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GSK Embraces PARP Promise With Tesaro Buy

KEVIN GROGAN kevin.grogan@informa.com

GlaxoSmithKline PLC has thrown its hat back into the oncology ring, specifically into the PARP inhibitor space, by making a $5.1bn bid to acquire **Tesaro Inc.**.

The offer, which has been unanimously approved by Tesaro's board of directors, values the firm at $75 per share, representing a premium of around 60% over its closing price on Friday (Nov. 30) and 110% over its 30-day average price. The attraction of the Waltham, Mass.-based company, which has been rumored to be up for sale for some time, is its PARP inhibitor *Zejula* (niraparib), which is currently approved for second-line maintenance treatment of platinum-sensitive ovarian cancer, regardless of BRCA mutation status.

However, to date it has struggled to have much commercial success in the PARP market and is way behind **AstraZeneca PLC**'s *Lynparza* (olaparib), which is approved for ovarian and breast cancer. The latter's third quarter sales were $169m, while Zejula revenues were $63m. **Clovis Oncology Inc.**'s *Rubraca* (rucaparib), which is approved for ovarian cancer, had revenues of $23m, while a fourth PARP, **Pfizer Inc.**'s *Talzenna* (talazoparib), got a green light from the FDA for metastatic breast cancer in October this year. *(Also see "AZ's Lynparza PARP Lead Likely To Lengthen With FDA Priority Review" - Scrip, 12 Nov, 2018.)*

There is much ground to make up on Lynparza but on a conference call, GSK Global Pharmaceuticals President Luke Miels said that Tesaro had done an excellent job despite a very constrained budget and there are a number of further growth areas for Zejula which will benefit from GSK's clout. R&D President Hal Barron added that the company believes Zejula will demonstrate benefit in patients with ovarian cancer beyond those who are BRCA-positive as frontline treatment.

Barron added that the company expected to see a shift from germline BRCA testing to testing for homologous recombination deficiencies (HRD), a group of mutational biomarkers which includes BRCA, significantly broadening the number of patients who could benefit from PARPs. He believes Zejula could increase market share by tapping into the first-line maintenance treatment market of ovarian cancer patients who carry gBRCA mutations as well as the larger population of patients without gBRCA mutations whose tumors are HRD-positive and HRD-negative. Results from the first of Tesaro's Zejula studies looking at those patients, called PRIMA, are expected in the second half of 2019, potentially making it the first PARP to have monotherapy data for the first-line market beyond the gBRCA population. *(Also see "QUADRA Supports Broader Use For Tesaro's PARP Inhibitor Zejula" - Scrip, 24 Apr, 2018.)*

Barron added that GSK would explore Zejula's efficacy beyond ovarian cancer into multiple tumor types. It is currently being investigated for use as a possible treatment in lung, breast and prostate cancer, both as a monotherapy and in combination with other medicines, including Tesaro's own anti-PD-1 antibody dostarlimab.

Commenting on the proposed deal, GSK CEO Emma Walmsley also noted that buying Tesaro "will strengthen our pharmaceuticals business by accelerating the build of our oncology pipeline and commercial

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Shareholders Say Yes
Takeda one step closer to Shire merger (p8)

New CAR-T King?
Other companies make claims to Celgene, bluebird's throne (p9)

Thank You, Next
Novartis India MD moves on just months after taking top job (p21)

from the editor

eleanor.malone@informa.com

As we hurtle towards 2019, welcome to the last issue of *Scrip* this year.

Companies are squeezing through the last few deals and business strategy updates before the end of 2018. GlaxoSmithKline's less-than-lauded acquisition of Tesaro (cover story) marking the UK big pharma's return to the oncology drug market was not exactly a marquee deal but it does flag up the difference in outlook between current management and that of Andrew Witty's team, who engineered the complex business swap with Novartis less than five years ago.

Also executing a strategic pivot is Boehringer Ingelheim, which is cancelling plans to develop and commercialize biosimilars for markets outside the US, even though it had already won approval for its version of the world's top-selling medicine *Humira* (adalimumab) last year (p4).

Mallinckrodt is splitting itself in two (p6) to better position the two halves of its business, while a merger with OncoMed has given AIM-listed Mereo BioPharma the access to Nasdaq that eluded it as a standalone firm earlier this year (p7).

Takeda's merger with Shire has advanced once step closer to completion, meanwhile, with both companies' shareholders now having approved the deal (p8).

Elsewhere in this week's issue you will find detailed coverage from the American Society of Hematology (ASH) meeting that took place earlier this month in San Diego. From the latest data in blood cancers to beta-thalassemia, Mandy Jackson and Emily Hayes have it covered.

I wish all our readers a restful and rejuvenating holiday.

Scrip

LEADERSHIP
Phil Jarvis, Mike Ward, Karen Coleman

SUBSCRIPTIONS
Dan Simmons, Shinbo Hidenaga

ADVERTISING
Christopher Keeling

DESIGN SUPERVISOR
Gayle Rembold Furbert

DESIGN
Paul Wilkinson

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

CUSTOMER SERVICES
US Toll-Free: +1 888 670 8900
US Toll: +1 908 547 2200
UK & Europe: +44 (20) 337 73737
Australia: +61 2 8705 6907
Japan: +81 3 6273 4260
Email: clientservices@pharma.informa.com

TO SUBSCRIBE, VISIT
scrip.pharmaintelligence.informa.com

TO ADVERTISE, CONTACT
christopher.keeling@informa.com

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SEASON'S GREETINGS

Wishing our readers a joyful holiday season and all the best for 2019.

The next issue will be on January 4, 2019. For online access please contact clientservices@pharma.informa.com

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AML Paradigm Shift: Doctors Welcome Many New Approvals And Approaches
https://bit.ly/2Lc4yR1
This year's ASH meeting reflected a peak of development success, with many new approvals and many more in the pipeline.

CVS CEO Larry Merlo On What Comes Next After Aetna Merger
https://bit.ly/2C6xmrt
One day after CVS' $70bn acquisition of Aetna closed, CEO Larry Merlo spoke at the Forbes Healthcare Summit about why the vertical integration makes sense and how it will contribute to lower healthcare spending.

Set, Ready, Afford: China Rushes To Access Innovation Amid New Drug Dash
https://bit.ly/2QwhPZZ
2018 is set to break the record for new drug approvals in China, which have included some immuno-oncology and powerful antiviral therapies. Providing access to these high-priced medicines to more patients in the populous country was high on the minds of several multinationals during a recent conference in Shanghai.

Pharma: Be Prepared For Tougher Price Negotiations For IO Combos And Expansions In Europe
https://bit.ly/2BaCn0q
Payers are increasingly likely to implement new strategies to manage price negotiations for immuno-oncology combinations, as competition heats up among the drug class. Mechanisms allowing for the negotiation of different prices for combination therapies do not exist at present, but payers insist that new tools must emerge.

Ninlaro Looking Positive In MM Maintenance On Back Of TOURMALINE Data
https://bit.ly/2RVK3uw
Takeda's Ninlaro seems to have proved its mettle in the first major placebo-controlled trial assessing a proteasome inhibitor as a single-agent maintenance therapy in multiple myeloma.

AbbVie's Rova-T Disappoints As Second-Line SCLC Trial Halted
https://bit.ly/2BWE8zR
Enrolment In the Phase III TAHOE study has been halted due to shorter overall survival in the Rova-T arm compared with the control arm.

inside:

CONTINUED FROM COVER

footprint." As well as Zejula, the company is getting hold of a solid tumor field force, with around 250 sales representatives in the US and major EU markets, plus oncology-focused regulatory and payer relations teams.

The initial reaction to the deal from investors was mixed. Analysts at Deutsche Bank noted that they continued to believe Lynparza will remain the leader in PARP "given its first-to-market advantage and arguably preferable safety/tolerability."

They added that given the marketing strength of AstraZeneca and partner Merck combined behind Lynparza, "GSK may struggle to compete purely based on commercial/marketing support." The Deutsche Bank team went on to say that the deal "will clearly help GSK's growth profile in the medium term," but doesn't seem to do much to address [its] pipeline challenge given that acquired pipeline assets are either me-too drugs (PD-1) or seem to be high risk (TIM3/LAG3).

The analysts concluded by saying that the deal "marks a strategic U-turn from GSK's decision to exit its oncology commercial business in 2014. While this is a sunk decision, the need to acquire to rebuild a commercial presence in oncology is likely to smart with some investors."

In addition to Zejula, TESARO has several oncology assets in its pipeline including antibodies directed against PD-1, TIM-3 and LAG-3 targets. *Published online 3 Dec 2018*

Tesaro's Pipeline Beyond Niraparib

DRUG NAME	TARGET	DEVELOPMENT PHASE
TSR-022	TIM-3	Phase I
TSR-033	LAG-3	Phase I
TSR-042	PD-1	Phase I
Undisclosed	LAG-3 and PD-1	Discovery
Undisclosed	Undisclosed IO targets	Discovery

Boehringer Bails On Biosimilars Outside US

KEVIN GROGAN kevin.grogan@informa.com

Boehringer Ingelheim GMBH has decided that its biosimilars business is going to focus on the US market and is pulling the plug on plans to develop them in the rest of the world.

The German group gave a clue that it sees its biosimilars future across the Atlantic by telling *Scrip*'s sister publication *Pink Sheet* in October that despite having bagged European approval back in November last year for *Cyltezo*, its biosimilar of **AbbVie Inc.**'s blockbuster *Humira* (adalimumab), it does not plan to launch in the EU and will concentrate on a US launch. However, BI has now said that it is taking that stance with the rest of its biosimilars portfolio, although the latter is empty at present.

Last week, *Bioprocess International* reported that the company had decided to focus on launching its biosimilar products solely in the US and BI spokesperson Ralph Warsinsky confirmed the strategy to *Scrip*. Noting that the company believes "the introduction of high-quality, lower-cost biosimilars is critical for both patients and the sustainability of the healthcare system," he said that "at this point in time, future biosimilars activities will be driven out of the US market, including partnership opportunities, while BI is stopping development activities for the rest of the world."

He went in to say that "our focus is on bringing Cyltezo to the US market and we are committed to making it available to patients as soon as possible and certainly before 2023."

US is land of opportunity for BI biosimilar

AbbVie has entered into seven patent litigation settlements with companies to date, the latest being with **Pfizer Inc.**, which allow for staggered entry of Humira biosimilars. **Amgen Inc.** has a five-month lead over **Samsung Bioepis Co. Ltd.**, whose licensing agreement takes effect on June 30, 2023. **Mylan NV** is next, followed by **Sandoz Inc.**, **Fresnius SE & Co KGAA** and **Momenta Pharmaceuticals Inc.**. Pfizer is eligible to launch at the same time as Momenta, in November 2023. *(Also see "Pfizer Decides Not To Challenge AbbVie's Humira Biosimilar Patents" - Pink Sheet, 1 Dec, 2018.)*

As for BI, it is the only company that has not settled its Humira patent dispute with AbbVie, having claimed that the latter has engaged in a "pattern of pursuing numerous overlapping and non-inventive patents for the purpose of developing a 'patent thicket,' using the patenting process itself as a means to seek to delay competition." AbbVie denies the claim and a court in Delaware is looking at the case. BI has said that because of the US

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15th Legal Affairs CONFERENCE

#LAC19

26-27 MARCH 2019
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17th Biosimilar Medicines CONFERENCE

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28-29 MARCH 2019
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OPENING COCKTAIL WITH PARTICIPANTS FROM THE LEGAL AFFAIRS CONFERENCE ON 27 MARCH

For the first time, in Amsterdam

The 2019 Medicines for Europe Legal Affairs Conference will take place, for the first time, in Amsterdam.

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The conference will address:

- A General Counsel discussion on international develop-ments around IP and competition
- What to expect from the pharma incentives review and from the Supplementary Protection Certificate (SPC) Regulation
- The SPC Manufacturing Waiver: what conclusions can be drawn?
- Brexit: the IP landscape and business strategies for the sector
- What's new on Biosimilars: opportunities or challenges for biosimilar medicine developers?
- The latest developments at the European Patent Office

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Biosimilars: Shared Journey to Access

For the very first time, Amsterdam, the Netherlands, will be the host city of our annual Biosimilar Medicines Conference, taking place on 28th and 29th of March 2019. As a key milestone in the biosimilar policy agenda, this 17th edition aims at fostering a multi-stakeholder forum conducive to achieving the needed advances. Delivering biological treatments to those in need as well as unlocking re-investment opportunities in the healthcare system will concentrate participants' attention.

During these two interactive days, leaders and world experts in biosimilar medicines will gather and debate the evolving biosimilar medicines landscape and new trends. Discussion will focus on setting aims and implementing good practices to achieve the depth, breadth and speed of the use of biosimilar medicines as a lever to realise the access benefits.

The various sessions will cover all relevant areas of healthcare policy, market access, scientific developments, regulatory and clinical experience.

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CONTINUED FROM PAGE 4

patent fight, it will not commercialize its Humira biosimilar in the EU, unlike rivals Sandoz, Amgen, Samsung Bioepis and Mylan, which all launched their adalimumab products in mid-October as soon as Humira lost patent protection in Europe. Its priority for Cyltezo is clear and if BI wins the litigation with AbbVie and does indeed get onto the US market before 2023, the company could find itself in pole position in a very lucrative market – branded Humira sales in the third quarter sales were $5.12bn, of which $3.55bn were in the US.

BI had also been developing BI 695502, its version of **Roche**'s blockbuster *Avastin* (bevacizumab) and a look at clinicaltrials.gov revealed that a Phase III study comparing the two drugs in combination with chemotherapy for non-small cell lung cancer had a completion date of Nov. 16. However, BI told *Scrip* that it stopped development of BI 695502 earlier this year, deciding not to proceed with the program "based on recent chemistry, manufacturing and controls (CMC) development challenges and the subsequent impact on potential launch timelines." The company stressed that "we continue our ongoing commitment to patients enrolled in BI 695502 clinical studies," adding that it is important to note that the decision was not based on any safety or efficacy findings. BI's decision to scale down its biosimilars presence comes just over a year after fellow German group Merck KGaA completed the €656m sale of its biosimilars business to Fresenius. *(Also see "Fresenius Covers All Bases With Akorn Acquisition And Merck Biosimilar Buy" - Scrip, 25 Apr, 2017.)*

There appear to be no other projects running, given that a click on the biosimilar links on BI's website is met with an error message. Also, in 2015, the firm terminated clinical development for its biosimilar version of another Roche blockbuster, namely *Rituxan/MabThera* (rituximab).

Just a week ago, the FDA gave the green light to **Teva Pharmaceutical Industries Ltd.** and **Celltrion Inc.**'s *Truxima*, making it the first US-approved biosimilar of Rituxan, the third approval of a biosimilar across the Atlantic in a month, after the thumbs-up for Sandoz's Humira copy *Hyrimoz* and **Coherus BioSciences Inc.**'s *Udenyca*, a biosimilar to *Neulasta* (pegfilgrastim). *(Also see "Keeping Track: US FDA Enters Year's Final Stretch With Tsunami Of Novel Approvals " - Pink Sheet, 1 Dec, 2018.)*

These approvals, plus BI's strategy change, show that the US, which has lagged behind Europe in terms of creating a regulatory biosimilars pathway, is evolving into a viable market, helped in no small manner by the support of FDA commissioner Scott Gottlieb, who has regularly raised concerns about the development and commercial hurdles for biosimilars in the US. *(Also see "Momenta Is Exiting Biosimilars; Is That A Bellwether For Biosimilar Sentiment? " - Scrip, 2 Oct, 2018.)*

In comments following the Truxima approval, Gottlieb noted that as part of the FDA's Biosimilars Action Plan unveiled in July, it is advancing new policies to make development more efficient "and to enable more opportunities for biosimilar manufacturers to make these products commercially successful and competitive. Our goal is to promote competition that can expand patient access to important medicines."

Published online 4 December 2018

Mallinckrodt Creating Two Companies: Generics And Innovative Specialty Drugs

JESSICA MERRILL jessica.merrill@informa.com

Mallinckrodt PLC will soon begin operating as two independent publicly traded companies – an innovative specialty drug marketer, and a generic and active pharmaceutical ingredient developer. That's after the company announced plans to spin out its specialty generics and API business Dec. 6, pending final board approval. The spin-out is expected to be completed in the second half of 2019.

The decision is part of a strategy to position some of the business into a new pure-play specialty pharmaceutical company, even as the company has sought to reduce its dependence on *H.P. Acthar Gel* (corticotropin injection). Acthar has been a controversial product, because it is an older medicine that underwent an enormous price hike.

"Specialty generics and specialty pharmaceutical brands have distinct business models and each has been impacted by the divergent set of market dynamics," CEO Mark Trudeau said in a same-day conference call. "The planned separation will allow the respective management teams to focus on and commit to the long-term strategic priorities aligned with each company's stakeholders."

Trudeau is expected to remain CEO of the new innovative company, which will be named at a later date and trade on the New York Stock Exchange.

Chief Financial Officer and President of the Specialty Generics business Matthew Harbaugh will become CEO of the new generics and API company upon completion of the spin-out, which will be executed through a pro-rata distribution of common stock to Mallinckrodt's shareholders.

The generics company will assume the Mallinckrodt name and ticker symbol. Although Mallinckrodt is based in the UK, the generics business is based in the US and will be headquartered in the St. Louis area.

The generics business has been a de-prioritized business at Mallinckrodt for some time, and it has been reported under discontinued operations in the company's financial updates as it has explored strategic alternatives.

The decision to break out the business will be refreshing and provide an opportunity to direct its own cash flow into reinvestments, Harbaugh said.

"In the last few years, the specialty generics business has assumed a supporting player role within Mallinckrodt," he said.

INNOVATIVE PHARMA: A $2.3BN BUSINESS

The better known innovative pharma business will have net sales in excess of $2.3bn, with a portfolio of hospital products includ-

Mallinckrodt splits company in two

> 'In the last few years, the specialty generics business has assumed a supporting player role within Mallinckrodt' – Mark Trudeau, CEO

ing *INOmax* (nitric oxide) gas, *Ofirmev* (acetaminophen) injection and Acthar for a range of autoimmune conditions.

Acthar attracted negative attention because it is an old drug that saw a steep jump in price, mostly under its prior owner Questcor, from $1,640 to $34,034 a vial since 2001.

Mallinckrodt acquired the product in 2014, but sales have come under pressure more recently. Acthar sales declined 6% year-over-year to $290.1m in the third quarter. The drug accounted for about 45% of the company's continuing operations – excluding the discontinued generics business – in the third quarter.

Mallinckrodt acquired **Sucampo Pharmaceuticals Inc.** for $1.2bn, including debt, earlier this year in an effort to diversify its portfolio. The company gained *Amitiza* (lubiprostone), a marketed drug for various constipation indications, and *Rescula* (unoprostone) for lowering ocular pressure, which is sold in Japan. Amitiza is poised to face generic competition in the near-term, so the longer-term benefits of the deal were focused on the late-stage pipeline, which includes two Phase III drugs for rare conditions.

Amitiza will go to the specialty generics business, which Harbaugh said was appropriate because it is managed through established commercial partnerships that resemble some of the company's other non-promoted brands for pain, addiction treatment and attention-deficit hyperactivity disorder (ADHD). An authorized generic version of the drug also is expected to launch in the US in 2021 under a settlement with **Par Pharmaceutical** . It is marketed by **Takeda Pharmaceutical Co. Ltd.** in the US.

The generic business generated $850m for the 12 months ended Sept. 28, including seven months of sales of Amitiza.

The specialty generic business also will have a leading acetaminophen business, a portfolio of API and generic finished-dose forms of controlled substances and a strong US manufacturing footprint, the company said. The business will employ 1,600.

"We anticipate roughly 40% of the business will come from APIs, approximately 35% will come from specialty generic dosage products and the remaining 25% will come from Amitiza and other non-promoted brands," Harbaugh said. "Specialty generics also has an ANDA pipeline of complex generics that we believe positions the business for growth longer term." The business is on track to launch as many as five new products in 2019, he said.

One of the challenges, however, will be around potential opioid litigation liability.

Leerink analyst Ami Fadia, in a same-day note, said the news could be incrementally positive for the innovative specialty company, because it could be a source of liquidity to further bolster the pipeline, but the headwinds facing the generic business could be problematic. "We believe the addition of Amitiza to this business is a positive as it provides a source of cash flows at least in the near term," Fadia said. "However, we believe investors will struggle with the lack of visibility into the pipeline on which very little has been disclosed so far, continued macro headwinds in generics, and the outstanding opioid litigation overhang."

Published online 6 December 2018

Mereo Makes It Stateside With OncoMed Merger

KEVIN GROGAN kevin.grogan@informa.com

The UK's **Mereo BioPharma Group PLC** is to get the US listing it had been seeking by merging with troubled California-based **Oncomed Pharmaceuticals Inc.**, adding cash and a couple of investigational cancer drugs.

In an interview with *Scrip* just after the deal was announced (Dec. 5), Mereo CEO Denise Scots-Knight noted that after postponing plans for a US offering in April, which would have raised in the region of $80m, the company decided late in the third quarter of this year to appoint Evercore as an advisor to look for US firms listed on NASDAQ which were doing strategic reviews. One of the options they came up with was OncoMed, a firm which itself had hired Leerink to look at its options after a series of setbacks. The latest of those came in September when **Celgene Corp.** decided against taking up an option on OncoMed's cancer drug navicixizumab, a move which battered its share price. The drug, an anti-DLL4/VEGF bispecific antibody, has shown promise in a Phase Ib trial in combination with paclitaxel in patients with platinum-resistant late-stage ovarian cancer, but pipeline prioritization at Celgene led to the rights being returned.

At the beginning of 2018, another Celgene-partnered drug, the anti-RSPO3 antibody rosmantuzumab, was discontinued after disappointing interim Phase I data. 2017 also saw the failure of a Phase II trial of Celgene-partnered demcizumab in pancreatic cancer, while **Bayer AG** declined to license the Wnt pathway inhibitors vantictumab and ipafricept.

Nevertheless, Scots-Knight is enthusiastic about the prospects for navicixizumab, but acknowledged that "it needs significant

investment to advance it so we are looking to partner that or do some sort of transaction." OncoMed also has the anti-TIGIT candidate etigilimab which is in Phase I and Celgene has an option to acquire the drug.

The all-equity reverse merger will see Mereo own 75% of the combined entity and issue new American Depositary Receipts (ADRs) to OncoMed investors, rather than shares from its present listing on London's AIM, giving them 25% of the company. In addition, the latter will also get contingent value rights (CVRs) based on what happens to navicixizumab and etigilimab.

Based on Mereo's closing share price of 190 pence on Dec. 4, the shares underlying the ADRs represent an aggregate value of $57.4m, a premium of 34% over OncoMed's market capitalization of $42.9 million the day before the deal was unveiled. As of September 30, the pro-forma cash resources of the combined business were $115.5m, including $70.9m from OncoMed, which extends Mereo's runway into 2020.

Scots-Knight noted that the deal broadened the firm's asset base and strengthened Mereo's cash position. The plan to initiate the ADR program on NASDAQ, in addition to the continued listing on the AIM "will facilitate a deep engagement with the broadest range of appropriate investors."

The companies noted that the Redwood City-based firm's workforce will be cut back to just "a core employee base to meet the obligations for the ongoing OncoMed operations." CEO John Lewicki will stay on as an advisor as partnership opportunities for the navicixizumab program are explored and Mereo's eight-member board will be expanded to include "two new biopharmaceutical industry-experienced OncoMed independent non-executive directors," They are Michael Wyzga, currently chief financial officer of **Aura Biosciences Inc.** and Deepa Pakianathan of Delphi Ventures.

As well as finalizing the merger, which is due to complete in the first half of next year, Scots-Knight told *Scrip* that 2019 would be a busy one for Mereo's own pipeline when the company expects "several value inflection points." Much of the focus will be on its anti-sclerostin antibody acquired from **Novartis AG** called BPS-804 (setrusumab), which is in Phase IIb for osteogenesis imperfecta (OI), or brittle bone disease.

Scots-Knight noted that six-month data from an open-label high-dose arm should be available in the first half of 2019, with 12-month dose ranging data expected in the second half. A Phase II study is also running in the US and Europe on MPH-966 (alvelestat), licensed from **AstraZeneca PLC** last October for the treatment of severe alpha-1 antitrypsin deficiency and top-line data are expected late in the second half of 2019.

She added that after the successful completion of Phase II studies "we are in the midst of partnering discussions" for BCT-197 (acumapimod) for acute exacerbations of chronic obstructive pulmonary disease, which was licensed from AstraZeneca in October last year. Scots-Knight said the firm was talking to regulators about the future clinical program which needs to be finalized before any partnering deal can be confirmed. Mereo is also looking to partner BGS-649 (leflutrozole), which licensed from Novartis, for hypogonadotropic hypogonadism in obese men.

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Clear 'Yes' From Shareholders On Takeda/Shire Deal

IAN HAYDOCK ian.haydock@informa.com

Takeda Pharmaceutical Co. Ltd.'s proposed acquisition of larger company **Shire PLC** has passed another key final hurdle, easily receiving approval at an Extraordinary General Meeting of the Japanese firm's shareholders held in Osaka on Dec. 5, followed by a similar vote of approval later in the day from Shire investors.

The deal needed a two-thirds majority and in the event around 88% of Takeda shareholders who exercised their vote were in favor of the $62.4bn transformational transaction - the biggest-ever M&A deal by any Japanese company and the fifth-biggest ever globally in the pharma sector.

Specifically, the vote put to Takeda investors was on a proposal to delegate to the Takeda board the decision regarding offering terms for the issuance of new Takeda shares to implement the acquisition.

"The Takeda shareholder approval condition required for the Acquisition to be implemented has therefore been satisfied," Takeda said in a statement just after the vote.

Similar clearance came in an EGM at Dublin, Ireland-based Shire later the same day, the steps removing the last potential pitfall on the way to the expected Jan.8, 2019 completion date, following generally smooth anti-trust approvals in major jurisdictions.

Takeda's share price was volatile in trading in Tokyo on Dec 5 around the expected nod, and closed the day around 1.4% higher, given the approval has largely been built into investor expectations. In the statement, Takeda President and CEO Christophe Weber said he was "delighted" in shareholders' strong support, which he said sets the stage for the merged entity to become "a more competitive, agile, highly profitable, and therefore more resilient company".

The shareholder support provides solid – while not unanimous –endorsement of his vision for the 237 year-old company, where he took over as CEO in April 2015 and has since overseen massive R&D reorganization, a stronger focus on core areas, and a string of divestments.

The effective merger with Shire will bring a portfolio and bolster the later-stage pipeline in rare diseases, plasma operations, a significantly stronger presence in the key US market – which Weber sees as still strongly supporting and rewarding innovation – and an increased scale that will finally take the Japanese company into the top 10 pharma groups globally.

Takeda shareholders in addition overwhelmingly approved the appointment as external directors to Takeda's board of three existing Shire external directors (Ian Clark, Olivier Bohuon and Steven Gillis), effective upon closing.

FINAL UNCERTAINTIES LIFTING

Takeda's share price has been lingering around five-year lows following the May confirmation of deal talks with Shire, given un-

certainties around investor concern over the funding of the huge transaction and the influence of lingering opposition from some influential shareholders on the direction of the vote.

On top of this, there has been what Deutsche Bank noted was incremental shorting from merger arbitrage funds, but its analysts now expect these suppressive factors to disappear following the vote, for which they note the market had priced in a "c.85% probability of a yes".

Takeda President and CEO Christophe Weber said he was 'delighted' in shareholders' strong support

Takeda shares should "sustain a strong upward trajectory into mid-2019," Deutsche Bank predicted in a Dec. 3 note.

While there had been strong opposition to the Shire deal from some shareholder quarters, including a group linked to the founding family which together hold around 10% – including former chairman Kunio Takeda – in the event these proved inconsequential.

Institutional investors (split roughly equally between Japan and overseas) hold around 66% of Takeda, and were seen to be generally in favor of the acquisition, and positive on the Japanese firm's plans to pay down its related debt through financing instruments and planned disposals.

Even so, Takeda is taking on around $30bn in debt in relation to the massive transaction, which is expected to reduce its credit ratings, although the company shas repeatedly stressed that post-closing divestments – which observers expect to include Shire's eye care business – and continued cost controls will help it pay down debt as quickly and as far as possible.

Reflecting this, the Deutsche Bank analysts said in their Dec. 3 analysis that they "continue to be comfortable with Takeda's capacity to pay its dividend and remain investment grade", with the deal seen as "strongly accretive to Core EPS [earnings per share] (+c40%) into the medium term". Following the Shire shareholder approval, the acquisition still remains subject to a formal sanctioning of a scheme of arrangement by a court in Jersey (Channel Islands), which is expected on Jan. 3 and is the last pre-completion procedural hurdle.

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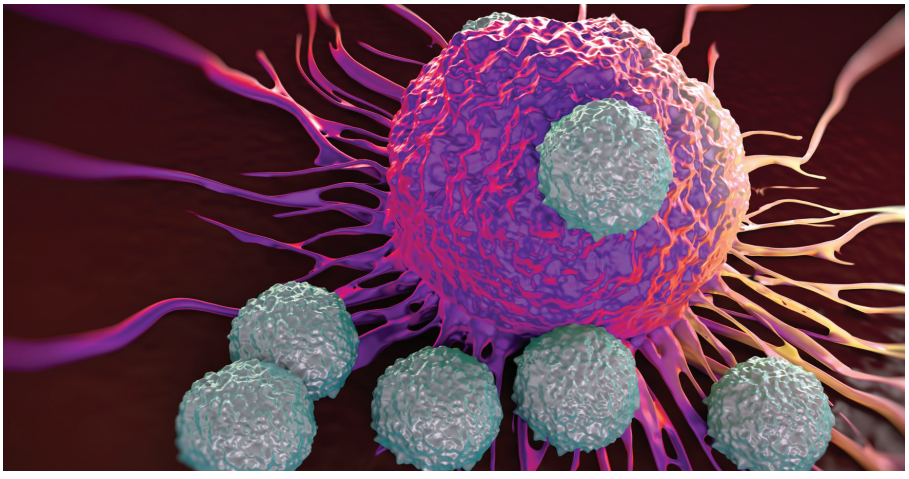
From the editors of PharmAsia News.

Poseida, Legend/Janssen Look To Snag Celgene/ Bluebird's BCMA Crown

MANDY JACKSON mandy.jackson@informausa.com

While **Celgene Corp.** and **bluebird bio Inc.** have the most advanced BCMA-targeting chimeric antigen receptor T-cell (CAR-T) therapy in the clinic for the treatment of relapsed or refractory multiple myeloma, data presented at the American Society of Hematology (ASH) meeting on Dec. 3 in San Diego show that CAR-T therapies against the same target from **Poseida Therapeutics Inc.**, partners **Legend Biotech Corp.** and **Janssen Pharmaceutical Cos.**, and others are quickly gaining ground.

Early Phase I data showing strong responses in the first 12 patients treated with Celgene's and bluebird's bb21217 – the partners' next-generation CAR-T asset targeting B-cell maturation antigen (BCMA) – were presented at ASH on Dec. 2, but not for their pivotal-stage candidate bb2121.



However, data for several other autologous BCMA-targeting CAR-T candidates also were presented on Dec 3, including results from 44 patients treated with Celgene's JCARH125, the BCMA-targeting CAR-T program it bought in the $9bn acquisition of Juno Therapeutics Inc. earlier this year.

Data for Poseida's P-BCMA-101 showed a 100% response rate for patients treated with the top dose (n=3), which will be the dose tested in the company's Phase II study. Also, there were limited cases of cytokine release syndrome (CRS) and neurotoxicity that frequently are seen with CAR-T therapies and can be severe. The small, private firm intends to move rapidly into a pivotal trial starting in the first half of 2019 based on these results with the goal of generating data that will support submission of a biologic license application (BLA) to the US FDA by the end of 2020.

Meanwhile, data for Legend/Janssen's LCAR-B38M from the Phase I/II LEGEND-2 clinical trial that Legend conducted in China included results from twice as many

patients – 57 as of the data cutoff versus 23 in Poseida's data set – and also showed strong response rates and low rates of CRS and neurotoxicity in advanced relapsed or refractory multiple myeloma.

However, while Legend is taking this CAR-T candidate into a confirmatory Phase II trial in China in 2019, Janssen's Phase Ib/II trial for the related investigational new drug (IND) JNJ-68284528 for the US and other markets began just this year.

CHINA-FIRST LCAR-B38M DATA SUPPORT BIG PHARMA BACKING

Nanjing, China-based Legend and **Johnson & Johnson** subsidiary Janssen reported at ASH that in patients with a median of three prior rounds of treatment the overall response rate (ORR) was 88%, including a complete response (CR) rate of 74%, very good partial response (VGPR) rate of 3% and partial response (PR) of 11%. The companies noted that 39 of the 42 patients with a CR were determined to be MRD-negative, which is believed to be a marker of a good prognosis.

With a median of 12 months of follow-up, median progression-free survival (PFS) across all patients was 15 months and PFS was 24 months for patients with minimal residual disease (MRD)-negative CRs. MRD negativity increasingly is viewed as a marker of a good prognosis.

Investigator Wan-Hong Zhao of The Second Affiliated Hospital of Xi'an Jiaotong University in Xi'an, China noted during the ASH presentation for LCAR-B38m that median overall survival (OS) has not been reached, but OS at 12 months was 75%.

The data presented at ASH included only patients enrolled in the study at Zhao's institution, but not the 17 patients enrolled at three other hospitals in China.

CRS occurring at a rate of 90% was among the most common adverse events along with pyrexia (91%), thrombocytopenia (49%), and leukopenia (47%). Grade 3/4 AEs were experienced by 65% of treated patients, the most common of which were leukopenia (30%), thrombocytopenia (23%) and increased aspartate aminotransferase (21%).

CRS was mostly grade 1 (47%) or grade 2 (35%), but 7% experienced grade 3 CRS. One patient had grade 1 neurotoxicity, which included aphasia, agitation and seizure-like activity. There were 17 deaths in the study and follow-up period due to progressive disease (n=14), suicide after disease progression (n=1), esophagitis (n=1), and pulmonary embolism and acute coronary syndrome (n=1).

Janssen and Legend entered into a worldwide collaboration and license agreement nearly a year ago to jointly develop and commercialize LCAR-B38M, which is directed against two distinct BCMA epitopes to confer high avidity and affinity binding of the CAR-T therapy to BCMA-expressing cells. Janssen paid $350m up front under the deal. *(Also see "China Looms Large Seeking New Funding, Deals At J.P. Morgan" - Scrip, 10 Jan, 2018.)*

A short investor called previously reported LCAR-B38M data into question recently and Legend quickly refuted those claims, with Chief Scientific Officer Frank Fan confirming again to *Scrip* during the ASH meeting that: "Legend has never omitted any clinical data whatsoever. The allegations were and remain completely groundless. Shortly after we officially responded to Flaming Research's anonymous, false report, it was removed from the web site." *(Also see "China CAR-T Front-Runner Allegations Reveal Soft Underbelly Of Development Race" - Scrip, 28 Sep, 2018.)*

Indeed, Janssen Vice President, Late-Stage Development and Global Medical Affairs for Oncology, Hematology and Supportive Care, Craig Tendler and Vice President, Oncology Clinical Research, Sen Zhuang confirmed the pharma's confidence in LCAR-B38M in an interview with *Scrip*.

"The study results that are being reported, it's is an important validation of what we hoped was initially true – that this particular CAR-T against the BCMA target is active and looks from an efficacy point of view to have a profile that's very competitive in terms of CR rates, and a high proportion of our patients that are achieving CR that are being reported at this meeting are MRD-negative," Tendler said. "All the signs are there from the study that was conducted in China that this is a highly active and efficacious CAR-T."

The data, he said, give Janssen and J&J the confidence necessary to throw their massive resources behind LCAR-B38M research and development as well as manufacturing.

Zhuang noted that Janssen will report results from its recently initiated study for JNJ-68284528 as soon as possible – potentially at ASH 2019.

TINY POSEIDA SEEKS A SEAT AT THE THRONE

San Diego-based Poseida is developing its lead CAR-T candidate P-BCMA-101 on its own. The company closed a $30.5m Series B venture capital round in April to fund its development of autologous and allogeneic CAR-T therapies and gene therapies. *(Also see "Finance Watch: VC Investment Soars In Q1, Putting Biopharma On Track For A Record Year" - Scrip, 15 Apr, 2018.)*

Of the three patients treated with the high dose of more than 1bn CAR-T cells, the responses included a PR in a patient who was MRD-negative and two VGPRs. Investigator Tara Gregory of the Colorado Blood Cancer Institute said during the ASH presentation that response rates were dose-dependent, ranging from 50% at the lowest dose to 100% at the top dose.

Poseida treated 23 patients with relapsed or refractory multiple myeloma in its Phase I study and reported "meaningful responses" for 15 out of 19 patients evaluable by International Myeloma Working Group (IMWG) criteria. Those responses included 13 patients with a stringent CR (sCR; five were MRD-negative), CR, VGPR or PR, and two patients dosed during the past 60 days who were described as having a "minor response" and continued to show improvement.

The company said P-BCMA-101 was well tolerated with two mild and transient instances of suspected CRS – one grade 1 and one grade 2 – and one possible neurotoxicity, but none of those adverse events were observed at the two highest doses tested in cohorts 4 and 5. Gregory noted that the slow expansion of P-BCMA-101 cells relative to other BCMA-targeting CAR-T therapies may account for the low incidence of CRS.

"These data suggest that our CAR-T product candidate, which is comprised of a high percentage of stem cell memory T cells (Tscm), has the potential to be truly differentiated and result in more gradual peak expansion leading to deep responses and lower toxicity as observed so far in this trial," Poseida CEO Eric Ostertag said in a company statement. "Although CRS and neurotoxicity have been significant risk factors in other CAR-T therapies with reported rates as high as 90% for some products, we have observed very little CRS or neurotoxicity and, when it has been suspected, it has been mild and transient."

P-BCMA-101 was granted a regenerative medicine advanced therapy (RMAT) desig-

nation by the FDA in November. *(Also see "Keeping Track: Yupelri Is Latest Novel Drug Approved, But Bad News For Biosimilars" - Pink Sheet, 11 Nov, 2018.)*

The initial Celgene and bluebird BCMA-targeting CAR-T therapy – bb2121 – already has moved into a pivotal trial. Data from the Phase II KarMMa study are expected to support regulatory submissions in 2019 seeking approval to treat relapsed or refractory multiple myeloma.

The companies' Phase I trial for bb2121 in this setting at ASH 2017 showed very high response rates, including a 94% ORR and 56% CR in this advanced myeloma population. *(Also see "Celgene's CAR-T Leadership Goals Advance At ASH 2017" - Scrip, 12 Dec, 2017.)* Progression-free survival data were presented from the Phase I study in June at this year's American Society of Clinical Oncology (ASCO) meeting.

The high response rates in the Phase I trial for bb2121 set a high bar for the follow-on candidate bb21217, which is enriched for memory T-cells to potentially improve CAR-T cell persistence and duration of efficacy, and for JCARH125.

The data presented at this year's ASH meeting for 12 patients treated with bb21217 at a dose of 150m CAR-T cells showed objective responses in 10 patients (83%), including three with a CR or sCR, two with VGPR and four with a PR. Among four patients who responded to treatment and had evaluable bone marrow samples, all four were MRD-negative.

Adverse events were described by Celgene and bluebird as manageable and consistent with known CAR-T therapy toxicities, including CRS and neurotoxicity.

There were four grade 1, three grade 2, one grade 3 and no grade 4 cases of CRS, for a total of eight out of the 12 bb21217-treated patients (67%). Neurotoxicity was experienced by three out of 12 patients (25%), including one Grade 1, one Grade 2 and one Grade 4 case, but there were no deaths from this side effect, which resolved during the study.

However, bb21217's developers have now divided patients into two groups based on tumor burden to determine in the treated patients and in individuals enrolled later at higher doses whether tumor burden plays a role in developing severe neurotoxicity, investigator Nina Shah from the University of California, San Francisco noted during the ASH presentation.

Data for JCARH125 were presented from 44 patients treated with the first three doses in the Phase I dose escalation portion of the Phase I/II EVOLVE clinical trial. The ORR was 82% with a median follow-up of 11 weeks. The ORR was 79% at the lowest dose level of 50m CAR-T cells, including a 43% rate of sCR or CR. Asked about responses based on dose level, EVOLVE investigator Sham Mailankody of **Memorial Sloan Kettering Cancer Center** said during the ASH presentation that it's too early to compare across doses.

EVOLVE required patents to have had at least three prior lines of therapy, but in reporting the study's safety results Celgene noted that patients were heavily pretreated with a median of seven prior lines of therapy. Grade 1/2 CRS was experienced by 71% of trial participants with grade 3/4 CRS reported for 9% of patients; grade 1/2 neurotoxicity was observed in 18% of patients, while 7% experienced grade 3/4 neurotoxicity. Other grade 3/4 adverse events included neutropenia (86%), anemia (50%), thrombocytopenia (43%) and infection (14%).

One patent with grade 4 CRS and a neurological event described as confusion died during the trial, but Mailankody noted that the patient had a history of chronic kidney disease associated with multiple myeloma and that the individual developed a lack of pharyngeal reflex, acute kidney injury and *Klebsiella pneumoniae* sepsis as a nosocomial infection. The patient died 19 days after treatment with JCARH125.

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Roche/Abbvie's Venclexta Outshines Agios IDH Inhibition In AML At ASH

EMILY HAYES emily.hayes@informa.com

Updated data for **Roche/AbbVie Inc.**'s BCL-2 inhibitor *Venclexta* in frontline treatment of acute myeloid leukemia looks robust – perhaps threatening **Agios Pharmaceuticals Inc.**'s IDH1/2 inhibitors *Idhifa* and *Tibsovo* – but clinical experts caution against comparing the two mechanisms, particularly without randomized data.

New data on all three drugs was presented at the American Society of Hematology (ASH) meeting Dec. 1-4 in San Diego.

The market for AML is being watched closely as the competitive dynamics have intensified. Eight new drugs have been approved by the US FDA for acute myeloid leukemia in the last two years, including Agios' Tibsovo and Idhifa, the latter of which is partnered with **Celgene Corp.**, and Roche/Abbvie's Venclexta.

> 'It is a different field today than it was a year ago. Absolutely, it is different,' said John Hayslip, medical director at AbbVie.

The spate of recent approvals followed decades of a stagnant treatment landscape for the disease and reflects substantial investment by the pharmaceutical industry, despite a relatively niche market.

"It is a different field today than it was a year ago. Absolutely, it is different," said John Hayslip, medical director at AbbVie.

About 21,000 new cases of AML are diagnosed every year in the US. Younger patients (those in their 40s to 60s) theoretically can get high-intensity chemotherapy and have a chance at complete remission, but

fewer than half of newly diagnosed patients are actually candidates for that regimen.

Drug development has been focused on frontline treatment of older patients who can't tolerate high intensity chemotherapy, relapsed/refractory disease and on genetic mutations across lines of therapy.

Tibsovo (ivosidenib) and Idhifa (enasidenib) were each approved within the last year and a half by the US FDA for use as monotherapy in relapsed/refractory AML based on single-arm studies.

Venclexta (venetoclax) got a supplementary approval in November for frontline AML in older patients not eligible for standard induction chemotherapy in combination with low-dose cytarabine (LDAC) or hypomethylating agents, such as azacitidine, also based on single-arm studies. US clinicians interviewed by *Scrip* said that LDAC is not commonly used or favored and may be hard to access at specialty pharmacies, so approval of Venclexta and other new AML drugs in combination with hypomethylating agents is important.

At ASH, Roche/Abbvie presented updated data for the studies supporting the approval of Venclexta and Agios presented data from studies of Tibsovo and Idhifa in frontline IDH-mutated AML. Agios plans to file Tibsovo as a monotherapy in IDH-mutated frontline AML by the end of January.

VENCLEXTA AML UPDATE WELL-RECEIVED

Clinicians described the updated Venclexta data at the ASH meeting as robust. In the M14-358 study, the rate of complete response plus complete response with at least partial blood count recovery (CR+CRh) was 67% for Venclexta with azacitidine and 71% for Venclexta with decitabine, another hypomethylating agent.

The percent of patients negative for minimal residual disease (MRD) after treatment is becoming an important endpoint, and in M14-358, 48% on Venclexta/azacitidine (29/60) and 39% on Venclexta/decitabine (9/23) achieved this.

Furthermore, in patients with IDH mutations, the rate of complete response with or without recovery of blood count (CR/CRi) was 90% for Venclexta/azacitidine (18/20) and 100% (5/5) for Venclexta/decitabine.

In a second study presented at the meeting – M14-387 – the CR/CRi rate for Venclexta/LDAC was 54% and 21% of patients (17/82) achieved MRD-negativity. The CR/CRi rate for those with IDH mutations was 25%.

Phase III studies testing Venclexta with azacitidine or LDAC in previously untreated AML patients who are ineligible for intensive chemotherapy are ongoing.

Patients who are older and not able to undergo intensive chemotherapy can now achieve the benefits of a high remission rate through Venclexta combinations, Hayslip said.

But the story for venetoclax and the BCL-2 target more generally in AML is just beginning, and there is a push to expand the patient groups who can benefit, he said.

"These studies are about Venclexta plus low-intensity [chemotherapy] treatment, but if Venclexta can do this for patients who can't receive more intensive therapies, what can it do for patients who are younger and fitter?" the exec asked.

Cleveland Clinic AML specialist Aaron Gerds said that the presentation of updated data at the meeting adds to the robustness of the Venclexta narrative as it evolves and noted that a lot of doctors are comfortable with the drug as they have already used it in chronic lymphocytic leukemia (CLL). However, he added the caveat that single-arm studies can be misleading and that robust results can dissipate later in a randomized trial.

Peter Emanuel, director of oncology services at CHI St. Vincent at Little Rock, said that in his view venetoclax is the most exciting among the new drugs right now for AML due to broader applicability, versus applicability in particular subsets.

PRESSURE ON AGIOS SHARES

The robust performance of the Venclexta combination, particularly in patients with IDH1/2 mutations, exceeding the results for the IDH2 inhibitor Idhifa as a single agent in frontline AML, as well as safety concerns, put pressure on Agios shares, Leerink Swann analyst Andrew Berns said in a Dec. 3 note.

Agios' stock price fell 13.66% on Dec. 3 to a close of $56.81 and closed down another 4.86% on Dec. 4 at $54.05.

Idhifa and Tibsovo both were approved with a boxed warning for IDH-differentiation syndrome, a condition caused by the rapid proliferation and differentiation of myeloid cells that can be fatal if not treated.

On Nov. 29, the FDA issued a safety communication about differentiation syndrome associated with Idhifa urging greater monitoring and aggressive management of the condition, and the agency also presented a safety meta-analysis drawing attention to the adverse event at the ASH meeting.

Both Gerds and Emanuel told *Scrip* that they did not see the risk as a barrier to use and that it may be managed by experienced prescribers. Gerds, who chairs the communications committee at ASH, said a learning curve can be expected with new drugs.

However, Leerink's Berens saw the FDA's safety presentation and efficacy data for Idhifa as monotherapy as part of the Leukemia & Lymphoma Society "Beat AML" umbrella development program for targeted drugs in newly diagnosed AML as negative. The objective response rate in 27 patients treated with Idhifa was 44%, the LLS reported at the meeting.

Berens said that some doctors at the meeting had the impression that the IDH inhibitors – in particular Idhifa – have diminished activity compared with Venclexta. However, the analyst also said that the Idhifa monotherapy data presented at the meeting "do not represent an accurate assessment of the IDH inhibitor development plan and opportunity."

While Berens sees Venclexta as a significant competitor, he saw two other studies reported by Agios – Tibsovo as a monotherapy in frontline patients not eligible for other therapies and Idhifa or Tibsovo with "7+3" frontline chemotherapy induction – as more relevant for the company.

The monotherapy study tested Tibsovo in a subset of 34 patients (out of a total Phase I study population of 258) who had IDH1 mutant newly diagnosed AML (primary and secondary) and were ineligible for standard treatment. In the subset, the drug demonstrated a CR+CRh rate of 42.4% and an objective response rate of 57.6%.

Agios CEO David Schenkein pointed out in an interview that these patients were very sick with very limited options. Half had previously had azacitidine as a treatment for myelodysplasia and would not be eligible to have it again as a repeat treatment in combination with venetoclax.

Safety was consistent with prior reports. The rate of IDH-differentiation syndrome of any grade was 17.6% and cases were managed with corticosteroids and diuretics, Agios reported. No permanent treatment discontinuations or deaths were reported.

These data will be submitted as part of Agios' planned FDA filing in IDH-mutated frontline AML next month. In the combination study, patients received Tibsovo or Idhifa

with standard induction and consolidation chemotherapy plus maintenance treatment in newly diagnosed AML (primary and secondary) with IDH1 or IDH2 mutations. In this study, 60 got Tibsovo and 93 got Idhifa.

For those on Tibsovo, the ORR was 80% for efficacy-evaluable patients. In a subset of those who had complete responses, elimination of MRD was achieved in 17%.

The rate of Grade 3+ IDH-differentiation syndrome was 3%.

For Idhifa, the overall best response rate was 72% in efficacy-evaluable patients. The rate of Grade 3+ IDH-differentiation syndrome was 1%.

Agios and Celgene are planning to start the Phase III, randomized-controlled HOVON 150 AML/AMLSG 29-18 study of Tibsovo or Idifa in 1,000 newly diagnosed IDH-mutated AML patients eligible for intensive chemotherapy by the end of the year. The study will test the IDH inhibitors in combination with 7+3 chemotherapy induction and consolidation chemotherapy followed by maintenance treatment for up to two years.

Gerds cautioned against comparing Venclexta with the IDH inhibitors. Venclexta targets the BCL-2 pathway whereas the IDH inhibitors are targeting particular mutations. Also, the studies did not include a direct comparator and results may change when a direct comparator is added and/or when trials get larger. Comparing the data for Venclexta with IDH inhibitors is not just like comparing apples vs. oranges, but "apples vs. elephants," Gerds told *Scrip*.

Emanuel said that more data is needed to know whether Venclexta or an IDH inhibitor should be used upfront, but that it would make more scientific sense that if a patient has a genetic abnormality to go first to a drug that targets that specific abnormality.

Schenkein said that his company showed compelling data for Tibsovo and Idhifa with azacitidine in newly diagnosed AML at the American Society of Clinical Oncology (ASCO) meeting this year that were similar to what has been seen with Venclexta.

But he added that he doesn't view Venclexta as competition. In treatment of older patients, none of the drugs are curative at this time, he noted. "The reality is that patients are going to need all of these medicines," Schenkein said.

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Imbruvica, Darzalex 'Practice-Changing' In Front-Line CLL, Myeloma

MANDY JACKSON mandy.jackson@informausa.com

AbbVie Inc./Johnson & Johnson's *Imbruvica* (ibrutinib) and J&J's *Darzalex* (daratumumab) were two of the biggest stars on the main stage during the late-breaker session that ended the annual American Society of Hematology (ASH) meeting on Dec. 4 in San Diego.

Tait Shanafelt of the Stanford University School of Medicine

Source: Courtesy of ASH

Investigators presented data that they described as practice-changing, because of the efficacy and safety gains compared with the standards of care for younger previously untreated patients with chronic lymphocytic leukemia (CLL) and older newly diagnosed individuals with multiple myeloma. In both cases, progression-free survival (PFS) and overall survival (OS) were improved, but notably for CLL patients, safety also was significantly improved by replacing chemotherapy with Imbruvica.

NO MORE CHEMO: IMBRUVICA ENDS NEED FOR TOXIC THERAPY

The study evaluating the Bruton's tyrosine kinase (BTK) inhibitor Imbruvica plus **Roche/Genentech Inc.**'s and **Biogen**'s anti-CD20 antibody *Rituxan* (rituximab) versus the standard-of-care chemotherapy regimen fludarabine, cyclophosphamide and Rituxan (FCR) was sponsored by the National Cancer Institute (NCI) and the ECOG-ACRIN Cancer Research Group, with funding from the NCI and **Pharmacyclics Inc.**, an AbbVie company.

CLL and small lymphocytic leukemia (SLL) patients in the clinical trial were randomized on a 2:1 basis to receive 420 mg per day of Imbruvica until disease progression and seven cycles of Rituxan (IR) or six courses of FCR. There were 77 PFS events and 14 deaths across both arms of the study in the intent-to-treat group at a median follow-up of 33.4 months.

With 37 patients who progressed out of 354 enrolled in the IR group and 40 out of 175 who progressed in the FCR group, the risk of progression was reduced by a statistically significant 65% (HR=0.35; p<0.0001). In terms of OS, four patients treated with IR died and 10 treated with FCR died (HR=0.17; p=0.0003, but p=0.0005 was the pre-specified boundary for superiority).

Grade 3 and 4 treatment-related adverse events (TEAEs) were observed in 58% of IR-treated patients and in 72% of FCR-treated patients (p=0.042). The grade 3 and 4 TEAEs reported most frequently for FCR-treated patients were neutropenia (44% versus 23% in the Imbruvica arm; p<0.0001) and infections (18% versus 7%; p<0.0001).

"These definitive results show why large trials like this that test new therapies in an effort to achieve clinically meaningful benefit for patients, are so important," Richard Little of the Cancer Therapy Evaluation Program at the NCI said in a statement from the institute.

Lead investigator Tait Shanafelt, the **Stanford University School of Medicine** professor of hematology who presented the data at ASH, noted during a Dec. 3 press conference at the meeting that the study is a registrational trial with a design and endpoints that were signed off by the US FDA.

AbbVie and J&J have not revealed whether they will seek approval for Imbruvica plus Rituxan for previously untreated younger CLL patients, but they will discuss the study results with regulators, Danelle James, head of clinical science at Pharmacyclics, told *Scrip* in an interview at ASH.

> 'The totality of the data supports that chemotherapy is not the best way to treat these patients in CLL in the front-line setting'

James pointed to the ECOG-ACRIN study and other data presented at the meeting as compelling evidence that chemotherapy should no longer be the standard of care in many CLL settings.

For instance, data from the Phase III iLLUMINATE study presented on Dec. 3 showed that the combination of Imbruvica and Genentech's next-generation anti-CD20 agent *Gazyva* (obinutuzumab) significantly improved PFS versus Gazyva plus the chemotherapy drug chlorambucil in newly-diagnosed CLL or SLL. With a median of 31.3 months of follow-up, median PFS was not reached in the Imbruvica/Gazyva arm, but was 19 months in the Gazyva/chlorambucil arm (HR=0.23).

The FDA accepted a supplemental new drug application (sNDA) for Imbruvica in combination with Gazyva based on the iLLUMINATE results in October. The drug already is approved in the front line as a monotherapy – long-term follow-up data from newly diagnosed and relapsed/refractory CLL patients also were presented during the ASH meeting, showing sustained remissions for up to seven years for patients treated with Imbruvica, but without chemotherapy.

"The totality of the data supports that chemotherapy is not the best way to treat these patients in CLL in the front-line setting," James said.

But while combining two targeted therapies to boost efficacy and improve safety relative to long-used chemotherapy drugs may be practice-changing, Shanafelt noted in a statement issued by ASH that one remaining question about the use of the IR regimen rather than FCR is the impact of Imbruvica's cost of about $10,000 per month – a question that fell outside the scope of the ECOG-ACRIN study.

One way that AbbVie/Pharmacyclics and J&J are working to limit the financial impact of long-term or chronic Imbruvica dosing, is by testing Imbruvica in various combination regimens to see if the drug can be administered alongside other novel therapies over fixed durations, James explained. "We have to look beyond the cost of therapy to the cost to society and the cost to the individual patient [of chemotherapy] – keeping the patient out of hospital without the need for supportive care and treatment of infections and being able to go back to work all benefit the patient and society; that's what the drug is bringing from a value perspective," Craig Tendler, vice president of late-stage development and global medical affairs for oncology, hematology and supportive care at J&J subsidiary **Janssen Pharmaceutical Cos.**, said in an interview.

That said, Tendler noted that "for some patients, it may be difficult to stay on the treatment for long periods of time. We are looking at combinations that can show the same improvement with a fixed duration of treatment," including studies with AbbVie and Genentech's Bcl2 inhibitor *Venclexta* (venetoclax). Venclexta also has been successful in combination with Gazyva in the front-line CLL setting.

Shanafelt noted during the press conference and his ASH late-breaker presentation that two ECOG-ACRIN trials will be initiated soon to test 12-month regimens of Imbruvica plus Gazyva versus Imbruvica plus Venclexta – one of which will enroll CLL patients aged 70 and older with the other testing the combination regimens in patients 70 and younger. Efficacy and safety will be evaluated as well as the cost-effectiveness of these short-term regimens using novel targeted medicines.

DARZALEX DAZZLES IN OLDER FRONT-LINE PATIENTS

J&J had a good ASH meeting between Imbruvica, its anti-BCMA chimeric antigen receptor T-cell (CAR-T) therapy LCAR-B38M in multiple myeloma and its anti-CD38 antibody Darzalex, which it licensed from **Genmab AG** in 2012. Darzalex was tested in combination with **Celgene Corp.**'s *Revlimid* (lenalidomide) and dexamethasone (D-Rd) versus Revlimid and dexamethasone (Rd) in the Phase III MAIA study that enrolled 737 newly diagnosed multiple myeloma patients who were ineligible for high-dose chemotherapy and autologous stem cell transplant. Top-line results were reported in October.

MAIA participants tended to be older patients, ranging from 45 to 90 years old with a median age of 73. Lead investigator Thierry Facon of Claude Huriez Hospital in Lille, France noted during the Dec. 3 ASH press conference and his Dec. 4 presentation of the MAIA data that 44% of patients were 75 or older, which was a little higher than in the real-world multiple myeloma setting where about a third of patients are 75 or older. With a median follow-up of 28 months, D-Rd significantly reduced the risk of death versus Rd by 44% (HR=0.56; p<0.0001). Median PFS was not reached in the D-Rd arm of the study, but it was 31.9 months in the Rd arm.

Responses to treatment also were improved by the addition of Darzalex to the Rd standard of care in these older, newly-diagnosed patients with complete responses in 48% of those treated with D-Rd and in 25% of patients treated with Rd. The percentage of patients who were minimal residual disease (MRD)-negative was three times greater for D-Rd compared with RD – 21% versus 7%. MRD-negativity is believed to be a predictor of a good prognosis.

The PFS, CR and MRD improvements did not come without a safety trade-off, however, with higher rates of some grade 3 and 4 TEAEs, including neutropenia (50% for D-Rd versus 35% for Rd), lymphopenia (15% versus 11%) and pneumonia (14% versus 8%). TEAEs more common for Rd-treated patients included anemia (20% for Rd versus 12% for D-Rd) and thrombocytopenia (9% versus 7%).

Tendler noted that Janssen also is looking at shorter-term combination therapy regimens in multiple myeloma to see if Darzalex or any of the company's other drugs or drug candidates can be combined with other agents to achieve remission during a fixed duration of therapy that can be maintained after treatment stops.

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'Totality Of Data' Make A Case For Luspatercept In Beta-Thalassemia, MDS

MANDY JACKSON mandy.jackson@informausa.com

Luspatercept met the primary endpoints in its first two Phase III tests – in transfusion-dependent beta-thalassemia and myelodysplastic syndromes (MDS) in the BELIEVE and MEDALIST studies, respectively – but **Acceleron Pharma Inc.** CEO Habib Dable pointed to key secondary endpoints in both clinical trials that could be the most important data points to treating physicians.

Results from the two studies were presented on Dec. 1 and 2 at the American Society of Hematology (ASH) annual meeting in San Diego. Luspatercept – a first-in-class erythroid maturation agent (EMA), which is believed to regulate late-stage red blood cell maturation – is being developed by Acceleron in partnership with **Celgene Corp.** The companies expect to submit the drug for approval in the US and EU for the treatment of beta-thalassemia and MDS in the first half of 2019.

Dable told *Scrip* in an interview at the ASH meeting that discussions with payers about the results are under way to determine reimbursement prospects for luspatercept, but he noted that the totality of the data from the studies will be important to support commercial use and reimbursement, not just the primary endpoints.

The MDS market is larger than the beta-thalassemia opportunity, but luspatercept was tested in both diseases in transfusion-dependent patient populations that are in need of new therapies, because they have essentially no options besides regular red blood cell (RBC) transfusions. The exception is in MDS, where patients sometimes are treated off-label with erythropoietin-stimulating agents (ESAs) – to the tune of about $500m per year in the US alone, according to Acceleron's research.

The BELIEVE trial in beta-thalassemia sought to cut RBC transfusion use by at least one-third and MEDALIST was designed to show that luspatercept could eliminate the need for transfusions in MDS. Reduction or elimination of regular blood transfusions would decrease the time patients have to spend at transfusion clinics as well as cut the small risk of infection and immunogenicity associated with transfusions and the longer-term risk of iron overload that requires chelation therapy to prevent liver and heart damage.

The primary endpoint in BELIEVE was a 33% or greater reduction in transfusion dependence for beta-thalassemia patients during weeks 13-24, and 21.4% of luspatercept-treated patients (48 out of 224) achieved this measure during that 12-week period versus 4.5% who were given a placebo (five out of 112), which was statistically significant ($p<0.0001$).

However, BELIEVE investigator Maria Domenica Cappellini from the **University of Milan** said during her ASH presentation – and Dable said when discussing the data – that a secondary endpoint assessing the reduction in transfusion dependence during any consecutive 12-week period during the 48-week study was more clinically meaningful than the primary endpoint. That secondary endpoint was achieved by 70.5% of patients in the luspatercept arm (158 out of 224) versus 29.5% in the placebo arm (33 out of 112; $p<0.0001$). Cappellini noted that because the beta-thalassemia population is heterogeneous, different patients respond at different times to treatment.

In real world practice, Dable noted, doctors don't ask patients how they did during a particular 12 weeks, but how they did since the last time the physician saw the patient.

"If you look at any 12-week period, we were able to show similar results as we did in our Phase II of 69% and 70% reductions … so that becomes very meaningful to patients," he said.

The Phase II study for luspatercept in transfusion dependent beta-thalassemia also used week 13-24 transfusion reduction as the primary endpoint, so regulators agreed to the same primary endpoint for Phase III, but the Acceleron CEO said there's "nothing magical" about that period of time post-treatment.

He noted that in both beta-thalassemia and low-risk MDS, "it was really important to us to demonstrate safety and efficacy in terms of the totality of the data" across the Phase III studies' primary and secondary endpoints. And, as in the beta-thalassemia pivotal trial, Dable said the MEDALIST study in MDS had a secondary endpoint that is more important to doctors than the primary endpoint necessary for regulatory approvals.

MEDALIST JUMPS OVER HI-E HURDLE

"Our primary endpoint in MDS is actually transfusion independence, but quite frankly that's not necessarily the way doctors treat [patients]," he said. "The clinically meaningful endpoint, referred to as HI-E, or hematologic improvement-erythroid, is really determined by the International Working Group's guidelines on how patients [are assessed]."

In the 229-patient MEDALIST trial, 38% of patients treated with luspatercept achieved transfusion independence versus 13% who received a placebo ($p<0.0001$). The study enrolled very low-, low- and intermediate-risk MDS patients with ring sideroblasts (high levels of iron in the blood) who require regular blood transfusions. Leerink analyst Martin Auster noted in a Nov. 1 report about Acceleron that investors were looking for at least a 30% reduction in transfusion dependence and Auster pointed out that doctors have said a 20%-25% reduction would be clinically meaningful.

But when it came to HI-E, Dable said, "we had approximately 53% response rates versus 12%" and "that was very similar to what we saw with approximately 55% in our Phase II."

In terms of both the BELIEVE and MEDALIST studies, he added, "arguably, the primary endpoints are not necessarily the clinically meaningful endpoints. We were very happy that in both primaries as well as our secondaries that we were able to hit highly statistically significant numbers in terms of demonstrating efficacy of the drug in both studies."

Top-line results were reported from both studies in June and July.

Rates of grade 3 or higher treatment-emergent adverse events (TEAEs) in BELIEVE were 29.1% (65/223) for luspatercept-treated patients and 15.6% (17/109) in the placebo group. Serious adverse event rates

were 15.2% (34/223) and 5.5% (6/109), respectively. The most common grade 3 or 4 events were anemia, increased liver iron concentration, hyperuricemia, hypertension and syncope.

There were eight thromboembolic events of any grade (two were grade 3 or 4) among the 223 luspatercept-treated patients (3.6%), including deep vein thrombosis, pulmonary embolism, portal vein thrombosis, ischemic stroke, thrombophlebitis, and one thromboembolic event was reported among the 109 placebo-treated patients (0.9%).

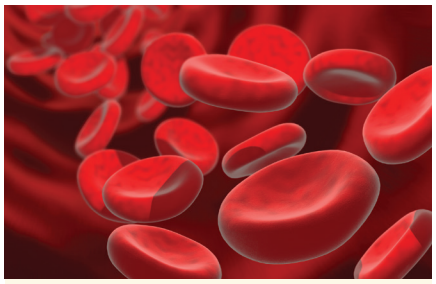
Cappellini noted during her presentation that all eight luspatercept-treated patients with thromboembolic events had multiple risk factors for such events – including a beta-thalassemia diagnosis – and all eight patients had undergone a splenectomy, which also is a risk factor for thromboembolic events.

Evercore ISI analyst Umer Raffat noted in a Dec. 1 report that "the commercial opportunity for luspatercept is primarily in [the] MDS indication," but said that "from an investor perspective, the real focus [of the BELIEVE data] was safety: mainly because the drug is understood to 'work' in this indication, and investors [are] looking to take read-across on safety to the important MDS indication."

Raffat was satisfied with Capellini's explanation that the BELIEVE population and the eight luspatercept patients with thromboembolic events had inherent risk factors for these events. Overall, he said, the safety and efficacy data are supportive of luspatercept approval in beta-thalassemia.

The safety results in MDS patients in the MEDALIST trial were similar across the luspatercept and placebo arms of the study. Grade 3 or 4 TEAEs were reported in 42.5% of luspatercept-treated patients (65/153) and in 44.7% in the placebo group (34/76). Three patients progressed to acute myeloid leukemia (AML) in the luspatercept arm (2%) and one placebo-treated patient progressed to AML (1.3%). TEAEs leading to death were reported among five patients in the luspatercept group (3.3%) and four patients in the placebo arm (5.3%).

Moffitt Cancer Center President and CEO Alan List, who presented the MEDALIST data, described luspatercept during his Dec. 2 ASH plenary session presentation as "well-tolerated" with no significant differences between TEAEs and severe adverse events across the study's two arms.



The companies expect to submit the drug for approval in the US and EU for the treatment of beta-thalassemia and MDS in the first half of 2019

PAYER TALKS WILL ACCELERATE FOLLOWING ASH DATA

Acceleron and Celgene are engaged in extensive research mode and discussions with payers about how they'll view reimbursement for luspatercept, Dable said, noting that those discussions will intensify now that the BELIEVE and MEDALIST data have been presented.

"We estimate that there's approximately 40,000 patients in the US and Europe that would fall under the definition of the MEDALIST population that we included in our Phase III; that is a roughly split 50-50," he explained. "When you look at the entry criteria for the BELIEVE study in beta-thalassemia patients, we estimated that there's an addressable population of about 20,000 between the US and Europe, but 90%-95% are outside the US, so it's going to be imperative for us to have detailed conversations with payers across a number of countries so we're able to understand what are the important metrics."

However, ongoing studies in additional MDS and beta-thalassemia patients may add another 45,000 patients to luspatercept's addressable market.

While MEDALIST enrolled MDS patients who were not helped by ESAs or who were not eligible for treatment with ESAs, the Phase III COMMAND study is enrolling 350 lower-risk MDS patients in the front-line setting to evaluate luspatercept head-to-head against ESAs. Acceleron and Celgene estimate the ESA-eligible, low-risk MDS market at another 25,000 patients in the US and Europe.

List said during a Dec. 1 press conference highlighting the MEDALIST and BELIEVE results that he expects luspatercept to be effective versus ESAs, because the drug was effective in MEDALIST regardless of patients' erythropoietin levels.

In beta-thalassemia, the ongoing Phase II BEYOND study is recruiting 150 non-transfusion dependent patients, which Dable noted can be a more symptomatic population, since they're not undergoing regular transfusions. That indication adds another 20,000 US and European patients to luspatercept's addressable market.

Another ongoing Phase II study in myelofibrosis is recruiting 40 patients with disease-induced anemia to be treated with luspatercept monotherapy, and another 30 patients who will receive the drug in combination with **Incyte Corp.**'s JAK inhibitor *Jakafi* (ruxolitinib) to treat both disease-induced and JAK inhibitor-induced anemia.

The myelofibrosis indication, when added to the beta-thalassemia and MDS markets, could bring luspatercept's market to 120,000 patients in the US and Europe. Excluding myelofibrosis and any other anemias that Acceleron and Celgene may pursue, the companies estimate peak sales of their drug could reach as high as $2bn in the US and Europe.

It remains to be seen if those estimates will hold up as gene and cell therapies for beta-thalassemia – some with data presented at ASH – make their way to the market, but Dable said Acceleron welcomes the competition.

"Innovation is great, especially in a space without any therapies," he said. "If luspatercept is approved, if the gene therapies are approved, we feel there will be an opportunity for both therapies. There will be patients that respond on luspatercept and some that don't. If there's alternatives for those patients, we welcome it."

Cappellini said during the Dec. 1 press conference that for gene therapies to be successful in beta-thalassemia they would need to go beyond reducing transfusion dependence to curing the disease by eliminating the need for transfusions entirely.

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Roche's Tecentriq Becomes Second In PD-1/L1 Family To Gain First-Line Lung Cancer Approval

EMILY HAYES emily.hayes@informa.com

At long last, **Roche**'s anti-PD-L1 *Tecentriq* was approved on Dec. 6 by the US FDA for use with the company's VEGF inhibitor *Avastin* and chemotherapy for first-line, metastatic non-squamous, non-small cell lung cancer (NSCLC), though patients with EGFR and ALK mutations were excluded, eliminating an expected labeling advantage.

Approval was supported by the results of the Phase III IMpower150 study, one of eight trials that are part of the pivotal NSCLC program testing Tecentriq (atezolizumab) in a variety of lung cancer settings.

IMpower150 tested the drug and chemotherapy (carboplatin or paclitaxel) with or without Avastin (bevacizumab) in previously untreated metastatic non-squamous NSCLC. The study included 1,202 patients, most of whom – 1,045 – did not have EGFR or ALK mutations.

Median overall survival was 19.2 months for the Tecentriq/Avastin combination versus 14.7 months for chemotherapy alone in the wild-type population, a significant reduction in risk (HR=0.78).

The drug demonstrated efficacy in subgroups with EGFR and ALK mutations as well as liver metastases in IMpower150 and it had been hoped that this would give Tecentriq an advantage relative to PD-1/L1 competitors, which excluded these populations from trials. However, the final label does not indicate the drug for NSCLC patients whose tumors have these mutations.

Roche submitted its supplemental filing to the FDA in May for the first-line NSCLC indication – the most valuable indication for PD-1/L1 inhibitors – and the application had a user fee date of Dec. 5, following a three-month delay, as the agency requested additional information.

Tecentriq's new approval adds to its previously approved indications in second-line NSCLC and urothelial cancer – and the new first-line indication makes it the first PD-1/L1 inhibitor approved in the first-line metastatic NSCLC setting.

Roche reported results from another study that could support an additional first-line lung cancer study, known as IMpower130, in October. That study combined Tecentriq with **Celgene Corp.**'s *Abraxane* (nab-paclitaxel) and carboplatin.

MERCK DOMINATES NSCLC

Results from IMpower150 were presented at the American Association for Cancer Research meeting in April, but were overshadowed by data for **Merck & Co. Inc.**'s competing PD-1 inhibitor *Keytruda* (pembrolizumab) in the KEYNOTE-189 first-line non-squamous NSCLC study. *(Also see "Roche's IMpower150 Gets AACR Applause But Merck's KEYNOTE-189 Big Winner " - Scrip, 17 Apr, 2018.)*

Keytruda became the first PD-1/L1 inhibitor approved by the FDA for first-line NSCLC in mid-2017.

In the KEYNOTE-189 study, Keytruda demonstrated a dramatically improved, significant overall survival benefit (HR=0.49) on top of a significant progression-free survival (PFS) benefit (HR=0.52), with consistent results across levels of PD-L1 expression, setting a standard for the whole field.

The counter-argument from Roche in April was that it wasn't fair to compare the data from IMpower150 with KEYNOTE-189, because KEYNOTE-189 used a different backbone – **Eli Lilly & Co.**'s *Alimta* (pemetrexed) and platinum-based chemotherapy.

However, Roche announced results in September for Tecentriq in the IMpower132 study using a similar backbone as KEYNOTE-189 that were disappointing. In that trial, the Tecentriq/chemo combination demonstrated a 40% improvement in PFS, but had not hit the overall survival mark yet. *(Also see "Tecentriq's Small-Cell Lung Cancer Success Takes Edge Off Roche's IO Position" - Scrip, 25 Sep, 2018.)*

Bristol-Myers Squibb Co.'s PD-1 inhibitor *Opdivo* (nivolumab) also has faltered in the race for the first-line NSCLC crown, having announced a three-month delay on Oct. 19 for its supplemental biologic license application (sBLA) filed with the FDA for the combination of Opdivo with a low-dose of the company's CTLA4 inhibitor *Yervoy* (ipilimumab) in first-line NSCLC.

Fueled by use in lung cancer, Keytruda has begun to overtake Opdivo in sales for recent quarters. Bristol reported $1.79bn for Opdivo in this year's third quarter, up 42% from the same period in 2017. *(Also see "Amid PD-1 Uncertainty, Bristol Under Pressure For M&A Activity" - Scrip, 25 Oct, 2018.)*

That compares to $1.89bn – an 80% increase from $1.05bn in the third quarter of 2017 – for Merck's Keytruda. *(Also see "Keytruda Is King, But Merck Faces Questions About Business Development" - Scrip, 25 Oct, 2018.)* **AstraZeneca PLC**'s PD-L1 inhibitor *Imfinzi* (durvalumab) has also fallen short in first-line metastatic NSCLC – missing the mark when used in combination with the CTLA4 inhibitor tremelimumab in the Phase III MYSTIC study, the company reported in mid-November. *(Also see "Mystic Miss Not Make Or Break For Imfinzi" - Scrip, 16 Nov, 2018.)* However, Imfinzi did get the first approval for stage III NSCLC. *(Also see "AstraZeneca's PACIFIC Update Bolsters Imfinzi's Lead In Stage III Lung Cancer" - Scrip, 25 Sep, 2018.)*

Published online 7 December 2018

Congratulations to our Scrip Awards Winners

2018

www.scripawards.com

We would like to thank everyone who attended the 14th Annual Scrip Awards, held on November 28th at the Hilton on Park Lane, London.

The evening, hosted by Rt Hon Lord (William) Hague, was a celebration of excellence across all parts of the pharmaceutical, biotech and allied industries and recognized both corporate and individual achievements.

SAVE THE DATE: Scrip Awards 2019
Wednesday 4 December
The Hilton on Park Lane, London

Scrip Awards
Pharma intelligence | informa

The winners

Best Technological Development in Clinical Trials – Tech Sponsor-focused
Medidata's Medidata Rave Engage

Best Technological Development in Clinical Trials – Clinical Sponsor-focused
Covance's Xcellerate CRA Dashboard

Best Use of Real-World Evidence
PAREXEL, EMD Serono and Intermountain Healthcare's Multiple Sclerosis Algorithms Development and Validation project

Financing Deal of the Year – Private
BioNTech's $270m Series A financing

Financing Deal of the Year – Public
Ablynx's $200m US IPO on NASDAQ

Best Partnership Alliance
F-star and Denali Therapeutics to develop a multi-specific platform for delivery of medicines across the blood-brain barrier

Best Contract Research Organization – Specialist Providers
Cytel

Best Contract Research Organization – Full-Service Providers
IQVIA

Business Development Team of the Year
Evotec's business development team

Masters Speciality Pharma's Best Company in an Emerging Market Award
WuXi Biologics

Licensing Deal of the Year – Sponsored by Worldwide Clinical Trials
AstraZeneca and MSD for Lynparza and selumetinib

Executive of the Year – For Small Cap & Private Pharma Companies
Raman Singh, CEO of Mundipharma

Executive of the Year – For Large & Medium Cap Companies
Vas Narasimhan, CEO of Novartis

IQVIA's Clinical Advance of the Year Award
GW Pharmaceuticals' Phase III GWPCARE4 trial of Epidiolex for refractory epilepsy

Community Partnership of the Year Award – Sponsored by Medidata Solutions
Beximco Pharma with DSM Nutritional Products and Sight & Life Global Nutrition Research Institute to improve nutrition in rural Bangladesh

WuXi AppTec's Biotech Company of the Year Award
AveXis

Syneos Health's Best New Drug Award
Novartis's Kymriah (tisagenlecleucel)
Kite Pharma/Gilead Sciences' Yescarta (axicabtagene ciloleucel)

Pharma Company of the Year
MSD

Scrip's Lifetime Achievement Award
Sir John Bell

Novartis Targets Chronic Urticaria As Ligelizumab Enters Late-Stage Trials

JOHN DAVIS john.davis@informa.com

With data from a positive Phase II study in hand, **Novartis AG** says it will now compare its investigational anti-IgE antibody, ligelizumab (QGE031) with its marketed anti-IgE MAb, *Xolair* (omalizumab), in two head-to-head Phase III studies, PEARL 1 and PEARL 2, that it is initiating in patients with chronic spontaneous urticaria (CSU).

Novartis is considered to be a leader in immune-dermatology with recently launched products such as the anti-IL-17A, *Cosentyx* (secukinumab), making an impact in the marketplace. Sales of more mature products like the 2003-launched blockbuster-selling Xolair (marketed in collaboration with **Genentech Inc.** in the US) are also still growing because, it says, of better awareness of conditions like CSU – in the third quarter of 2018 Novartis reported that Xolair sales rose by 8% to $255m.

BIOSIMILAR COMPETITION

However, biosimilar versions of omalizumab are on the horizon, such as **Glenmark Pharmaceuticals Ltd.**'s GBR310, which has completed Phase I and is targeting the start of a Phase II study for mid-2019. And Xolair is under pressure in its other indication, severe allergic asthma , from newer agents including **GlaxoSmithKline PLC**'s *Nucala* (mepolizumab), **Teva Pharmaceutical Industries Ltd.**'s *Cinqair* (reslizumab) and **AstraZeneca PLC**'s *Fasenra* (benralizumab).

That said, current therapies for CSU including histamine H1 antagonists and Xolair can be unsatisfactory, with some patients continuing to suffer intense pain and itching, which Novartis is addressing with ligelizumab and a second potential CSU candidate product, LOU064, in early clinical studies.

Ligelizumab, a high-affinity anti-IgE antibody, has met the primary endpoint in a Phase IIb study by showing a clear dose-response relationship and improvements over Xolair. Ligelizumab showed a rapid onset of action and an improved and sustained efficacy in patients whose symptoms were not adequately controlled by H1-antagonists, Novartis announced on Dec. 4.

CLINICAL STUDIES

In the two Phase III studies, more than 2,000 patients will be randomized to one of two doses of ligelizumab, or omalizumab 300mg, given every four weeks for one year, or placebo. Patients initially randomized to placebo will be switched to one of the doses of ligelizumab at week 24 until week 52. The primary outcome will measure absolute change from baseline in the urticaria measure, UAS7, at Week 12.

Patients will include adolescents aged over 12 years and adults, who continue to have symptoms despite the use of antihistamines, and will come from 48 countries including the US, Germany and Japan. Symptoms include spontaneous swelling of the skin and itchy hives which can have a negative impact on sleep and work productivity.

Selected Urticaria Candidates In Clinical Studies

COMPANY	COMPOUND	ACTIVITY	STATUS
Novartis AG	ligelizumab (QCE031)	anti-IgE MAb	Phase III
Allakos Inc.	AK002	MAb targeting Siglec-8	Phase II
Novartis AG	LOU064	Bruton's tyrosine kinase inhibitor	Phase II
Roche AG	quilizumab	anti-IgE MAb	Phase II
Roche AG	fenebrutinib (RG7845)	Bruton's tyrosine kinase inhibitor	Phase II
GlaxoSmith-Kline plc	GSK2646264	spleen tyrosine kinase (Syk) inhibitor	Phase I

Source: Biomedtracker.

There are a handful of other companies with potential chronic urticaria in clinical development, according to Informa Pharma's database, *Biomedtracker*, as shown in the table above.

In addition, **JDP Therapeutics Inc.** is developing *Qzytir*, an intravenous cetirizine formulation, for the treatment of acute urticaria, for use in hospital and urgent care settings. Qzytir has completed Phase III studies and met primary and secondary endpoints, the company reported in June 2018.

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Revolving Door: Novartis India Managing Director Quits

ANJU GHANGURDE anju.ghangurde@informa.com

Milan Paleja, vice chairman and managing director of **Novartis India**, is moving on, just months after taking over the top job at the Swiss multinational's Indian operations.

This is also the second time in less than 12 months that Novartis India will see the exit of an MD. Previous head Jawed Zia was appointed effective March 1, 2018 but left soon after to join **Abbott India** as vice president (established pharmaceuticals).

Novartis said that Paleja had informed the board of directors on Dec. 5 of his decision to step down as the vice chairman and managing director, effective close of business hours on May 31, 2019. It said he would be "embracing challenges" outside the company. Paleja had moved into the corner office at Novartis India effective June 1, 2018 for a five-year term.

"The Board requested the Nomination and Remuneration Committee to identify and recommend a suitable successor for the role of managing director of the company," Novartis India informed the Bombay Stock Exchange on Dec. 5.

Second Novartis MD exit in under nine months

DISTURBING SIGNALS?

Paleja's exit has sparked some speculation around the revolving door situation at the helm of Novartis India, with some industry watchers claiming that such frequent top-level changes send "disturbing signals" to various stakeholders including employees, investors and business partners.

"Two successive exits in such a short span of time are less likely to be routine," an industry expert said. Others, however, indicated that the company has a good talent base and established systems and process that will facilitate a neat transition.

Paleja, who joined Sandoz India in 1982 in the finance function, had over the years held positions of increasing responsibility in consumer health, Sandoz and pharmaceuticals, at country and regional level, in diverse geographies including Singapore, South Africa and Switzerland. He was also Country President and Head (Pharmaceuticals) of Novartis Indonesia, where he is said to have pioneered innovative access models and turned around the business.

More recently, at an interaction with *Scrip* at the time of Novartis Pharmaceuticals CEO Paul Hudson's visit to India, Paleja enthusiastically referred to the potential of Modicare – India's massive National Health Protection Scheme (NHPS), which expects to cover 100 million poor and vulnerable families with health cover for secondary and tertiary care hospitalization.

"What would be important for us as a company and an industry is to work with the government to see how they can expand the coverage and further it is opened to even innovative medicines, which can be very helpful and where we are very keen to partner," Paleja said at the time.

Published online 5 December 2018

Lilly CEO Made New IFPMA President On Health Budget Mandate

JO SHORTHOUSE joanne.shorthouse@informa.com

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) has elected **Eli Lilly & Co.** chairman and CEO David Ricks as its new president for a two-year term, succeeding **Pfizer Inc.**'s outgoing CEO, Ian Read.

Ricks' term as president will see IFPMA focusing on ways to tackle the pressures on health budgets, while also expanding healthcare system offering. High on the IFPMA agenda for the next two years will be universal health overage, incentivizing innovation, meeting the chronic health needs of an aging world population and stepping up the power of private-public partnerships.

David Ricks said: "We need to redouble efforts to avoid undermining the last-half century's hard-won gains in health. Our industry is committed to develop medicines and vaccines that help people live longer, healthier, more productive lives. We are also committed to work in partnership with the public and private sectors to develop evidence-based and forward-looking solutions that improve health and encourage innovation".

CONTINUED ON PAGE 23

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.

PIPELINE WATCH, 30 NOVEMBER – 6 DECEMBER 2018

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

Phase III

Event Type	Lead Company/Partner	Drug	Indication	Comments	Change To LOA (%)	LOA (%)
Phase III Published Results	Merck & Co., Inc.	Keytruda (pembrolizumab)	Head and Neck Cancer	KeyNote-040; The Lancet, Nov. 30, 2018	0	100
Phase III Published Results	AbbVie Inc./J&J	Imbruvica (ibrutinib) Plus rituximab	Chronic Lymphocytic Leukemia	ALLIANCE; NEJM, Dec. 2, 2018	0	100
Phase III Final Results	Daiichi Sankyo Co., Ltd.	quizartinib	Acute Myeloid Leukemia	QUANTUM-R; Meaningful Benefit	0	89
Phase III Updated Results	Acceleron Pharma/Celgene	luspatercept	Thalassemia	BELIEVE; Reduced RBC Transfusion Burden	-2	62
Phase III Updated Results	AbbVie Inc./Roche	Venclexta (venetoclax) Plus Rituximab	Chronic Lymphocytic Leukemia	MURANO; Reduced Risk Disease Progression	0	100
Phase III Updated Results	AbbVie Inc./Johnson & Johnson	Imbruvica (ibrutinib) Plus rituximab	Waldenstrom Macroglobulinemia	INNOVATE; Continued Efficacy	0	100
Phase III Updated Results	Swedish Orphan Biovitrum/Sanofi	Eloctate (efmoroctocog alfa)	Hemophilia A	ASPIRE; Effective Over Four Years	0	100
Phase III Updated Results	Swedish Orphan Biovitrum/Sanofi	Alprolix (eftrenonacog alfa)	Hemophilia B	B-YOND; Effective Over Four Years	0	100
Phase III Updated Results	Verastem, Inc.	Copiktra (duvelisib)	Chronic Lymphocytic Leukemia	DUO Ext; Sustained Efficacy	0	100
Phase III Updated Results	Takeda	Ninlaro (ixazomib)	Multiple Myeloma	TOURMALINE-MM1, MM3; Clinical Benefits	0	100
Phase III Updated Results	Seattle Genetics, Inc./Takeda	Adcetris (brentuximab vedotin)	Hodgkin's Lymphoma	ECHOLON-1; Sustained Responses	0	100
Phase III Updated Results	Acceleron Pharma/Celgene	luspatercept	Myelodysplastic Syndrome	MEDALIST; Positive Results	0	41
Phase III Updated Results	bluebird bio	LentiGlobin gene therapy	Thalassemia, Sickle Cell Anemia	Clinical Responses Observed	-5	65

Source: Biomedtracker | Informa, 2018


David Ricks

David Ricks: A Life At Lilly

Ricks joined Lilly in 1996 as a business development associate and held several management roles in US marketing and sales before moving to Lilly Canada.

He was general manager of Lilly Canada from 2005 to 2008, after roles as director of pharmaceutical marketing and national sales director in that country.

He then served as president and general manager of Lilly China from 2008 to 2009.

He was made president of Lilly USA, the company's largest affiliate, in 2009 and served until 2012.

Ricks served as president of Lilly Bio-Medicines from 2012 to 2016.

Lilly's board made him CEO and chairman in 2017.

IFPMA holds official relations with the United Nations and partners with the global health community to find sustainable solutions that improve health.

Ricks will continue to be supported by the two IFPMA vice presidents, **Roche** CEO Severin Schwan and Isao Teshirogi, president and CEO of **Shionogi & Co. Ltd.**

In the last two years, under Read's presidency, IFPMA has helped to establish Access Accelerated, in which more than 20 biopharmaceutical companies are partnering with governments, civil society, the World Bank and the Union for International Cancer Control, to tackle the growing burden of non-communicable diseases in low- and middle-income countries.

It has also created the AMR Industry Alliance, a 100-strong private-sector coalition to provide sustainable solutions to curb antimicrobial resistance. IFPMA also launched Pat-INFORMED, a partnership between the biopharmaceutical industry and World Intellectual Property Organization designed to make data on the patent status of the most commonly used medicines easily accessible, so that procurement agencies can find the patent status of medicines anywhere in the world.

"It is only by leveraging our collective experience, skills, resources and networks that we will be able to achieve lasting change," said Read. *Published online 5 Dec 2018*

APPOINTMENTS

Executive	To Company	New Role	From Company	Previous Role	Effective Date
Paresh N. Soni	Cardax Inc	Chief Clinical and Regulatory Strategist and Scientific Advisory Board Member	Amarin Corp	Head, Development and Senior Vice President	28-Nov-18
Katharine Knobil	Kaleido Biosciences Inc	Chief Medical Officer and Head, Research and Development	GlaxoSmithKline plc	Chief Medical Officer	3-Dec-18
Daniel Kirby	Omeros Corp	Vice President and Head, Commercial	Celgene	US Commercial Lead	3-Dec-18
Justin McCue	Omeros Corp	Vice President, Chemistry, Manufacturing and Controls	Celgene	Head, CAR T-cell Development	3-Dec-18
Rita Laeufle	Oncolytics Biotech Inc	Chief Medical Officer	SFJ Pharmaceuticals	Vice President, Clinical Development and Medical Affairs	29-Nov-18
Ivan Horak	Tessa Therapeutics Pte Ltd	President, Research and Development	Symphogen	Chief Scientific Officer, Chief Medical Officer, and Head, Global Research and Development	29-Nov-18

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

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General Enquiries:

Jo Kirkpatrick | Tel: +44 (0) 20 7017 7180 | Email: jo.kirkpatrick@informa.com