UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
PURSUANT TO SECTION 13 OR 15(d)
OF THE SECURITIES EXCHANGE ACT OF 1934

Date of report (Date of earliest event reported): October 5, 2018

ZIOPHARM Oncology, Inc.
(Exact Name of Registrant as Specified in Charter)

Delaware	**001-33038**	**84-1475642**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

One First Avenue, Parris Building 34, Navy Yard Plaza
Boston, Massachusetts **02129**
(Address of Principal Executive Offices) **(Zip Code)**

(617) 259-1970
(Registrant's telephone number, including area code)

Not applicable
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425).

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12).

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b)).

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c)).

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act (17 CFR 230.405) or Rule 12b-2 of the Exchange Act (17 CFR 240.12b-2).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 5.02 Departure of Directors or Certain Officers; Election of Directors; Appointment of Certain Officers; Compensatory Arrangements of Certain Officers.

In connection with the entry by Ziopharm Oncology, Inc., or the Company, into a new strategic transaction with Precigen, Inc., or Precigen, which is further described in the press release referenced in Item 7.01 below, on October 5, 2018, Randal J. Kirk resigned from the Company's Board of Directors, or the Board, effective immediately. Mr. Kirk has served as a member of the Board since 2011 and his decision to resign was not due to any disagreement with the Company's operations, policies or practices. The Company thanks Mr. Kirk for his service.

Item 7.01 Regulation FD Disclosure.

On October 9, 2018, the Company, together with Precigen, a wholly owned subsidiary of Intrexon Corporation, issued a press release announcing the amendment of their prior collaborations and entry into an exclusive license agreement. A copy of the press release is furnished herewith as Exhibit 99.1 to this Current Report on Form 8-K. Members of management of the Company plan to hold a conference call on October 9, 2018 at 8:00 a.m. Eastern time to discuss the new transaction. Information about how to access the conference call is in the press release attached as Exhibit 99.1. Presentation slides will be used in connection with the conference call and are available on the Company's website at www.ziopharm.com, and furnished herewith as Exhibit 99.2.

The information contained in this Item 7.01, including Exhibits 99.1 and 99.2, are being "furnished" and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, or the Exchange Act, or otherwise subject to the liability of that section or Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended, or the Securities Act. The information in this Item 7.01, including Exhibits 99.1 and 99.2, shall not be incorporated by reference into any registration statement or other document pursuant to the Securities Act or into any filing or other document pursuant to the Exchange Act, except as otherwise expressly stated in any such filing.

Item 8.01 Other Events.

Clinical Programs Update

In the press release described above, the Company updated guidance on the timing of its response to the request for more information from the U.S. Food and Drug Administration, or the FDA, regarding the clinical hold placed on the investigational new drug, or IND, application for the Company's third-generation Phase 1 trial to evaluate CD19-specific CAR-T therapies under technology referred to as point-of-care. The Company expects to respond to the FDA's request for more information in the second half of 2019.

The Company also updated its guidance on its planned Phase 1 trial of Sleeping Beauty-modified TCRs to treat solid tumors. As previously disclosed, the IND application for this Phase 1 trial, which is being led by and conducted at the National Cancer Institute, or the NCI, remains on track to be submitted in the fourth quarter of 2018. The Company today updated that it currently expects the NCI to initiate the trial and begin treating patients in 2019 following IND clearance.

The information contained in this Current Report on Form 8-K speaks only as of the date hereof. While the Company may elect to update the information in this Current Report on Form 8-K in the future, the Company disclaims any obligation to do so except to the extent required by applicable law.

Caution Concerning Forward Looking Statements

This Current Report on Form 8-K may contain forward-looking statements made in reliance upon the safe harbor provisions of Section 27A of the Securities Act and Section 21E of the Exchange Act. Forward-looking statements include all statements that do not relate solely to historical or current facts, and can be identified by the use of words such as "may," "will," "expect," "project," "estimate," "anticipate," "plan," "believe," "potential," "should," "continue" or the negative versions of those words or other comparable words. These forward-looking statements include, but are not limited to, statements regarding the expected timing of the completion of clinical trials or studies related to Sleeping Beauty-modified TCRs and CD19-specific CAR-T therapies, the expected timing for the Company's response to the FDA, the expected timing for the filings or amendments of its IND applications and the expected timing for the initiation and readouts of the Company's upcoming clinical trials. These forward-looking statements are not guarantees of future actions or performance. These forward-looking statements are based on information currently available to the Company and its current plans or expectations, and are subject to a number of uncertainties and risks that could significantly affect current plans. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied by, the forward-looking statements. These risks and uncertainties include, but are not limited to: the expected benefits of the strategic transaction; changes in the Company's financial condition and cash needs, funding or other strategic opportunities that become available to the Company, the Company's ability to finance its operations and business initiatives and obtain funding for such activities; whether chimeric antigen receptor T cell (CAR-T) approaches, Ad-RTS-hIL-12, TCR and NK cell-based therapies, or any of other product candidates will advance further in the preclinical research or clinical trial process, including receiving clearance from the FDA to conduct its clinical trials and whether and when, if at all, they will receive final approval from the FDA or equivalent foreign regulatory agencies and for which indications; whether chimeric antigen receptor T cell (CAR-T) approaches, Ad-RTS-hIL-12, TCR and NK cell-based therapies, and the Company's other therapeutic products it develops will be successfully marketed if approved; the strength and enforceability of the Company's intellectual property rights; competition from other pharmaceutical and biotechnology companies; as well as other risk factors contained in the Company's periodic and interim reports filed from time to time with the Securities and Exchange Commission, including but not limited to, the risks and uncertainties set forth in the "Risk Factors" section of the Company's Annual Report on Form 10-K for the fiscal year ended December 31, 2017 and subsequent reports that the Company may file with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and the Company does not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press release of Ziopharm Oncology, Inc. dated October 9, 2018.
99.2	Presentation slides dated October 9, 2018.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

ZIOPHARM ONCOLOGY, INC.

Date: October 9, 2018

By: /s/ Robert Hadfield
Name: Robert Hadfield
Title: General Counsel and Secretary

Ziopharm and Precigen Redefine Relationships, Announce New License Agreement

Ziopharm to Host Conference Call at 8 a.m.

BOSTON and GERMANTOWN, MD, October 9, 2018 – Ziopharm Oncology, Inc. (Nasdaq: ZIOP) and Precigen, Inc., a wholly-owned subsidiary of Intrexon Corporation (Nasdaq: XON), today announced a new definitive license agreement to replace all existing agreements between the companies that will provide Ziopharm with certain exclusive and non-exclusive rights to technology controlled by Precigen, Inc.

Through the new agreement, Ziopharm will primarily focus its resources on developing its Controlled IL-12 and *Sleeping Beauty* (SB) T-cell receptor (TCR) platform technologies which have the capability to treat solid tumors, while Intrexon further establishes Precigen as a therapeutics company concentrating on immuno-oncology, autoimmune and infectious disease therapies. Both companies will be better positioned to independently focus on their respective platforms and markets with full developmental and financial controls.

With this exclusive license, Ziopharm now has full developmental control and exclusivity utilizing SB for TCRs targeted towards neoantigens and public antigens. The existing Cooperative Research and Development Agreement (CRADA) with the National Cancer Institute related to SB-generated T cells expressing TCRs to target neoantigens buried within solid tumors will be transferred to Ziopharm, and Ziopharm will maintain this exclusive relationship with the NCI for this program. Ziopharm will build on its IL-12 platform utilizing Precigen's RheoSwitch® gene switch with both the existing human adenovirus program and now with rights to pursue next-generation viral technologies. Using the SB system, Ziopharm will continue to advance its CD19-specific chimeric antigen receptor (CAR) program, while retaining rights to a second, unnamed CAR target. Precigen gains exclusive rights for all other CAR-T therapies, including CD33-specific CAR-T therapies, subject to the agreement with Merck KGaA.

"This is a new day for Ziopharm, as we have the power and flexibility to advance IL-12 and *Sleeping Beauty*-generated TCRs ," said Ziopharm Chief Executive Officer Laurence Cooper, M.D., Ph.D. "We now have focused the company on the two platforms to drive the most shareholder value and transitioned a significant portion of our CAR-T program to Precigen. The ability of both Ziopharm and Precigen to autonomously execute their respective operating plans on their independent platforms, while sharing in future economics, enables both parties to undertake more efficient 'divide and conquer' drug-development plans to the benefit of all constituents."

In partial consideration for the termination of the former agreements, in addition to the grant of the revised limited exclusive license, the companies agree that Ziopharm will retire all outstanding shares of its Series 1 Preferred Stock held by Intrexon, including any accrued dividends, valued at approximately $156.9 million, as of Sept. 30, 2018. Additionally, the companies have terminated Intrexon's contractual right to a seat on Ziopharm's board. Randal J. Kirk, Chairman and Chief Executive Officer of Intrexon, who has served as a director on the board of Ziopharm since 2011, has stepped down from that position, effective immediately, and Ziopharm plans to fill all vacant seats in the near term.

"In 2011 with Ziopharm, we entered into our first exclusive collaboration and therewith granted a field that was far broader than any other. Today's announcement is about seeing Ziopharm's tighter focus and about our desire

to invest in Precigen. We believe that Ziopharm will succeed under the license to develop and bring to market important new cancer therapeutics, and we look forward to enjoying benefits from these while we continue our investments in Precigen," commented Mr. Kirk.

Ziopharm will receive a low single digit, capped royalty on Precigen products in the field of point-of-care (P-O-C) CAR T-cell therapies. Precigen will receive milestone payments on late-stage regulatory events as well as commercial royalties in the low to high single-digit range for certain CAR and IL-12 targets that Ziopharm develops. Precigen will receive capped commercial royalties in low- to mid-single digits for the TCR products that Ziopharm develops. Further details on the terms of the transaction will be available within SEC filings respectively filed by Intrexon and Ziopharm.

Ziopharm Clinical Programs Update

Ziopharm today updated guidance on the timing of its response to the request for more information from the U.S. Food and Drug Administration (FDA) regarding the clinical hold placed on the investigational new drug (IND) application for its third-generation Phase 1 trial to evaluate CD19-specific CAR-T therapies under P-O-C technology. Ziopharm expects to respond to the FDA's request for information in the second half of 2019.

Ziopharm also affirmed its guidance on the planned Phase 1 trial to evaluate SB-modified TCRs to treat solid tumors. As disclosed in Ziopharm's second quarter business update, the IND application for this Phase 1 trial, which is being led by and conducted at the National Cancer Institute, remains on track to be submitted in the fourth quarter of 2018 followed by enrollment of patients beginning in 2019, pending regulatory clearance.

Conference Call and Slide Webcast

Ziopharm will host a webcast and conference call today, October 9, at 8 a.m. ET. The call can be accessed by dialing 1-844-309-0618 (U.S. and Canada) or 1-661-378-9465 (international). The passcode for the conference call is 9789556. To access the slides and live webcast or the subsequent archived recording, visit the "Investors Events and Presentations" section of the Ziopharm website at www.ziopharm.com. The webcast will be recorded and available for replay on the Company's website for two weeks.

About Ziopharm Oncology, Inc.

Ziopharm Oncology is a Boston-based biotechnology company focused on the development of next-generation immunotherapies utilizing gene- and cell-based therapies to treat patients with cancer. Ziopharm is focused on the development of two platform technologies designed to deliver safe, effective and scalable cell- and viral-based therapies for the treatment of multiple cancer types: Controlled IL-12 and *Sleeping Beauty* for genetically modifying cells. These programs are being advanced in collaboration with MD Anderson Cancer Center and the National Cancer Institute.

About Precigen: Advancing Medicine with Precision™

Founded in 2017, Precigen is a dedicated discovery and clinical stage biopharmaceutical company advancing the next generation of gene and cellular therapies using precision technology to target the most urgent and intractable diseases in oncology, autoimmune disorders, and emerging specialty therapy areas. Our technologies enable us to find innovative solutions for affordable biotherapeutics in a controlled manner. Precigen operates as an innovation engine progressing a preclinical and clinical pipeline of well-differentiated unique therapies toward clinical proof-of-confidence and commercialization. Precigen was founded as a wholly-owned subsidiary of Intrexon Corporation (Nasdaq: XON) and leverages Intrexon's proprietary technology platforms to advance human health. Learn more about Precigen at www.precigentherapeutics.com.

About Intrexon Corporation

Intrexon Corporation (Nasdaq: XON) is Powering the Bioindustrial Revolution with Better DNA™ to create biologically-based products that improve the quality of life and the health of the planet. Intrexon's integrated technology suite provides its partners across diverse markets with industrial-scale design and development of complex biological systems delivering unprecedented control, quality, function, and performance of living cells.

We call our synthetic biology approach Better DNA®, and we invite you to discover more at www.dna.com or follow us on Twitter at @Intrexon, on Facebook, and LinkedIn.

Trademarks

Intrexon, RheoSwitch, Powering the Bioindustrial Revolution with Better DNA, and Better DNA are trademarks of Intrexon and/or its affiliates. Other names may be trademarks of their respective owners.

Forward-Looking Statements Disclaimer

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts, and in some cases can be identified by terms such as “may,” “will,” “could,” “expects,” “plans,” “anticipates,” and “believes.” These statements include, but are not limited to, statements regarding Ziopharm’s and Intrexon’s goals, expectations, financial or other projections, intentions or beliefs, including statements regarding Ziopharm’s and Intrexon’s business and strategic plans; the expected benefits of the strategic transaction, such as creating shareholder value, growth potential, market profile, enhanced competitive position and flexibility; the progress and timing of the development of Ziopharm’s research and development programs, including the expected timing for its response to the U.S. FDA and of the filing of its IND applications; the timing for the initiation and readouts of Ziopharm’s upcoming clinical trials; expected additions to Ziopharm’s board of directors; and statements regarding future performance. Although Ziopharm’s and Intrexon’s management teams believe that the expectations reflected in such forward-looking statements are reasonable, investors are cautioned that forward-looking information and statements are subject to various risks and uncertainties, many of which are difficult to predict and generally beyond the control of Ziopharm and Intrexon, that could cause actual results and developments to differ materially from those expressed in, or implied or projected by, the forward-looking information and statements. These risks and uncertainties include among other things, the uncertainties inherent in research and development, future clinical data and analysis, including whether any of Ziopharm’s and Intrexon’ product candidates will advance further in the preclinical research or clinical trial process, including receiving clearance from the U.S. Food and Drug Administration or equivalent foreign regulatory agencies to conduct clinical trials and whether and when, if at all, they will receive final approval from the U.S. FDA or equivalent foreign regulatory agencies and for which indication; the strength and enforceability of Ziopharm’s and Intrexon’s intellectual property rights; Ziopharm’s ability to attract qualified board candidates; competition from other pharmaceutical and biotechnology companies as well as risk factors discussed or identified in the public filings with the Securities and Exchange Commission made by Ziopharm and Intrexon, including those risks and uncertainties listed in Ziopharm’s and Intrexon’s annual reports on Form 10-K for the year ended December 31, 2017 and subsequent Quarterly Reports on Form 10-Q filed by Ziopharm and Intrexon with the Securities and Exchange Commission. We are providing this information as of October 9, 2018, and neither Ziopharm nor Intrexon undertake any obligation to update or revise the information contained in this press release whether as a result of new information, future events or any other reason.

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Exhibit 99.2

Ziopharm ONCOLOGY

A New Day for Ziopharm Oncology

October 9, 2018

Forward-Looking Statements

This presentation contains certain forward-looking information about Ziopharm Oncology, Inc. that is intended to be covered by the safe harbor for "forward-looking statements" provided by the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements are statements that are not historical facts, and in some cases can be identified by terms such as "may," "will," "could," "expects," "plans," "anticipates," and "believes." These statements include, but are not limited to, statements regarding the expected benefits of the strategic transaction including entry into an exclusive license agreement with Precigen, Inc., the progress, timing and results of preclinical and clinical trials involving the Company's product candidates including the development of Sleeping Beauty-modified TCRs and CD19-specific CAR-T therapies, the expected timing for the Company's response to the U.S. Food and Drug Administration (FDA) in regards to its investigational new drug (IND) application for its third-generation Phase 1 trial to evaluate CD19-specific CAR-T therapies under technology referred to as point-of-care, the expected timing for the filings or amendments of IND applications for its other product candidates and the progress of the Company's research and development programs. All of such statements are subject to certain risks and uncertainties, many of which are difficult to predict and generally beyond the control of the Company, that could cause actual results to differ materially from those expressed in, or implied by, the forward-looking statements. These risks and uncertainties include, but are not limited to: whether chimeric antigen receptor T cell (CAR^+ T) approaches, Ad-RTS-hIL-12, TCR and NK cell-based therapies, or any of our other therapeutic candidates will advance further in the preclinical or clinical trials process and whether and when, if at all, they will receive final approval from the FDA or equivalent foreign regulatory agencies and for which indications; whether chimeric antigen receptor T cell (CAR^+ T) approaches, Ad-RTS-hIL-12, TCR and NK cell-based therapies, and our other therapeutic products will be successfully marketed if approved; the strength and enforceability of our intellectual property rights; competition from other pharmaceutical and biotechnology companies; and the other risk factors contained in our periodic and interim SEC reports filed from time to time with the Securities and Exchange Commission, including but not limited to, our Annual Report on Form 10-K for the fiscal year ended December 31, 2017, and subsequent reports that the Company may file with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements that speak only as of the date hereof, and we do not undertake any obligation to revise and disseminate forward-looking statements to reflect events or circumstances after the date hereof, or to reflect the occurrence of or non-occurrence of any events.

Ziopharm ONCOLOGY

Agenda (beginning 8 am ET October 9, 2018)

- On the Call
  - Laurence Cooper, MD, PhD, CEO
  - David Mauney, MD, EVP, CBO and Interim COO
  - David Connolly, VP, Corporate Communications and IR
  - Rob Hadfield, General Counsel
- Introduction / Overview
  - Laurence Cooper
- Terms of New Agreement
  - David Mauney
- Clinical Programs Update
  - Laurence Cooper
- Q&A

Ziopharm ONCOLOGY

The New Ziopharm

Ziopharm ONCOLOGY

The “New Ziopharm” with Full Autonomy

- Immunotherapy pipeline focused on solid tumors
- New, simplified licensing agreement with Intrexon/Precigen
- Preferred stock issued to Intrexon fully retired
- Revised Board of Directors
- Strategic flexibility for corporate development, sublicensing
- Aligned financial incentives and resources

Refined Focus on Controlled IL-12 *Sleeping Beauty* for All TCR Targets and Two CAR Targets

Exclusive worldwide rights

Platform #1
Controlled IL-12

Ad-RTS-hIL-12 plus veledimex for brain cancer, other solid tumors

- Monotherapy
- Combination with immune checkpoint inhibitors
- Optionality on next-gen delivery

Platform #2
Sleeping Beauty

Sleeping Beauty

- **TCRs targeting neoantigens for solid tumors**
- CD19-specific CAR and second unnamed CAR target

Ziopharm ONCOLOGY

The New Ziopharm

Terms of New Agreement

Ziopharm ONCOLOGY

Historic Overview of Ziopharm and Intrexon Relationship

- January 2011 – Intrexon and Ziopharm enter into Exclusive Channel Collaboration (ECC)* agreement
  - Established 50-50 share of net profits; Ziopharm is Intrexon's exclusive oncology partner; Limited sub-licensing rights
- January 2015 – Intrexon, Ziopharm and MD Anderson announce Exclusive Licensing Agreement for CAR-T, TCR, NK Cell programs specifically for development of nonviral adoptive cell therapies
- March 2015 – Intrexon-Ziopharm announce global CAR-T collaboration with Merck KGaA
- June 2016 – Intrexon and Ziopharm renegotiate ECC
  - 80-20 Ziopharm-Intrexon sales royalties (changed from 50-50); 50-50 on sub-licensing agreement remains; Intrexon received $120M in preferred stock plus 12% annually
- January 2017 – Intrexon and Ziopharm announce Collaborative Research and Development Agreement (CRADA) with National Cancer Institute (NCI) – *Sleeping Beauty*-modified TCRs for solid tumors
- March 2017 – Intrexon announces restructuring, formation of Precigen for all health care assets
- October 2018 – ECC terminated, replaced with new licensing agreement

* Intrexon transferred rights to Precigen when it was launched in 2017
** Now, with the exception of CD19

Ziopharm ONCOLOGY

New License for Exclusive Rights to Controlled IL-12, *Sleeping Beauty* TCRs and *Sleeping Beauty* CD19-CAR

Controlled IL-12 Platform

- **Exclusive rights** to Ad-RTS-hIL-12 plus veledimex
- Ziopharm **gains optionality for next-generation technologies** for RTS-IL-12

Sleeping Beauty Platform

- **Exclusive rights** to T cells genetically modified with *Sleeping Beauty* to express TCRs
- **Exclusive rights** to *Sleeping Beauty* CD19-specific CAR-T and rights to second unnamed CAR target

Ziopharm gains broad sub-licensing rights providing flexibility to pursue partnerships with lower sub-licensing fees to Precigen, than previous ECC agreement

Non-exclusive rights to pursue additional programs

Milestone payments upon commencement of later stage clinical and regulatory milestones

Tiered royalty payments based on net sales

Ziopharm ONCOLOGY

Additional Terms of 2018 Licensing Agreement with Precigen

- Preferred stock valued at approximately $156.9 million* retired
- R.J. Kirk resigns from Ziopharm Board of Directors
- Ziopharm retains collaboration with MD Anderson Cancer Center and the approximately $31.7 million** available from prepayments
- Ziopharm will assume full control of CRADA with NCI for TCRs
- CAR-T development by Precigen remains subject to Merck KGaA
  - Precigen retains worldwide rights to CD33 and all other CAR targets, excluding Ziopharm's CD19 and 2nd unnamed CAR target with *Sleeping Beauty* platform
  - Ziopharm receives capped royalties on Precigen CAR products

* As of Sept. 30, 2018
** As of June 30, 2018

Ziopharm ONCOLOGY

The New Ziopharm

Clinical Programs Update

Ziopharm ONCOLOGY

Focused on Controlled IL-12, *Sleeping Beauty*-TCRs to Target Solid Tumors plus Two CAR Targets

Controlled IL-12: Turning cold tumors hot by activating patient's immune response

	Indication	Preclinical	Phase 1	Phase 2	Phase 3
Ad-RTS-hIL-12 + veledimex	rGBM	Monotherapy (expansion)			
	rGBM	In combination w/ OPDIVO®			
	Pediatric brain tumor	Monotherapy			
	New indication	Initiated in 1H2019			

Sleeping Beauty: Non-viral genetic modification of TCR-T cells and CAR-T cells to infuse an immune response

TCRs targeting neoantigens	Multiple solid tumors	IND 4Q2018	NIH NATIONAL CANCER INSTITUTE
CAR-T	Leukemia/lymphoma	CD19 2nd Gen shortened manufacture	THE UNIVERSITY OF TEXAS MD Anderson Cancer Center Making Cancer History®
	Leukemia/lymphoma	3rd Gen w mbIL15 (P-O-C) IND in 2H2019	
	Unnamed target*		

P-O-C = "Point-of-Care" for very rapid manufacturing
* Ziopharm holds rights to second, unnamed CAR target

Initiated Planned

Ziopharm ONCOLOGY

Controlled IL-12 Platform for Brain Tumors

- Monotherapy of Ad-RTS-hIL-12 + veledimex has shown improved survival benefit of 12.7 months median overall survival (mOS) in 15 patients*; Low-dose steroid use improved survival
  - Adult: Phase 1 expansion cohort with 20 mg of veledimex underway to expand clinical data
    - Seven patients treated to date
  - Pediatrics: Wide open for drug development
    - First pediatric patient survival past 10-month mark reported as of August 2018; Second patient treated in September
- Combination trial with OPDIVO (nivolumab): Biopsy, biomarker data supportive of combination
  - Actively enrolling; three patients treated to date; up to 18 planned

- Administered intratumorally at resection
- Oral veledimex modulates and turns on/off local expression of IL-12

** mOS of 12.7 months at 12.9 months follow-up compares favorably to historical controls of 5 to 8 months mOS. Was presented in "A Phase 1 study of Ad-RTS-hIL-12 + veledimex in adult recurrent glioblastoma," at 2017 Society of Neuro-Oncology by Antonio Chiocca, M.D., Ph.D., Brigham and Women's / Dana-Farber Cancer Center*

Ziopharm ONCOLOGY

Market Opportunity for IL-12 in rGBM – Three Paths to Commercialization to be Explored

Monotherapy

- Adult rGBM
- Pediatric gliomas

Combination with anti-PD-1

- Adult rGBM

~70,000
new adult cases world wide each year

12,390[1]
new cases in the U.S. each year

14,576[2]
new cases in Europe each year

Recurrence = 90%
US – 11,151[1]
EU – 13,118[2]

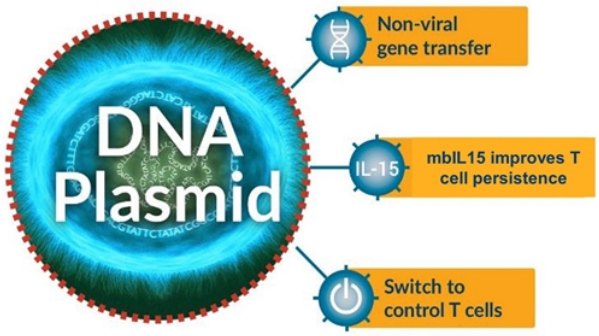
1. http://www.abta.org/about-us/news/brain-tumor-statistics/
2. GlobalData information, June 2016

Ziopharm ONCOLOGY

Status of Investigational New Drug Application for Third-Generation Trial to Evaluate CD19-specific CAR-T Therapy

- Per disclosures in June and August 2018, FDA requested additional pre-clinical process development, placed clinical hold on IND
- Guidance update on “point-of-care” (“P-O-C”):
  - FDA mandated a 70% cell viability threshold
  - Ziopharm and MD Anderson executing on cell viability improvements
  - Anticipate filing amended IND in 2H2019
- Second-generation *Sleeping Beauty* trial at MD Anderson Cancer Center ongoing
  - Dosing, CAR design, reduced manufacturing and release testing time
  - Encouraging clinical data

Genetic modification of T cells with *Sleeping Beauty* system to produce T cells in < 2 days



Potential advantage over off-the-shelf

- Third-party OTS cells require lymphodepletion, but mbIL15 may enable avoidance

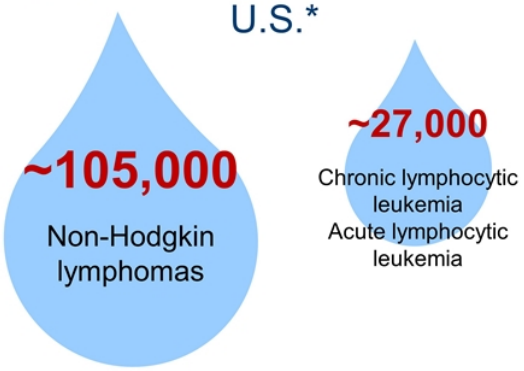
Ziopharm ONCOLOGY

Market Opportunity for CD19-Specific CAR-T

"Point-of-care"

- Reduced cost and complexity with < 2-day manufacturing
- Potential to avoid lymphodepletion with SB system and mbIL15

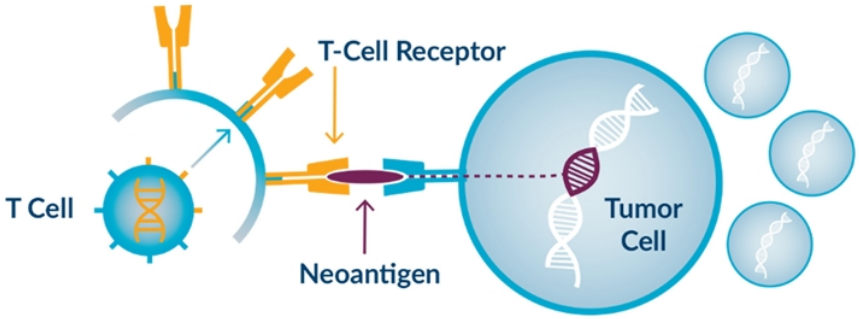
Estimated new cases of lymphomas and leukemias in U.S.*



- *Updated Data on Blood Cancers, 2018,* Leukemia & Lymphoma Society
- CA Cancer J Clin. 2016 Sep 12 [Epub ahead of print]

Ziopharm ONCOLOGY

Sleeping Beauty Provides Manufacturing Solution for Autologous Personalized TCR-T Therapies Targeting Neoantigens for Each Patient



Neoantigens → the key to targeting solid tumors

Intracellular antigens that are unique to each patient's cancer

TCRs	**T cells**	**TCR⁺ T cells**	***Sleeping Beauty***
• Neoantigens can only be recognized by TCRs (& not CARs)	• Infuse autologous T cells as cannot be targeted by off-the-shelf T cells	• Eliminate bulky solid tumors with infusions of genetically modified T cells	• The gene therapy platform to express multiple TCRs in T cells

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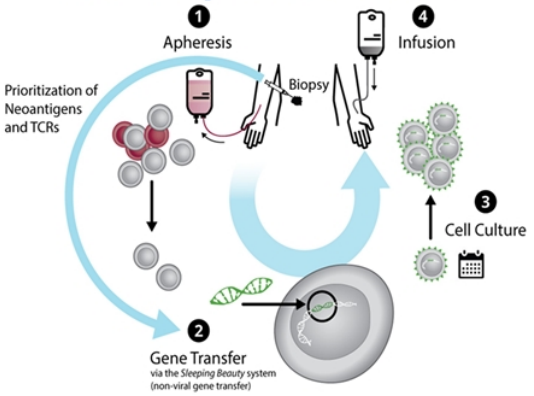
T cells Targeting Neoantigens has Demonstrated Clinical Success in Solid Tumors (History on our Side)

Ziopharm provides technology to commercialize T-cell targeting of TCRs

Four steps to success



Cancer Immunotherapy Based on Mutation-Specific CD4+ T Cells in a Patient with Epithelial Cancer

Eric Tran,[1] Simon Turcotte,[1]* Alena Gros,[1] Paul F. Robbins,[1] Yong-Chen Lu,[1] Mark E. Dudley,[1]† John R. Wunderlich,[1] Robert P. Somerville,[1] Katherine Hogan,[1] Christian S. Hinrichs,[1] Maria R. Parkhurst,[1] James C. Yang,[1] Steven A. Rosenberg[1]‡

Limited evidence exists that humans mount a mutation-specific T cell response to epithelial cancers. We used a whole-exomic-sequencing-based approach to demonstrate that tumor-infiltrating lymphocytes (TIL) from a patient with metastatic cholangiocarcinoma contained CD4+ T helper 1 (T_H1) cells recognizing a mutation in erbb2 interacting protein (**ERBB2IP**) expressed by the cancer. After adoptive transfer of TIL containing about 25% mutation-specific polyfunctional T_H1 cells, the patient achieved a decrease in target lesions with prolonged stabilization of disease. Upon disease progression, the patient was retreated with a >95% pure population of mutation-reactive T_H1 cells and again experienced tumor regression. These results provide evidence that a CD4+ T cell response against a mutated antigen can be harnessed to mediate regression of a metastatic epithelial cancer.

The human immune system has evolved to recognize and eliminate cells expressing foreign, nonself antigens. All malignant tumors has or other genetic may generate ne potentially trigge Indeed, mutation ly be found infi and likely play efficacy of ado other immunot

However, limited evidence exists demonstrating that the human immune system can mount an endogenous, mutation-specific T cell response

Mutated PPP1R3B Is Recognized by T Cells Used To Treat a Melanoma Patient Who Experienced a Durable Complete Tumor Regression

Yong-Chen Lu,[a] Xin Yao,[a] Yong F. Li,[b] Mona El-Gamil,[b] Mark E. Dudley,[a] James C. Yang,[a] Jorge R. Almeida,[c] Daniel C. Douek,[c] Yardena Samuels,[c] Steven A. Rosenberg,[a] and Paul F. Robbins[a]

Adoptive cell therapy with tumor-infiltrating lymphocytes (TILs) represents an effective treatment for patients with metastatic melanoma. However, most of the Ag targets recognized by effective melanoma-reactive TILs remain elusive. In this study, patient 2369 experienced a complete response, including regression of bulky liver tumor masses, ongoing beyond 7 y following adoptive TIL transfer. The screening of a cDNA library generated from the autologous melanoma cell line resulted in the isolation of a mutated protein phosphatase 1, regulatory (inhibitor) subunit 3B (PPP1R3B) gene product. The mutated PPP1R3B peptide represents the immunodominant epitope recognized by tumor-reactive T cells in TIL 2369. Five years following adoptive transfer, peripheral blood T lymphocytes obtained from patient 2369 recognized the mutated PPP1R3B epitope. These results demonstrate that adoptive T cell therapy targeting a tumor-specific Ag can mediate long-term survival for a patient with metastatic melanoma. This study also provides an impetus to develop personalized immunotherapy targeting tumor-specific, mutated Ags. *The Journal of Immunology*, **2013, 190: 6034–6042.**

Patients with metastatic melanoma have a poor prognosis, as the five-year survival rate in this population is ~5% (1). Other than the conventional chemotherapy, the available treatments include IL-2, anti-CTLA-4 Ab (ipilimumab, BRAF V600E inhibitor vemurafenib, and adoptive cell therapy. Among these treatments, adoptive cell therapy can be an effective salvage treatment, after patients have progressed after other therapies (2).

Adoptive cell therapy involves the transfer of autologous T cells with antitumor activity to the cancer-bearing patient. Tumor-infiltrating lymphocytes (TILs) within surgically resected melanoma deposits can be grown to large numbers in culture medium containing IL-2, while retaining reactivity against autologous tumor. On three sequential clinical trials, patients were treated with the adoptive transfer of autologous TILs after ex vivo expansion in conjunction with high-dose IL-2 following a lymphodepleting preparative regimen (3). Adoptive TIL transfer mediated the objective regression of metastatic melanoma in an in 72% of patients. including the induction of an in vivo activity of TILs (5, 6). The ex vivo culture of TILs with the stimulation of IL-2 can reverse this inhibitory state, resulting in their activation and clonal expansion. Despite the strong antitumor activities of TILs ex vivo, the majority of patients receiving adoptive TIL transfer have not experienced durable regression. One potential explanation for these findings is that TIL targeting Ags derived from essential genes may mediate long-term regression more effectively than those targeting nonessential gene products that can be downregulated, leading to tumor escape (7). However, most of the Ags recognized by adoptive transferred TILs that mediated long-term complete regressions remain elusive (8). To further examine this hypothesis, we identified the immunodominant target of a TIL product that was administered to a patient with metastatic melanoma who experienced a durable complete regression without tumor recurrence.

Materials and Methods

nature medicine LETTERS

Immune recognition of somatic mutations leading to complete durable regression in metastatic breast cancer

Nikolaos Zacharakis[1], Harshini Chinnasamy[1], Mary Black[1], Hui Xu[1], Yong-Chen Lu[1]*, Zhili Zheng[1], Anna Pasetto[1], Michelle Langhan[1], Thomas Shelton[1], Todd Prickett[1], Jared Gartner[1], Li Jia[1], Katarzyna Trebska-McGowan[1], Robert P. Somerville[1], Paul F. Robbins[1], Steven A. Rosenberg[1]*,

The New England Journal of Medicine

BRIEF REPORT

T-Cell Transfer Therapy Targeting Mutant KRAS in Cancer

Eric Tran, Ph.D., Paul F. Robbins, Ph.D., Yong-Chen Lu, Ph.D., Todd D. Prickett, Ph.D., Jared J. Gartner, M.Sc., Li Jia, M.Sc., Anna Pasetto, Ph.D., Zhili Zheng, Ph.D., Satyajit Ray, Ph.D., Eric M. Groh, M.D., Isaac R. Kriley, M.D., and Steven A. Rosenberg, M.D., Ph.D.

SUMMARY

CELL THERAPY USING EX VIVO EXPANDED TUMOR-INFILTRAT-

Clockwise from top left:

1. Science. 2014 May 9;344(6184):641-5
2. Nat Med. 2018 Jun;24(6):724-730
3. N Engl J Med. 2016, Dec 8;375(23):2255-2262
4. J Immunol. 2013 Jun 15;190(12):6034-42

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NCI Advancing *Sleeping Beauty* to Target Neoantigens in Solid Tumors with TCR-expressing T cells

Preclinical Data

original article

Stable, Nonviral Expression of Mutated Tumor Neoantigen-specific T-cell Receptors Using the *Sleeping Beauty* Transposon/Transposase System

CRADA

ZIOPHARM and Intrexon Announce CRADA with NCI

NIH NATIONAL CANCER INSTITUTE

Clinical Protocol

Completed

Validation

Complete 4Q 2018

Patient Data in 2019

- **IND for TCR-T to be submitted in 4Q 2018** (unaffected by CAR program)
- All four steps being tested at NCI
- Multiple solid tumor types can benefit from this approach

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Ziopharm Will be First to Use Non-Viral Approach to Manufacture TCR-T

Neoantigens

- Likely, best chance to target solid tumors

TCR-T

- Undertaken using the cutting edge science at NCI

Sleeping Beauty

- Superior technology to commercialize TCR-T

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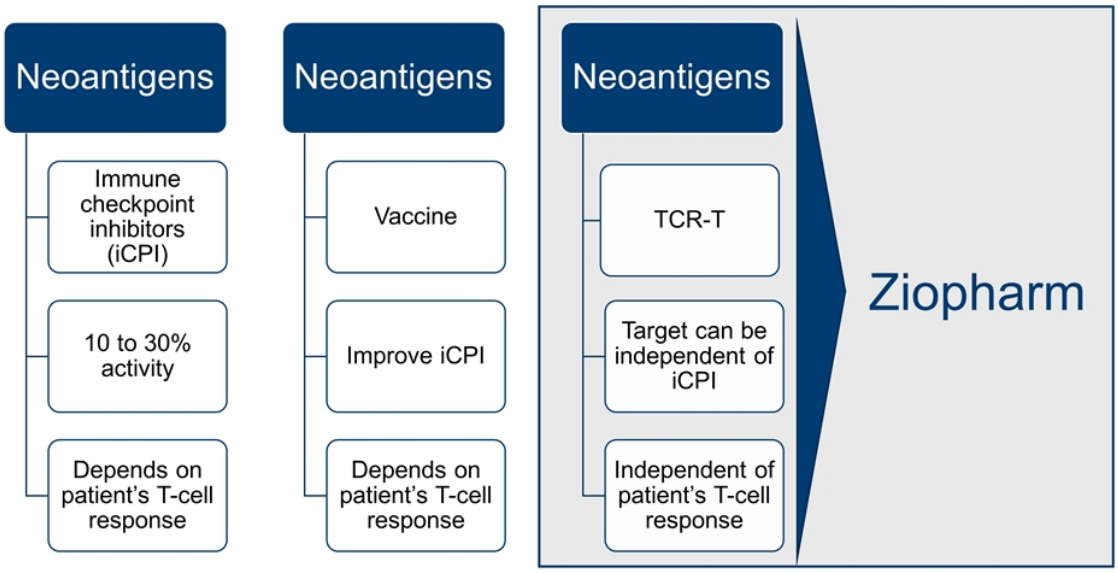
Market Opportunity for TCR-T in Solid Tumors

Prospect of TCR-T dwarfs the opportunity for CAR-T



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The New Ziopharm
New Day

Ziopharm
ONCOLOGY

Key Investment Highlights: Expected Milestones and Value Inflection Points

New Ziopharm on Day 1

- ✓ Large platform opportunities currently in clinic and more in 2019
- ✓ Strategic autonomy
- ✓ Preferred stock retired
- ✓ Three new board members with 75+ years experience in life sciences

- **Fourth Quarter 2018**
  - NCI to submit IND for TCR
  - Updated IL-12 data at Society of Neuro-Oncology
  - Additional board members
- **First Half 2019**
  - Complete enrollment in IL-12 monotherapy expansion and in IL-12 combo trial with nivolumab
  - Initiate new phase 1 trial for IL-12 and immune checkpoint inhibitor
  - Begin enrollment in TCR trial with SB-modified T cells
  - Data updates across all programs
  - Investor & Analyst Day
- **2H19**
  - Resubmit third-generation (“P-O-C”) CD19 CAR T IND

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