A META-ANALYSIS OF BIOMARKERS IN THREE RANDOMIZED, PHASE 2 STUDIES OF MM-121, A LIGAND-BLOCKING ANTI-ERBB3 ANTIBODY, IN PATIENTS WITH OVARIAN, LUNG, AND BREAST CANCERS

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Aim: Heregulin (HRG)-driven ErbB3 signaling mediates resistance to standard-of-care (SOC) cancer therapy in a variety of preclinical models. MM-121, a HRG-blocking anti-ErbB3 antibody, underwent clinical evaluation to determine if patients with advanced malignancies would derive benefit from the addition of MM-121 to their standard therapy. Potential predictive biomarkers were identified from a pre-specified set of mechanistic markers.

Methods: Randomized Phase 2 studies were conducted in: i) platinum-resistant ovarian cancer, ii) EGFR wt NSCLC, and iii) ER/PR + , HER2- mBC. Patients were randomized to SOC therapy, with or without MM-121. Safety and clinical activity data from these studies have previously been presented. Tumor tissue was acquired from each patient and five pre-specified biomarkers were measured and correlated with clinical benefit: HRG, betacellulin, EGFR, HER2, and ErbB3. Protein levels were determined by quantitative IHC (qIHC) and mRNA levels by RT-PCR and RNA in-situ hybridization (RNA-ISH).

Results: Among 464 patients (220 ovarian, 115 breast, 129 lung), RNA-ISH data were available from 224 patients (157 ovarian, 67 lung), qIHC from 252 (174 ovarian, 78 lung), and RT-PCR from 175 (105 ovarian, 57 breast, 13 lung). Of the five biomarkers, the most predictive of response was HRG mRNA: patients with detectable HRG in pre-treatment biopsies or high HRG in archived tissue blocks responded poorly to SOC therapy and benefited most from MM-121. In addition, benefit was largely restricted to patients with low ErbB2. Hazard ratios for PFS were calculated, defining biomarker positive (BM+) patients: Ovarian cancer, detectable HRG and low ErbB2; Lung cancer, detectable HRG; and, Breast cancer, high HRG. PFS hazard ratios with 95% CI and prevalence of the BM+ and BM- subpopulations are provided below.

Conclusions: Heregulin is a potential biomarker for poor response to SOC therapy and a potential predictor of clinical benefit from MM-121 in late-stage ovarian, lung, and breast cancers.

Disclosure: G. MacBeath is an employee of Merrimack Pharmaceuticals and holds stock in the company; B. Adiwijaya is an employee of Merrimack Pharmaceuticals, the sponsor of this clinical research, and holds stock in the company; J. Liu is an unpaid advisor for Merrimack Pharmaceuticals and was a Principal Investigator for one of the clinical studies included in this analysis; L.V. Sequist is an unpaid advisor for Merrimack Pharmaceuticals and was a Principal Investigator of one of the clinical studies included in this analysis; E. Pujade-Lauraine serves as an unpaid advisor to Merrimack Pharmaceuticals and Sanofi. He was also a lead investigator for one of the clinical studies included in this analysis; M. Higgins is an unpaid advisor to Merrimack Pharmaceuticals and Sanofi. She was a Principal Investigator of one of the clinical studies included in this analysis; I. Tabah-Fisch is an employee of Sanofi, a sponsor of the clinical studies summarized in this abstract, and holds stock in the company; J. Pearlberg is an employee of Sanofi, a sponsor of this clinical research, and holds stock in the company; V. Moyo, W. Kubasek, R. Nering and A. Czibere: Is an employee of Merrimack Pharmaceuticals, a sponsor of the clinical research, and holds stock in the company.

Table: 246P

<table>
<thead>
<tr>
<th>Study</th>
<th>BM+ n/N*</th>
<th>BM+ Prevalence</th>
<th>PFS HR in study</th>
<th>PFS HR in measured BM</th>
<th>PFS HR in BM+</th>
<th>PFS HR in BM-</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ovarian</td>
<td>69/150</td>
<td>46%</td>
<td>1.03 [0.74-1.42]</td>
<td>1.10 [0.74-1.63]</td>
<td>0.40 [0.21-0.76]</td>
<td>2.02 [1.17-3.50]</td>
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<tr>
<td>Lung</td>
<td>36/67</td>
<td>54%</td>
<td>0.82 [0.55-1.21]</td>
<td>0.91 [0.51-1.61]</td>
<td>0.39 [0.18-0.82]</td>
<td>2.43 [1.07-5.55]</td>
</tr>
<tr>
<td>Breast</td>
<td>21/57</td>
<td>37%</td>
<td>0.75 [0.48-1.15]</td>
<td>0.68 [0.38-1.23]</td>
<td>0.35 [0.13-0.94]</td>
<td>0.99 [0.47-2.08]</td>
</tr>
</tbody>
</table>

*n = BM + , N = patients with measured biomarkers

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