MERRIMACK PHARMACEUTICALS INC
Form 10-K
February 27, 2015
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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, 2014

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 001-35409

Merrimack Pharmaceuticals, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**04-3210530**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
One Kendall Square, Suite B7201	
Cambridge, MA	**02139**
(Address of principal executive offices)	**(Zip Code)**

Registrant s telephone number, including area code: (617) 441-1000

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

Title of each class	**Name of each exchange on which registered**
Common Stock, $0.01 par value	**NASDAQ Global 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 Section 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 website, 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 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	x	Accelerated filer	¨
Non-accelerated filer	¨ (Do not check if a smaller reporting company)	Smaller 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

Aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the last sale price for such stock on June 30, 2014: $707,644,419.

As of February 13, 2015, there were 106,934,746 shares of Common Stock, $0.01 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A in connection with its 2015 Annual Meeting of Stockholders. Portions of such proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this Annual Report on Form 10-K, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words anticipate, believe, estimate, expect, intend, may, plan, predict, project, target, potential, will, would, could, s expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this Annual Report on Form 10-K include, among other things, statements about:

- our plans to develop and commercialize our most advanced product candidates and companion diagnostics;
- our ongoing and planned discovery programs, preclinical studies and clinical trials;
- the timing of the completion of our clinical trials and the availability of results from such trials;
- our collaborations with Baxter International Inc., Baxter Healthcare Corporation and Baxter Healthcare SA, which we collectively refer to as Baxter, and PharmaEngine, Inc., or PharmaEngine, related to MM-398;
- our ability to establish and maintain additional collaborations;
- the timing of and our ability to obtain and maintain regulatory approvals for our product candidates;
- the rate and degree of market acceptance and clinical utility of our products;
- our intellectual property position;
- our commercialization, marketing and manufacturing capabilities and strategy;
- the potential advantages of our Network Biology approach to drug research and development;
- the potential use of our Network Biology approach in fields other than oncology; and

our estimates regarding expenses, future revenues, capital requirements and needs for additional financing.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. We have included important factors in the cautionary statements included in this Annual Report on Form 10-K, particularly in Part I, Item 1A. Risk Factors, that could cause actual results or events to differ materially from the forward-looking statements that we make. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments that we may make.

You should read this Annual Report on Form 10-K and the documents that we have filed as exhibits to this Annual Report on Form 10-K completely and with the understanding that our actual future results may be materially different from what we expect. We do not assume any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

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PART I

Item 1. Business

Overview

We are a biopharmaceutical company discovering, developing and preparing to commercialize innovative medicines consisting of novel therapeutics paired with companion diagnostics for the treatment of cancer. We were founded by a team of scientists from The Massachusetts Institute of Technology and Harvard University who sought to develop a systems biology-based approach to biomedical research. The core of our approach to systems biology is to apply multidisciplinary and multitechnology capabilities to build functional and predictive computational models of biological systems, such as cell signaling networks, that allow us to engineer treatments that are directed at the mechanisms of disease. Our mission is to employ these insights to provide patients, physicians and the healthcare system with the medicines, tools and information to deliver integrated healthcare solutions that improve both the quality of outcomes and the efficiency of care.

We currently have six targeted therapeutic oncology candidates in clinical development. Our most advanced program is our investigational agent MM-398. We have initiated a New Drug Application, or NDA, submission with the U.S. Food and Drug Administration, or FDA, for MM-398 as a treatment for metastatic pancreatic cancer in combination with 5-fluorouracil, or 5-FU, and leucovorin in patients who have been previously treated with gemcitabine. Additionally, we have multiple product candidates in preclinical development and a discovery effort advancing additional candidate medicines. We have tailored each of our six most advanced product candidates to target specific disease mechanisms that our research suggests are common across many solid tumor types. We believe that these product candidates have the potential to address major unmet medical needs.

We are also developing *in vitro* and *in vivo* companion diagnostics for use with each of our oncology therapeutic product candidates. Our *in vitro* companion diagnostic agents employ biophysical or biochemical markers of cancer, or biomarkers, which we have identified using our systems biology approach. Our *in vivo* companion diagnostics take the form of imaging agents that may help identify patients likely to benefit from our therapeutic products by measuring deposition of our products in the tumor. We believe that companion diagnostics will allow us to improve the efficiency and productivity of our clinical development and enhance the potential efficacy and pharmacoeconomic benefit of our therapeutics.

We have also entered into an agreement to utilize our manufacturing expertise to develop, manufacture and exclusively supply bulk drug to a third party, who will in turn process the drug into finished product and commercialize it globally.

Our Most Advanced Product Candidates

The table and descriptions below summarize key information about our six most advanced therapeutic product candidates, MM-398, MM-302, MM-121, MM-111, MM-151 and MM-141. All of these product candidates are designed for intravenous administration. None of our product candidates are approved for any indication by the FDA or any other regulatory agency.

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Each of the product candidates described below is a targeted therapy, designed to efficiently act on selected cancer cells. These targeted therapies are either nanotherapeutics that are designed to preferentially deliver cytotoxic therapies to the tumor tissue, such as MM-398 and MM-302, or monoclonal antibodies or monoclonal antibody-derived molecules that are designed to block oncogenic signaling pathways, such as MM-121, MM-111, MM-151 and MM-141.

Program	Clinical Status	Commercial Rights (Territory)
MM-398 (nanotherapeutic encapsulation of irinotecan)	Initiated an NDA submission with the FDA as a treatment for metastatic pancreatic cancer in combination with 5-FU and leucovorin in patients who have been previously treated with gemcitabine	Merrimack (United States)
	Announced top-line results of a Phase 3 clinical trial in combination with 5-FU and leucovorin in patients with metastatic pancreatic cancer whose cancer had progressed on treatment with gemcitabine (NAPOLI-1 trial)	PharmaEngine (Taiwan)
	Conducting investigator-sponsored Phase 1 clinical trials as a monotherapy in patients with glioma and in combination with cyclophosphamide in patients with pediatric solid tumors	Baxter (rest of world outside of United States and Taiwan)
	Conducting a Phase 1 translational clinical trial designed to identify predictive biomarkers associated with MM-398	
MM-302 (ErbB2 (HER2) targeted antibody drug conjugated liposomal doxorubicin)	Conducting a Phase 2 clinical trial in combination with trastuzumab in patients with ErbB2 (HER2)-positive, locally advanced or metastatic breast cancer	Merrimack (worldwide)
MM-121 (ErbB3 targeted monoclonal antibody)	Conducting a Phase 2 clinical trial in combination with docetaxel or pemetrexed in patients with heregulin positive, advanced non-small cell lung cancer	Merrimack (worldwide)
	Announced top-line results from four Phase 2 clinical trials in combination with chemotherapies and other targeted agents in patients with ovarian, breast and non-small cell lung cancers	
MM-111 (ErbB3 and ErbB2 (HER2) targeted bispecific antibody)	Conducting a Phase 2 clinical trial in combination with paclitaxel and trastuzumab in patients with advanced gastric, esophageal and gastroesophageal junction cancers. In February 2015, we stopped enrolling patients in this clinical trial prior to full enrollment based on a recommendation from the Data Safety Monitoring Board, or DSMB, for the clinical trial, which cited shorter progression	Merrimack (worldwide)

	free survival, or PFS, on the treatment arm relative to the control arm in the overall patient population. We do not plan to invest in additional development of MM-111 at this time.	
MM-151 (EGFR (ErbB1) targeted triclonal antibody)	Conducting a Phase 1 clinical trial as a monotherapy and in combination with irinotecan in patients with solid tumors	Merrimack (worldwide)

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Program	Clinical Status	Commercial Rights (Territory)
MM-141 (IGF-1R and ErbB3 targeted tetravalent bispecific antibody)	Conducting a Phase 1 clinical trial as a monotherapy, in combination with everolimus and in combination with nab-paclitaxel and gemcitabine in patients with solid tumors	Merrimack (worldwide)

MM-398

MM-398 overview

Our most advanced product candidate is MM-398 (irinotecan liposome injection), also known as nal-IRI. MM-398 is a nanoliposomal encapsulation of the marketed chemotherapy drug irinotecan. In 2014, we announced results of a Phase 3 clinical trial of MM-398 in patients with metastatic pancreatic cancer whose cancer had progressed on treatment with the chemotherapy drug gemcitabine. Based on the results of that trial, which are described below, we have initiated an NDA submission with the FDA for MM-398 as a treatment for metastatic pancreatic cancer in combination with 5-FU and leucovorin in patients who have been previously treated with gemcitabine. In November 2014, the FDA granted us a fast track designation for this NDA, which allows for a rolling submission of the application. Although our Phase 3 clinical trial of MM-398 focused on pancreatic cancer, we believe that MM-398 may have potential uses in a number of other solid tumor indications, including colorectal cancer, lung cancer, breast cancer, gastric cancer, glioma and pediatric solid tumors.

We hold development and commercialization rights for MM-398 in the United States. In September 2014, we established a collaboration with Baxter for the development and commercialization of MM-398 outside of the United States and Taiwan. PharmaEngine holds the development and commercialization rights to MM-398 in Taiwan.

In July 2011, the FDA granted MM-398 orphan drug designation for the treatment of pancreatic cancer. In September 2011, the European Medicines Agency, or EMA, granted MM-398 orphan medicinal product designation for the treatment of pancreatic cancer.

The encapsulated ingredient of MM-398, irinotecan, is a well-known and widely used chemotherapy. The activated form of irinotecan is SN-38, which functions by inhibiting topoisomerase I, an essential enzyme involved in DNA transcription and replication, and promoting cell death. Dosing with free irinotecan, as with other chemotherapies, is limited by significant adverse effects and rapid clearance that, in turn, limit efficacy. In addition, as with other chemotherapies, the efficacy of irinotecan is limited by tumor resistance mechanisms. MM-398 has demonstrated extended circulation in comparison to free irinotecan in the clinical setting.

MM-398 Phase 3 clinical trial for metastatic pancreatic cancer

In 2014, we announced results from our Phase 3 clinical trial of MM-398 in patients with metastatic pancreatic cancer whose cancer had progressed on treatment with gemcitabine. This clinical trial, which we refer to as the NAPOLI-1 study, was a randomized, open label Phase 3 clinical trial designed to evaluate two MM-398 regimens, 80 mg/m^2 combined with 5-FU and leucovorin every two weeks, and 120 mg/m^2 as a monotherapy every three weeks. Each arm was compared to a control arm of 5-FU and leucovorin. A total of 417 patients at over 100 sites in North America, South America, Europe, Asia and Australia were randomized across the three arms. The primary endpoint of this trial was a statistically significant difference in overall survival between MM-398, alone or in combination with 5-FU and

leucovorin, against the common control arm of the combination of 5-FU and leucovorin. Overall survival is a measure of the time to death from treatment randomization. The combination of MM-398 with 5-FU and leucovorin achieved the primary endpoint for this trial, with a statistically significant survival advantage compared to the control arm. The combination of MM-398 with 5-FU and leucovorin achieved an overall survival of 6.1 months, a 1.9 month improvement over the 4.2 month survival demonstrated by the control arm of 5-FU and leucovorin alone. The primary log-rank analysis of overall survival for the MM-398 combination arm was statistically significant (p=0.0009) with a corresponding stratified hazard

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ratio of 0.57. A hazard ratio, or HR, is a measure of how often a particular event happens in one group compared to how often it happens in another group over time. In cancer research, hazard ratios are often used in clinical trials to measure survival at any point in time in a group of patients who have been given a specific treatment compared to a control group given another treatment or a placebo. A hazard ratio of one means that there is no difference in survival between the two groups, while a hazard ratio of greater than one or less than one means that survival was better in one of the groups. A statistically significant advantage in PFS was also observed in the combination arm, with a median of 3.1 months compared to 1.5 months in the control arm. PFS is the time from the initiation of treatment to tumor progression based on an increase of at least 20% in the sum of measured tumor diameters with no new tumors. The combination arm also showed a statistically significant difference in objective response rate compared to the control arm (16% and 1%, respectively, $p<0.001$). Objective response rate is the sum of the complete response rate, which measures the disappearance of all target and non-target tumors, plus the partial response rate, which measures the overall tumor regression based on a decrease of a least 30% of the sum of measured tumor diameters with no new tumors according to Response Evaluation Criteria in Solid Tumors (RECIST v1.1).

The most common non-hematologic Grade 3 and higher adverse events in the MM-398 combination arm were fatigue (14%), diarrhea (13%) and vomiting (11.1%). Hematologic Grade 3 and higher adverse events included neutropenia, which was observed in 20% of patients as determined by objective laboratory values, and febrile neutropenia, which was observed in 2% of patients.

The MM-398 monotherapy arm did not achieve a statistically significant survival advantage compared to the control arm in this trial, with a 4.9 month median overall survival compared to 4.2 months in the control arm. For the monotherapy arm, the stratified hazard ratio for overall survival was 0.93 with a corresponding p-value of 0.5545. In general, patients experienced a higher level of adverse events with the MM-398 monotherapy dose and treatment schedule compared to patients who received the combination of MM-398 with 5-FU and leucovorin.

MM-398 other clinical trials

MM-398 previously met its primary efficacy endpoints in two Phase 2 clinical trials, one in pancreatic cancer patients and one in gastric cancer patients. We are also collaborating with several investigators to conduct additional trials of MM-398, including an investigator-sponsored Phase 2 clinical trial in colorectal cancer, an investigator-sponsored Phase 1 clinical trial in glioma and an investigator-initiated Phase 1 clinical trial in pediatric solid tumors, which is being conducted under our investigational new drug application, or IND.

MM-398 companion diagnostic development

We believe that deposition of nanotherapeutics such as MM-398 in the tumor may be important to efficacy. We are exploring development of *in vivo* companion diagnostics that take the form of imaging agents that may serve as surrogate biomarkers for estimating MM-398 deposition in patient tumors. The companion diagnostic may help identify patients most likely to benefit from nanotherapeutics, and direct those patients with low deposition tumors towards alternate therapy strategies (that may or may not still involve nanotherapeutics). We are currently evaluating various agents imaged by MRI and other modalities to assess the potential for predicting drug deposition. We conducted a Phase 1 translational study at one site in the United States designed to test the feasibility of an MRI-based approach to assess large-particle delivery and tumor macrophage uptake using a marketed iron supplement as an imaging agent and to identify predictive biomarkers associated with MM-398 in various cancers, and recently opened an expansion phase to this translational study that will enroll triple negative breast cancer patients, hormone receptor positive breast cancer patients and breast cancer patients with brain metastases. As part of our preclinical and clinical translational research, we are also investigating functional *in vitro* biomarkers that may be predictive of efficacy in poorly vascularized tumors.

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MM-302

MM-302 overview

MM-302 is an antibody drug conjugated liposomal doxorubicin that targets the ErbB2 (HER2) receptor. Doxorubicin is a marketed chemotherapy that is a member of the anthracycline class of chemotherapies. The addition of anthracyclines to the treatment of both solid and liquid tumors has historically improved outcomes for patients and, specifically, has been an effective component of breast cancer treatment for decades, with free doxorubicin-based regimens providing consistent clinical benefit. However, significant adverse events, including acute and chronic cardiotoxic effects, have limited the use of traditional anthracyclines in combination with targeted therapies, such as trastuzumab, for treatment of ErbB2 (HER2) positive breast cancer. Liposomal doxorubicin (Doxil®), which has been shown to reduce cardiotoxicity associated with free doxorubicin, has been approved for use in certain settings, but has not been approved for use in the United States for the treatment of breast cancer. We designed MM-302 to target and bind to cancer cells that overexpress ErbB2 (HER2) and thereby release doxorubicin at the site of the tumor, while minimizing uptake into normal cells, including those of the heart.

We believe that MM-302 may offer advantages in comparison with other forms of doxorubicin, namely free doxorubicin and liposomal doxorubicin. Our clinical development strategy is to demonstrate that MM-302 has favorable efficacy and safety compared to doxorubicin for the treatment of metastatic breast cancer where concerns over cardiac safety, particularly in combination with trastuzumab, have led to a decline in the use of anthracyclines despite proven efficacy.

MM-302 Phase 2 clinical trial

In August 2014, we initiated a global, open-label, randomized Phase 2 clinical trial of MM-302 in combination with trastuzumab (Herceptin®) in patients with ErbB2 (HER2) positive, locally advanced or metastatic breast cancer. The trial was designed with input from the FDA to support a potential accelerated approval application. The trial has also been reviewed by the EMA, and we intend to use data from the trial, if positive, to support conditional marketing authorization in Europe. This clinical trial, which we refer to as the HERMIONE trial, is expected to enroll approximately 250 patients who will be randomized (1:1) to receive either MM-302 and trastuzumab or chemotherapy of their physician s choice (capecitabine, gemcitabine or vinorelbine) and trastuzumab. Eligible patients for the HERMIONE trial must have received prior treatment with trastuzumab in any setting, and pertuzumab (Perjeta®) and ado-trastuzumab emtansine (T-DM1, Kadcyla®) in the locally advanced or metastatic setting, but have not been treated with an anthracycline-based regimen. The primary endpoint of the trial is PFS. Secondary endpoints include overall survival, objective response rate, safety and tolerability. The trial will be conducted at approximately 60 sites in the United States, Canada and Europe.

Prior to initiating the HERMIONE trial, we conducted a Phase 1 clinical trial of MM-302 in patients with advanced ErbB2 (HER2) positive breast cancer. The purpose of that Phase 1 clinical trial was to assess the safety of MM-302 and identify the maximum tolerated dose. Reported interim results from this trial showed a median PFS of 5.7 months (95% CI [3.1-10.9]) in a heavily pretreated (median of four prior lines of therapy) population of 47 patients receiving a therapeutic dose of MM-302 (30 mg/m2 or greater) alone or in combination with trastuzumab. Patients who had not received prior anthracycline-based chemotherapy treatment had a median PFS of 10.9 months (95% CI [1.7-NC]) and a 35% objective response rate. The most common adverse events in the Phase 1 clinical trial were fatigue, nausea and decreased appetite. Neutropenia was the most common Grade 3/4 adverse event, occurring in seven patients, of which six were in the monotherapy arms and one was in the combination arm. One dose limiting toxicity, febrile neutropenia, was observed in the Phase 1 clinical trial, and the dose was subsequently withheld from the patient. The patient went on to continue study treatment for three additional cycles. Cardiac events, which are a side effect that has

limited the use of anthracyclines, were infrequent in the Phase 1 clinical trial, with three out of 47 patients (6%) experiencing declines in ejection fraction. None of these events were serious adverse events. Consistent with the design of this Phase 1 clinical trial to principally test for safety and dosage tolerance, it was not designed to test for statistical significance of anti-tumor activity.

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MM-302 companion diagnostic development

We believe that deposition of nanotherapeutics such as MM-302 in the tumor may be important to efficacy. We are exploring development of *in vivo* companion diagnostics that take the form of imaging agents that may help identify patients likely to benefit from nanotherapeutics by enabling the measurement of deposition in patient tumors and excluding those patients with low deposition whose tumors are therefore unlikely to respond to treatment with a nanotherapeutic. We are currently evaluating nanotherapeutic formulations of liposomal agents imaged by PET/CT scan and other modalities to assess the potential for measuring deposition.

MM-121

MM-121 overview

MM-121 is a fully human monoclonal antibody that targets ErbB3, a cell surface receptor that is activated by the ligand heregulin. An antibody is a type of protein normally produced by cells of the immune system that binds to just one epitope, or chemical structure, on a protein or other molecule. MM-121 was designed to inhibit cancer growth directly, restore a tumor s sensitivity to drugs to which it has become resistant, and delay the development of resistance by a tumor to other agents.

Research suggests that ErbB3 signaling is primarily activated through binding of its ligand heregulin, and that it is often critical to the growth and survival of tumors. Further data shows that the use of ErbB3 signaling as a resistance mechanism by cancer cells to a variety of cancer therapies often occurs across patient populations and tumor types. Since MM-121 directly inhibits binding of heregulin to ErbB3 and as such prevents activation of this critical pathway, we believe that MM-121 may be effective when given in combination with various standard therapies, offering the following potential advantages compared to existing therapies alone:

- the ability to synergistically or additively inhibit tumor growth, based on our preclinical research involving a broad range of combination therapies;
- the ability to delay the development of resistance to other agents, based on research by us and others demonstrating that ErbB3 signaling is upregulated in response to treatment with other therapies; and
- the ability to restore sensitivity to drugs, based on our preclinical research involving several cell types and xenograft models that are resistant to targeted therapies or chemotherapies.

Based on the central role of heregulin and ErbB3 in cancer growth and survival, we believe that MM-121 may be applicable to a broad range of metastatic tumors, including lung, prostate, breast, ovarian, colon and pancreatic cancers. Our preclinical studies of several hundred tumor samples and the analysis of tumor samples from our Phase 2 clinical trials suggest that MM-121 may be able to target heregulin-dependent ErbB3 signaling that is relevant in approximately 35-50% or more of cancer patients with these types of tumors.

MM-121 Phase 2 clinical trials

We have evaluated MM-121 in multiple Phase 1 and Phase 2 clinical trials in combination with both chemotherapies and other targeted agents across a wide spectrum of solid tumor patient populations, including patients with ovarian,

breast and lung cancers. The goal of our MM-121 clinical program is to explore the efficacy and safety of MM-121 in combination with other targeted ErbB agents such as erlotinib, chemotherapies such as paclitaxel, and anti-hormonal agents such as exemestane, and to evaluate biomarkers that identify patients most likely to benefit from MM-121. We have sought to assess whether efficacy is improved by measuring the ability of various MM-121 combinations to enhance anti-tumor activity or to delay resistance or restore sensitivity to the other therapies.

We announced new or updated results in 2014 from the four Phase 2 clinical trials described below. Our three Phase 2 clinical trials in metastatic cancers, which are the trials in ovarian, breast and lung cancers listed immediately below, enrolled a total of 464 patients and evaluated whether MM-121 in combination with a

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standard of care therapy was more effective than the standard of care therapy alone in prolonging PFS. As ErbB3 signaling was expected to be active in only a subset of patients, pre-treatment biopsies were collected from patients in the lung and ovarian studies and archived tumor tissue in all three studies to assess heregulin, along with four other pre-specified biomarkers. Secondary analyses included evaluation of the pre-specified biomarkers, as well as overall survival and safety data. Across the studies, there was a consistent but modest and tolerable increase in adverse events when MM-121 was combined with erlotinib, paclitaxel and exemestane. Most adverse events were reported as mild to moderate in severity and included diarrhea, fatigue, vomiting, rash, hypokalemia and stomatitis.

Phase 2 clinical trial of MM-121 in combination with paclitaxel for platinum resistant or refractory advanced ovarian cancer

This clinical trial was designed as a global, open-label, randomized Phase 2 clinical trial evaluating whether the combination of MM-121 and paclitaxel was more effective in prolonging PFS than paclitaxel alone in patients (n=220) with locally advanced/metastatic or recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer, and who had received at least one prior platinum-based chemotherapy regimen and were platinum-resistant or refractory. The study analysis was conducted after 171 events. Of the 220 patients in this clinical trial, biomarker data were available for 151 patients.

	Full Population (N=220)		**Heregulin Positive, ErbB2 (HER2) Low (N=57 of 151)**	
	MM-121 + Paclitaxel	Paclitaxel	MM-121 + Paclitaxel	Paclitaxel
Median PFS	3.7 months	3.7 months	5.7 months	3.5 months
Hazard Ratio	1.05 (95% CI [0.76-1.44])		0.37 (95% CI [0.18-0.76])	
p-value	0.77		0.007	

The HR for PFS is a measurement of the chance of disease progression for the treatment arm relative to the control arm, with an HR of less than one indicating that a patient will likely progress less quickly on the treatment arm than on the control arm, and an HR of more than one indicating the opposite. Because a trial represents a sample of a much larger population, the reported HR from a trial is an estimate of the true HR. The confidence interval, or CI, given after the HR reflects the amount of certainty in the estimate of the HR. An HR value that is not contained within a 95% CI is unlikely to be the true HR. The addition of MM-121 did not significantly enhance paclitaxel activity in an unselected platinum-resistant ovarian cancer population. A subset of heregulin positive patients (38%) who also had low ErbB2 (HER2) levels, however, responded poorly to paclitaxel alone and had improved PFS with the addition of MM-121. There was a consistent but modest and tolerable increase in adverse events when MM-121 was combined with paclitaxel. Further confirmatory studies of MM-121 in ovarian cancer are being considered.

Phase 2 clinical trial of MM-121 in combination with exemestane in metastatic ER/PR+, ErbB2 (HER2) negative breast cancer

This clinical trial was a randomized, double-blinded, placebo-controlled Phase 2 clinical trial evaluating whether the combination of exemestane and MM-121 was more effective in prolonging PFS than exemestane plus placebo in postmenopausal ER/PR+ metastatic breast cancer patients (n=115) who have previously failed anti-estrogen therapy. The primary objective was to compare PFS between the groups. The clinical trial was powered to detect a HR of less than 0.5. The study analysis was conducted after 84 events. Of the 115 patients in this clinical trial, biomarker data were available for 76 patients.

	Full Population (N=115)		**Heregulin Positive (N=34 of 76)**	
	MM-121 + Exemestane	Exemestane	MM-121 + Exemestane	Exemestane
Median PFS	3.7 months	2.5 months	3.8 months	1.9 months
Hazard Ratio	0.77 (95% CI [0.5-1.2])		0.26 (95% CI [0.11-0.63])	
p-value	0.25		0.003	

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The addition of MM-121 did not significantly enhance exemestane activity in an unselected metastatic breast cancer population. There was a consistent but modest and tolerable increase in adverse events when MM-121 was combined with exemestane. Further confirmatory studies of MM-121 in breast cancer are being considered.

Phase 2 clinical trial of MM-121 in combination with erlotinib in EGFR wild-type non-small cell lung cancer

This clinical trial was a global, open-label, randomized parallel cohort Phase 2 clinical trial evaluating whether the combination of MM-121 and erlotinib was more effective in prolonging PFS than erlotinib alone in epidermal growth factor receptor, or EGFR, wild-type (wt) non-small cell lung cancer, or NSCLC, patients (n=129). The reported cohort was previously referred to as Group A, and is the cohort for which sufficient biomarker data was available for biomarker analysis. The primary objective was to compare PFS between the groups. The study analysis was conducted after 105 events. Of the 129 patients enrolled, biomarker data were available for 69 patients.

	Full Population (N=129)		**Heregulin Positive (N=37 of 69)**	
	MM-121 + Erlotinib	Erlotinib	MM-121 + Erlotinib	Erlotinib
Median PFS	1.9 months	1.8 months	1.9 months	1.6 months
Hazard Ratio	0.81 (95%CI [0.55-1.2])		0.35 (95% CI [0.16-0.76])	
p-value	0.29		0.008	

The addition of MM-121 did not significantly enhance erlotinib activity in an unselected NSCLC population. A subset of heregulin positive patients (54%), however, responded poorly to erlotinib alone and had improved PFS with the addition of MM-121. There was a consistent but modest and tolerable increase in adverse events when MM-121 was combined with erlotinib. Further confirmatory studies of MM-121 in NSCLC are being considered, although likely not in combination with erlotinib.

Phase 2 neoadjuvant clinical trial of MM-121 in combination with paclitaxel for ErbB2 (HER2) negative breast cancer

This clinical trial was a randomized, open label Phase 2 neoadjuvant clinical trial of MM-121 in combination with paclitaxel, an established chemotherapy, in patients with ErbB2 (HER2) negative breast cancer. The primary efficacy endpoint of this trial was pathologic complete response, or pCR, rate at time of surgery. pCR measures the absence of invasive cancer in breast and lymph node tissue following neoadjuvant therapy. The trial enrolled 200 patients across the following two populations of ErbB2 (HER2) negative breast cancer patients:

Group A: patients whose tumors are estrogen receptor, or ER, positive and ErbB2 (HER2) negative and have not undergone prior treatment or surgery; and

Group B: patients whose tumors are ER negative, ErbB2 (HER2) negative and progesterone receptor negative, often referred to as triple negative breast cancer, or TNBC, and have not undergone prior treatment or surgery.

Each population of patients was randomized (2:1) to receive either MM-121 in combination with paclitaxel or paclitaxel alone. Following treatment with MM-121 and/or paclitaxel, patients received standard treatment with doxorubicin and cyclophosphamide, two marketed chemotherapies, prior to surgical resection.

In 2014, we announced updated results that included data from both groups. In Group A, patients with an evaluable resection in the treatment arm who received the combination of MM-121 and paclitaxel achieved a pCR rate of 10.6% (95% CI [5.3-20.6]) compared to a pCR rate of 3.3% (95% CI [0.6-16.7]) for those in the control arm. In Group B, patients with an evaluable resection in the treatment arm who received the combination

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of MM-121 and paclitaxel achieved a pCR rate of 42.9% (95% CI [30.8-55.9]) compared to a pCR rate of 51.7% (95% CI [34.4-68.6]) for those in the control arm. There was no formal quantitative endpoint specified for this study.

MM-121 recently initiated Phase 2 clinical trial

In February 2015, we initiated a global, open-label, biomarker-selected, randomized Phase 2 clinical trial of MM-121 in combination with docetaxel or pemetrexed versus docetaxel or pemetrexed alone in patients with heregulin positive, locally advanced or metastatic NSCLC. As part of this trial, we expect to enroll approximately 120 heregulin positive patients that will be randomized (2:1) to receive either MM-121 plus the investigator s choice of docetaxel or pemetrexed, or the investigator s choice of docetaxel or pemetrexed alone. Eligible patients for the trial must have failed prior treatment with no more than two lines of therapy for locally advanced or metastatic disease. The primary endpoint of the trial is PFS. Secondary endpoints include overall survival, objective response rate, safety and tolerability. We plan to conduct the trial at sites in the United States, Canada and Europe.

MM-121 companion diagnostic development

We are developing a companion diagnostic that is focused on measuring certain mechanistically related biomarkers to determine whether a tumor is dependent on ErbB3 signaling and therefore amenable to treatment with MM-121. In 2014, we announced updated biomarker results from a meta-analysis of three randomized clinical trials of MM-121 in patients with ovarian, breast and lung cancers. This analysis included biomarker and efficacy results that had previously been disclosed, as well as additional biomarker data from the Phase 2 metastatic breast cancer trial that had not previously been reported. This meta-analysis highlighted heregulin as the principal biomarker for MM-121 efficacy. High levels of heregulin mRNA correlated with favorable hazard ratios in all three settings: in ovarian cancer, heregulin-high patients had a PFS HR of 0.37 (95% CI [0.18 0.76]) (57 of 151 evaluable patients; prevalence of 38%); in breast cancer, heregulin-high patients had a PFS HR of 0.26 (95% CI [0.11 0.63]) (34 of 76 evaluable patients; prevalence of 45%); in lung cancer, heregulin-high patients had a PFS HR of 0.35 (95% CI [0.16 0.76]) (37 of 69 evaluable patients; prevalence of 54%). In ovarian cancer, the definition of biomarker positive also required that patients have low ErbB2 (HER2) levels. In breast cancer, where only ErbB2 (HER2) negative patients were enrolled in the clinical trial, this requirement was not needed. In lung cancer, where ErbB2 (HER2) levels are naturally low, this requirement was also not needed.

Heregulin mRNA was measured in two different ways in the Phase 2 clinical trials. For archived tissue samples obtained through surgical removal of tumor tissue, which was the source of tissue in the breast cancer clinical trial, heregulin mRNA was measured by reverse transcriptase polymerase chain reaction (RT-PCR). This is a commonly used quantitative assay that provides a measure of the amount of heregulin mRNA in a block of tissue. In tissue samples obtained through a biopsy procedure, which was the source of tissue in the ovarian and lung cancer studies, heregulin mRNA was measured by RNA in situ hybridization (RNA-ISH). This is an assay in which a section of tissue is stained for heregulin mRNA and scored by a certified pathologist. Both of these assays have been transferred to certified diagnostic laboratories for use in future clinical trials of MM-121.

MM-111

MM-111 overview

MM-111 is a bispecific antibody designed to inhibit ErbB3 signaling in cancer cells that are characterized by overexpression of the ErbB2 (HER2) cell surface receptor. A bispecific antibody is a type of antibody that is able to bind simultaneously to two distinct target cell proteins or receptors. In the case of MM-111, these targets are the ErbB2 (HER2) receptor and the ErbB3 receptor. Our research and that of others suggest that the ErbB2 (HER2)

receptor triggers tumor growth and survival when it binds together with the ErbB3 receptor and another protein called heregulin. MM-111 is designed to anchor to both receptors, ErbB2 (HER2) and ErbB3, on the cell surface and block heregulin s ability to transmit tumor growth signals.

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We have evaluated the safety of MM-111 in combination with a range of therapies across ErbB2 (HER2) positive solid tumors, including gastric, esophageal, gastroesophageal junction, breast, ovarian and bladder cancers. In 2013, we obtained orphan drug designation in the United States for MM-111 for the treatment of gastric, esophageal and gastroesophageal junction cancers.

As discussed below, we have stopped enrollment into our Phase 2 clinical trial of MM-111 based on a recommendation from the DSMB for the clinical trial, which cited shorter PFS on the treatment arm relative to the control arm in the overall patient population. We do not plan to invest in additional development of MM-111 at this time.

MM-111 Phase 2 clinical trial

In 2013, we enrolled our first patient in a Phase 2 clinical trial of MM-111 for the treatment of advanced gastric, esophageal and gastroesophageal junction cancers. Overexpression of the ErbB2 (HER2) cell surface receptor has been reported in 7% 34% of gastric cancers. This Phase 2 clinical trial was designed to evaluate whether MM-111 is effective in gastric, esophageal and gastroesophageal junction cancer patients overexpressing the ErbB2 (HER2) receptor. The clinical trial enrolled patients who would traditionally receive trastuzumab-based therapy due to their ErbB2 (HER2) score of 3+ on the HercepTest®, or their ErbB2 (HER2) score of 2+ on the HercepTest® and their positive FISH status (FISH positive), and randomized those patients to receive either MM-111 in combination with paclitaxel and trastuzumab or paclitaxel and trastuzumab. In February 2015, we stopped enrolling patients in this clinical trial prior to full enrollment based on a recommendation from the DSMB for the clinical trial, which cited shorter PFS on the treatment arm relative to the control arm in the overall patient population. We do not expect to enroll any new patients in this clinical trial. A preliminary analysis shows that a vast majority of the patients in this clinical trial were below the threshold of heregulin levels that we believe are necessary to benefit from MM-111.

MM-111 companion diagnostic development

The current focus of our companion diagnostic development for MM-111 is the development of assays to quantify heregulin in patient samples from our clinical trials. We are testing additional quantitative assays for other biomarkers in archived and pretreatment patient biopsies from our clinical trials to generate data to support our biomarker hypotheses. This diagnostic is in preclinical development.

MM-151

MM-151 overview

MM-151 is an oligoclonal therapeutic consisting of a mixture of three fully human monoclonal antibodies designed to bind to non-overlapping epitopes of EGFR (ErbB1). An oligoclonal therapeutic is a mixture of two or more distinct monoclonal antibodies. EGFR (ErbB1) has long been recognized as an important drug target in several malignancies, including lung, breast, colon, pancreatic and head and neck cancers. We are conducting a Phase 1 clinical trial of MM-151 in patients with refractory solid tumors.

Based on our preclinical research, we believe that MM-151 may offer the following advantages over other EGFR (ErbB1) inhibitors:

MM-151 is designed to block the signal amplification that our research suggests occurs in the EGFR (ErbB1) pathway. Binding to multiple epitopes of EGFR (ErbB1) may result in superior signal inhibition compared to currently marketed EGFR (ErbB1) therapies, which only bind to one epitope.

MM-151 is designed to inhibit the signaling that results from the binding of a full range of EGFR (ErbB1) ligands. In contrast, currently marketed therapies block the signaling of only a subset of these ligands. As a result, a broader patient population may derive clinical benefit from MM-151.

Tumors treated with marketed monoclonal antibodies directed at EGFR (ErbB1), such as cetuximab and panitumumab, often develop resistance to these therapies. We hypothesize that this resistance often

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results from the production by the tumor of a different type of ligand that binds to EGFR (ErbB1). Because MM-151 is designed to block a full range of EGFR (ErbB1) ligands, resistance to treatment with MM-151 may be delayed or reduced compared to existing therapies.

We believe that there may be the potential to expand MM-151 into indications in which targeted EGFR (ErbB1) therapies are not currently approved, but which our preclinical research indicates should contain patients who will respond to these therapies. Potential indications include lung cancer, triple negative breast cancer and colorectal cancer.

MM-151 Phase 1 clinical trial

We are conducting a Phase 1 clinical trial of MM-151 as a monotherapy and in combination with irinotecan in patients with solid tumors. The Phase 1 clinical trial will assess the safety of MM-151 and determine the recommended Phase 2 dose. Four sites are participating in this trial.

MM-151 companion diagnostic development

We are focusing our diagnostic efforts for MM-151 on the identification of key biomarkers that will indicate which patient populations are likely to benefit from MM-151 treatment.

MM-141

MM-141 overview

MM-141 is a fully human tetravalent bispecific antibody designed to inhibit signaling of the PI3K/AKT/mTOR pathway initiated by the insulin-like growth factor 1 receptor, or IGF-1R, and ErbB3 cell surface receptors. A tetravalent bispecific antibody is a single molecule that has four binding sites, two for each of two different target cell surface receptors. PI3K/AKT/mTOR signaling is often activated in cancers in response to stress induced by chemotherapies or targeted anti-cancer medicines and is believed to play a significant role in promoting tumor cell survival. We are conducting a Phase 1 clinical trial of MM-141 as a monotherapy and in a combination therapy setting in patients with solid tumors. In 2014, we obtained orphan drug designation in the United States for MM-141 for the treatment of pancreatic cancer.

We designed MM-141 to suppress the PI3K/AKT/mTOR signaling pathway by reducing the levels of IGF-1R and ErbB3 receptor complexes that trigger the pathway. Based on our preclinical research, we believe that MM-141 may offer the following advantages compared to antibodies that solely target IGF-1R or ErbB3:

MM-141 is a tetravalent antibody that binds to both IGF-1R and ErbB3 with high affinity and avidity.

MM-141 is designed to block pro-survival signaling of major activators of PI3K/AKT/mTOR, such as heregulin, IGF-1 and IGF-2.

MM-141 is designed to block mutual compensation in IGF-1R and ErbB3 mediated activation of PI3K/AKT/mTOR by co-inhibiting both targets.

MM-141 is designed to degrade IGF-1R and ErbB3 containing receptor complexes that are commonly activated in tumors in response to PI3K/AKT/mTOR inhibition by a small molecule or an antibody.

MM-141 appears not to activate the immune system, which reduces the chance of off-target adverse events.

MM-141 Phase 1 clinical trial

We are conducting a Phase 1 clinical trial of MM-141 in both a monotherapy and a combination therapy setting in patients with solid tumors. This is a Phase 1 dose-escalation clinical trial evaluating safety and tolerability and pharmacokinetic and pharmacodynamic properties of MM-141 as a monotherapy and in

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combination with everolimus or with nab-paclitaxel and gemcitabine. The purpose of this trial is to assess the safety of MM-141 and identify the recommended Phase 2 dose. The monotherapy and combination of MM-141 with nab-paclitaxel and gemcitabine portions of this Phase 1 clinical trial are complete, and the combination of MM-141 with everolimus is ongoing. In the monotherapy arm, no dose-limiting toxicities were observed at any of the studied dose levels. In the nab-paclitaxel and gemcitabine combination arm, the observed safety profile of MM-141 in combination with nab-paclitaxel and gemcitabine was comparable to expected toxicities reported with the chemotherapy combination when used alone.

MM-141 Phase 2 clinical trial

We anticipate initiating a Phase 2 clinical trial of MM-141 in combination with nab-paclitaxel and gemcitabine in front-line pancreatic cancer in 2015.

MM-141 companion diagnostic development

We are conducting research and development on an *in vitro* companion diagnostic for MM-141 that will help to determine which patients will derive benefits from the drug alone or in combination with other therapies, while experiencing a satisfactory safety profile. This research is focused on identifying pathway-relevant biomarkers and assessing their correlation with the magnitude of patient response to MM-141. Thus far, we have identified serum-free IGF-1 as a useful stratification criteria and intend to use a proprietary, validated test to prospectively select patients with high serum-free IGF-1 levels for inclusion into the Phase 2 clinical trial of MM-141.

Preclinical Product Candidates

We are developing our preclinical product candidates for a range of solid tumor indications. Our most advanced preclinical candidates are MM-310, a targeted nanotherapeutic, and MM-131, a multispecific antibody.

Network Biology

Network Biology is what we call our proprietary systems biology-based approach to biomedical research. The goal of Network Biology is to understand how the complex molecular interactions that occur within cell signaling pathways, or networks, regulate cell decisions and how network dysfunction leads to disease. This platform utilizes proprietary, dynamic biological data generated in a high-throughput method in which we test multiple biological or chemical parameters using engineering, analytical and modeling expertise, and from which we build computational models of cell biology to further our drug discovery, design and predictive development. To execute Network Biology, we have developed an expertise in generating kinetic data, describing molecular changes or interactions over time, to illuminate the dynamic interactions that occur within biological systems. We apply Network Biology throughout the research and development process, including for target identification, lead compound design and optimization, diagnostic discovery, *in vitro* and *in vivo* predictive development and the design of clinical trial protocols.

Our models are constructed and validated using internally generated and proprietary data sets. Following the validation of a comprehensive model of a cell signaling network, we are able to use the model for drug discovery. Contrary to traditional methods, a significant portion of our discovery work takes place *in silico*, or using the model for simulation. We believe that this approach is more efficient and productive for drug discovery and development than traditional approaches.

As one example, we identified ErbB3, the target of MM-121, using our proprietary model of the ErbB signaling network after conducting a sensitivity analysis on its signaling process. Although the ErbB pathway has been

extensively targeted by cancer therapeutics, we believe that understanding the relative importance of the different components of the ErbB network is central to identifying an attractive drug target and a therapeutic

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directed at this target. In this case, we built a computational model of the ErbB signaling network that includes the most potent ErbB receptor ligands, as well as known and novel ErbB inhibitors. We populated the model with proprietary dynamic data that we generated from our experiments. The model describes in mathematical equations 700 biochemical reactions representing the ErbB signal transduction network, and identified ErbB3 as the key node in response to both ErbB3- and EGFR (ErbB1)-binding ligands. We then used this insight to develop MM-121.

Ultimately, we believe that Network Biology will result in better treatments for complex diseases by providing broader insight into disease and the potential therapeutic alternatives for physicians and patients. Using Network Biology, we are incorporating the identification of biomarkers and the development of companion diagnostics into the drug development process. We believe that integrated medicines may enable physicians to deliver the right drug to the right set of patients at the right time. This may improve patient outcomes by providing improved therapeutics along with the diagnostic information to guide physician treatment decisions, reduce the overall costs of treating and caring for cancer patients, and provide a basis for seeking favorable reimbursement of approved drugs from payors because of the benefits to patients.

In addition to improving patient care, we believe that Network Biology can increase the productivity of biomedical research, increase the probability of approval for new drugs and produce more precisely targeted therapeutics. We believe that our therapeutic oncology product candidates will have a greater probability of success than product candidates based on conventional drug development because Network Biology provides us with:

- a multidisciplinary, integrated approach to understanding complex biology;
- simulation and modeling capabilities that aid in the efficiency and productivity of development; and
- the capability to design and build a broad range of therapeutic product candidates without being limited to a particular drug design technology or target class.

Although our initial focus is oncology, we believe that our Network Biology approach is applicable to a broad range of therapeutic areas beyond cancer, including bone and joint conditions, infectious disease, inflammation, central nervous system disease and other areas of medicine with high unmet needs. While we may pursue some of these disease areas directly ourselves, because of the potential of very broad applicability of our Network Biology approach, our plan is to pursue many or all of these other areas through collaborations, licenses and other arrangements with third parties. As an example, in 2010, we established Silver Creek Pharmaceuticals, Inc., or Silver Creek, to apply our Network Biology approach to the research and development of regenerative medicines to repair the heart. Silver Creek is currently a majority owned subsidiary.

Therapeutic Design Capabilities

We apply the insights about cell signaling dynamics that we gain from Network Biology across a range of therapeutic technologies to design drug candidates that we believe can be efficiently delivered to the selected molecular target. We believe that the best therapies for the oncology indications that we are pursuing are targeted therapies that, in contrast with conventional chemotherapies, are highly selective for the molecular mechanisms that we are seeking to affect and, as a result, offer the potential for significant efficacy and safety benefits. Two such targeted therapies are human monoclonal antibodies and nanotherapeutics.

Human monoclonal antibodies

Human monoclonal antibodies are a key component of many of our targeted therapies based on their range of favorable attributes, including their significant target specificity and avidity relative to small molecules and their well understood pharmacokinetic properties. We have designed antibodies for use as stand-alone

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therapeutics and have incorporated antibodies into other therapeutics, such as targeted nanotherapeutics, as targeting or docking agents. We work with several antibody formats, including the following:

Fully human recombinant monoclonal antibodies and fragments of fully human recombinant monoclonal antibodies that include the antibody binding domain. Monoclonal antibodies and antibody fragments are proteins that bind specifically to one defined site on a cell surface protein or receptor.

Multispecific antibody formats, which are comprised of two or more antibodies or antibody fragments linked to a common scaffold molecule to produce a single molecule that specifically binds to distinct epitopes on two or more target cell surface proteins or receptors.

Oligoclonal antibody mixtures, which are comprised of defined ratios of two or more recombinant human monoclonal antibodies that target two or more distinct epitopes on a single cell surface protein or receptor.