

NOVARTIS REPORTS RESPONSE DATA FOR CAR T IN DLBCL

5:34 PM, JUN 07, 2017 | BY JAIME DE LEON

Novartis AG (NYSE:NVS; SIX:NOVN) said chimeric antigen receptor (CAR) T cell therapy **tisagenlecleucel-T** (CTL019) led to a best objective response rate (ORR) of 59% in the pivotal Phase II JULIET trial to treat relapsed or refractory diffuse large B cell lymphoma. The interim data were released in an abstract ahead of next week's International Conference on Malignant Lymphoma in Lugano.

Tisagenlecleucel-T led to a 43% complete response rate and a 16% partial response rate. The three-month ORR was 45%, including complete and partial response rates of 37% and 8%, respectively. The analysis included 51 patients with at least three months of follow-up or earlier discontinuation who received a single infusion of tisagenlecleucel-T following restaging, bridging therapy and lymphodepleting chemotherapy. Sixty percent of patients received three or more lines of chemotherapy and 51% had a prior autologous stem cell transplantation (ASCT).

Of the 141 patients enrolled in the trial, nine (6%) discontinued due to an inability to manufacture an adequate dose of CAR T cells. Novartis said process improvements over the course of the study improved the manufacturing success rate to 97% for the last 30 patients, and the company is "confident" it will be able to meet the required manufacturing demands moving forward.

Of the 85 patients treated in the trial, 57% experienced cytokine release syndrome (CRS) of any grade, and 26% experienced grade 3/4 CRS. There were no CRS-associated or treatment-related deaths, and no cases of cerebral edema. Grade 3/4 neurologic adverse events occurred in 13% of patients.

FDA's Oncologic Drugs Advisory Committee (ODAC) will meet on July 12 to discuss a BLA for tisagenlecleucel-T to treat relapsed or refractory B cell acute lymphoblastic leukemia (ALL) in patients ages three to 25, the first such meeting for a CAR T cell therapy. The candidate is under FDA Priority Review, with a PDUFA date in early October (see [BioCentury Extra, June 6](#)).

Novartis CMO Vasant Narasimhan told BioCentury the company plans to submit a BLA to FDA for tisagenlecleucel-T to treat DLBCL shortly after the PDUFA date for the ALL indication. Concurrent with that submission, the company plans to submit an MAA to EMA for the product in both indications.

Tisagenlecleucel-T comprises autologous T cells loaded with a lentiviral vector expressing **CART-19**, which consists of a cancer antigen-binding domain targeting **CD19** linked to CD3zeta/CD137 immunostimulatory domains. It has breakthrough therapy designation from FDA to treat acute ALL and relapsed and refractory DLBCL.

A BLA for another CAR T cell therapy targeting CD19, axicabtagene ciloleucel (**KTE-C19**) from **Kite Pharma Inc.** (NASDAQ:KITE), is under FDA Priority Review to treat refractory aggressive non-Hodgkin's lymphoma (NHL). Its PDUFA date is Nov. 29.

In a cohort of 77 DLBCL patients in the Phase II portion of the Phase I/II ZUMA-1 trial, axicabtagene ciloleucel led to an ORR of 82%, including a 49% complete response rate. Six-month ORR and complete response rates were 36% and 31%, respectively. Among the overall ZUMA-1 population, which also included patients with primary mediastinal B cell lymphoma (PMBCL) and transformed follicular lymphoma (FL), the respective incidences of grade three or higher CRS and neurologic events were 18% and 34% at the interim analysis and 13% and 28% at the primary analysis. One-year follow-up data from ZUMA-1 are expected by year end.

There were two KTE-C19-related deaths in ZUMA-1: one from hemophagocytic lymphohistiocytosis and one from cardiac arrest "in the setting" of CRS (see [BioCentury Extra, Sept. 26, 2016](#)).

Kite also disclosed last month that a patient with non-Hodgkin's lymphoma (NHL) died from treatment-related cerebral edema in an expansion cohort of ZUMA-1 (see [BioCentury Extra, May 8](#)).

Kite gained \$5.46 to \$82.10 on Wednesday.

ACTELION'S CADAZOLID HIT-AND-MISS IN PHASE III STUDIES

12:51 PM, JUN 08, 2017 | BY JAIME DE LEON

Actelion Ltd. (SIX:ATLN) said **cadazolid** (ACT-179811) missed the primary endpoint in the Phase III IMPACT 2 trial, but met the primary endpoint of the identical Phase III IMPACT 1 study to treat *Clostridium difficile*-associated diarrhea (CDAD). Both primary endpoints measured whether clinical cure rates following 10-day courses of cadazolid were non-inferior to vancomycin treatment.

The studies enrolled a total of 1,263 patients and defined clinical cure as resolution of diarrhea and no further need for therapy maintained for two days after the end of treatment. Actelion said it will continue to analyze the results. Cadazolid is a chimeric quinolonyl-oxazolidinone antibiotic.

Johnson & Johnson (NYSE:JNJ) is expected to gain cadazolid through its pending \$30 billion acquisition of Actelion. The Swiss biotech is spinning out its drug discovery operations and some clinical programs into newco **Idorsia Ltd.** (Allschwil, Switzerland), but cadazolid is not included in the spinout (see **BioCentury, Feb. 3 & BioCentury, May 26**).

BC EXTRA | CLINICAL NEWS

CYCLIN D3-CDK6 LEVELS PREDICT TUMOR RESPONSE TO CDK4/6 INHIBITORS

2:14 PM, JUN 08, 2017 | BY MICHAEL LEVITEN

In an **article** published online in *Nature* on Wednesday, scientists reported that high levels of tumor cyclin D3-cyclin-dependent kinase 6 (**CDK6**) correlated with long-term tumor regression after blockade of **CDK4** and CDK6. Inhibitors of CDK4 and CDK6 are approved to treat breast cancer, and are in clinical trials for a variety of cancers.

The team, led by Piotr Sicinski of **Dana-Farber Cancer Institute**, tested CDK4/6 inhibitor **Kisqali** ribociclib in melanoma xenograft models. Among xenografts from 33 melanoma patients, three had long-term regression and all three tumors were derived from patient cells with high pre-xenograft levels of cyclin D3 and CDK6. In contrast, non-regressing tumors all had low pre-xenograft levels of cyclin D3 and CDK6.

Cyclin D3 and CDK6 form a complex in cells known to be key drivers of cell proliferation.

Novartis AG (NYSE:NVS; SIX:NOVN) markets Kisqali to treat breast cancer.

In mechanistic studies, cells with high levels of cyclin D3-CDK6 underwent apoptosis after CDK4/6 treatment, while low expressing tumors underwent cell cycle arrest. This was demonstrated in patient-derived acute T-cell lymphoblastic leukemia (T-ALL) cells *in vitro*, and was confirmed in the melanoma xenograft studies.

The researchers said high levels of cyclin D3-CDK6 complex inhibited two key metabolic enzymes needed to make the antioxidants NADPH and glutathione and provide a pro-survival function. The CDK4/6 inhibitors blocked this pathway and caused cell death.

The mechanistic studies used the CDK4/6 inhibitor **Ibrance** palbociclib, which **Pfizer Inc.** (NYSE:PFE) markets to treat breast cancer.

The team concluded that cyclin D3-CDK6 levels could be used to select the optimal patient population for CDK4/6 inhibitor therapy.

BC EXTRA | COMPANY NEWS

J&J TAPS MAMMEN FOR R&D JOB; HAIT TO LEAD EXTERNAL INNOVATION

2:15 PM, JUN 08, 2017 | BY MARY ROMEO

Johnson & Johnson (NYSE:JNJ) hired Mathai Mammen to succeed William Hait as global head of R&D. Hait will take on a newly created role as global head of external innovation. Mammen is joining J&J from the Merck Research Labs division of **Merck & Co. Inc.** (NYSE:MRK), where he is SVP of cardiovascular and metabolic diseases, immunology and oncology.

Hait will oversee the company's Johnson & Johnson Innovation unit, including the company's Innovation Centers, JLABS and JJDC, as well as the company's cross-sector lung cancer and obesity initiatives and its "World Without Disease" innovation strategy.

Mammen is to join J&J on June 26. Both executives' transitions are to become fully effective Jan. 1, 2018.

In his 10 years at J&J, Hait reorganized the company's oncology R&D to focus on the tumor microenvironment,

spurring the creation of biomarker and translational medicine groups and the company's acquisition of cancer drugs. He also formed J&J's Disease Interception Accelerator (DIA), an incubator-like group that seeks to predict and prevent progression to disease in at-risk populations (see [BioCentury, Aug. 30, 2010](#) & [BioCentury, March 2, 2015](#)).

BC EXTRA | COMPANY NEWS

SCICLONE GOING PRIVATE IN \$605M DEAL

3:20 PM, JUN 08, 2017 | BY CHRIS LIEU

SciClone Pharmaceuticals Inc. (NASDAQ:SCLN) said it will be acquired by an investor syndicate led by GL Capital Management for \$11.18 per share in cash, or about \$605 million. Other investors include Bank of China Group Investment, CDH Investments, Ascendent Capital Partners and Boying Investments. The deal is expected to close by year end, and is subject to approval by shareholders.

The price is an 11% premium to SciClone's close of \$10.10 on Wednesday, the day before the deal was announced.

U.S.-based SciClone is developing treatments in oncology, infectious disease and cardiovascular disorders with a focus on the Chinese pharmaceutical market. SciClone's **Zadaxin** thymalfasin, a synthetic thymosin alpha-1, is approved as an immune system enhancer and to treat HBV and HCV infections and certain cancers.

SciClone said the decision was based on the "challenges of continuing to operate as an independent U.S.-based, publicly traded company in the complex, competitive and increasingly price-sensitive China pharmaceuticals market." Spokesperson Jane Green declined to disclose additional details.

The deal includes a breakup fee of \$15.8 million, which SciClone would pay. It also includes a 60-day "go-shop" period, where the company would pay a reduced fee of \$7.9 million if it accepts a superior proposal. If the deal is terminated due to regulatory approvals, the investors would pay a \$21 million fee to SciClone.

In November 2016, SciClone received an unsolicited cash bid from a consortium led by GL Capital and ABM Management to acquire all outstanding shares not already owned for \$11.18 per share. ABM Management is part of Ally Bridge Group.

GL Capital was founded in 2010 by Jeffrey Li, a former CEO of the China division of **Novartis AG** (NYSE:NVS; SIX:NOVN). He was responsible for commercial and sales in the territory.

In March, GL Capital, Ally Bridge and Giant Star Global proposed to take private **Shandong Luoxin Pharmaceutical Group Stock Co. Ltd.** (HKSE:8058) for HK\$17 per share.

SciClone added \$0.80 to \$10.90 on Thursday.

BC EXTRA | CLINICAL NEWS

INOVIO RESUMES VGX-3100 HPV CANCER PROGRAM

3:46 PM, JUN 08, 2017 | BY JAIME DE LEON

Inovio Pharmaceuticals Inc. (NASDAQ:INO) gained \$0.80 (11%) to \$8.19 on Thursday after the company said FDA lifted a clinical hold on its Phase III program of **VGX-3100** to treat cervical dysplasia caused by HPV. The company plans to immediately begin a pair of Phase III trials of the candidate.

FDA placed the hold on Inovio's development program for VGX-3100 last October and requested additional data on the shelf life of the company's redesigned Collectra electroporation device used to administer the product (see [BioCentury Extra, Oct. 24, 2016](#)).

The REVEAL 1 and confirmatory REVEAL 2 trials of VGX-3100 each will enroll 198 patients with high-grade squamous intraepithelial lesions (HSIL) attributable to HPV 16 or 18 infection. HSIL, which is a precursor to cervical cancer, is also known as cervical intraepithelial neoplasia (CIN) grade 2 or 3. The trials' primary endpoint is regression of cervical HSIL and virologic clearance of HPV in the cervix.

In February, Inovio granted **ApolloBio Corp.** (NEEQ:430187) rights to VGX-3100 in Greater China to treat or prevent pre-cancerous infections and dysplasias tied to HPV (see [BioCentury Extra, Feb 13](#)).

VGX-3100 is a DNA-based therapeutic vaccine targeting the E6 and E7 proteins of HPV 16 and 18.

FDA ASKS ENDO TO REMOVE OPIOID FROM MARKET

4:06 PM, JUN 08, 2017 | BY JAIME DE LEON

FDA requested that **Endo International plc** (NASDAQ:ENDP) voluntarily remove its reformulated pain drug **Opana ER oxymorphone extended release** from the U.S. market. The agency said it is the first time it has “taken steps” to remove a marketed opioid pain medicine “due to the public health consequences of abuse.”

The agency said it would withdraw Opana ER's approval if Endo does not comply with the request. Endo said it is reviewing the request and evaluating its options.

FDA cited a concern that the opioid analgesic's benefits may not outweigh its risks. In March, the agency's Drug Safety and Risk Management and Anesthetic and Analgesic Drug Products advisory committees voted 18-8, with one abstention, that the benefits of Opana ER following a 2012 reformulation no longer outweigh its risks. According to Endo, while the committee members believed concerns over the drug's misuse, abuse and diversion overshadowed its benefits, some panelists expressed the preference that Opana ER remain on market with additional risk-mitigating regulatory restrictions.

On Thursday, FDA said postmarketing data from studies following the drug's reformulation showed a “significant shift” in its route of abuse, from nasal to injection. The agency said the latter method of abuse “has been associated with a serious outbreak of HIV and hepatitis C, as well as cases of a serious blood disorder (thrombotic microangiopathy).”

FDA added that it had declined Endo's request to include language in Opana ER's label which would have described potentially abuse-deterrent properties, because “the data did not show that the reformulation could be expected to meaningfully reduce abuse.”

Addressing the opioid addiction epidemic is among the political challenges new FDA Commissioner Scott Gottlieb faces. The Senate confirmed his appointment last month ([see BioCentury, March 31](#)).

Endo sank \$1.86 (14%) to \$11.92 in after-hours trading on Thursday. It had gained \$1.38 (11%) to \$13.78 during regular trading.

NEWLINK FALLS AFTER GENENTECH RETURNS IDO INHIBITOR

4:23 PM, JUN 08, 2017 | BY ALICIA PARKER

NewLink Genetics Corp. (NASDAQ:NLNK) fell \$4.38 (41%) to \$6.24 on Thursday after it said the **Genentech Inc.** unit of **Roche** (SIX:ROG; OTCQX:RHHBY) will return rights to cancer candidate **navoximod** (GDC-0919), an inhibitor of **indoleamine 2,3-dioxygenase** (INDO; IDO).

Genentech had held navoximod's rights under a 2014 deal in which it paid \$150 million up front. The return of navoximod's rights does not end the companies' deal, in which they will continue to discover and develop **tryptophan-2,3-dioxygenase** (TDO2; TDO)/IDO inhibitors. Genentech is now also eligible for single-digit royalties tied to navoximod ([see BioCentury Extra, Oct. 20, 2014](#)).

Data presented at this month's **American Society of Clinical Oncology** (ASCO) meeting showed that navoximod plus **PD-L1 mAb Tecentriq** atezolizumab led to a partial response rate of 10% in a Phase Ib trial in patients with advanced or metastatic solid tumors. NewLink shares had slipped 9% to \$14.46 on May 18, the day after an abstract with earlier data from the study was released after market hours. With Thursday's move, the shares are off 61% since closing at \$16.10 on May 17.

On a conference call Thursday, NewLink said it will focus on the development of IDO inhibitor **indoximod** (**NLG8189**) and its prodrug **NLG802**. In April, NewLink reported data from a Phase II trial showing that **indoximod** plus **Keytruda** pembrolizumab led to an overall response rate (ORR) of 52% and a 10% complete response rate in patients with melanoma ([see BioCentury Extra, April 4](#)).