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Merrimack Pharmaceuticals Identifies Heregulin as Patient Response Biomarker for MM-121 and Standard of Care Therapy Across Multiple Cancers

Studies indicate that 30-50 percent of patients most at risk of progression may benefit from MM-121

Data presented at the 2014 ASCO Annual Meeting from three Phase 2 studies in metastatic lung, breast and ovarian cancer

CAMBRIDGE, Mass., June 2, 2014 (GLOBE NEWSWIRE) -- Merrimack Pharmaceuticals, Inc. (Nasdaq:MACK) today reported that expression of heregulin (HRG), the principal ligand that binds to and activates the ErbB3 receptor, is associated with poor response to standard of care therapy for patients with platinum-resistant ovarian cancer, ER/PR+ HER2- breast cancer and EGFR wild-type non-small cell lung cancer. Heregulin-driven drug resistance pathways were found to be active in approximately 30-50 percent of patients tested.

Results from three Phase 2 studies further showed that patients with heregulin-positive tumors experienced a statistically significant reduction in their risk of progression when they received a combination of MM-121 with their standard of care therapy as compared to patients who received the standard of care therapy alone. MM-121 is specifically designed to block heregulin binding to ErbB3.

Top line data from these trials had previously been released. Detailed biomarker data for all three studies were presented at the American Society of Clinical Oncology (ASCO) Annual Meeting, May 30-June 3, 2014, at McCormick Place in Chicago.

"These data suggest a significant clinical role for heregulin-driven ErbB3 signaling as a mechanism of resistance to multiple standard of care therapies regardless of the cancer indication studied. Moreover, these studies demonstrate that targeting heregulin-positive tumors with MM-121 appeared to sensitize patients to exemestane, erlotinib and paclitaxel in metastatic breast, lung and ovarian cancers, respectively, and significantly lower their risk of tumor progression," said Akos Czibere, MD, PhD, Senior Medical Director at Merrimack. "We look forward to advancing MM-121 into definitive studies that will allow us to prospectively screen patients for heregulin."

In addition to identifying heregulin as the principal biomarker for MM-121, the benefit from MM-121 in these studies was enhanced in patients with low levels of HER2, the dimerization partner of ErbB3. In ovarian and breast cancers, biomarker-positive patients were defined as having high heregulin and low HER2. In lung cancer, where HER2 levels are naturally low, biomarker-positive patients were defined as having high heregulin. Biomarker data across the three studies are as follows:

Study	Biomarker Positive			
	No. of Patients	Hazard Ratio	Prevalence	P-value
Ovarian	57	0.37 (95% CI [0.18 - 0.79])	37%	0.009
Breast	17	0.31 (95% CI [0.1-0.98])	31%	0.045
Lung	36	0.38 (95% CI [0.18-0.8])	54%	0.011

"The consistency of these findings across three different cancer indications and the benefit achieved with MM-121 in these studies is evidence of the importance of ErbB3 signaling in cancer. It also strengthens our confidence in systems biology and its applicability to drug discovery and development. With these findings, we are now preparing our diagnostic assays for use in future clinical studies for MM-121 as well as for use in the clinical development of our other ErbB3-targeted therapies," said Gavin MacBeath, Ph.D., Co-Founder and Senior Vice President at Merrimack. "These data lay the foundation for the development of ErbB3 inhibitors in oncology."

The three Phase 2 studies that were presented enrolled a total of 473 patients and evaluated whether MM-121 in combination with a standard of care therapy was more effective than the standard of care therapy alone in prolonging progression free

survival (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.

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.

To access clinical posters presented at ASCO 2014, click [here](#).

Study Results:

Phase 2 Study of MM-121 in Combination with Paclitaxel in Platinum-Resistant/Refractory Ovarian Cancers

This study was designed as a global, open-label, randomized Phase 2 study evaluating whether the combination of MM-121 and paclitaxel was more effective in prolonging PFS than paclitaxel alone in patients (n=223) 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 223 patients in this study, biomarker data were available for 150 patients.

	Full Population (N=223)		Heregulin Positive, HER2 low (N=57 of 150)	
	MM-121 + Paclitaxel	Paclitaxel	MM-121 + Paclitaxel	Paclitaxel
Median PFS	3.75 months	3.58 months	5.8 months	3.5 months
Hazard Ratio	1.027 [95% CI 0.741 - 1.425]		0.37 (95% CI [0.18 - 0.79])	
p-value	0.864		0.009	

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 (37%) who also had low 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 in ovarian cancer are being considered.

Phase 2 Study of MM-121 in Combination with Exemestane in Metastatic ER/PR+, HER2 Negative Breast Cancer

This study was a randomized, double-blinded, placebo-controlled Phase 2 study 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=118) who have previously failed anti-estrogen therapy. The primary objective was to compare PFS between the groups. The study was powered to detect a hazard ratio (HR) of < 0.5. The study analysis was conducted after 84 events. Of the 115 patients in this study, biomarker data were available for 55 patients.

	Full Population (N=115)		Heregulin Positive, HER2 low (N=17 of 55)	
	MM-121 + Exemestane	Exemestane	MM-121 + Exemestane	Exemestane
Median PFS	3.7 months	2.5 months	[7.7 months]	[2.7 months]
Hazard Ratio	0.77 (95% CI [0.5- 1.2])		0.31 (95% CI [0.1-0.98])	
p-value	0.25		0.045	

The addition of MM - 121 did not significantly enhance exemestane activity in an unselected metastatic breast cancer population. A subset of heregulin positive patients (31%) who also had low HER2 levels, however, responded poorly to exemestane 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 exemestane. Further confirmatory studies in breast cancer are being considered.

Phase 2 Study of MM-121 in Combination with Erlotinib in EGFR Wild-Type Non-Small Cell Lung Cancer

This study was a global, open-label, randomized parallel cohort study evaluating whether the combination of MM-121 and erlotinib was more effective in prolonging PFS than erlotinib alone in EGFR wild-type (wt) non-small cell lung cancer (NSCLC) patients (n=132). The primary objective was to compare PFS between the groups. The study analysis was conducted after 105 events. Of the 132 patients in this study, biomarker data were available for 67 patients.

	Full Population (N=132)		Heregulin Positive (N=36 of 67)	
	MM-121 + Erlotinib	Erlotinib	MM-121 +Erlotinib	Erlotinib
Median PFS	1.9 months	1.8 months	1.9 months	1.7 months
Hazard Ratio	0.81 (95%CI [0.55 - 1.2])		0.38 (95% CI [0.18-0.8])	
p-value	p=0.29		p=0.011	

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 in NSCLC are being considered, although they would likely not rely on erlotinib as the backbone therapy.

About MM-121

MM-121 is a fully human monoclonal antibody that targets ErbB3, a cell surface receptor that is activated by the ligand heregulin. Heregulin-driven ErbB3 signaling has been implicated as a mechanism of tumor growth and resistance to targeted, cytotoxic and anti-endocrine therapies. When used in the combination setting, MM-121 is designed to block ErbB3 signaling in order to restore or enhance the anti-tumor effect of a combination therapy partner.

MM-121 has been investigated in four Phase 2 and six Phase 1 clinical studies covering a broad spectrum of patient populations and drug combinations. An extensive translational component of the MM-121 clinical program was designed to establish clinically useful biomarkers that were initially identified using Merrimack's systems biology approach and confirmed in preclinical studies. Sanofi and Merrimack entered into an exclusive, global license and collaboration agreement for MM-121 in 2009.

About Merrimack

Merrimack is a biopharmaceutical company discovering, developing and preparing to commercialize innovative medicines paired with companion diagnostics for the treatment of cancer. Merrimack seeks to gain a deeper understanding of underlying cancer biology through its systems biology-based approach and develop new insights, therapeutics and diagnostics to improve outcomes for cancer patients. Merrimack currently has six oncology therapeutics in clinical development and three additional candidates in late stage preclinical development. For more information, please visit Merrimack's website at www.merrimackpharma.com.

Forward-Looking Statements

To the extent that statements contained in this press release are not descriptions of historical facts, they are forward-looking statements reflecting the current beliefs and expectations of management made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995, as amended. Forward-looking statements include any statements about Merrimack's strategy, future operations, future financial position and future expectations and plans and prospects for Merrimack, and any other statements containing the words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," "hope" and similar expressions. In this press release, Merrimack's forward-looking statements include statements about the potential effectiveness and tolerability of its investigational therapeutics in certain patient populations or subpopulations, its ability to develop a predictive diagnostic, the initiation of future clinical studies, and its ability to translate clinical data into future clinical success. Such forward-looking statements involve substantial risks and uncertainties that could cause Merrimack's clinical development programs, future results, performance or achievements to differ significantly from those expressed or implied by the forward-looking statements. Such risks and uncertainties include, among others, availability of data from ongoing clinical trials, expectations for regulatory approvals, development progress of Merrimack's companion diagnostics and other matters that could affect the availability or commercial potential of Merrimack's drug candidates or companion diagnostics. Merrimack undertakes no obligation to update or revise any forward-looking statements. Forward-looking statements should not be relied upon as representing Merrimack's views as of any date subsequent to the date hereof. For a further description of the risks and uncertainties that could cause actual results to differ from those expressed in these forward-looking statements, as well as risks relating to Merrimack's business in general, see the "Risk Factors" section of Merrimack's Quarterly Report on Form 10-Q filed with the Securities

and Exchange Commission (SEC) on May 6, 2014 and other reports Merrimack files with the SEC.

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