Adaptimmune Therapeutics PLC
Form 10-K
March 13, 2017
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

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

For the fiscal year ended December 31, 2016

OR

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

Commission File Number 001-37368

ADAPTIMMUNE THERAPEUTICS PLC

(Exact name of Registrant as specified in its charter)

England and Wales	**Not Applicable**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)

101 Park Drive, Milton Park **Abingdon, Oxfordshire OX14 4RY** **United Kingdom** (Address of principal executive offices)	**(44) 1235 430000** (Registrant s telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Name of exchange on which registered**
American Depositary Shares, each representing 6 Ordinary Shares, par value £0.001 per share	The NASDAQ Global Select 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.

o Yes x No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act.

o Yes x No

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.

x Yes o 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).

x Yes o No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K (§ 229.405 of this chapter) 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.

x

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 definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act.

Large accelerated filer o | Accelerated filer x
Non-accelerated filer o (Do not check if a smaller reporting company) | Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act).

o Yes x No

As of June 30, 2016, the last business day of the registrant s most recently completed second fiscal quarter, the aggregate market value of the registrant s ordinary shares, par value £0.001 per share, held by non-affiliates was approximately $386,305,126.

As of March 8, 2017 the number of outstanding ordinary shares, par value £0.001 per share, of the Registrant is 424,775,092.

DOCUMENTS INCORPORATED BY REFERENCE

The following documents (or parts thereof) are incorporated by reference into the following parts of this Form 10-K: Certain information required by Part III of this Annual Report on Form 10-K is incorporated from our definitive proxy statement pursuant to Regulation 14A, to be filed with the Commission not later than 120 days after the close of our fiscal year ended December 31, 2016.

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GENERAL INFORMATION

In this Annual Report on Form 10-K (Annual Report), Adaptimmune, the Group, the Company, we, us and our refer to Adaptimmune Therapeutics plc and its consolidated subsidiaries, except where the context otherwise requires. Adaptimmune® and SPEAR are registered trademarks of Adaptimmune.

Information Regarding Forward-Looking Statements

This Annual Report contains forward-looking statements that are based on our current expectations, assumptions, estimates and projections about us and our industry. All statements other than statements of historical fact in this Annual Report are forward-looking statements.

These forward-looking statements are subject to known and unknown risks, uncertainties, assumptions and other factors that could cause our actual results of operations, financial condition, liquidity, performance, prospects, opportunities, achievements or industry results, as well as those of the markets we serve or intend to serve, to differ materially from those expressed in, or suggested by, these forward-looking statements. These forward-looking statements are based on assumptions regarding our present and future business strategies and the environment in which we expect to operate in the future. Important factors that could cause those differences include, but are not limited to:

- our ability to advance our NY-ESO SPEAR T-cells to a point where GlaxoSmithKline, or GSK, exercises the option to license the product and the scope and timing of performance of our ongoing collaboration with GSK;

- our ability to successfully advance our MAGE-A10, MAGE-A4 and AFP SPEAR T-cells through clinical development and the timing within which we can recruit patients in to and treat patients in our clinical trials;

- our ability to further develop our commercial manufacturing process for our SPEAR T-cells, transfer such commercial process to third party contract manufacturers and for such third party contract manufacturers to manufacture SPEAR T-cells to the quality and on the timescales we require;

- the success, cost and timing of our product development activities and clinical trials;

- our ability to successfully advance our SPEAR T-cell technology platform to improve the safety and effectiveness of our existing SPEAR T-cell candidates and to submit Investigational New Drug Applications, or INDs, for new SPEAR T-cell candidates;

- the rate and degree of market acceptance of T-cell therapy generally, and of our SPEAR T-cells;

- government regulation and approval, including, but not limited to, the expected regulatory approval timelines for TCR therapeutic candidates;

- patents, including, any inability to obtain third party licenses, legal challenges thereto or enforcement of patents against us;

- the level of pricing and reimbursement for our SPEAR T-cells, if approved for marketing;

- general economic and business conditions or conditions affecting demand for our SPEAR T-cells in the markets in which we operate, both in the United States and internationally;

- volatility in equity markets in general and in the biopharmaceutical sector in particular;

- fluctuations in the price of materials and bought-in components;

- our relationships with suppliers and other third-party providers;

- increased competition from other companies in the biotechnology and pharmaceutical industries;

- claims for personal injury or death arising from the use of our SPEAR T-cell candidates;

- changes in our business strategy or development plans, and our expected level of capital expenses;

- our ability to attract and retain qualified personnel;

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- regulatory, environmental, legislative and judicial developments including a regulatory requirement to place any clinical trials on hold or to suspend any trials;

- a change in our status as an emerging growth company under the Jumpstart Our Business Start-ups Act of 2012, or JOBS Act);

- uncertainty about the future relationship between the United Kingdom and the European Union; and

- additional factors that are not known to us at this time.

Additional factors that could cause actual results, financial condition, liquidity, performance, prospects, opportunities, achievements or industry results to differ materially include, but are not limited to, those discussed under Risk Factors in Part I, Item 1A in this Annual Report and in our other filings with the Securities and Exchange Commission (the SEC). Additional risks that we may currently deem immaterial or that are not presently known to us could also cause the forward-looking events discussed in this Annual Report not to occur. The words believe, may, will, estimate, continue, anticipate, intend, expect and similar words are intended to identify estimates and forward-looking statements. Estimates forward-looking statements speak only at the date they were made, and we undertake no obligation to update or to review any estimate and/or forward-looking statement because of new information, future events or other factors. Estimates and forward-looking statements involve risks and uncertainties and are not guarantees of future performance. Our future results may differ materially from those expressed in these estimates and forward-looking statements. In light of the risks and uncertainties described above, the estimates and forward-looking statements discussed in this Annual Report might not occur, and our future results and our performance may differ materially from those expressed in these forward-looking statements due to, inclusive of, but not limited to, the factors mentioned above. Because of these uncertainties, you should not make any investment decision based on these estimates and forward-looking statements.

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Item 1. Business

Overview

We are a clinical-stage biopharmaceutical company committed to developing novel immunotherapies primarily to treat cancer. Our vision is to be a world leader in discovering, developing and commercializing T-cells to transform the treatment of patients with serious diseases. Our comprehensive SPEAR (Specific Peptide Enhanced Affinity Receptor) T-cell platform enables us to identify cancer targets, find and genetically optimize T-cell receptors (TCRs), and produce SPEAR T-cells for administration to patients. Unlike certain other autologous immunotherapies our SPEAR T-cells are able to target intracellular and extracellular targets and solid and haematologic tumors.

Our SPEAR T-cell platform is being utilized to maximize both patient and disease indication coverage. First, we are using our platform to identify and validate cancer testis antigens for development of SPEAR T-cells. These antigens have very low expression on normal tissues and are therefore preferred targets for our SPEAR T-cells. However, within a given disease indication, the frequency of expression of these targets may be low, and may not be uniformly expressed in every cell within a tumor. As a result, we are developing multiple SPEAR T-cells to different target antigens within any disease indication to increase treatment potential for any given disease. We have three SPEAR T-cells in clinical trials which are directed to cancer testis antigens, NY-ESO-1, MAGE-A4 and MAGE-A10. The targets to which these SPEAR T-cells are directed are expressed in multiple disease indications including non-small cell lung cancer (NSCLC), melanoma, urothelial (bladder) cancers and head and neck cancers, with each of these indications being addressed by at least two of the SPEAR T-cells.

Second, we are developing SPEAR T-cells directed to non-cancer testis antigens which are closely related to a specific disease indication. The first of these SPEAR T-cells is our AFP SPEAR T-cell which is directed to hepatocellular cancer. Further targets closely associated with other cancers are also being validated.

Finally, we are identifying peptides to different Human Leukocyte Antigen (HLA) types ensuring that for any given target, for example NY-ESO, MAGE-A10, MAGE-A4 or AFP, we can address patient populations with different HLA types.

We have Phase 1/2 clinical trials ongoing with our NY-ESO and MAGE-A10 SPEAR T-cells and during 2016 opened two additional INDs for our AFP and MAGE A-4 SPEAR T-cells. Our NY-ESO SPEAR T-cell has shown promising initial results in clinical trials with a 50% response rate and 18-month median survival rate reported in synovial sarcoma (a solid tumor) and a 91% response rate at day 100 post autologous stem cell transplant in multiple myeloma. The NY-ESO SPEAR T-cell has shown a promising tolerability profile to date in all clinical trials. Our NY-ESO SPEAR T-cell therapy has breakthrough therapy designation in the United States and has also received orphan drug designation from the U.S. Food and Drug Administration (FDA), and European Commission for the treatment of soft tissue sarcoma. The European Medicines Agency (EMA) has also granted PRIME regulatory access for the Company s NY-ESO SPEAR T-cell therapy for the synovial sarcoma indication. We expect further clinical data during 2017.

In addition, we continue to use our SPEAR T-cell platform to identify further target peptides which provide additional coverage for any existing indications or which show high expression in specific cancers. We have identified over 30 intracellular target peptides and have 12 research

programs evaluating these peptides.

We also recognize that further development of our SPEAR T-cells will assist in enhancing efficacy and durability of response. We therefore have a number of next generation SPEAR T-cell strategies to further develop and engineer our SPEAR T-cells in addition to the initiation of combination therapy approaches, the first of which is with Merck & Co., Inc s (Merck) KEYTRUDA®. To enable continued innovation and development, we also have collaborations with third parties intended to promote further next generation solutions. These include our collaboration with Universal Cells, Inc. (Universal Cells) and our collaboration with Bellicum Pharmaceutical Inc. (Bellicum). With Universal Cells, we are looking to develop affinity engineered donor T cells that are universally applicable to all patients. While these universal cells would be specific for a given HLA type and target antigen, they would overcome the current limitation of autologous therapies that need to be manufactured specifically for each patient. The enhanced T-cell technology being developed involves selective engineering of cell surface proteins, without the use of nucleases, to develop universal T-cell products. If successful, this will enable us to treat large patient populations with an off-the-shelf product. Our Bellicum collaboration was announced in December 2016 and under the collaboration, we will evaluate Bellicum s GoTCR technology (inducible MyD88/CD40 co-stimulation, or iMC) with our SPEAR T-cells for the potential to create enhanced T-cell therapeutics.

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Our Clinical Product Pipeline

NY-ESO

Our SPEAR T-cell therapy targets the NY-ESO-1 and LAGE-1a cancer antigens which are present in multiple different tumor types. We are conducting Phase 1/2 clinical trials in patients with solid tumours and haematological malignancies including synovial sarcoma, multiple myeloma, NSCLC and ovarian cancer. A pilot trial in myxoid round cell liposarcoma (MRCLS) started in December 2016. We are planning to start a pivotal trial in synovial sarcoma, which is dependent on the start and performance of comparability studies. Clinical trials are ongoing in the United States and clinical trial applications have been approved in both Canada and the United Kingdom.

MAGE-A10

Our second SPEAR T-cell therapy, targeting the MAGE-A10 peptide, is currently in clinical trials in the United States. The MAGE-A10 trial in NSCLC was initiated in late 2015. A three tumor trial in urothelial (bladder) cancers, melanoma and head and neck cancers was initiated at The University of Texas MD Anderson Cancer Center (MD Anderson) in October 2016 and the trial is currently being initiated at other sites in the United States and Canada. Initial data for our MAGE-A10 clinical trials is anticipated in late 2017 or early 2018.

AFP SPEAR T-cell

An IND for our AFP SPEAR T-cell for the treatment of hepatocellular cancer was opened in 2016. Clinical trial sites in the United States and Europe will be initiated in 2017. Initial data from the AFP clinical trials is anticipated in late 2017 or early 2018.

MAGE-A4 SPEAR T-cell

An IND for our MAGE-A4 SPEAR T-cell program in urothelial (bladder) cancers, melanoma, head and neck cancer, ovarian cancer, NSCLC, esophageal cancer and gastric cancers is now open. Initial data on our MAGE-A4 SPEAR T-cell program is anticipated in late 2017 or early 2018.

The following table summarizes the status of our current clinical trials:

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Business Strategy

Our strategic objective is to be a world leader in discovering, developing and commercializing TCR-based T-cell therapies that transform the clinical outcomes of patients with cancer. In order to achieve our objective, we are focused on the following strategies:

Advance our clinical studies for our AFP, MAGE-A10 and MAGE-A4 SPEAR T-cells and advance clinical studies with our NY-ESO SPEAR T-cell beyond the setting of synovial sarcoma where preliminary evidence of efficacy and safety is established. We have four SPEAR T-cells with open INDs covering multiple indications and we plan to advance all four SPEAR T-cells further during 2017 with the aim of providing initial tolerability data for SPEAR T-cells other than our NY-ESO SPEAR T-cell. We are also advancing clinical studies for our NY-ESO SPEAR T-cell in indications other than synovial sarcoma, and clinical trials are already being extended to additional sites within the United States and within Europe. We are also planning to advance into pivotal trials in synovial sarcoma with our NY-ESO SPEAR T-cell. Discussions with the FDA in relation to the planning of that pivotal trial are ongoing.

Continue to use our SPEAR T-cell platform to generate SPEAR T-cells for cancers where existing therapeutic approaches are limited. We intend to continue to generate TCR therapeutic candidates from our fully integrated technology platform, which enables the systematic identification and validation of suitable target peptides, T-cell cloning, engineering of TCRs and preclinical testing processes. The first of our two approaches uses cancer testis antigens and aims to select multiple cancer testis antigens for any given indication to maximize the patient coverage that can be obtained with our SPEAR T-cell products. The second approach relies on the identification of targets which are closely associated with a particular cancer and where the SPEAR T-cells can then be specifically targeted to that cancer.

Continue to understand, further enhance and improve effectiveness and persistence of our SPEAR T-cell therapies. We continue to evaluate and work to understand the mechanism of action of our SPEAR T-cells, in particular the best approaches for enhancing effectiveness and persistence of our SPEAR T-cells. We continue to further develop our TCR therapeutic candidates by exploring the addition of other components in our lentiviral vector, which would be expressed in the SPEAR T-cells alongside the engineered TCR. In addition, we are planning to evaluate the combination of our SPEAR T-cell therapies with other immunotherapy approaches. A combination trial with Merck s KEYTRUDA® (pembrolizumab) in patients with multiple myeloma is planned to start in 2017.

Optimize and expand our process development and manufacturing capabilities to maintain our leadership position in the TCR space. Our commercial-ready cell manufacturing process (cell process 1.5), has been reviewed by the FDA and the FDA has allowed us to proceed with implementation of cell process 1.5 into our ongoing NY-ESO SPEAR T-cell trials. We continue to optimize the manufacture, supply, associated analytical expertise and quality systems for our SPEAR T-cell therapies to ensure that our manufacturing capability is sufficient for later-stage clinical trials and, potentially, initial commercial supply. We continue to work with third party contract manufacturers in both the United States and Europe to plan for commercial manufacture of our SPEAR T-cells. In addition, during 2016 we completed the shell and core construction for a new state of the art current good manufacturing practice (cGMP) manufacturing and office

facility and continue to fit-out the facility, which is intended to support the clinical development and initial commercialization of SPEAR T-cells. We are planning to have manufacturing capability towards the end of 2017 and will initially manufacture SPEAR T-cells to support our clinical trials.

Expand our intellectual property portfolio. We intend to continue building on our technology platform, comprising intellectual property, proprietary methods and know-how in the field of TCRs and T-cells. These assets form the foundation for our ability not only to strengthen our product pipeline, but also to defend and expand our position as a leader in the field of T-cell therapies.

Our SPEAR T-cell Therapies

The Immune System and T-cells

The immune system plays an important role in targeting and destroying cancer cells. Specifically, T-cells, which are a type of white blood cell, and their receptors create a natural system that is designed to scan the body for diseased cells. In general, cells process proteins internally and then convert these proteins into peptide fragments which are then presented on the cell surface by a protein complex called the Human Leukocyte Antigen, or HLA. T-cells naturally scan all other cells in the body for the presence of abnormal peptide fragments, such as those generated from infectious agents. Recognition of this peptide-HLA complex takes place through the TCR expressed on the T-cells. Binding of naturally occurring TCRs to cancer targets, however, tends to be very poor because cancer proteins appear very similar to naturally occurring proteins on healthy cells and TCRs that recognise what the body sees as self-proteins are eliminated during early human development. Even when TCRs recognize cancer cells expressing novel proteins caused by mutations, elements of the immune system, or the cancer itself often suppress the T-cell response.

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Target Identification and Validation

Before developing any engineered T-cell or TCR it is important to identify and validate a suitable target cancer peptide. The target must be expressed primarily only on the cancer cells of interest and with expression in normal non-cancerous tissue only where a risk to the patient would be deemed acceptable. Careful validation and identification of targets is important to ensuring that any engineered TCR is specific to the targeted cancer and does not bind to the same target on non-cancer cells, or that the TCR does not recognize a similar peptide derived from a protein in normal cells. Our target identification platform is focused on three approaches. First, we are using our platform to validate cancer testis antigens. These targets have very low expression on most normal tissues in adults and are therefore preferred targets for our SPEAR T-cells. However, within a given indication, the frequency of expression of these targets may be low, and may not be uniformly expressed in every cell within a tumor. As a result, we are developing multiple SPEAR T-cells to different target peptides in selected disease indications to increase the probability of treating patients with a given disease indication and potentially the ability for re-treatment of patients with a different SPEAR T-cell. We have three SPEAR T-cells in clinical trials which are directed to cancer testis antigens, NY-ESO-1, MAGE-A4 and MAGE-A10. The targets to which these SPEAR T-cells are directed are expressed in multiple disease indications including NSCLC, melanoma, urothelial (bladder) cancers and head and neck cancers, with each of these indications being addressed by at least two of the SPEAR T-cells.

The second type of approach is directed to non-cancer testis antigens which are closely related to a specific disease indication. The first of these SPEAR T-cells is our AFP SPEAR T-cell which is directed to hepatocellular cancer. Further targets closely associated with other cancers are also in development.

Finally, we are identifying targets to different HLA types ensuring that for any given target, we can address patient populations with different HLA types.

Affinity Engineering

Following identification of a suitable target peptide, we identify TCRs that are capable of binding to that target peptide. We then engineer those identified TCRs to enhance and optimize their ability to target and bind to the cancer peptides, thereby enabling a highly targeted immunotherapy. The optimized TCR then undergoes extensive preclinical safety testing prior to administration to patients. Our SPEAR T-cell platform technology enables us to develop a pipeline of targets and TCR therapeutic candidates that we believe may be effective in a variety of cancer types that are unresponsive to currently available and experimental therapies. We have two SPEAR T-cells already in clinical trials (NY-ESO, MAGE-A10), two additional programs with open INDs are planned to enter the clinic in 2017 (AFP and MAGE-A4) and a pipeline of SPEAR T-cells in development.

Administration to Patients

The process for treating a patient with an engineered TCR therapeutic candidate involves extracting the patient s T-cells and then combining the extracted cells with our delivery system containing the gene for our affinity-enhanced TCR, through a process known as transduction. Our delivery system uses a type of self-inactivating (SIN) virus, known as SIN-lentivirus, to transduce the patient s T-cells and is referred to as a lentiviral vector. The transduced T-cells are then expanded and infused into the patient. When these T-cells encounter a recognized HLA-peptide complex, they multiply and initiate the destruction of the targeted cancer cells. The following diagram summarizes the process for manufacturing and administering our SPEAR T-cells.

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Our NY-ESO SPEAR T-cell therapy

Our first SPEAR T-cell targets the NY-ESO-1 and LAGE-1a target peptides and is currently in clinical trials in the United States. Phase 1/2 studies are ongoing in synovial sarcoma, MRCLS, NSCLC and ovarian cancer indications. GSK has an exclusive option over our NY-ESO SPEAR T-cell program. For further details please see Core Alliances and Collaborations - *GSK Collaboration and License Agreement* below.

Our NY-ESO SPEAR T-cell therapy has received orphan drug designation from the FDA and European Commission for the treatment of soft tissue sarcoma. The EMA has also granted PRIME regulatory access for the Company s NY-ESO SPEAR T-cell therapy for the synovial sarcoma indication, and this product has breakthrough designation in the United States. NY-ESO SPEAR T-cells overall continue to demonstrate a generally acceptable benefit:risk profile to date.

As of January 5, 2017, 61 subjects have received NY-ESO SPEAR T-cells in our sponsored studies. The most common (>15%) adverse events in these subjects considered by investigators to be at least possibly related to our NY-ESO SPEAR T-cells include: fever, diarrhea, fatigue, rash, nausea, anemia, dyspnea, cytokine release syndrome (CRS), lymphopenia, leukopenia, cough, ALT increased, AST increased, hypotension, sinus tachycardia, neutropenia, and thrombocytopenia. Adverse events with a severity of grade 3 or higher and considered by investigators to be at least possibly related and occurring in more than one patient include: lymphopenia, leukopenia, anemia, neutropenia, febrile neutropenia, diarrhea, CRS, thrombocytopenia, hypophosphatemia, fever, rash, dyspnea, hypotension, hypoxia, colitis, decreased appetite, dehydration, graft versus host disease, hyponatremia, and musculoskeletal chest pain. There has been one fatal (grade 5) bone marrow failure which was considered related to study treatment by the investigator in the trial. Internal investigations have not identified a mechanism by which the NY-ESO SPEAR T-cells may have caused bone marrow failure. For further details on adverse events please see Part II Item 1A Risk Factors

Our SPEAR T-cells may have undesirable side effects or have other properties that could halt their clinical development, prevent regulatory approval, limit their commercial potential or otherwise result in significant negative consequences .

- *Our synovial sarcoma program*:

Soft tissue sarcomas can develop from tissues like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. There are approximately 50 types of soft tissue sarcomas, including synovial sarcoma, which is a malignant tumor of the soft tissues arising often around joints. Synovial sarcoma is associated with a characteristic chromosomal translocation, and represents about nine percent of all soft tissue sarcomas. This disease is more common in children and young adults, and typically presents at an age ranging from 15 to 40 years. The majority of patients who develop metastatic soft tissue sarcomas are currently incurable, with 75% to 80% of patients not surviving past two to three years. First line therapy typically involves radiotherapy and chemotherapy, as well as surgical resection where possible. There are limited additional treatment options for unresectable, recurrent and metastatic synovial sarcoma, which is nearly always fatal, and systemic therapy is mainly used to provide palliation and slow disease progression.

There are four cohorts in the Phase 1/2 pilot study:

- Cohort 1 (patients with high NY-ESO-1 antigen expression and lymphodepletion with cyclophosphamide and

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fludarabine) enrollment in this first cohort is now complete.

- Cohort 2 (patients with low NY-ESO-1 antigen expression and lymphodepletion with cyclophosphamide and fludarabine) enrollment continues in this cohort. Indications of a clinical response have also been observed in cohort 2 for one patient out of the 4 evaluable patients treated to date.

- Cohort 3 (patients with high NY-ESO-1 antigen expression and lymphodepletion with cyclophosphamide alone) only one confirmed response was observed in evaluable patients treated in cohort 3 and as a result, this cohort has now closed. The data from this cohort 3 suggest that fludarabine may be required as part of the pre-conditioning regimen.

- Cohort 4 (patients with high NY-ESO-1 antigen expression and lymphodepletion with a modified (lower) dose of cyclophosphamide and fludarabine) given the lack of response seen in cohort 3, cohort 4 is open and enrolling patients.

The current synovial sarcoma trials are also being extended to sites outside of the United States with clinical trial applications approved in both the United Kingdom and Canada.

NY-ESO SPEAR T-cells continue to demonstrate a generally acceptable benefit:risk profile to date in synovial sarcoma trials. As of September 30, 2016, our NY-ESO SPEAR T-cells demonstrated a 50% (6/12) response rate in cohort 1 or 60% (6/10) response rate in patients receiving the target cell dose. The median survival rate for patients in cohort 1 is approximately 18 months (80 weeks) as of September 30, 2016.

The diagram below illustrates the best response rate for patients in cohort 1 as of September 30, 2016. Response rate has been determined using Response Evaluating Criteria in Solid Tumors (RECIST) 1.1 criteria. The dotted line denotes the level of decrease in target lesion required for a partial response.

As of January 5, 2017, 24 subjects have received NY-ESO SPEAR T-cells in our synovial sarcoma program. The most common (>30%) adverse events in this trial (all cohorts) considered by investigators to be at least possibly related to our NY-ESO SPEAR T-cells include fever, anemia, lymphopenia, leukopenia, CRS, fatigue, nausea, dyspnea, rash, sinus tachycardia, cough, neutropenia, and thrombocytopenia. Adverse events with severity grade 3 or higher considered by investigators to be at least possibly related and occurring in more than one patient include lymphopenia, leukopenia, anemia, neutropenia, thrombocytopenia, CRS, hypophosphatemia, fever, dyspnea, febrile neutropenia, hypotension, hypoxia, musculoskeletal chest pain, and rash. One patient experienced a fatal bone marrow failure which was considered related to study treatment by the investigator in the trial. Internal investigations have not identified a mechanism by which the NY-ESO SPEAR T-cells may have caused bone marrow failure.

We are in discussions with the FDA in relation to the initiation of a pivotal trial in the synovial sarcoma indication, including discussions relating to trial design and the requirement for comparability testing for use of our manufacturing process. The start of the pivotal trial is dependent on the start and performance of analytical comparability studies between the current and the commercial processes. Should comparability studies be delayed or the results not be acceptable to us or the FDA then the start of the pivotal trial will be delayed.

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- *Our MRCLS program*:

Soft tissue sarcomas can develop from tissues like fat, muscle, nerves, fibrous tissues, blood vessels, or deep skin tissues. There are more than 50 types of soft tissue sarcomas, including MRCLS, which is mostly located in the limbs (most frequently in the thighs). MRCLS is associated with a characteristic chromosomal translocation, and represents about 30 to 35 percent of liposarcomas and 5 to 10 percent of all adult soft tissue sarcomas. MRCLS commonly presents at an age ranging from 35 to 55 years.

A pilot trial in MRCLS is now active at sites in the United States. Initial data from this trial is expected in late 2017 or early 2018 depending on patient recruitment.

This is an open-label pilot study in patients to assess preliminary safety and efficacy in this new indication. Initially, 10 patients will be enrolled. If further characterization of the treatment is required, up to five additional patients may be enrolled. Eligible patients will be HLA-A*02:01, HLA-A*02:05 and/or HLA-A*02:06 with advanced (metastatic or inoperable) MRCLS whose tumor express NY-ESO-1 (defined as ≥30% of tumor cells that are 2+ or 3+ by immunohistochemistry). Patients will receive preconditioning with fludarabine and cyclophosphamide at the same dose that is being used in cohort 4 of our ongoing synovial sarcoma Phase 1/2 study.

- *Our Ovarian program:*

Ovarian cancer ranks fifth in cancer deaths among women, accounting for more deaths than any other cancer of the female reproductive system. About 85 to 90 percent of ovarian cancers are cancerous epithelial tumors or epithelial ovarian carcinomas. It is estimated that approximately 22,440 women will receive a new diagnosis of ovarian cancer, and approximately 14,080 women will die of this disease in the United States in 2017. This cancer mainly develops in older women, and approximately half of all ovarian cancers occur in women 63 years of age or older.

The primary trial objective is to determine the safety and tolerability of our NY-ESO TCR therapeutic candidate with chemotherapy preconditioning in patients who have refractory or resistant Stage 3/4 ovarian cancer.

To date, no objective clinical responses have been reported in patients. The initial patients received a preconditioning regimen which consisted of cyclophosphamide alone. The protocol for the ovarian study has now been amended to include a preconditioning regimen which includes both fludarabine and cyclophosphamide. Further data from this trial with the modified preconditioning regimen is expected in late 2017 or early 2018 depending on the rate of patient recruitment.

- *Our Melanoma program:*

No objective responses have been observed in the four patients treated to date in this trial. As a result, no further patients will be enrolled in the trial. A combination study with immune check point inhibitors (CPI) was previously being considered but is no longer being considered given the changes in the underlying standard of care for melanoma patients and the likely difficulty in recruiting patients to such a combination study.

- *Our Myeloma program:*

Multiple myeloma is a cancer formed by malignancies of plasma cells, which are found in the bone marrow and are an important part of the immune system. It is estimated that approximately 30,280 new cases of multiple myeloma will be diagnosed in the United States in 2017 (17,490 in men and 12,790 in women). Multiple myeloma is characterized by several features, including low blood counts, bone and calcium problems, infections, kidney problems, monoclonal gammopathy, and by the proliferation of malignant plasma cells within bone marrow. The risk of multiple myeloma goes up as people age, and less than one percent of cases are diagnosed in people younger than 35. Most people diagnosed with this cancer are at least 65 years of age.

Enrollment in the myeloma trial (with autologous stem-cell transplantation, or ASCT) was completed in July 2014. The Phase 1/2, open-label, two-site clinical trial in 25 multiple myeloma patients who were eligible for ASCT was open to patients with high risk or relapsed multiple myeloma, who have few remaining treatment options and short life expectancy. Prior to enrollment in the clinical trial, patients had received on average three prior therapies and the trial included six patients that had a prior ASCT. Sixty percent of tumors contained cytogenetic abnormalities that represent negative prognostic indicators. Disease response was assessed in accordance with the International Uniform Response Criteria for myeloma assessment and the additional criteria of nCR which was consistent with the methods employed by the Bone Marrow Transplantation Clinical Trials.

Interim results from this Phase 1/2 clinical trial in multiple myeloma patients were reported in Nature Medicine, published on July 20, 2015. Nature Medicine reported response rates in patients with active disease at the time of transplant, with a 59%

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CR/nCR as compared to 24-38% CR/nCR rates at 100 days in other studies treating myeloma with stem cell transplants alone and with stem cell transplants with bortezomib, respectively.

A 91% response rate at day 100 has been previously reported for patients and as of January 27, 2017 there is a median survival rate of approximately three years. Survival data is illustrated in the following Kaplan Meier plot.

As of January 5, 2017, 25 subjects have received NY-ESO SPEAR T-cells in our myeloma transplant program. The most common (>30%) adverse events in this trial considered by investigators to be at least possibly related to our NY-ESO SPEAR T-cells include diarrhea and rash. Adverse events with severity grade 3 or higher considered by investigators to be at least possibly related and occurring in m