine therapy.

Researchers reported that median PFS was 16.4 months for abemaciclib/fulvestrant vs. 9.3 months for fulvestrant alone, a highly significant result, at the ASCO meeting on June 3.

Furthermore, the objective response rate (ORR) was 48.1% for abemaciclib/fulvestrant, with 3.5% complete responses, vs. 21.3% and no complete responses for fulvestrant alone.

"This response rate is to the best of our knowledge, the highest reported in an endocrine-resistant population," said lead investigator George Sledge, chief of medical oncology at Stanford University Medical Center, in presenting results at the meeting. Top-line results were released in March. *(Also see "Can Lilly's Abemaciclib Overcome Third Place Finish In CDK4/6 Race?" - Scrip, 21 Mar, 2017.)*

Overall survival data are not mature.

Grade 3 adverse events included diarrhea (13.4% vs. 0.4%), neutropenia (23.6% vs. 1.3%) and nausea (2.7% vs. 0.9%), the company reported. The rate of Grade 4 neutropenia was 2.9% vs. 0.4%.

Diarrhea has been an adverse event of concern for abemaciclib. The trial protocol was changed to lower the starting dose from 200 mg to 150 mg to minimize effects – diarrhea typically occurred in the first cycle, and intensity and frequency were strongly related to the starting dose. The discontinuation rate due to diarrhea was 6.6% prior to the protocol change and 1.6% after.

"Diarrhea was readily manageable with dose reduction and standard anti-diarrheal medication," Sledge reported.

Lilly is now planning to file for approval of abemaciclib as a monotherapy based on MONARCH 1 and as a combination treatment in the second-line setting based on MONARCH in the second quarter and then submit a supplemental filing in the third quarter with data from the MONARCH 3 first-line trial. Abemaciclib is also being studied in Phase III in the adjuvant setting in high-risk, hormone receptor-positive, human receptor 2-negative breast cancer.

The MONARCH 2 data show the magnitude of benefit the company wanted to see, "supporting filing across indications over the next couple of quarters," Levi Garraway, senior vice president of global development and medical affairs at Lilly Oncology, commented in an interview at the ASCO meeting.

Two other CDK4/6 inhibitors are already on the market: Pfizer's Ibrance (palbociclib), which was approved in early 2015, and

Shutterstock: dorsto&media

> Until survival data are available, CDK4/6 inhibitors may not move to first-line use

Novartis AG's *Kisqali* (ribociclib), which was just approved in March. *(Also see "Novartis Sets 'Flexible Pricing' For Kisqali To Compete Against Pfizer's Ibrance" - Scrip, 14 Mar, 2017.)*

Lilly is differentiating abemaciclib partly through continuous dosing – Ibrance and Kisqali require a break in dosing to minimize neutropenia effects.

Garraway said the company took the view that continuous dosing might be preferable to intermittent dosing because in metastatic breast cancer, cells are dividing all the time.

"Intuitively, it seems obvious that intermittent inhibition of a cell cycle inhibitor, when you have 10 billion tumor cells capable of dividing at any point, would be less ideal than continuous," so Lilly set out to develop a drug that could be dosed continually in the hopes that it would translate into better efficacy, Garraway said.

Lilly sees this as a differentiating quality, along with the ability to penetrate the blood brain barrier, which is important for breast cancer patients who develop brain metastases, a feared complication.

Datamonitor Healthcare analysts think that the dosing, in addition to the benefit seen in MONARCH 2, position Lilly well for approval and competition (*see table below*). "Abemaciclib's tolerability profile is highlighted by its continuous dosing regimen. Both Ibrance and

Kisqali require time off treatment with each cycle. This, in conjunction with its strong efficacy data presented here, may give abemaciclib an advantage over its competitors, particularly in advanced HR+/HER2- breast cancer patients at later lines of therapy," the analysts concluded in a report.

In the PALOMA-3 study, Pfizer's Ibrance with fulvestrant demonstrated a median PFS advantage of 4.9 months compared to fulvestrant alone (9.5 months vs. 4.6 months).

Rates of neutropenia were lower for abemaciclib, Datamonitor Healthcare analysts noted – 46% in MONARCH 2 vs. 65% for Ibrance in PALOMA-3 and 60% for Kisqali in the MONALEESA-2 study, which included letrozole instead of fulvestrant.

The PFS advantage for combination therapy over fulvestrant alone in MONARCH 2 was 7.1 months vs. 4.9 months for Ibrance in the PALOMA-3 study, but Vanderbilt University breast oncologist Ingrid Mayer noted in a discussion about the results at the ASCO meeting that there were differences in trial design. Prior chemotherapy was not allowed in MONARCH 2, whereas it was allowed in PALOMA-3. Also, the number of lines of endocrine therapy in MONARCH 2 was limited to one, whereas it was unlimited in PALOMA-3.

This was a patient population with much less prior treatment than in PALOMA-3, which probably explains the difference in the duration of PFS, said Mayer, who is director of breast cancer clinical research at Vanderbilt Health.

IBRANCE FAILS OVERALL SURVIVAL TEST

Survival results for Pfizer's Ibrance in the Phase II PALOMA-1 study presented in the same session as MONARCH 2 raised questions about the role of the CDK4/6 class in first-line advanced breast cancer.

PALOMA-1 had supported the initial accelerated approval based on a PFS benefit. Researchers said that the analysis presented at the ASCO meeting represented the longest overall survival data available for any CDK4/6 inhibitor. Overall survival has been a difficult endpoint, largely due to the long post-progression treatment and follow-up for this disease, investigators said.

The open label PALOMA-1 study compared palbociclib with letrozole to letrozole alone in 165 patients. Median PFS was dramatically higher for the test drug arm (20.2 months vs. 10 months, hazard ratio 0.49). But overall survival was only numerically improved – 37.5 months for the combination vs. 34.5 months for letrozole alone (hazard ratio 0.90). Very few patients – less than 3% -- had palbociclib as a post-study therapy, investigators reported.

Mayer noted that the OS was not achieved, but the study was small and "clearly underpowered to show any potential difference."

"We eagerly await results from the [Phase III] MONALEESA-2 and PALOMA-2 trials to tell us if overall survival is indeed going to be seen in first-line use of CDK4/6 inhibitors plus endocrine therapy," Mayer said.

> 'The MONARCH 2 data supports filing across indications over the next couple of quarters'

Until survival data are available, CDK4/6 inhibitors may not be needed in first-line treatment, she said.

Using an aromatase inhibitor first, followed by CDK4/6 inhibition with fulvestrant in the second line and an mTOR inhibitor in the third line represents one treatment strategy. Another is to use a CDK4/6 inhibitor with fulvestrant up front, fulvestrant in the second line and an mTOR inhibitor with an aromatase inhibitor in the third line. Both of these strategies would give a patient 40 months of progression-free survival before chemotherapy was needed.

The decision about whether to use a CDK4/6 inhibitor upfront may come down to biology, Mayer said. Patients with primary endocrine therapy resistance are unlikely to respond for very long to an aromatase inhibitor alone and could benefit from a CDK4/6 inhibitor up front. On the other hand, those with a long disease-free interval and acquired resistance to endocrine therapy could defer the fulvestrant and CDK4/6 inhibitor combination for second-line therapy, she said.

But the clinician also stressed that CDK4/6 inhibitors have a valuable role to play in treatment today. Due to good quality of life, the long duration of benefit and delay in the start of chemotherapy, the class should absolutely be used in combination with endocrine therapy at some point in treatment of ER+ metastatic breast cancer, Mayer concluded.

Published online 8 June 2017

Comparison Of Trial Data For CDK4/6 Inhibitors In Breast Cancer

	PALOMA-1	PALOMA-2	MONALEESA-2	PALOMA-3	MONARCH 2
Design	Phase II, open label, first line	Phase III, placebo controlled, first line	Phase III, placebo controlled, first line	Phase III, placebo controlled, second line	Phase III, placebo controlled, second line
Endocrine partner	Letrozole	Letrozole	Letrozole	Fulvestrant	Fulvestrant
CDK4/6 inhibitor	Palbociclib	Palbociclib	Ribociclib	Palbociclib	Abemaciclib
Patients on study	165	666	668	521	669
Primary endpoint: PFS hazard ratio	0.49	0.58	0.56	0.46	0.55
Primary endpoint: PFS, median (difference)	20.2 vs. 10.2 months (10 months)	24.8 vs.14.5 (10.3 months)	25.3 vs. 16 months (9.3 months)	9.5 vs. 4.6 (4.9 months)	16.4 vs. 9.3 (7.1 months)

Source: I. Mayer, ASCO 2017

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
Visit scrip intelligence.com for the entire pipeline with added commentary.

Selected clinical trial developments for the week 2–8 June 2017

LEAD COMPANY/PARTNER	COMPOUND	INDICATION	COMMENTS
Phase III Results Published			
Takeda Pharmaceutical Co. Ltd./ Seattle Genetics Inc.	*Adcetris* (brentuximab vedotin)	cutaneous T-cell lymphoma	The Lancet online, on June 6, 2017.
Roche	*Perjeta* (pertuzumab) plus trastuzumab and chemo	breast cancer	APHINITY; NEJM online on june 5, 2017 .
Sun Pharmaceutical Industries Ltd.	tildrakizumab	plaque psoriasis	reSURFACE 1, 2; The Lancet online, June 5, 2017.
Phase III Completed			
AbbVie Inc./Johnson & Johnson	*Imbruvica* (ibrutinib)	chronic lymphocytic leukemia	RESONATE: long-term follow-up shows sustained survival benefit.
Phase III Interim/Top-line Results			
Johnson & Johnson	*Zytiga* (abiraterone) plus androgen deprivation and prednisone	prostate cancer, metastatic, hormone-naïve	LATITUDE; improved overall survival and PFS .
Actelion Pharmaceuticals Ltd.	cadazolid	Clostridium difficile associated diarrhea	IMPACT-1. -2; disappointing mixed results .
AbbVie Inc.	upadacitinib (ABT-494), oral JAK1 inhibitor	rheumatoid arthritis	SELECT-NEXT; promising efficacy .
Merz Pharmaceuticals GMBH	*Xeomin* (incobotulinumtoxinA)	sialorrhea in Parkinson's disease	SIAXI; positive results.
Teva Pharmaceutical Industries Ltd.	fremanezumab	episodic migraine prevention	HALO-2; positive results, adding to chronic migraine results.
Pfizer Inc.	dacomitinib	non-small cell lung cancer	ARCHER 1050; clinical benefits observed.
CytoDyn Inc.	PRO-140	HIV/AIDS	Encouraging results.
Phase III Initiated			
Eli Lilly & Co.	abemaciclib	early breast cancer	monarchE; as adjuvant therapy .
Alkermes PLC	ALKS-3831	schizophrenia	ENLIGHTEN-Early; supportive study.
Phase III Announced			
Can-Fite BioPharma Ltd.	piclidenoson	rheumatoid arthritis	ACRobat; to compete with methotrexate.
Bristol-Myers Squibb Co./ Seattle Genetics Inc.	*Opdivo* (nivolumab) plus brentuximab vedotin	Hodgkin's lymphoma	CHECKMATE-812.
Phase II Suspended			
NewLink Genetics Corp.	indoximod plus taxane chemotherapy	breast cancer	Missed endpoint, studies continue in other indications.
Phase II Completed			
Takara Bio Inc.	TBI-1401	melanoma	Oncolytic virus and ipilimumab shows antitumor activity.

Source: Biomedtracker

Actelion Setback Ahead Of J&J Deal Closure

SUKAINA VIRJI sukaina.virji@informa.com

Actelion Pharmaceuticals Ltd. has reported one hit and one miss in the Phase III IMPACT program of its novel anti-infective cadazolid versus vancomycin in the treatment of *Clostridium difficile*-associated diarrhea (CDAD). The program is one that will be taken over by **Johnson & Johnson** shortly when the healthcare giant completes its $30bn acquisition of Actelion, expected in the coming weeks.

In the pivotal program for cadazolid, IMPACT 1 met its primary endpoint, while the identical second study IMPACT 2 did not. Cadazolid demonstrated an "acceptable" tolerability and safety profile in the IMPACT program, Actelion added.

The company "will now work diligently to complete the analyses of the full study results and detailed results will be made available through scientific disclosure at upcoming congresses and in peer-reviewed publications," it said.

It is likely that regulatory authorities will expect Actelion to conduct another positive Phase III trial to be assured of marketing authorization. *Scrip* recently spoke to the CEO of **Tetraphase Pharmaceuticals Inc.** which suffered a similar setback with its lead compound, the antibiotic eravacycline, in 2015. That company was asked to conduct another Phase III trial, data from which are expected later this year.

IMPACT 1 and 2 compared the efficacy and safety of cadazolid (250 mg administered orally twice daily for 10 days) versus vancomycin (125 mg administered orally four times daily for 10 days). A total of 1,263 patients worldwide participated in the IMPACT program, which assessed as primary endpoint whether the clinical response after administration of cadazolid was non-inferior to vancomycin in patients with CDAD.

Cadazolid, a novel quinoxolidinone antibiotic, is an inhibitor of *C difficile* protein synthesis, leading to suppression of toxin production and spore formation.

There are two antibiotics with a specific label for C difficile infection, Merck & Co's *Dificid* (fidaxomicin) and vancomycin. Recurring infection (seen in up to 25% of cases) is a major challenge as the antibiotic treatment can deplete the protective microbiome in the gut, and about a quarter of patients experience a recurrence after the initial episode, with 40- 65% of these patients having further *C difficile* recurrence.

A number of vaccine-based approaches are in late-stage clinical development.

The transaction with J&J includes the acquisition of Actelion's pulmonary arterial hypertension (PAH) franchise plus late-stage development programs. Earlier-stage programs will be spun off prior to the close of the deal into a new company called Idorsia, led by Actelion's CEO and founder Jean-Paul Clozel, with CHF1bn in launch cash.

J&J subsidiary Janssen Biotech will have the option to license in Idorsia's lead program: ACT-132577, an orally active dual endothelin receptor antagonist for which a Phase III trial design is in the works.

Published online 8 June 2017

APPOINTMENTS

Prana Biotechnology Ltd. has named ***David Stamler*** chief medical officer and senior vice president, clinical development. Stamler was previously vice president, clinical development and therapeutic head, movement disorders at Teva Pharmaceutical Industries Ltd.

Richard E. Walters has been appointed **Octapharma AG**'s USA vice president of commercial development. Walters has more than 30 years of industry leadership experience and spent eight years as vice president US sales and corporate accounts for CSL Behring. Most recently, he was vice president of sales and marketing with General Medical Services of Summit, N.J.

Silence Therapeutics PLC has named ***Torsten Hoffmann*** chief operating officer. Hoffmann joins Silence from Proteros biostructures GMBH, where he was chief scientific officer and managing director and before this, he was chief scientific officer and executive vice president at Zealand Pharma AS.

Saratha Rajeswaran has joined the **ABPI (Association of the British Pharmaceutical Industry)** as executive director government affairs and devolved nations. Before this appointment, Rajeswaran was associate director of public affairs at Edelman. She has previously worked in senior advisory roles in politics as special advisor to UK MPs Theresa Villiers and Theresa May.

Orphan disease and cancer focused **Gamida Cell Ltd.** has appointed Nobel Prize Laureate ***Professor Roger Kornberg*** and ***Michael Perry***, an immune-oncology expert and recently retired Novartis AG executive, to its board of directors. Kornberg has been a professor of structural biology at Stanford Medical School since 1978 and won the Nobel Prize for Chemistry in 2006. He began his career at a postdoctoral research fellow at the laboratory of molecular biology in Cambridge and was later an assistant professor of biological chemistry at Harvard Medical School. Perry held various roles at Novartis including senior vice president, chief scientific officer, global BD&L, chief scientific officer, cell & gene therapy unit and global head, cellular therapy/VP, integrated hospital care franchise. Currently, he is on the board of Avita Medical Ltd., Arrowhead Pharmaceuticals Inc. and AmpliPhi BioSciences Corp.

Allergy Therapeutics PLC has appointed ***Tunde Otulana*** to its board of directors as a non-executive director; ***Thomas Lander***, non-executive director, will be retiring from his position – June 30, 2017. Otulana has more than 20 years' experience in the industry and is senior vice president and chief medical officer of Mallinckrodt PLC. He has previously worked for Boehringer Ingelheim Pharmaceuticals Inc. as senior vice president, clinical development and medical affairs. Otulana spent over six years working at the US FDA as medical officer and medical team leader in the division of pulmonary-allergy drug products.

Scrip Awards 2017

Pharma intelligence | informa

Deadline extended - enter before 16.06.2017

The 13th Annual Scrip Awards

2017

www.scripawards.com

29 November 2017 | London Hilton on Park Lane

General Enquiries:

Natalia Kay | Tel: +44 (0) 20 7017 5173 | Email: natalia.kay@informa.com

Sponsorship and Table Booking Enquiries:

Chris Keeling | Tel: +44 (20) 337 73183 | Mobile: +44 (0) 7917 647 859

Email: christopher.keeling@informa.com

Event Sponsors

aptuit HUYA bioscience international inc Research ICON A Symbol of Excellence Lachman CONSULTANTS PPD WORLDWIDE CLINICAL TRIALS 药明康德 WuXi AppTec

Headline Sponsor

QuintilesIMS