Atara Biotherapeutics, Inc.
Form 10-K
March 04, 2016

UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

x ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the fiscal year ended December 31, 2015

OR

¨TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934
For the transition period from to

Commission File Number 001-36548

ATARA BIOTHERAPEUTICS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware (State or other jurisdiction of incorporation or organization)	46-0920988 (I.R.S. Employer Identification No.)
701 Gateway Blvd., Suite 200 South San Francisco, CA (Address of principal executive offices)	94080 (Zip Code)

Registrant’s telephone number, including area code: (650) 278-8930

Securities registered pursuant to Section 12(b) of the Act: Common Stock, par value $0.0001 per share, traded on The Nasdaq Stock Market

Securities registered pursuant to Section 12(g) of the Act: None

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. YES ¨ NO x

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. YES ¨ NO x

Indicate by check mark whether the Registrant: (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. YES x NO ¨

Indicate by check mark whether the Registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit and post such files). YES x NO ¨

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§229.405) is not contained herein, and will not be contained, to the best of Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ¨

Indicate by check mark whether the Registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definition of "large accelerated filer", "accelerated filer", and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨		Accelerated filer	x
Non-accelerated filer ¨	(Do not check if a small reporting company)	Small reporting company	¨

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). YES ¨ NO x

The aggregate market value of common stock held by non-affiliates of the Registrant, based on the closing sales price for such stock on June 30, 2015 as reported by The Nasdaq Stock Market, was $698,303,925. The calculation of aggregate market value excludes 11,292,937 shares held by executive officers, directors and stockholders that the Registrant has concluded are affiliates of the Registrant. Exclusion of such shares should not be construed to indicate that any such person possesses the power, direct or indirect, to direct or cause the direction of the management or policies of the registrant or that such person is controlled by or under common control with the Registrant.

The number of outstanding shares of the Registrant's Common Stock as of February 15, 2016 was 28,692,220.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive proxy statement relating to its 2016 Annual Meeting of Stockholders are incorporated by reference into Part III of this Report where indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

ATARA BIOTHERAPEUTICS, INC.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Such forward-looking statements, which represent our intent, belief or current expectations, involve risks and uncertainties and other factors that could cause actual results and the timing of certain events to differ materially from future results expressed or implied by such forward-looking statements. In some cases you can identify these statements by forward-looking words such as "believe," "may," "will," "estimate," "continue," "anticipa "intend," "could," "would," "project," "plan," "expect" or the negative or plural of these words or similar expressions. Forward-looking statements in this Annual Report on Form 10-K include, but are not limited to, statements about:

- our expectations regarding the timing of initiating clinical trials, enrolling clinical trials and reporting results of clinical trials for our T-cell programs;
- the likelihood and timing of regulatory approvals for our product candidates;
- the potential market opportunities for commercializing our product candidates;
- our expectations regarding the potential market size and the size of the patient populations for our product candidates, if approved for commercial use;
- our expectations regarding the timing of reporting results from our Phase 1 clinical trial of STM 434;
- estimates of our expenses, capital requirements and need for additional financing;
- our expectation that our existing capital resources will be sufficient to enable us to fund our planned operations through 2018;
- our expectations regarding the timing of reporting results from clinical trials being conducted by Memorial Sloan Kettering Cancer Center ("MSK") of the T-cell product candidates we licensed in 2015;
- our ability to develop, acquire and advance product candidates into, and successfully complete, clinical trials;
- the initiation, timing, progress and results of future preclinical studies and clinical trials and our research and development programs;
- the scope of protection we are able to obtain and maintain for our intellectual property rights covering our product candidates;
- our use of proceeds from our public offerings of common stock;
- our financial performance;
- developments and projections relating to our competitors and our industry; and
- our ability to sell or manufacture approved products at commercially reasonable values.

These statements are only current predictions and are subject to known and unknown risks, uncertainties and other factors that may cause our or our industry's actual results, levels of activity, performance or achievements to be materially different from those anticipated by the forward-looking statements. We discuss many of these risks in this report in greater detail under the heading "1A. Risk Factors" and elsewhere in this report. You should not rely upon forward-looking statements as predictions of future events. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risks and uncertainties.

In this Annual Report on Form 10-K, unless the context requires otherwise, "Atara," "Atara Biotherapeutics," "Company," "we," "our," and "us" means Atara Biotherapeutics, Inc. and, where appropriate, its subsidiaries.

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PART I

Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company focused on developing meaningful therapies for patients with severe and life-threatening diseases that have been underserved by scientific innovation. We have two groups of product candidates: (a) allogeneic or third-party derived antigen-specific T-cells, and (b) molecularly targeted biologics.

T-cells are a type of white blood cell. Cytotoxic T-cells, otherwise known as cytotoxic T lymphocytes, or CTLs, have been shown to have the ability to kill cancer cells. Our T-cell product candidates arise from a platform technology designed to produce off-the-shelf, partially human leukocyte antigen, or HLA, matched cellular therapeutics utilizing CTLs. We licensed rights to these product candidates from Memorial Sloan Kettering Cancer Center, or MSK, in June 2015. Our initial T-cell product candidates target viral- or cancer-specific antigens and are designed to harness the body's immune system to counteract specific viral infections and cancers. Our most advanced T-cell product candidate, EBV-CTL, is in Phase 2 clinical trials for malignancies associated with Epstein Barr Virus, or EBV, including EBV-associated post-transplant lymphoproliferative disorders, or EBV-PTLD. EBV-PTLD is a cancer affecting some patients who have received an allogeneic hematopoietic cell transplant, or HCT, a solid organ transplant, or SOT, or are otherwise immunocompromised. Our second T-cell product candidate, CMV-CTL, is in Phase 2 clinical trials for cytomegalovirus, or CMV, an infection that occurs in some patients who have received an HCT or SOT or are otherwise immunocompromised. Our third T-cell product candidate, WT1-CTL, targets cancers expressing the antigen Wilms Tumor 1, or WT1, and is currently in Phase 1 clinical trials. In addition, we entered into a sponsored research collaboration with MSK to discover and develop additional T-cell product candidates. In October 2015, we entered into exclusive license and research agreements with another academic institution. These agreements enable us to access a technology complementary to that which was licensed from MSK and to pursue development of EBV and CMV-CTLs for other indications such as nasopharyngeal carcinoma, or NPC, gastric cancer, and multiple sclerosis, or MS. We are working with this academic institution on the submission to the FDA of one or more investigational new drug applications, or INDs, for these new indications.

Our molecularly targeted product candidates are biologics that inhibit myostatin and activin, members of the Transforming Growth Factor-Beta, or TGF-ß, protein superfamily, which play roles in the growth and maintenance of muscle and many other body tissues. Our lead molecularly targeted product candidate is STM 434. We commenced a Phase 1 clinical trial of STM 434 for ovarian cancer and other solid tumors in 2014. We have five additional molecularly targeted product candidates that modulate the TGF-ß pathway in preclinical development.

In clinical trials that enrolled patients with EBV-PTLD following HCT or SOT, efficacy following treatment with EBV-CTL compares favorably with historical data in these patient populations. In rituximab-refractory patients with EBV-PTLD after HCT, treatment with EBV-CTL resulted in one-year overall survival of approximately 60% in two separate clinical trials in comparison with historical data where median survival, or the time by which 50% of patients had died, was 16-56 days. In the setting of rituximab-refractory EBV-PTLD after SOT, similar results were observed, with one-year overall survival of approximately 60% in EBV-CTL-treated patients in comparison with an expected historical one-year survival of 36% in patients with high risk disease similar to the patients treated in the trials. In February 2015, the U.S. Food and Drug Administration, or the FDA, granted breakthrough therapy designation for EBV-CTL in the treatment of rituximab-refractory EBV-PTLD after HCT. Breakthrough therapy designation is an FDA process designed to accelerate the development and review of drugs intended to treat a serious condition when early trials show that the drug may be substantially better than current treatment. In June 2015, we met with the FDA

to discuss late-stage development to support a potential approval in this indication. Based on guidance from the FDA, we submitted a special protocol assessment, or SPA, for a single arm pivotal trial in rituximab-refractory EBV-PTLD after HCT. We received feedback from the FDA regarding this SPA in which the FDA indicated that a single arm trial with response rate as the primary endpoint may provide an adequate basis for approval but it would be unlikely to grant an SPA for our proposed trial. We intend to continue the dialogue with the FDA regarding this trial design under breakthrough designation and expect to initiate this pivotal trial towards the end of 2016. Additionally, we intend to initiate a randomized pivotal trial in patients with EBV-PTLD after SOT towards the end of 2016. In February 2016, the FDA granted orphan drug designation for EBV-CTL for the treatment of patients with EBV-PTLD after HCT or SOT.

Results from ongoing Phase 2 trials of CMV-CTL have demonstrated similar efficacy in the setting of refractory CMV infection after HCT, with response rates exceeding 60% in patients with CMV viremia and disease resistant to multiple approved and investigational anti-viral therapies. We expect to meet with the FDA in the middle of 2016 to discuss late phase development with CMV-CTL to support approval.

While we evaluate the path to registration for both EBV-CTL and CMV-CTL in these initial indications, we intend to concurrently explore the clinical utility of these T-cell product candidates or other cellular therapies in other relevant disease states to expand their potential applicability. In addition, we believe that T-cells can be directed at a broad range of other targets to create future

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product candidates. We believe that viral antigens are well suited to adoptive immunotherapy given that people with normal immune systems are able to mount robust responses to these viral targets, but immunocompromised patients and some cancer patients are not.

Our lead molecularly targeted product candidate, STM 434, a soluble ActR2B receptor that binds to Activin A, is in a Phase 1 clinical trial that will enroll approximately 70 patients with ovarian cancer and other solid tumors. In October 2015, we received orphan drug designation from the FDA for STM 434 in ovarian cancer, and we believe that novel therapies for clear cell and granulosa cell tumors could qualify for breakthrough therapy designation if supported by appropriate clinical data. Based on its mechanism of action, we also believe that STM 434 has the potential to be the first product to target tumor growth and proliferation through the inhibition of Activin A. STM 434 has a well-characterized mechanism of action and was developed initially, along with our other in-licensed molecularly targeted biologic product candidates, at Amgen, Inc., or Amgen. We are evaluating the remaining five pre-clinical molecularly targeted product candidates to determine the best path forward. Where appropriate, we intend to conduct preclinical studies and file INDs with the FDA for these candidates.

In December 2015, we announced results from a Phase 2 proof-of-concept clinical trial for PINTA 745, a molecularly targeted product candidate, for the treatment of protein energy wasting in patients with end stage renal disease. The trial did not meet its primary endpoint, defined as the percent change from baseline in lean body mass as measured by dual energy x-ray absorptiometry at week 12 following weekly treatment with PINTA 745. PINTA 745 also did not improve physical function, measures of glycemic control and markers of inflammation. There were no treatment related serious adverse events observed in the trial. We intend to complete the trial as designed; however, as a consequence of these results, we have suspended further clinical development of PINTA 745.

Our business model is to license or acquire, develop and commercialize novel therapeutics for serious unmet medical needs with validated targets and established proof of concept. Based on the properties of each of these molecules, including efficacy, safety, pharmacokinetics, affinity and other characteristics, we match each program to clinical indications that we believe maximize its therapeutic potential and may result in an expedited path to market. We believe our management team has the breadth and depth of experience to execute this model. Our management team includes:

- Isaac E. Ciechanover, M.D., our President and Chief Executive Officer, was Executive Director for Business Development at Celgene Corporation, or Celgene. At Celgene, he led the company’s venture capital efforts and led licensing and acquisition activities with an aggregate transaction value of more than $6.7 billion. Those efforts included striking licensing and partnership transactions with cancer therapeutics companies Agios Pharmaceuticals, Inc., Acceleron Pharma Inc. and PTC Therapeutics Inc. Prior to founding Atara, Dr. Ciechanover was a Partner with Kleiner Perkins Caufield & Byers, a leading venture capital firm.
- Christopher Haqq, M.D., Ph.D., our Chief Medical Officer, was Vice President for Clinical Research and Development at Cougar Biotechnology, which was acquired by Johnson & Johnson in 2009. At Cougar Biotechnology, he was the lead clinician for a pivotal prostate cancer trial leading to market approval for Zytiga (abiraterone acetate). He has served as medical monitor for more than ten clinical trials and has contributed to drug development programs for a wide range of molecules, and served as an attending oncology physician and director of a translational laboratory at the University of California, San Francisco.
- Mitchall G. Clark, our Chief Regulatory and Quality Officer, was previously Senior Vice President of Global Regulatory Affairs at Abraxis Bioscience, Inc., or Abraxis, where he submitted and managed five INDs for oncology and cardiovascular drugs, including Abraxane (nanoparticle albumin-bound paclitaxel).
- Gad Soffer, our Chief Operating Officer, previously held various roles at Celgene, including most recently Global Project Leader for Abraxane following Celgene’s acquisition of Abraxis, where he led successful regulatory submissions for pancreatic cancer and non-small cell lung cancer.

- John F. McGrath, Jr., our Chief Financial Officer, was previously Executive in Residence and Operating Partner at Kleiner Perkins Caufield & Byers. Prior to that time, he served as Vice President and Chief Financial Officer for Network Equipment Technologies, Inc., a publicly traded company. He has served on the board of directors of the Presidio Fund, a publicly traded mutual fund, and on the boards of directors and as Audit Committee chairman of publicly traded companies Actel Corporation and Endwave Corporation.
- Heather Turner, our General Counsel and Secretary, was previously Senior Vice President, General Counsel and Secretary at Orexigen Therapeutics, Inc., a publicly traded company. Prior to that time, she served as Associate General Counsel - Corporate for Conor Medsystems, Inc., a publicly traded company, and an associate at Cooley LLP, a law firm.

Our T-Cell Product Candidates

T-cells are a critical component of the body’s immune system and can be harnessed to counteract viral infections and some cancers. By focusing the T-cells on specific proteins involved in cancers and infections, the power of the immune system can be

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employed to combat these diseases. In June 2015, we exclusively licensed from MSK worldwide rights to three clinical stage T-cell product candidates. We also have an exclusive option to exclusively license from MSK worldwide rights to certain other T-cell programs that are discovered or developed by MSK pursuant to sponsored research funded by us.

Our T-cell product candidates arise from a platform technology designed to produce off-the-shelf, cellular therapeutic options for patients with unmet medical needs. Our initial T-cell product candidates target viral- or cancer-specific antigens. In October 2015, we entered into exclusive license and research agreements with another academic institution. These agreements enable us to access a technology complementary to that which was licensed from MSK and to pursue development of EBV and CMV-CTLs for other indications such as NPC, gastric cancer, and MS. We are working with this academic institution on the submission to the FDA of one or more INDs for these new indications.

Our most advanced T-cell product candidate, EBV-CTL, is in Phase 2 clinical trials for the treatment of EBV-associated malignancies. EBV is the virus that causes mononucleosis and is associated with a number of more severe diseases, including certain malignancies and neurologic conditions, such as MS. EBV-CTL received breakthrough therapy designation from the FDA in February 2015 for the treatment of patients with rituximab-refractory EBV-PTLD after HCT, based on data from two separate clinical trials conducted by MSK. Since licensing our T-cell product candidates, the IND under which these trials were conducted has been transferred to us. In June 2015, we met with the FDA to discuss late-stage development to support a potential approval in this indication. Based on guidance from the FDA, we submitted an SPA for a single arm pivotal trial in rituximab-refractory EBV-PTLD after HCT. We received feedback from the FDA regarding this SPA in which the FDA indicated that a single arm trial with response rate as the primary endpoint may provide an adequate basis for approval but it would be unlikely to grant an SPA for our proposed trial. We intend to continue the dialogue with the FDA regarding this trial design under breakthrough therapy designation and expect to initiate this pivotal trial towards the end of 2016. Additionally, we intend to initiate a randomized pivotal trial in patients with EBV-PTLD after SOT towards the end of 2016. In February 2016, the FDA granted orphan drug designation for EBV-CTL for the treatment of patients with EBV-PTLD after HCT or SOT.

Our second T-cell product candidate, CMV-CTL, targets CMV, an infection that can result in blindness, illness or death, depending on the tissue it affects, in those with weakened immune systems. CMV is also associated with certain malignancies, including glioblastoma multiforme, or GBM. CMV-CTL is currently being investigated in Phase 2 clinical trials sponsored and conducted by MSK for CMV infections that occur in some patients who have received an HCT.

Our third clinical stage T-cell product candidate, WT1-CTL, targets WT1. Abnormal expression of WT1 is seen in a variety of hematologic and solid tumors, including MM, PCL, and ovarian cancer. This product candidate is currently in Phase 1 clinical trials sponsored and conducted by MSK.

Clinical experience with our T-cell product candidates is broad, including in immunocompromised states, as well as in solid and hematologic malignancies. Clinical data for EBV-CTL, CMV-CTL and WT1-CTL have been published in the journal Blood and presented at major scientific conferences. We are focusing our initial development and regulatory activities on EBV-CTL in the post-HCT and post-SOT setting and CMV-CTL in the post-HCT setting, which we believe offer a rapid path to marketing approvals if supported by additional clinical data. However, we intend to concurrently explore the clinical utility of our T-cell product candidates in other relevant disease states.

T-cell Technology Platform

Our T-cell product candidates share a common technology under which T-cells are collected from the blood of third-party donors and then exposed to a selected viral antigen in order to activate them against that particular virus. The resulting activated T-cells are expanded in number, characterized and stored for future therapeutic use in an appropriate partially HLA matched patient, providing an off-the-shelf, cellular therapeutic option for patients. Because these T-cells are off-the-shelf, patients often only need to wait days until they receive treatment. In addition to expanding the activated T-cells, the manufacturing process also leads to substantial reduction in the number of alloreactive cells, which can cause graft versus host disease, or GvHD. We believe this may reduce the risk of GvHD, a serious complication in immunocompromised recipients.

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The process through which EBV-CTLs are generated is shown in the diagram below. First, B-cells derived from the blood of a third-party donor are exposed to a specific strain of the EBV virus to create EBV transformed B lymphoblastoid cell lines, or EBV BLCLs. The BLCLs are irradiated to prevent the BLCLs from growing and then co-cultured with T-cells derived from the blood of the same third-party donor. In this co-culture process, the BLCLs present EBV antigen to the T-cells to activate the T-cells against the EBV virus. These activated EBV-specific T-cells are then sensitized and expanded, while the potentially alloreactive cells contained in the same culture are not expanded. When complete, the cultures are assessed for EBV reactivity, HLA restriction, the absence of allo-specificity and microbial sterility. Once fully characterized in this way, the cell lines are cryopreserved and stored for future therapeutic use as an off-the-shelf therapy.

The donor's blood contains a mix of T-cells, some that have the potential to target EBV-infected cancer cells, and others called alloreactive or allospecific T-cells, which have the potential to target cells recognized as foreign. Administration of bulk third-party lymphocytes that contain a relatively high proportion of allospecific T-cells has the potential to cause severe and life-threatening toxicities such as GvHD when these allospecific T-cells recognize the recipient's native cells as foreign. Our manufacturing process enriches the product for the desired EBV-CTLs while depleting the undesirable allospecific T-cells as they are not stimulated to expand and eventually die. The existing manufacturing process typically results in an approximately 70-fold expansion in the number of EBV-CTLs and reduces by a factor of approximately 20 the number of GvHD-causing allospecific T-cells, compared with the prevalence of these two types of cells in a sample of bulk donor lymphocytes.

In addition to being evaluated for expansion before release for use in clinical trials, cells are also evaluated for HLA restriction. HLA restriction refers to the fact that any given T-cell line will only recognize such T-cell line's target—in this case an EBV protein—when it is bound to a particular HLA. For example, an EBV-CTL restricted by a particular HLA known as HLA A*02:01 will only kill EBV-infected cells that show that same EBV protein when bound to HLA A*02:01. This process identifies EBV-CTLs that are specific to the desired target, limiting undesirable off-target killing of other cells.

An appropriate cell line for use in a particular patient is typically defined as being matched with at least two of eight HLA alleles and restricted through a shared HLA allele. In an analysis conducted by MSK and reported at the 2015 American Association for Cancer Research, or AACR, annual meeting, an appropriate cell line was determined to be available for all but one of 200 consecutive unrelated transplant recipients and 100 cord blood transplant recipients. This analysis was based on evaluating these potential patients against a bank of approximately 330 HLA characterized EBV-CTL lines that MSK had generated to date. MSK's clinical experience has yielded an empirically derived, proprietary approach to selecting the appropriate cell line for use in individual patients. We believe this algorithm will ultimately allow us to deliver the therapy efficiently by focusing on a limited set of EBV-CTL lines without compromising our ability to treat a wide range of patients with diverse HLA types.

A similar process is used to generate and characterize CMV-CTL and WT1-CTL, and we also plan to utilize this process to generate diverse banks of targeted cytotoxic T-cell lines against other antigens of interest.

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EBV-Targeted T-Cells for EBV-PTLD and Other EBV Associated Diseases

EBV is a member of the Herpes virus family and is one of the most common viruses in humans. It is present in all populations, infecting more than 95% of all individuals within the first four decades of life. In healthy individuals, EBV causes infectious mononucleosis, a generally benign self-limiting condition. Following the acute phase of EBV infection, the virus remains present in a small number of B-cells throughout the body; however, it is kept in check by the intact immune system. Though benign in the vast majority of people, EBV has been demonstrated to be involved in the development of many malignancies. In immunocompromised patients, EBV causes lymphomas and other lymphoproliferative disorders, collectively called EBV-PTLD. EBV-PTLD most commonly affects patients after HCT or after SOT. Even in patients with intact immune systems, EBV is associated with various hematologic malignancies and solid tumors including Hodgkin lymphoma, Burkitt's lymphoma, other B-cell malignancies, nasopharyngeal carcinoma and gastric cancer. EBV is also associated with certain diseases of the central nervous system, including multiple sclerosis.

The approximate estimated number of patients per year in the United States and European Union with EBV associated diseases is highlighted in the figure below.

Indication	Estimated Number of Patients
EBV-PTLD after HCT	1,400
EBV-PTLD after SOT	1,700
EBV positive Diffuse Large B cell lymphoma	5,800
EBV positive chemotherapy refractory Hodgkin lymphoma	2,100
EBV positive nasopharyngeal carcinoma	6,000
EBV positive gastric cancer	16,500
Primary and secondary progressive multiple sclerosis	>400,000

EBV-PTLD is a rare but serious complication in recipients of HCT. EBV-PTLD is often severe and sudden in onset and results in death in the majority of HCT patients who develop the disease. A study conducted by the Karolinska Institute that was reported in the journal Haematologica noted a three-year survival rate of just 20%. According to the U.S. Department of Health and Human Services, there were 8,338 allogeneic transplants in the United States in 2013, and according to the European Society for Blood and Marrow Transplantation, there were 14,950 allogeneic transplants in the European Union. While autologous transplants, or those obtained from the same individual, still comprise the majority of all transplants in the United States and European Union, the relative proportion of allogeneic transplants, or those obtained from a third-party donor, has increased over time, and we believe this trend will continue due to the increasing utilization of haploidentical transplants and reduced intensity transplants.

The monoclonal antibody, rituximab, is typically used off-label to treat EBV-PTLD, producing initial responses in approximately 55% of treated patients and durable responses in approximately 20% of treated patients. However, for those who relapse after rituximab therapy or fail to respond to rituximab, or for those with CD20 negative lymphoma (which is known to be unlikely to respond to rituximab), EBV-PTLD is frequently lethal. For example, it was reported in 2014 in the journal Bone Marrow Transplantation that the median survival period from diagnosis of rituximab-refractory EBV-PTLD in adult HCT patients was 33 days, and in 2014 it was reported in the journal

Haematologica that median survival was 16 days. In 2008, it was reported in the journal Bone Marrow Transplantation that the median survival period from the time of diagnosis in a group of EBV-PTLD patients who received rituximab was 56 days. Taken together, these studies suggest a range of median overall survival, or OS, in the setting of rituximab failure of 16-56 days.

MSK is conducting two separate clinical trials of EBV-CTL that enroll a heterogeneous group of patients with a variety of EBV-associated malignancies, including, but not limited to, EBV-PTLD after HCT and EBV-PTLD after SOT. These trials are referred to as Study 95-024, initiated in 1995, and Study 11-130, initiated in 2011. Results from these two trials supported the granting of breakthrough therapy designation by the FDA for EBV-CTL in February 2015 for the treatment of rituximab-refractory EBV-PTLD after HCT. Data from these trials was presented at a clinical trials plenary session at the April 2015 AACR Annual Meeting and was subsequently updated at an oral presentation at the June 2015 American Society of Clinical Oncology, or ASCO, Annual Meeting.

In Study 95-024, patients with EBV-PTLD following HCT were treated with EBV-CTL manufactured from T-cells derived from either the primary HCT donor or an unrelated third-party donor. The term primary HCT donor refers to the donor who provided hematopoietic stem cells for the HCT. As one measure of efficacy, response rate was evaluated in these patients. The response rate refers to the proportion of patients treated with EBV-CTL who had either a complete or partial response as best response to treatment when measured by radiographic imaging of the tumor. In a complete response, no visible evidence of tumor following treatment was observed. In a partial response, the tumor was reduced in size by more than 50% but less than 100%.

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In both the primary HCT donor and third-party donor cohorts, similar response rates of approximately 60% were achieved. Such response rates suggest that the efficacy of treatment with primary donor derived and third-party donor derived EBV-CTL are comparable. The similarity in efficacy observed following treatment with third party and primary donor derived EBV- CTL is important, as there are significant limitations associated with a therapy derived from the primary transplant donor. First, it can take approximately eight weeks to generate an EBV-CTL line from blood remaining from the primary HCT donor. In this amount of time and based on historical data, approximately half of those patients who had either failed to respond or who had relapsed after rituximab would likely have succumbed to their EBV-PTLD and died before the cell line was available for therapeutic use. Second, due to the limited quantities of certain HCT donor materials such as umbilical cord blood, it is not possible to make a primary donor derived EBV-CTL line for all patients. Additionally, if the EBV-PTLD is of host rather than donor origin, T-cells derived from the primary HCT donor may not be able to recognize this host tumor, and therefore would not be expected to be effective in combatting the disease. Thus, we believe that the availability of off-the-shelf third-party derived EBV-CTL provides significant practical and therapeutic advantages in the treatment of rituximab-refractory EBV-PTLD. A median of two cycles of third-party derived EBV-CTL were administered in these trials. In each cycle, three doses of EBV-CTL were given weekly for three weeks. In addition, a number of patients with disease located in the central nervous system, or CNS, responded to treatment with EBV-CTL, suggesting that these cells are capable of passing through the blood-brain barrier.

The OS for patients with rituximab-refractory EBV-PTLD after HCT following treatment with third-party derived EBV-CTL was evaluated by MSK as well as presented at ASCO 2015 using industry standard Kaplan Meier, Or K-M, methods. One-year OS was approximately 60% in the patients from Study 95-024 and approximately 70% in the patients from Study 11-130.

Since these trials are ongoing, we expect that these K-M estimates of survival will evolve with ongoing follow-up of the patients and that a median OS may be reached in Study 11-130. However, we believe that these results compare favorably with the historically reported median survival of 16-56 days in the setting of rituximab failure. Moreover, patients who achieve a complete response after EBV-CTL treatment have been noted by MSK to experience durable remissions without relapse of their EBV lymphoma.

The time course of a complete response following multiple cycles of EBV-CTL in a patient with rituximab-refractory EBV-PTLD is shown below using sequential positron emission tomography, or PET, scans. Also shown are the timing of rituximab and EBV-CTL therapy depicted by the corresponding set of arrows, the levels of EBV DNA in the blood as measured by EBV polymerase chain reaction, or EBV PCR, a sensitive and specific technique to detect viral DNA depicted in the corresponding line, as well as the levels of CTL precursors per milliliter of blood, or CTLp/ml, depicted in the corresponding line. CTLp/ml identifies and enumerates activated T-cells.

This patient developed EBV viremia, or high levels of virus in the blood, early post-HCT as noted in the line labeled EBV PCR. Her viremia responded to rituximab, but recurred and it again responded to a second cycle of rituximab. In the interim, she developed a rapidly progressive diffuse large B-cell lymphoma, or DLBCL, that was EBV positive. By week 0, defined as the start of EBV-CTL therapy, the lymphoma is visible in the lymph nodes as well as in the liver and spleen. She received a first cycle of third party EBV-CTL after which she had a partial response. The patient received three subsequent cycles of EBV-CTL after which she achieved a complete response. In conjunction with each cycle of EBV-CTL, expansion of EBV-specific cytotoxic T-cells was detected, as shown

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in the line labeled CTLp/ml. While these expansions were not durable, they mediated her complete response. The PET scans, in which dark areas correspond to areas of high metabolic activity, show both normal metabolism of organs such as the heart and abnormal metabolism in areas of lymphoma. After treatment with T-cells, the abnormal areas of metabolism recede, indicating eradication of tumor cells. In the final image, no abnormal metabolic activity is observed, reflecting a complete response to EBV-CTL therapy.

The ability to switch from one cell line to another led to the discovery of a hierarchy of HLA restriction. This is highlighted by the example below, in which a patient received three EBV-CTL lines (A, B and C) with different HLA restrictions, but only went into complete response upon administration of a fourth unique EBV-CTL line (D) with a different HLA restriction. We believe that future patients can be treated using a cell line selection algorithm based in part on the hierarchy elucidated in this manner that enables a more efficient choice of EBV-CTL.

Across all patients enrolled in the two trials, reports of treatment related adverse events were low, with few possibly related grade 3 and grade 4 adverse events observed. One patient developed grade 1 skin GvHD responding to topical steroids with no systemic therapy required. No infusion related toxicities or cytokine release syndrome was observed.

In part due to these results, treatment with EBV-CTLs is recognized as a recommended treatment for persistent or progressive EBV-PTLD as set forth in the 2015 National Comprehensive Cancer Network Guidelines. In addition, in December 2013, the FDA granted MSK cost reimbursement for use of the EBV-CTL in MSK’s clinical trials.

Since licensing our T-cell product candidates, the IND under which Studies 95-024 and 11-130 were conducted has been transferred to us. In June 2015, we met with the FDA to discuss late-stage development to support a potential approval in EBV-PTLD after HCT. Based on guidance from the FDA, we submitted an SPA for a single arm pivotal trial in rituximab-refractory EBV-PTLD after HCT. We received feedback from the FDA regarding this SPA in which the FDA indicated that a single arm trial with response rate as the primary endpoint may provide an adequate basis for approval but it would be unlikely to grant an SPA for our proposed trial. We intend to continue the dialogue with the FDA regarding this trial design under breakthrough therapy designation and expect to initiate this pivotal trial towards the end of 2016.

EBV-PTLD after SOT

EBV-PTLD after SOT, also referred to as post-transplant lymphoproliferative disorder, is a spectrum of lymphoid malignant disease associated with the use of immunosuppressive drugs after SOT. Patients with EBV-PTLD, one of the most common neoplastic diseases after SOT, commonly present with stage 3 or 4 disease. Reduction in immunosuppression, antiviral therapy, or surgical resection are common treatments, but many patients with PTLD require systemic therapy, especially those with aggressive lymphoma morphology such as DLBCL. Chemotherapy remains undesirable in PTLD because of myelotoxic side effects of cytotoxic therapy and associated infections and toxic deaths. In addition, recipients of chemotherapy face the prospect of secondary malignancies in the future. Rituximab with or without chemotherapy is often used off-label after reduction in immunosuppressive therapy with a response rate of 44% to 60.5%. In the setting of rituximab-refractory EBV-PTLD after SOT, historical one-year survival of 36% is observed in patients with high risk disease. The rates of EBV-PTLD after SOT vary by organ transplant type and degree of immunosuppression with rates in the adult and pediatric settings ranging from <1% to 3.4% in kidney transplants, <1% to 4.4% in liver transplants, <1% to 15.0% in heart transplants, 2.4% to 9.8% in lung

transplants, 2.0% to 10.0% in heart/lung transplants, and 20.0% to 30.0% in bowel

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transplants. In addition, the rates of EBV-PTLD after SOT appear to be higher in children than in adults. One of the unique features of EBV-PTLD after SOT in comparison with the post-HCT setting is that the immunosuppression that ultimately gives rise to the lymphoma is in many cases required chronically and, as a result, the period of time during which an EBV-associated lymphoma may arise extends for the duration of immunosuppression. Although some cases of EBV-PTLD in SOT occur within the first year, many occur years after transplant.

In trials 95-024 and 11-130, patients with EBV-PTLD after SOT were treated with third-party derived EBV-CTL. All patients had failed to respond to or relapsed following rituximab treatment. Most had also progressed after receiving chemotherapy. Additionally, nearly all patients had high risk disease defined as those with age greater than or equal to 60 years, poor performance status, elevated LDH, or presence of disease in the central nervous system, or CNS. Response rate and OS results for these patients were also evaluated by MSK.

The response rate observed in the rituximab-refractory post SOT setting of greater than 50% and the one-year OS of approximately 60% are similar to those observed in the post HCT setting.

Since these trials are ongoing, we expect that these K-M estimates of survival may evolve with ongoing follow-up of the patients. Based on this data, we plan to solicit feedback from the regulatory authorities on the plan for late-phase development to support a potential marketing approval for EBV-CTL in the treatment of EBV-PTLD after SOT.

Other EBV-Associated Diseases

EBV-associated malignancies can occur even in immunocompetent patients, and include: Burkitt’s lymphoma, Hodgkin lymphoma, non-Hodgkin lymphoma such as DLBCL, or NHL, NK T-cell lymphomas, nasopharyngeal carcinoma, or NPC, and gastric cancer. Typically, these malignancies occur many years after primary EBV infection. For Burkitt’s lymphoma, approximately 15% to 30% of cases in the United States and European Union are associated with EBV. For Hodgkin lymphoma, approximately 20% to 50% of cases in the United States and European Union are associated with EBV; however, many of these are responsive to chemotherapy. Nearly 100% of NK T-cell lymphomas are associated with EBV. In NPC, the association with EBV is such that regardless of geography nearly 100% of the nonkeratinising tumors and all the tumor cells have been demonstrated to be monoclonally EBV-positive. EBV-positive gastric cancer can make up approximately 10% of all gastric cancers. In some of these tumor types, multiple EBV proteins are associated with the disease and in others, a smaller subset are made.

In the setting of CNS disease, a number of observations implicate EBV in the pathogenesis of MS. For example, MS patients are universally EBV seropositive, there are high levels of anti-EBV antibodies, their T-cells have altered immune function, there is an increase in spontaneous EBV-induced peripheral blood B-cell transformation, there is increased shedding of EBV from saliva, and EBV-infected B-cells and plasma cells accumulate in the brain.

We intend to explore the therapeutic utility of EBV-targeted cellular therapy in a number of these tumor types. We expect to develop specific cellular therapies that target the precise EBV antigen implicated in a disease. As we expand the use of EBV-targeted cellular therapy in these settings, we expect to present data at major scientific meetings and engage regulatory authorities to solicit agreement on the plan for late-phase development to support a marketing approval for EBV-CTL in the treatment of certain of these conditions.

CMV-Targeted T-cells for CMV Infection and Other CMV Associated Malignancies

CMV, also known as HHV-5, is a member of the Herpes virus family. CMV infection rate gradually increases throughout childhood, and, once infected, an individual carries the virus for life due to the ability of CMV to establish a latent state of infection. It is estimated that CMV infection affects 50% to 90% of the global adult population.

Immunocompromised patients, including HCT and SOT patients, human immunodeficiency, or HIV, patients, and to a lesser extent cancer patients, are at highest risk for developing significant disease syndromes caused by CMV, including interstitial pneumonia, gastrointestinal infection, central nervous system disease, hepatitis, retinitis, and encephalitis. CMV reactivations have also been reported to occur frequently in critically ill immunocompetent patients and are associated with prolonged hospitalization or death. Congenital CMV infection causes deaths and leaves children with permanent disabilities such as hearing loss, vision loss, or mental retardation.

In the oncology setting, CMV is commonly associated with glioblastoma multiforme, or GBM, where approximately 95% of tumors express CMV. In GBM, multiple CMV proteins are associated with the disease.

While there have been many advances in detecting and managing CMV infections, the virus continues to be one of the most important infectious diseases among immunocompromised patients. Antiviral drugs in the form of prophylaxis or preemptive

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treatment strategies have reduced morbidity and mortality, though adverse effects such as neutropenia and toxicity remain a challenge. The emergence of resistance to antiviral drugs also presents challenges to laboratory medicine and patient care.

The approximate estimated number of patients per year in the United States and European Union with refractory CMV infection and associated malignancies is highlighted in the figure below.

Indication	Estimated Number of Patients
Anti-viral resistant CMV after HCT	2,000
Anti-viral resistant CMV after SOT	1,300
Glioblastoma multiforme	21,000
Congenital CMV	9,000

CMV Viremia and Disease after HCT

Despite the use of prophylactic and preemptive therapy using small molecule antivirals, many post-HCT patients progress to develop overt, symptomatic CMV viral diseases such as retinal infections that risk permanent blindness, encephalopathy with the risk of permanent brain damage and other serious morbidities. In prophylactic therapy, immunocompromised patients are given antiviral drugs for several months after HCT. In preemptive therapy, patients are intensively monitored for CMV activity using sensitive laboratory methods, and short-term antiviral treatment is given only to those with significant viral counts (CMV viremia) before symptoms and overt CMV disease occur. However, the antiviral drugs used to treat CMV have significant toxicities, including marrow toxicity for ganciclovir, valganciclovir and cidofovir, and renal toxicity for foscarnet and cidofovir. In addition, CMV drug resistance mutations arise during this antiviral therapy.

MSK has conducted one Phase 1 clinical trial and two Phase 2 clinical trials of CMV-CTL that included patients with CMV viremia and CMV disease, in each case resistant to antiviral drug treatment. An interim summary of MSK's clinical experience was reported at the December 2014 ASH Annual Meeting. This analysis evaluated outcomes in patients who were treated with CMV-CTLs after failing a median of four different antiviral drugs. Following the ASH presentation, in January 2015, MSK provided us with a more current summary of its clinical experience to account for additional cycles of CMV-CTL therapy in which certain patients with stable disease and partial responses from the interim summary had converted to complete responses after additional CMV-CTL therapy. Response rates of greater than 60% were noted in patients with antiviral resistant CMV viremia as well as CMV disease. Responses in patients treated for viremia alone with CMV-CTLs were considered to be complete responses if the viremia resolved completely and partial responses if the viral load fell 100-fold or more. Responses in patients treated for overt disease were considered to be complete responses if all detectable CMV viremia and disease resolved and partial responses if patients became asymptomatic.

An additional subset analysis of MSK's clinical experience from the ongoing Phase 2 clinical trial and including patients treated under compassionate use was reported at the December 2015 ASH Annual Meeting. This analysis included patients with refractory CMV disease in the CNS who were treated with either primary donor derived or third-party derived CMV-CTL. Nearly all of these patients were treated with third-party derived CMV-CTL and one

was treated with a primary donor derived CMV-CTL. Patients had received a range of three to six prior therapies before treatment with CMV-CTL. The overall response rate was more than 70%, including seven complete responses and one partial response. Responses in these patients treated for CMV disease in the CNS were considered to be complete responses if all detectable CMV viremia and disease resolved and partial responses if patients became asymptomatic.

We believe this data suggests a high response rate among patients with otherwise refractory CMV viremia and disease. Overall, CMV-CTL therapy was well tolerated and no patients developed de novo GvHD, or a flare-up of prior GvHD, in association with infusion of CMV-CTLs.

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Two individual patient experiences following treatment with CMV-CTL are described below. The graph below shows the time course of a reduction in CMV viremia and a reciprocal increase in the proliferation of CMV-CTL following administration. The improvement in CMV viremia is evidenced by a decline in blood CMV DNA ascertained by CMV PCR. The reciprocal proliferation of CMV-CTL following administration is reflected by the release of interferon-gamma (IFNg[+]) in CMV-CTL detected via flow cytometry; interferon-gamma positivity identifies and enumerates activated T-cells.

The following retinal photographs depict improvement in CMV retinitis for a patient treated with CMV-CTL. The baseline images, labeled “a” and “b”, show the right and left retinae, respectively, at the start of CMV-CTL administration. Subsequent images “c” and “d” capture the response of the patient’s CMV retinitis at six weeks after first CMV-CTL administration. In the retinal images, the dark areas correspond to affected portions of the retina. The response of retinal disease to treatment with CMV-CTL suggests that, as was observed with EBV-CTL, the cells are able to reach areas of the body typically not accessible to systemic therapies.

Based on these results, we intend to continue to support the ongoing Phase 2 clinical trials of CMV-CTL and meet with health authorities to establish a plan for late-phase development to support potential marketing approvals in treatment of anti-viral resistant CMV viremia and symptomatic disease after HCT, including retinitis.

Other CMV-Associated Conditions and Malignancies

CMV is among the most common and important infectious agents among SOT patients. In transplant recipients, the factor that most strongly influences the degree of morbidity and mortality caused by CMV is the type and extent of immunosuppressive therapy. Reactivation can occur in any individual who is latently infected. However, no transplant patient is safe from CMV since this pathogen can also be acquired from the transplanted organ. CMV can also be community acquired following transplantation and is of particular concern in pediatric transplant patients. In SOT patients, particularly those who develop a primary infection during the first three months post-transplant, a specific CMV syndrome consisting of fever, malaise, arthralgia, and neutropenia may be observed. CMV infections have been associated with indirect effects, such as dysfunction or rejection of the transplanted organ; increased risk for bacterial or fungal opportunistic infections; development of EBV-associated post-transplant lymphoproliferative disorder;

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accelerated atherosclerosis in heart transplant patients; and decreased patient and graft survival. In the absence of antiviral intervention, symptomatic CMV infections occur in approximately: 50% to 75% of heart-lung transplant recipients, 23% of heart transplant recipients, 22% to 29% of liver and pancreas transplant recipients, 8% to 32% of kidney transplant recipients, 50% of kidney-pancreas transplant recipients, and 22% of small-bowel transplant recipients.

Malignant gliomas are the most common primary CNS neoplasms in humans. However, most patients who are diagnosed with a glioblastoma multiforme, which is the most common and malignant form of malignant glioma, still have a mean survival less than two years. In the last few years, multiple investigators have confirmed the presence of CMV in GBM, and multiple CMV gene products are now implicated in biologically relevant GBM signaling pathways. Preclinical studies published in 2013 in the journal Cancer Research indicate that CMV may be unique in its ability to promote oncogenesis in the setting of a prior tumor suppressor dysfunction. Given the emerging role of CMV in GBM, antiviral strategies that block CMV expression or stimulate immune attack of CMV-infected cells may prove beneficial as novel therapeutics for GBM, and both direct antiviral strategies and specific CMV-based immunotherapy approaches are showing early promise.

Based on the established proof of concept for CMV-CTL in the treatment of antiviral resistant CMV viremia and disease after HCT, we intend to explore the therapeutic utility of CMV-targeted cellular therapy in a number of other immunocompromised states, including potentially after SOT. In addition, the clinical data with both EBV-CTL and CMV-CTL have demonstrated the ability of these product candidates to access the brain and mediate clinical responses in difficult to treat CNS disease. As a result, we believe that CMV-targeted cellular therapy may provide a novel off-the-shelf cellular therapeutic option for patients with GBM, and we intend to explore its clinical utility in this setting as well. As we expand the use of CMV-CTL in these settings, we expect to present data at major scientific meetings and engage regulatory authorities to solicit agreement on the plan for late-phase development to support potential marketing approval for CMV-CTL in the treatment of certain of these conditions.

WT1 Targeted T-Cells for Hematologic Malignancies and Solid Tumors

WT1 is an intracellular protein that is overexpressed in a number of cancers, including multiple myeloma, or MM, and non-small cell lung, breast, pancreatic, ovarian, and colorectal cancers. We have two ongoing Phase 1 clinical trials sponsored and conducted by MSK with primary HCT donor derived WT1-CTL. The first is a dose escalation trial of WT1-CTL for residual or relapsed leukemia after HCT. The second is a dose escalation trial of WT1-CTL following T-cell depleted HCT for patients with relapsed or refractory MM, including PCL. In 2011, it was reported in the journal Blood that the prognosis of PCL is poor with a median survival of seven to eleven months and that survival is even shorter, two to seven months, when PCL occurs in the context of refractory or relapsing MM. At the ASH 2015 Annual Meeting, MSK presented results from this Phase 1 clinical trial of primary donor-derived WT1-CTLs. In this trial, response assessments were conducted utilizing criteria consistent with those defined by the International Myeloma Working Group.

- Patients with relapsed-refractory MM, including PCL were treated with allogeneic HCT followed by WT1-CTLs.
- At one year, a response rate of greater than 50% was observed in these patients. For these data, the response rate was determined by adding the complete responses to the partial responses and then dividing by the number of patients.
- Two patients who developed a complete response remain in remission for more than one year.
- There were no serious adverse events reported related to treatment with WT1-CTLs.

As these trials complete, we expect our collaborating investigators at MSK to present additional data at upcoming conferences. In addition, based on data from these trials, we expect to explore the clinical utility of WT1-CTL in these hematologic malignancies. In the setting of solid tumors, we believe that treatment with WT1-CTL may be potentiated through combination approaches with other agents.

Additional Platform Expansion Activities

We anticipate that our T-cell technology platform will have utility beyond the current set of targets to which it has been directed. We and MSK have agreed to collaborate on further research to develop additional cellular therapies, which may include T-cell programs targeted against other antigens and chimeric antigen receptor, or CAR-T, cell programs. Pursuant to the existing agreements with MSK, we have an option to license these additional cellular therapies. We believe that viral antigens are well suited to adoptive immunotherapy given that people with normal immune systems are able to mount robust responses to these viral targets, but immunocompromised patients and some cancer patients are not. We also intend to license or acquire additional product candidates or technologies to enhance our existing T-cell technology platform.

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Our Molecularly-Targeted Product Candidates

STM 434, a Targeted Therapy for Ovarian Cancer and Other Solid Tumors

Our lead molecularly targeted product candidate, STM 434, is in a Phase 1 clinical trial in ovarian cancer and other solid tumors, which commenced in 2014. In October 2015, we received orphan drug designation from the FDA for ovarian cancer. STM 434 is a soluble ActR2B receptor-IgG fusion protein that binds the signaling molecule human activin. STM 434 has the potential to be the first product to target tumor growth and proliferation by inhibiting multiple ActR2B ligands, including Activin A. A ligand is a protein that binds a receptor on a cell to trigger a signal. In ovarian cancer, Activin A is a novel and promising target. Published data, including a study in Clinical Cancer Research in 2008, as well as our preclinical data, suggest that Activin A is upregulated in patients with ovarian cancer, and blocking it reduces proliferation of tumor cells. In many solid tumor types, upregulation of Activin A is correlated with poorer prognoses.

Ovarian Cancer

Ovarian cancer is the fifth leading cause of cancer death in women in the United States. According to the National Cancer Institute, there were an estimated 22,192 new ovarian cancer cases and 14,180 ovarian cancer deaths in the United States in 2015. Surgery and cytotoxic chemotherapies are widely used to treat ovarian cancer; however, the outcomes have changed little in 40 years. There were estimated to be approximately 192,500 women suffering from ovarian cancer in the United States in 2012. According to the American Cancer Society, based on patients diagnosed between 2005 and 2011, the blended five-year survival rate is only 45.6% for ovarian cancer patients overall.

Ovarian cancers are divided into three distinct main subtypes:

- serous adenocarcinoma, which accounts for approximately 63% of ovarian tumors in the United States;
- clear cell cancers, which account for up to 11% of ovarian tumors in Western countries and a higher percentage in Asian countries. For example, clear cell cancers have been reported to account for approximately 23% of ovarian tumors in Japan; and
- granulosa cell tumors, which account for approximately 2% to 5% of ovarian tumors in the United States.

Limitations of Current Therapies for Ovarian Cancer

Despite the strong unmet need for better therapies, there have been few new treatment options introduced, and numerous studies, including a 2012 study published in Obstetrics & Gynecology, have shown that clinical outcomes have not improved significantly for several decades. The number of new cases and deaths in the United States per 100,000 people (all races), age-adjusted, is as follows:

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First Line Treatment

Surgical therapy for ovarian cancer that has not escaped the ovary can be curative. In other cases, palliative debulking surgery is done. However, for women with advanced or recurrent tumors that have escaped the ovary and involve critical anatomic structures, there are no curative therapies, and chemotherapy is generally employed. When chemotherapy is indicated, treatment for these subtypes vary but are generally based on a foundation of platinum chemotherapy. Response rates and outcomes vary among subtypes.

- Serous tumors have a reported response rate to chemotherapy of 72% to 73%, according to a 2005 study in the journal Clinical Cancer Research; however, most patients relapse, resulting in a median survival of approximately 40.8 months, according to a 2010 publication in the International Journal of Gynecological Cancer.
- Clear cell tumors have a platinum-based chemotherapy response rate of approximately 11% as reported in a 2006 study in the British Journal of Cancer. Median overall survival in patients with clear cell tumors is approximately 21.3 months.
- The data on post-surgery response rates to chemotherapy in the granulosa subtype of ovarian cancer is limited due to its rarity.

Recurrent Disease Treatment

For patients whose tumors did not respond to first line therapy, or for those whose tumors became unresponsive to platinum chemotherapy, a number of other chemotherapy options may be applied, including liposomal doxorubicin, topotecan and gemcitabine. Despite these therapies, the median survival of platinum chemotherapy resistant ovarian cancer is approximately 13 months.

Role of Activin A in Ovarian Cancer and Other Solid Tumors

Activin A, a secreted growth factor, is a member of the TGF-ß superfamily of growth factors, which also includes Activin B, Activin AB, GDF-11 and others. Activin A is widely understood to be involved in the growth and proliferation of ovarian cancer and other solid tumors. Some of the other secreted proteins in this superfamily, including Activin AB, have also been implicated in the growth of these tumors. As reported in BMC Medical Genomics in 2010, overexpression of Activin A in support cells called stroma is a key component of a metastasis-associated gene expression signature. This signature predicts shortened survival across a number of cancers including, ovarian, gastric and breast cancers. Overexpression of Activin A is now recognized as a common feature across advanced solid tumors including head and neck, colon, gastric, esophageal, pancreatic and non-small cell lung cancer. In addition to their role in regulating interactions between epithelial cells and stromal cells, activins may be involved in regulating stem cell survival.

Activin A has been found to play a role in the three principal subtypes of ovarian cancer: serous, clear cell and granulosa. For example, the mRNA precursor for activin has been found to be upregulated in approximately 30% of specimens of serous ovarian cancer. At the protein level, as published in 1997 in the Journal of Clinical Endocrinology and Metabolism, most typical serous ovarian cancers made serum Activin A.

Many women with ovarian cancer have high levels of Activin A. The utility of high Activin A in ovarian cancer will be explored in the currently ongoing Phase 1 clinical trial.

Genetic Linkages to Ovarian Cancer Subtypes

Mutations in the BRCA gene have been found in 5% to 10% of serous ovarian tumors, suggesting that there is a genetic link between the activin pathway and ovarian cancer. According to a 2012 publication in the journal PloS One,

these patients with BRCA mutations fail to produce the Activin A counter-regulators follistatin and inhibin, implying that these tumors may be unable to switch off activin signaling.

In clear cell ovarian cancer, studies have shown that mutations in the ARID1A gene contribute to tumor proliferation. Specifically, these mutations drive upregulation in the signaling cascade triggered by the ActR2B receptor. Mutations in the ARID1A gene were present in 46% and 55% of ovarian clear cell tumors, as reported in a 2010 publication in The New England Journal of Medicine and a 2014 publication in BMC Cancer, respectively. We believe that increased levels of activin mimic the effect of ARID1A mutations, and therefore play a similar role in clear cell ovarian cancer.

In granulosa cell ovarian cancer, mutations in the FOXL2 C134W gene have been suggested in several studies to drive the growth of tumors. This mutation was present in 97% of granulosa cell tumors as reported in a 2009 publication in The New England Journal of Medicine. In a normal cell, activin is under tight control—FOXL2 protein turns on follistatin when an activin signal is received, and follistatin, a natural inhibitor of activin, then shuts off the activin signal. However, in granulosa cell tumors, mutant FOXL2 C134W is not able to turn on follistatin, and activin signals continue unchecked. These studies have been reported in 2014 in

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the journal Biochemical and Biophysical Research Communications as well as in 2013 in the journal Molecular and Cellular Endocrinology.

Mechanism of Action of STM 434

We believe that STM 434 has the potential to be the first product to address directly the underlying biology of ovarian tumors.

Activin A is known to act through the ActR2B receptor on the surface of ovary cells. When the receptor receives the signal from Activin A, it initiates a cascade of gene transcription that leads to abnormal cell proliferation, cell migration, blood vessel formation and inhibition of programmed cell death. STM 434 is a ligand trap, which mimics the ActR2B receptor, binding Activin A and other ligands that would normally activate this receptor. Several ligand traps based on other receptors have been developed as therapeutic products and commercialized successfully. The choice of a ligand trap for STM 434 conforms mechanistically with the goal of binding Activin A and other secreted proteins associated with the ActR2B receptor and tumor growth.

Preclinical Studies

Preclinical testing of STM 434 was designed to confirm and quantify its effects in binding Activin A and other ligands with a receptor-like ligand trap. These studies were conducted with STM 217, a close analog of STM 434, which we refer to as STM 434/s. In addition, these studies were carried out in two types of mouse models: TOV-21G mice, which are analogous to patients with clear cell ovarian tumors and carry ARID1A mutations, and inhibin knockout mice, which are analogous to patients with granulosa cell tumors.

Results of the TOV-21G study have shown that blocking Activin A by using a soluble receptor, as both a single therapy and in combination with chemotherapy, led to a reduction in tumor size. In other experiments, knockout mice that were born without inhibin, and therefore had high activin levels that led to granulosa cell ovarian tumors, survived longer after treatment with STM 434/s in comparison to untreated mice. A 2007 publication in the journal Molecular Human Reproduction showed that the survival of the knockout mice was greatly improved when they were treated with an ActR2B-Fc fusion similar to STM 434. Other mouse tumor models tested, including renal cell carcinoma, melanoma and small cell lung cancer, were shown to be sensitive to activin levels and antitumor responses were seen when activins were inhibited.

TOV-21G Mouse Models (Clear Cell Ovarian Tumors)

In a preclinical study using TOV-21G mice, tumors derived from human clear cell ovarian carcinoma were shown to have high levels of serum Activin A, analogous to those observed in human ovarian cancer patients as described above.

In a subsequent preclinical study that we presented together with Amgen at the American Society of Clinical Oncology meeting in 2013, we evaluated STM 434/s in this TOV-21G model used as both a single agent and in combination with the chemotherapy agent 5-fluorouracil, or 5-FU. STM 434/s was administered subcutaneously weekly at 10.0 mg/kg beginning on day 12. 5-FU was administered for three cycles. The tumor was measured two to three times per week, up to day 52. Results from these experiments showed a statistically significant ($p<0.0001$) approximately 30% reduction in tumor volume for the agent. Results of the combination experiments demonstrated in the figure below showed an additive ($p<0.0001$) approximately 70% reduction in tumor growth.

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Additive Effect with 5-FU

In addition, this study examined the anticachectic effects of STM 434/s in this model. Cachexia is a condition associated with significant weight loss often seen in patients with solid tumor cancers. The results of this study showed that the administration of STM 434/s increased body weight of the mice. In addition to demonstrating the antitumor properties of STM 434/s, we believe that this data also demonstrates that an ActR2B soluble receptor may provide an additional benefit to patients by addressing cancer cachexia. We intend to investigate these attributes as part of our planned Phase 1 clinical trial.

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Inhibin Knockout Mouse Model (Granulosa Cell Tumors)

For granulosa cell studies, a knockout mouse model was used with STM 434/s. The study showed that serum Activin A levels in the knockout mice were elevated, and upon treatment with STM 434/s Activin A levels were significantly reduced.

STM 434/s treatment reduced the elevated circulating Activin A in the inhibin knockout mice to the levels in control mice. Serum Activin A was measured before and 14 days after treatment.

Further, this study showed that treatment with STM 434/s reduced ovary size to near normal in comparison to control mice treated with saline. A representative example of the observed reduction in size is shown below. In this study, STM 434/s was administered as a single dose of 30 mg/kg.

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Lastly, the knockout model treated with STM 434/s showed a statistically significant ($p<0.0001$) improvement in survival with approximately 90% alive at 133 days of age, as compared to knockout mice treated with saline, where more than 95% had died by this time.

In July 2014, Amgen provided us a draft report from a 2009 eight-week pharmacology study of STM 217, a compound closely related to STM 434 and which we also refer to as STM 434/s, in orchiectomized (neutered) male cynomolgus monkeys. This pharmacology study was designed to explore the ability of STM 217 to reverse the effects of androgen deprivation. In the study, two weekly doses of STM 217 were evaluated at 3 mg/kg and 10 mg/kg. The study found that STM 217 was effective in mitigating the muscle and bone loss that accompany androgen deprivation in this animal model.

In addition to the muscle and bone effects, clinical observations from the study included bleeding from the muzzle (similar to human nosebleeds) in some of the monkeys and one animal bleeding from a skin lesion over the buttock. In this study, it was not possible to determine if the bleeding was caused by STM 217. To further characterize this observation, we performed additional in vitro studies of STM 217 and STM 434. Platelets, a component of blood that helps stop bleeding, were evaluated, and neither STM 217 nor STM 434 impacted platelet function. We also evaluated BMP-9, a factor involved in bleeding and blood vessel development known to be mutated in humans with hereditary hemorrhagic telangiectasia, or HHT. Both STM 217 and STM 434 bound to BMP-9 in these studies, suggesting that the bleeding observed with STM 217 could also be observed with STM 434. The observations from the STM 217 report and the in vitro studies we conducted have been shared with the FDA.

As a result of these findings with STM 217, we altered our STM 434 Phase 1 clinical trial protocol to exclude patients at heightened risk of bleeding and enhance the monitoring of patients for bleeding or increased risk for bleeding. These changes were also shared with the FDA.

Phase 1 Clinical Trial in Ovarian Cancer and Other Solid Tumors

We commenced an open-label Phase 1 clinical trial of STM 434 in 2014 that will enroll approximately 70 patients. The initial dosing schedule for this trial was once every four weeks. This trial is being conducted in three parts:

- Part 1 — Dose escalation trial in patients with advanced solid tumors. Dosing initiated at 0.25 mg/kg. We plan to test up to the maximum tolerated dose, or MTD. Assuming no MTD is reached, we will test ascending doses of STM 434.
- Part 2 — Designed to obtain additional safety and exploratory efficacy data in patients with advanced ovarian cancer, including clear and granulosa cell tumors.
- Part 3 — Designed to study STM 434 in combination with chemotherapy in patients with ovarian cancer who have received prior treatment.

The objectives for our Phase 1 clinical trial are: to test if STM 434 monotherapy is safe and well tolerated; to obtain preliminary efficacy data in ovarian cancer and other solid tumors; to assess safety and preliminary efficacy of STM 434 with liposomal doxorubicin chemotherapy or the current standard of care; and to explore biomarkers predictive of response to treatment. Further objectives include collecting pharmacokinetic data during therapy with STM 434 and defining the recommended Phase 2 dose.

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Since initiating this trial in October 2014, we have continued to dose and enroll patients. Bleeding has been observed in a subset of patients. Some of these bleeding events were deemed by the treating investigators to be possibly related to treatment with STM 434. Following review of these events by the safety committee, consisting of the trial sponsor and the trial investigators, the associated doses were deemed safe and well tolerated, and the trial is continuing at escalating doses.

Based on data supporting the role of activin in the progression of other solid tumors and the inclusion criteria, we expect that a number of patients included in the dose escalation portion of the Phase 1 clinical trial will have solid tumors in organs other than the ovary. Other tumors may include pancreas, stomach and kidney tumors, where there is a high correlation between Activin A upregulation and the severity and outcome of disease. We expect to release initial data from this Phase 1 clinical trial in the first half of 2016.

Biomarker Approach

Activin expression is one of a few biomarkers associated with severity in a variety of tumors including ovarian tumors. For this reason, Activin A is one of 12 genes that are measured in colon cancer as part of the clinically validated OncotypeDX® colon cancer panel. Our Phase 1 clinical trial is testing whether high levels of Activin A measured at baseline before patients receive STM 434 predict whether they respond to treatment. If levels of Activin A can predict response, this biomarker may be valuable in late-phase trials to improve the trial design and maximize the proportion of patients who respond to STM 434.

In addition, we will be measuring follicle-stimulating hormone, or FSH, levels using a routine laboratory test, to determine the inhibition of activin by STM 434. It is well established that activin negatively regulates FSH, and we therefore can use FSH reduction as a surrogate for activin inhibition. We also plan to conduct ARID1A and FOXL2 mutation testing in our Phase 1 clinical trial. These mutations have been associated with tumor proliferation.

PINTA 745 for PEW in ESRD

In December 2015, we announced results from the a Phase 2 proof-of-concept clinical trial for PINTA 745, a molecularly targeted product candidate, for the treatment of protein energy wasting in patients with end stage renal disease. The trial did not meet its primary endpoint, defined as the percent change from baseline in lean body mass as measured by dual energy x-ray absorptiometry at week 12 following weekly treatment with PINTA 745. PINTA 745 also did not improve physical function, measures of glycemic control and markers of inflammation. There were no treatment related serious adverse events observed in the trial. We intend to complete the trial as designed; however, as a consequence of these results, we have suspended further clinical development of PINTA 745.

Molecularly Targeted Product Candidate Pipeline

Our molecularly targeted product candidate pipeline currently consists of five product candidates that were licensed from Amgen in addition to STM 434. The product candidates in this portfolio are closely related to one another in terms of the biology and align with our in-house expertise regarding development, manufacturing, intellectual property strategy and other critical activities. These products share association with the TGF-ß superfamily of growth factors. At the same time, they represent distinct modes of intervention with potentially different therapeutic applications. These distinctions relate to target specificity, pharmacokinetic/pharmacodynamic relationships and modality. We believe these product candidates have unique characteristics, and, in some cases, demonstrated activity in preclinical studies, which would make them attractive candidates for various indications, including cancer cachexia, a condition that is implicated in up to 30% of cancer deaths with limited existing treatments. We are evaluating these product candidates to determine the best path forward taking into account the results from the PINTA 745 Phase 2

proof-of-concept trial. Where appropriate, we intend to conduct preclinical studies and file IND applications with regulatory authorities for these candidates.

Our molecularly targeted product candidate pipeline licensed from Amgen includes the following:

- ATA 777, a fully human antibody targeting Activin A, which we believe will be well suited for non-oncology indications where chronic dosing and specificity to Activin A is beneficial;
- ATA M43, a fully human anti-ActR2A/2B monoclonal antibody with high affinity to both receptors that is mechanistically similar to programs targeting muscle wasting diseases;
- STM 217, a soluble ActR2B receptor-IgG Fc fusion protein and a close analog of STM 434; and
- ActR2B5, a soluble ActR2B receptor that can be fused to an IgG Fc receptor; and
- ATA 842, a humanized antibody targeting myostatin, designed to be more selective than similar programs in the clinic targeting oncologic, orthopedic and renal indications.

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Competition

The biotechnology and pharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our innovative technology, knowledge, experience and scientific resources provide us with competitive advantages, we face potential competition from many different sources, including major pharmaceutical, specialty pharmaceutical and biotechnology companies, academic institutions and public and private research institutions. Some of these potential competitors may have a more established presence in the market and significantly greater financial, technical and human resources than we have. Our commercial opportunity will be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer side effects or are less expensive than any products that we may develop.

T-Cell Product Candidates

Should our T-cell product candidates be approved for use, we will face substantial competition. In addition to the current standard of care for patients, commercial and academic clinical trials are being pursued by a number of parties in the field of immunotherapy. Early results from these trials have fueled continued interest in immunotherapy. In addition, if approved, our T-cell programs would compete with currently marketed drugs and therapies used for treatment of the following indications, and potentially with drug candidates currently in development for the same indications.

EBV-PTLD

There are currently no FDA or EMA approved products for the treatment of EBV-PTLD. However, some approved products and therapies are currently used off-label in this setting, and a number of companies and academic institutions that may license therapies to companies in the future are or may be developing new treatments. These therapies, as well as promotional efforts by competitors and clinical trial results of competitive products, could significantly diminish any ability to market and sell EBV-CTL. The current treatment for EBV-PTLD involves administration of rituximab as a single agent or in the SOT setting, in combination with chemotherapy regimens. Additionally, a number of companies and academic institutions are developing drug candidates for EBV-PTLD, including Cell Medica Ltd., or Cell Medica, which is conducting Phase 2 clinical trials for Cytorex EBV, an autologous EBV specific T-cell therapy, in NK/T-cell lymphoma.

CMV Infection

There are numerous approved products and therapies for the treatment of CMV infection, and a number of companies and academic institutions that may license therapies to companies in the future are or may be developing new treatments for CMV infection. These therapies, as well as promotional efforts by competitors and clinical trial results of competitive products, could significantly diminish any ability to market and sell the CMV-CTL. Drug therapies approved or commonly used for CMV infection include antiviral compounds such as ganciclovir, valganciclovir, cidofovir or foscarnet.

Additionally, a number of companies and academic institutions are developing drug candidates for CMV infection and other CMV-associated diseases, including Shire plc, or Shire, which has completed Phase 2 clinical trials of maribavir, a UL97 protein kinase inhibitor; Merck & Co., Inc., or Merck, which is conducting Phase 3 clinical trials of letermovir, a CMV terminase inhibitor; Vical Inc., or Vical, which is conducting Phase 3 clinical trials for ASP0113, a bivalent plasma DNA CMV vaccine; and ViraCyte, which is conducting Phase 1 clinical trials for Viralym-C, a CMV-specific third party cell therapy product. Chimerix, Inc., or Chimerix, recently announced that brincidofovir, a

lipid conjugated nucleotide analogue of cidofovir, did not meet the primary endpoints of its Phase 3 trials for the prevention of CMV infection in hematopoietic stem cell transplant recipients.

Multiple Myeloma including Plasma Cell Leukemia

Several products are approved for the treatment of relapsed or refractory multiple myeloma, including Kyprolis (marketed by Amgen Inc.), Revlimid and Pomalyst (marketed by Celgene Corporation), Velcade (marketed by Millennium Pharmaceuticals, Inc.) and Darzalex® (marketed by Janssen Research & Development, LLC). In addition, a number of companies and institutions are developing drug candidates for relapsed or refractory multiple myeloma, including: AB Science SA, which is conducting a Phase 3 clinical trial for masitinib, a tyrosine kinase inhibitor; and Adaptimmune Therapeutics PLC, which is conducting Phase 1 / 2 clinical trials for a TCR candidate targeting NY-ESO-1.

Molecularly Targeted Product Candidates

If approved, STM 434 would compete with currently marketed drugs and therapies used for treatment of the following indications, and potentially with drug candidates currently in development for the same indications.

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Ovarian Cancer

There are numerous approved products and therapies for ovarian cancer, and a number of companies are or may be developing new treatments for ovarian cancer and other solid tumors. These therapies, as well as promotional efforts by competitors and clinical trial results of competitive products, could significantly diminish any ability to market and sell STM 434. Approved drug therapies for ovarian cancer include chemotherapy with platinum compounds such as cisplatin or carboplatin and taxane compounds such as paclitaxel or docetaxel; bevacizumab in combination with chemotherapy compound such as liposomal, doxorubicin, paclitaxel or topotecan; olaparib in patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy; and hormone therapies including goserelin, leuprolide, tamoxifen, letrozole, anastrozole and exemestane.

We are aware of other companies engaged in clinical development of compounds for treatment of ovarian cancer. These include:

- PARP inhibitors such as Tesaro, Inc.’s niraparib;
- angiogenesis inhibitors, such as F. Hoffman-La R