SHERLOC: A Phase 2 Study of MM-121 in Combination with Docetaxel versus Docetaxel Alone in Patients with Heregulin Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

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List of Abbreviations

Abbreviation	Definition
AE	Adverse event
AESI	Adverse event of special interest
AKT	Protein kinase B
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASCO	American Society for Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
AUC_t	Area under the concentration-time curve
BTC	Betacellulin
C_{avg}	Average serum concentration
CBC	Complete blood count
CFR	Code of Federal Regulations
CI	Confidence interval
CL	Clearance
C_{max}	Maximum serum concentration
CMH	Cochran-Mantel-Haenszel (test)
C_{min}	Minimum serum concentration
CNB	Core needle biopsy
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CTG	Cell TiterGlo
DMC	Data Monitoring Committee
EC	Ethics Committee
ECG	Electrocardiogram
ECOG (PS)	Eastern Cooperative Oncology Group (performance status)
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
ErbB	Epidermal growth factor family of receptor tyrosine kinases
FDA	Food and Drug Administration
FFPE	Formalin-fixed, paraffin-embedded
FGF	Fibroblast growth factor
FL-IHC	Fluorescence-based immunohistochemistry
FNA	Fine needle aspiration
g	Gram
GCP	Good Clinical Practice
GnRH	Gonadotropin-releasing hormone
GR	Grade
HAHA	Human anti-human antibodies
HER2	Human epidermal growth factor receptor 2
HGF	Hepatocyte growth factor
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio

Abbreviation	Definition
HRG	Heregulin
IB	Investigator's Brochure
ICH	International conference on harmonization
Ig	Immunogenicity
IGF	Insulin-like growth factor
IGF-1R	Insulin-like growth factor 1 receptor
IHC	Immunohistochemistry
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion-Related Reaction
ISH	In-situ hybridization
ITT	Intent to treat
IV	Intravenous
IWRS	Interactive web response system
kg	Kilogram
LDH	Lactate dehydrogenase
LVEF	Left ventricle ejection fraction
mBC	Metastatic breast cancer
mcg	Micrograms
MedDRA	Medical Dictionary for Regulatory Activities
mg	Milligram
mOC	Metastatic ovarian cancer
mL	Milliliter
MM-121	Seribantumab
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mammalian target of rapamycin
NCI	National Cancer Institute
NRG	Neuregulin
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall survival
p.o.	Per os (oral administration)
PD-L1	Programmed death ligand 1
PET-CT	Positron emission tomography - computed tomography
PFS	Progression-free survival
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetic(s)
PP	Per Protocol
PR	Partial response
PTT	Prothrombin time
PWB	Physical well-being domain of FACT-L
Q2W	Every 2 weeks
Q3W	Every 3 weeks
QW	Weekly
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RNAi	Ribonucleic acid interface

Abbreviation	Definition
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event
SAF	Safety Population
SAP	Statistical Analysis Plan
SD	Stable disease
SmPC	Summary of Product Characteristics
TCGA	The Cancer Genome Atlas
TKI	Tyrosine kinase inhibitor
T_{max}	Time to maximum serum concentration
TTP	Time to Progression
ULN	Upper limit of normal
US	United States
USP	United States Pharmacopeial Convention
VD_{ss}	Volume of distribution at steady state
WBC	White blood cell

Study Synopsis

Sponsor:	Merrimack One Kendall Square Cambridge, MA USA 02139-1670
Protocol Title:	SHERLOC: A Phase 2 Study of MM-121 in Combination With Docetaxel versus Docetaxel Alone in Patients with Heregulin Positive, Locally Advanced or Metastatic Non-Small Cell Lung Cancer
Protocol Number:	MM-121-01-02-09
Phase of Development:	Phase 2
Trial Locations:	International
Number of sites:	Approximately 80-100 sites worldwide
Patient Population:	Patients who are candidates to receive single agent docetaxel therapy for non-small cell lung cancer (NSCLC) that is histologically classified as adenocarcinoma. Such patients have received either one or two lines of systemic therapy for locally advanced and/or metastatic disease, and shall have tumors that are positive for heregulin (HRG) mRNA as assessed by central testing.
Estimated Number of Patients:	Approximately 300 patients will be screened, and approximately 110-150 patients will need to be enrolled to support randomization of 80 HRG positive patients that meet the Per Protocol Population criteria according to Protocol version 4.0.
Primary Objective:	• To determine whether the combination of MM-121 plus docetaxel is more effective than docetaxel alone based on investigator assessed Progression-Free Survival (PFS) according to RECIST 1.1 in HRG positive patients (defined as HRG ISH score of ≥1+).
Secondary Objectives:	• To determine whether the combination of MM-121 plus docetaxel is more effective than docetaxel alone in HRG positive patients (defined as HRG ISH score of ≥ 1+) for the following clinical outcome parameters: o Overall Survival (OS) o Objective Response Rate (ORR) based on RECISTv1.1 o Time to Progression (TTP) • To describe the safety profile of MM-121 in combination with docetaxel • To characterize the pharmacokinetic (PK) profile of MM-121 when given in combination with docetaxel and of docetaxel when given in combination with MM-121
Exploratory Objective:	• To evaluate if mechanistically linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes
Study Design:	This study is a randomized, open-label, international, multi-center, phase 2 study in patients with NSCLC histologically classified as adenocarcinoma that has progressed following one or two lines of systemic therapy for locally advanced and/or metastatic disease, of which one must have been a platinum containing regimen. Following signing the pre-screening informed consent form, all patients will provide a tissue sample (which meets the requirements for collection and processing as outlined in the study lab manual) to the designated central lab facility for HRG testing. If adequate archived tissue is not available, patients should undergo a procedure (e.g. fine needle aspiration (FNA), core needle biopsy (CNB), thoracentesis, or excisional biopsy) to acquire the necessary tissue for HRG testing. For these procedures, investigators are asked to choose

	an easily accessible tumor lesion to minimize any possible risk associated with the collection of the tissue. As a general guideline, if the selected procedural location has an established serious complication rate of >2% at the institution completing the procedure, this is considered a high risk procedure and should be avoided. Upon receipt of a tissue sample at the central lab, the investigational site will be informed of the results within 7 days. Patients with a positive HRG status, defined as a HRG ISH score of ≥1+, will sign the full study consent form and continue with screening procedures. Patients with tumors that show no staining for HRG, HRG ISH score of 0, will not continue any further procedures for this study and will be considered screen failures. Minimal medical history for HRG negative patients will be collected. In order to obtain fresh tissue from all patients enrolled, all patients that receive a positive HRG result for eligibility based on testing of archived samples will also be required to undergo a fresh research biopsy (e.g. FNA, CNB, thoracentesis, or excisional biopsy) prior to first dose. It is important that no systemic therapy is administered between collection of this tissue and dosing on this study. An additional sample will not be requested from patients who underwent a fresh biopsy for eligibility testing. After all screening procedures and determination of eligibility for treatment randomization (including HRG positive ISH result) have been completed, eligible patients will be randomized in a 2:1 ratio (experimental arm versus comparator arm) using an Interactive Web Response System (IWRS). Randomization will be stratified based on the number of prior systemic therapies for locally advanced and/or metastatic disease (1 or 2) and prior anti-PD-1 or anti-PD-L1 will be capped at approximately 30% per group. Patients will be assigned to Arm A or Arm B: **Arm A (Experimental Arm)**: MM-121: fixed dose of 3000 mg intravenously (IV) on day 1 of each 21-day cycle Docetaxel: 75 mg/m^2 IV on day 1 of each 21-day cycle **Arm B (Comparator Arm):** Docetaxel: 75 mg/m^2 IV on day 1 of each 21-day cycle Treatment must start within 7 days following randomization. Patients are expected to be treated until investigator-assessed progressive disease or unacceptable toxicity. Tumor assessments will be measured and recorded by the local radiologist every 6 weeks (+/- 1 week) and evaluated using the RECIST guidelines (version 1.1). All patients that come off treatment for reasons other than progressive disease will have a scan at the time of the End of Treatment visit. After patients come off treatment, survival information and information about subsequent therapies will be collected until death or study closure, whichever occurs first. Final analysis will be triggered following the last recorded event as recorded in the database. In prior studies, MM-121 has been administered in combination with taxanes (paclitaxel and cabazitaxel) at the standard doses with no maximum tolerated dose (MTD) reached. However, no data was available for the combination of MM-121 and docetaxel prior to starting the current study. Therefore, enrollment into this backbone was paused after the twelfth patient was

	randomized to docetaxel or MM-121 + docetaxel and completed one full cycle of treatment, and the emerging safety data on both arms was reviewed by investigators, medical monitors and representatives from the sponsor. The safety review decided that enrollment to docetaxel alone or MM-121 + docetaxel can continue at the current dose level without modification as outlined in the study protocol. The DMC will monitor safety data over the course of the study in accordance with the DMC Charter.

Inclusion Criteria:	To be eligible for participation in the study, patients must meet the following criteria. Patients who are assessed to be HRG negative do not complete any screening procedures beyond HRG assessment.
	• Patients with cytologically or histologically documented NSCLC classified as adenocarcinoma that is presenting as either:
	  o Stage IV (metastatic disease) or
	  o Stage IIIB disease not amenable to surgery with curative intent or
	  o Recurrent or progressive disease following multimodal therapy (chemotherapy, radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced or metastatic disease)
	• Disease progression or evidence of recurrent disease during or after the last systemic therapy as documented by radiographic assessment
	• Received one prior platinum-based regimen for management of primary or recurrent disease
	• Received nivolumab, pembrolizumab, or other anti-PD-1 or anti-PD-L1 therapy, where available and clinically indicated
	• Clinically eligible for treatment with docetaxel once every three weeks per the investigator's judgment
	• Must have at least one lesion amenable to collection of tissue
	• A positive in-situ hybridization (ISH) test for heregulin with a score of $\geq$1+, as determined by centralized testing
	• ECOG performance status (PS) of 0 or 1
	• Screening ECG without clinically significant abnormalities
	• Women of childbearing potential, as well as fertile men and their partners, must be willing to abstain from sexual intercourse or to use an effective form of contraception (an effective form of contraception is an oral contraceptive or a double barrier method or as defined by country-specific guidelines) during the study and for 6 months, in males and females, following the last dose of study drug(s), or greater, as in accordance with the label requirements or institutional guidelines for docetaxel
	• $\geq$ 18 years of age
	• Able to provide informed consent, or have a legal representative able and willing to do so
	• Patients who have experienced a venous thromboembolic event within 60 days of signing the main consent form should have been treated with anti-coagulants for at least 7 days prior to beginning treatment and for the duration of treatment on this study

Exclusion Criteria:	To be eligible for randomization, patients must not meet any of the following criteria: • Known Anaplastic Lymphoma Kinase (ALK) gene rearrangement • Presence of exon 19 deletion or exon 21 (L858R) substitution of the EGFR gene • Pregnant or lactating

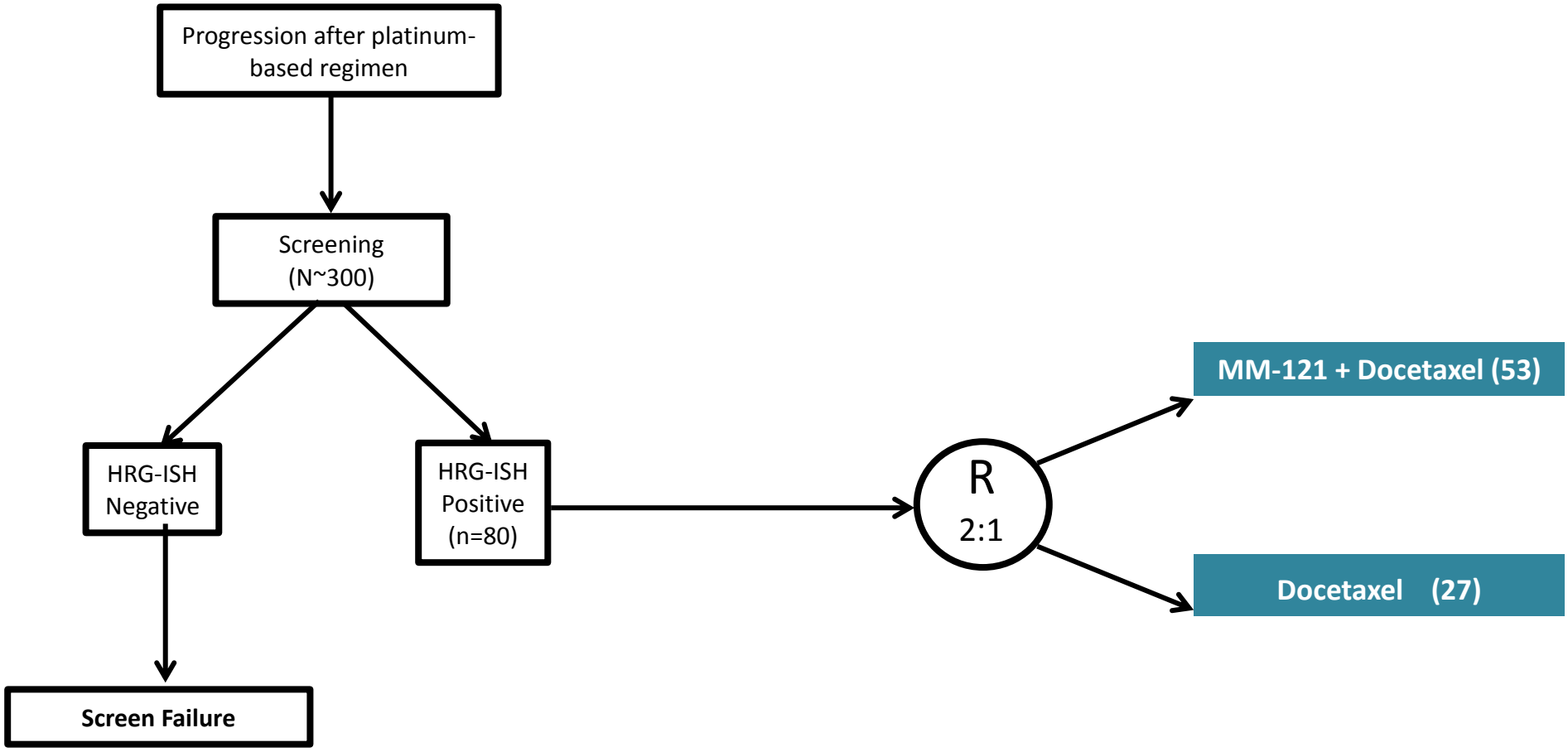
	• Prior radiation therapy to >25% of bone marrow-bearing areas
	• Received >2 prior lines of systemic anti-cancer drug regimens for locally advanced and/or metastatic disease
	  o Any type of maintenance therapy, e.g. pemetrexed maintenance following first line treatment with cisplatin and pemetrexed, is not considered a separate line of therapy
	• Prior treatment with an anti-ErbB3 antibody
	• Prior treatment with docetaxel for advanced/ metastatic disease
	• Received other recent antitumor therapy including:
	  o Investigational therapy administered within the 28 days or 5 half-lives, whichever is shorter, prior to the first scheduled day of dosing in this study
	  o Radiation or other standard systemic therapy within 14 days prior to the first scheduled dose in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation
	• CTCAE grade 3 or higher peripheral neuropathy
	• Presence of an unexplained fever > 38.5°C during screening visits that does not resolve prior to the first day of dosing. If the fever and active infection have resolved prior to randomization, the patient will be eligible. At the discretion of the investigator, patients with tumor fever may be enrolled.
	• Clinically active CNS metastasis
	• Use of strong CYP3A4 inhibitors
	• Any other active malignancy requiring systemic therapy
	• Known hypersensitivity to any of the components of MM-121 or previous CTCAE grade 3 or higher hypersensitivity reactions to fully human monoclonal antibodies
	• History of severe hypersensitivity reactions to docetaxel
	• Known hypersensitivity to polysorbate (Tween) 80 or arginine
	• Inadequate bone marrow reserve as evidenced by:
	  o ANC < 1,500/µl or
	  o Platelet count < 100,000/µl or
	  o Hemoglobin < 9 g/dL (5.59 mmol/L)
	• Serum/plasma creatinine > 1.5 x ULN
	• Inadequate hepatic function as evidenced by:
	  o Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 x ULN concomitant with Alkaline phosphatase (AP) > 2.5 x ULN
	  o Serum/plasma total bilirubin > ULN
	• Clinically significant cardiac disease, including: symptomatic congestive heart failure, unstable angina, acute myocardial infarction within 12 months of planned first dose, or unstable cardiac arrhythmia requiring therapy (including torsades de pointes)
	• Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; or active human immunodeficiency virus (HIV) infection, active hepatitis B infection or active hepatitis C infection
	• Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator

Length of Study:	It is intended that patients will be treated until radiographic disease progression per RECIST 1.1, death or intolerable toxicity, as assessed by the investigator. The primary analysis will be event driven. It is estimated that the accrual will be approximately 5-6 patients per month over an approximately 15 month period.
Investigational Product:	MM-121 is a clear liquid solution, supplied in sterile, single-use vials for injectable use at a concentration of 25 mg/mL. MM-121 Drug Product should be stored at 2-8°C.
Docetaxel:	Docetaxel is a commercially available pyrogen-free, non-aqueous solution for intravenous use supplied in multi-use vials containing either 4 mL or 8 mL of docetaxel at a concentration of 10 mg/mL. Docetaxel should be stored at 20-25°C (68 - 77°F) and should be retained in the original packaging to protect from light.
Sample Size:	The primary endpoint of the study is Progression-Free Survival (PFS). Approximately 61 PFS events in 80 patients are required to have at least 80% power to detect a 2 month improvement in median PFS with the combination of MM-121 plus docetaxel or MM-121 versus docetaxel alone with a baseline median PFS assumption of 3 months (i.e., hazard ratio ≤ 0.60), using a one-sided, stratified log-rank test at a significance level of 0.15 with a 2:1 ratio.
Statistical Considerations and Data Reporting:	**General:** Categorical variables will be summarized by frequency distributions (number and percentages of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). **Analysis Populations:** The primary analysis will occur on the Per Protocol (PP) population, defined as patients that meet all inclusion/exclusion criteria as defined in Protocol version 4.0 and that are confirmed HRG positive based on centralized analysis of tissue collected after progression on the most recent line of therapy (pre-treatment tissue sample). Due to the adjusted entry criteria, patients randomized prior to this amendment will be maintained as evaluable for the primary efficacy analysis where applicable. A thorough review of all patient level data will be performed on those already randomized. Those patients meeting the new entry criteria will be eligible to be part of the primary efficacy analysis and may contribute to the total sample size of 80 patients enrolled under Version 4.0 of the protocol, as long as no major protocol violations exist which would exclude them from the per protocol population. Major protocol violations include those not meeting the new entry criteria, those with no baseline measurable lesions, and those patients that never received at least 1 dose of study drug. The total number of patients randomized will not exceed the number needed to randomize 80 patients who qualify for the per protocol population of Version 4.0. It is estimated to be in the range of 110-150 patients. Patients that meet eligibility criteria but have existing protocol violations which would exclude them from the per protocol population will be analyzed as part of a sensitivity analysis by pooling them with the per protocol population. Any patient randomized and not meeting the new entry criteria will be pooled with all other patients and analyzed as part of a sensitivity analysis population.

	All patients previously randomized under previous protocols will be used either as part of the primary efficacy analysis in the per protocol population or in some form of sensitivity analysis. All patients dosed will contribute to the safety population. Patients that have signed informed consent, are identified as HRG positive based on centralized tissue analysis, and have successfully completed study entry criteria will be delineated into the following analysis populations • **Intent-to-Treat (ITT) population**: This population includes randomized patients. Patients will be analyzed in the randomized group. • **Per Protocol (PP)**: This population includes randomized and dosed patients. The PP population is the primary efficacy population and will only include patients that meet all inclusion/exclusion criteria as defined in Protocol Version 4.0 and that are confirmed HRG positive based on centralized analysis of tissue collected after progression on the most recent line of therapy (pre-treatment tissue sample). The PP will exclude those patients with major protocol violations, which will be defined in the SAP in more detail and assessed in an unbiased ongoing manner. Primary considerations for exclusion will be those patients with no measurable baseline tumor, non-evaluated baseline non-target tumor assessments, and incomplete tumor evaluations. Not all circumstances will result in exclusion, however a continual review of patient data will be performed to address data inconsistencies by the medical director, statistician, and clinical trial manager. Data will be reviewed without knowledge of progression/non-progression. • **Safety (SAF) population**: The safety population includes patients receiving at least one dose of study medication. Patients will be analyzed by the treatment received and not by the treatment to which they were randomized. All safety analyses will be performed on this population. • **PK population**: All treated patients with at least one PK assessment **Primary Efficacy Analysis:** PFS, based on investigator assessment is the primary endpoint of the study. PFS is defined as the time from randomization to the first documented radiographical progression of disease using RECIST 1.1, or death from any cause, whichever comes first. Details of censorship will be thoroughly explained in the SAP. The primary efficacy will be performed on the per protocol (PP) population using a stratified log-rank test. The Kaplan-Meier method will be used to estimate median PFS for each treatment group. A stratified Cox proportional hazard model will be used to obtain an estimate hazard ratio and corresponding 70% confidence intervals. Stratification factors include: Number of prior systemic treatments for locally advanced and/or metastatic disease (1, 2). **Secondary Efficacy Analysis:** Overall Survival (OS): Overall Survival (OS) is defined as the time from the date of randomization to the date of death from any cause. The Kaplan-Meier method will be used to estimate median OS for each treatment group. A stratified Cox proportional

	hazard model will be used to obtain an estimate hazard ratio and corresponding 95% confidence intervals. Objective Response Rate (ORR): Objective response rate (ORR) is determined by RECIST v1.1 (CR+PR). An estimate of the ORR and its 95% CI will be calculated. CMH tests will be performed as appropriate. Time to Progression (TTP): TTP is defined as the time from the date of randomization to the date of objective tumor progression. Those patients without objective tumor progression will be censored at the date of last tumor assessment documenting no objective progression. Patients who died prior to first scan will be censored on the date of death. Biomarkers and standard covariates will be analyzed with respect to OS, PFS, ORR, and TTP. Additional OS, PFS, ORR and TTP sensitivity analyses will be conducted using various study populations. In addition, OS and PFS will have different censoring rules applied to assess parameter sensitivity to changes in specifications. These will be clearly detailed in the statistical analysis plan (SAP). **Safety Analysis:** Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be coded using the latest MedDRA dictionary. Severity will be graded according to the NCI CTCAE version 4.03. Patients will be analyzed according to the treatment received. Pemetrexed patients will be summarized accordingly. Treatment-emergent adverse events (TEAEs), TEAE grade 3 and higher, TEAE-related, SAEs, and discontinuation due to AE will be reported by frequency and percent summaries. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient. Laboratory, vital signs, and ECG data will be summarized according to parameter type. **Pharmacokinetic Analysis:** Serum concentrations will be used to determine the MM-121 PK parameters and plasma concentrations will be used to determine docetaxel parameters as appropriate using population pharmacokinetic analysis. The resulting PK parameters will be associated with efficacy and safety endpoints as appropriate. Details will be provided in a separate population PK analysis plan. **Exploratory Translational Analyses:** Biomarker data will be explored from collected tissue and serum to assess potential associations with tumor response. Efficacy outcomes considered for exploratory biomarker analysis will include OS, PFS, and ORR. Kaplan Meier methods for displaying graphs and Cox proportional models will be used when estimating hazard ratios with 95% confidence intervals.

Study Schema



1 Introduction

1.1 Non-Small Cell Lung Cancer

Lung cancer is projected to be the leading cause of all cancer-related deaths worldwide in 2014. It is estimated that there will be 224,410 new cases diagnosed in 2014 alone, making up approximately 13% of all cancer diagnoses. For cases diagnosed during the period of 2003-2009, the 1- and 5-year survival rates were 43% and 17% respectively ("American Cancer Society Facts and Figures 2014," 2014). Over 80% of lung cancers are comprised of non-small cell lung cancers (NSCLC), and nearly two thirds of these are diagnosed at an advanced stage. A platinum-based doublet regimen with a third-generation agent (paclitaxel, docetaxel, gemcitabine, vinorelbine, pemetrexed) is considered standard of care worldwide for the treatment of advanced NSCLC (Kawaguchi et al., 2014). However, only one third of patients that receive this regimen reach an objective response during first-line therapy, and another 20-30% achieves stabilization of disease. Unfortunately, almost all patients ultimately see progression of their disease (Gridelli et al., 2008).

There are currently three agents approved for second-line treatment of advanced NSCLC. Docetaxel was the first regimen approved for second-line treatment after several phase 2 and phase 3 studies established the standard regimen (Shen et al., 2014). The dose of 75 mg/m^2 once every three weeks was shown to demonstrate longer survival and better quality of life than the best supportive care at that time, and was shown to demonstrate an increase in 1-year survival rates in comparison to vinorelbine or ifosfamide (Manegold et al., 2013). Pemetrexed received approval as second-line therapy due to its similarity in survival and response with lower toxicity levels than those of docetaxel, although statistically, it was not proven to be better or inferior to docetaxel (Hanna et al., 2004; Paz-Ares et al., 2008). Erlotinib was also approved on the basis of increased survival in comparison to best supportive care.

Although these regimens do show an increase in survival rates and better quality of life from supportive care, there is still much room for improvement. Docetaxel given at 75 mg/m^2 once every three weeks is associated with a 1-year survival of 30-40%. While this is a higher rate of survival, it is a clear indication that a more effective treatment for patients with advanced NSCLC is needed.

1.2 ErbB3

ErbB3 was first isolated and characterized in 1989 (Kraus et al., 1989). The ErbB3 receptor is a 148 kilodalton (kDa) transmembrane receptor tyrosine kinase belonging to the ErbB/EGFR family and was shown to be kinase dead (Citri et al., 2003). The ErbB family of transmembrane receptor tyrosine kinases impacts the physiology of cells and organs by eliciting ligand-dependent activation of multiple signal transduction pathways. Upon binding of HRG, the physiological ligand for the ErbB3 receptor, ErbB3 dimerizes with other ErbB family members, preferentially ErbB2.

Heregulin, the cognate ligand to ErbB3, has been shown to be involved in several different types of cancer: breast, ovarian, endometrial, colon, gastric, lung, thyroid, glioma, medulloblastoma, melanoma as well as squamous cell carcinomas of the head and neck (Breuleux, 2007; Stove & Bracke, 2005). In most of these tumor types, HRG regulates growth, invasion, and angiogenesis through the presence of either autocrine or paracrine HRG signaling. It is thought that autocrine HRG may give rise to constitutively activated ErbB2 and ErbB3, protecting these tumors against apoptosis and generating growth factor independence (Li et al., 2004; Mills & Yarden, 2010;

Sheng et al., 2010). Disruption of the heregulin autocrine loop by blocking HRG binding to ErbB3 or disruption of the ErbB2/ErbB3 dimer is considered to provide an important therapeutic measure to control cancer cell growth (Yarden & Pines, 2012; Yarden & Sliwkowski, 2001).

The role of ErbB3 and heregulin in the development and progression of multiple cancers has been well-established. ErbB2/ErbB3 heterodimers and heregulin have been identified as being instrumental for breast cancer cell growth (Holbro et al., 2003; Hutcheson et al., 2007; Perez-Nadales & Lloyd, 2004; Yarden & Sliwkowski, 2001). Elevated levels of tyrosine-phosphorylated ErbB3 are frequently found in breast tumors that overexpress ErbB2 (Lemoine et al., 1992; Naidu et al., 1998). In addition, ErbB3 expression has recently been shown to be predictive of poor prognosis in ovarian cancer (Tanner et al., 2006) and, nuclear expression of ErbB3 has been shown to correlate with the risk of disease progression and hormone-refractory status in prostate cancer (Koumakpayi et al., 2006).

There exist potential clinical implications of the HRG-activated ErbB2/3 and EGFR/ErbB3 heterodimers, as these are believed to be integrally involved in the resistance of several tumor types to targeted therapies or chemotherapy. Such heterodimers act as potent activators of cancer cell survival signaling through AKT and MAPK and have been associated with cancer cell insensitivity to both cytotoxic and targeted agents (Chakrabarty, Sánchez, Kuba, Rinehart, & Arteaga, 2012; Engelman et al., 2007; Sheng et al., 2010). Indeed, pioneering studies have demonstrated that high expression of kinase-dead ErbB3 can predict early escape from the anti-ErbB2 monoclonal antibody trastuzumab. In addition, the growth-inhibitory effects of ErbB1/2 tyrosine kinase inhibitors (TKIs) were previously found to be attenuated in the presence of HRG. (Hutcheson et al., 2007). Interestingly, ErbB3 has recently been shown to play an important role in TKI resistance in both breast and lung cancer cells (Engelman et al., 2007; Sergina et al., 2007). The experimental abrogation of ErbB3 resistance by small interfering RNA knockdown of ErbB3 restores potent pro-apoptotic activity to otherwise cytostatic ErbB TKIs, suggesting that anti-ErbB3 therapeutics may be useful in combination with other antitumor agents.

Furthermore, ErbB3 was also shown to promote resistance to chemotherapy in various cancer models. The chemotherapeutic drug doxorubicin upregulates HRG to activate the ErbB3/PI3K/AKT signaling axis in ovarian cancer cells and targeting of ErbB3 may significantly sensitize ovarian tumors to the killing effects of platinum-based or other chemotherapy regimens (Bezler, Hengstler, & Ullrich, 2012). Knuefermann et al. showed that co-expression of ErbB2 and ErbB3 in human breast cancer cell lines induced activation of PI3K/AKT signaling and was associated with an increased resistance to multiple chemotherapeutic agents, such as paclitaxel, doxorubicin, 5-fluorouracil, etoposide, and camptothecin (Knuefermann et al., 2003). These findings are in agreement with our clinical data obtained with MM-121. Yu et al. showed that the pemetrexed resistant A549 lung cell line expresses increased levels of ErbB3 and EGFR. Within this particular cell line, the knock-down of EGFR or ErbB3 by RNAi resensitized the cells to therapy (Yu et al., 2014).

Overall these data suggest a broad implication of HRG driven ErbB3 signaling in mediating resistance to chemotherapies making it an attractive target for therapeutic intervention when used in combination with cytotoxic therapies.

1.3 MM-121

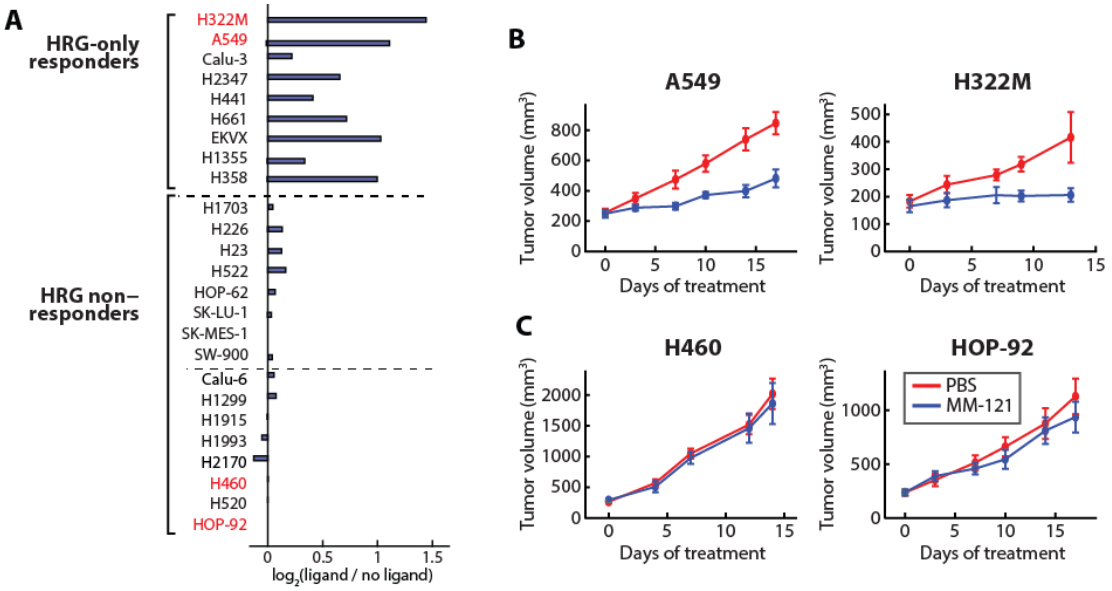
MM-121 is a fully human, monoclonal IgG2 antibody that binds to the HRG domain of the ErbB3 receptor with single digit nanomolar affinity and is being developed as an anti-cancer therapeutic. By preventing HRG from binding to the ErbB3 receptor, MM-121 effectively blocks

heterodimer formation of the ErbB3 receptor with e.g. ErbB2 and EGFR and as such potently blocks downstream signaling activation and cancer cell survival. Merrimack Pharmaceuticals originally identified the ErbB3 receptor as a novel therapeutic target using a systems biology approach which allows for a holistic understanding of the dynamics of a specific signaling pathway by applying mechanistic computational models and quantitative biology (Rajkumar, Stamp, Hughes, & Gullick, 1996; Schoeberl, Eichler-Jonsson, Gilles, & Müller, 2002; Sheng et al., 2010). In addition, the insights gained by computer simulations were also used to generate a preclinical biomarker hypothesis that was tested clinically in previous randomized Phase 2 studies and led to the identification of HRG as the principal biomarker for MM-121 efficacy.

1.3.1 Pre-Clinical Experience of MM-121 and NSCLC

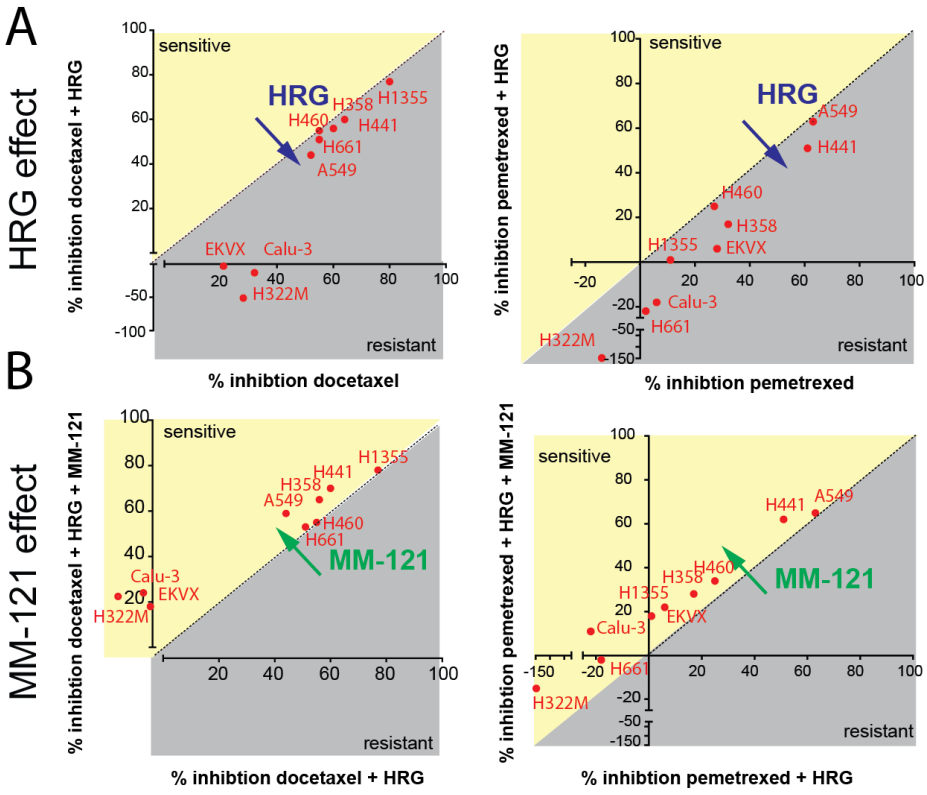
Pre-clinical data demonstrated single agent response to MM-121 in lung cancer cell lines (*in vivo*) in those cell lines that are receptive to heregulin (HRG) stimulation *in vitro*. *In vitro* studies carried out at Merrimack indicate that 9 out of 25 EGFR wild-type NSCLC cell lines are responsive to HRG: they exhibit increased cell proliferation in response to exogenously added HRG, as measured by CTG using 3D spheroid cultures (Figure 1A). Two HRG-responsive cell lines and two non-responsive cell lines were selected to assess single agent activity of MM-121 in subcutaneous mouse xenografts. The mice were dosed with 300 µg MM-121 every three days (Q3D). As shown in Figure 1B, the HRG-responsive cell lines also responded to MM-121 as a single agent *in vivo*. In contrast, H460 and Hop92, which were not responsive to HRG *in vitro*, did not respond to MM-121 *in vivo* (Figure 1C). High tissue HRG mRNA levels were measured in the MM-121-responsive xenograft tumors (data not shown). Interestingly, both human HRG mRNA, indicative of autocrine HRG signaling, and mouse HRG mRNA, indicative of stroma-derived paracrine signaling, were observed in the HRG-responsive tumors. These data indicate that a subset of EGFR wild-type NSCLC cell lines are responsive to HRG, that these cell lines elicit the production of HRG, and that the presence of HRG in tissue appears to be necessary for MM-121 response *in vivo* further supporting exclusion of patients whose tumors do not express HRG.

Figure 1: Capacity of HRG to induce proliferation in a panel of NSCLC cell lines in vitro is indicative of single-agent response to MM-121 in vivo.



As depicted in Figure 2, HRG induces resistance to pemetrexed and docetaxel in a panel of 9 lung cancer cell lines. HRG-driven ErbB3 signaling mediates survival signaling through the PI3K/AKT pathway and has been implicated as a general mechanism that imparts insensitivity to cytotoxic chemotherapy. As shown in Figure 2A, HRG induces resistance to pemetrexed and docetaxel in a subset of EGFR wild-type NSCLC cell lines. Proliferation was measured in the presence or absence of HRG in a panel of nine cell lines using 3D spheroid cultures. Full dose response curves were obtained but results are only shown for a single relevant dose of chemotherapy. In three of these cell lines – those most responsive to HRG – inhibition of cell viability by both docetaxel and pemetrexed was decreased upon the addition of HRG. In fact, HRG induced proliferation even in the presence of chemotherapy, as noted by the negative values for % inhibition. Importantly, when MM-121 was added in addition to HRG, sensitivity to both docetaxel and pemetrexed was restored in these cell lines (Figure 2B).

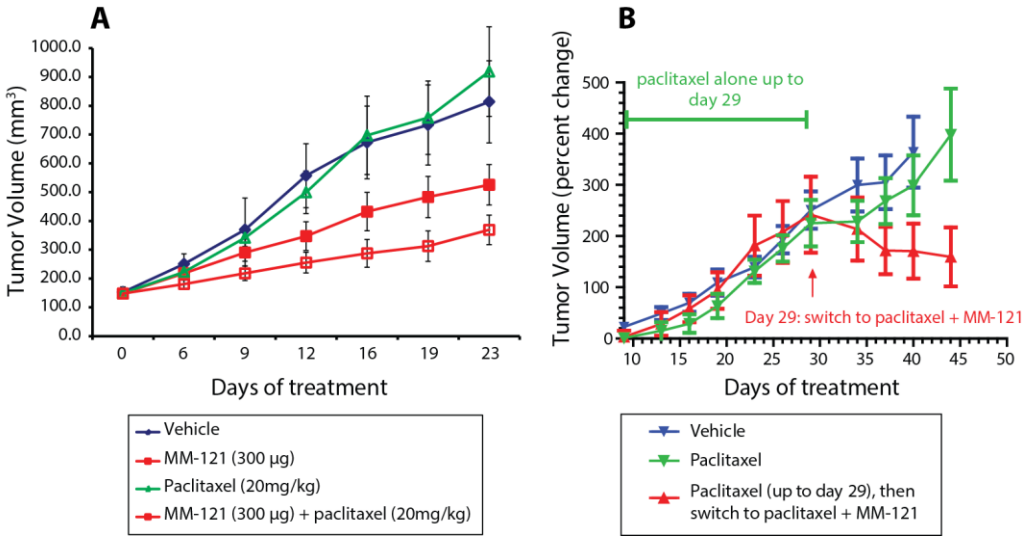
Figure 2: (A) 5nM HRG induces resistance to docetaxel (111nM) and pemetrexed (1111nM) in a 3D spheroid proliferation assay after 96hrs.
(B) MM-121 (1µM) restores sensitivity in NSCLC cell lines (A549, EKVX, H358, H322M, Calu-3, H661, H441, H1355, H430).



Based on Merrimack's preclinical research and previous clinical experience, HRG-induced ErbB3 signaling appears to be a general resistance mechanism for several standard-of-care therapies used to treat NSCLC and MM-121 may provide a way to sensitize tumor cells when this pathway is active. An *in vivo* example is shown in Figure 3A and Figure 3B. The combination of MM-121 and paclitaxel controls tumor growth significantly better than either agent alone (Figure 3A). Figure 3B describes the effect of drug scheduling. A549 tumors were grown in mice and only exposed to paclitaxel for the first 29 days. Single agent paclitaxel did

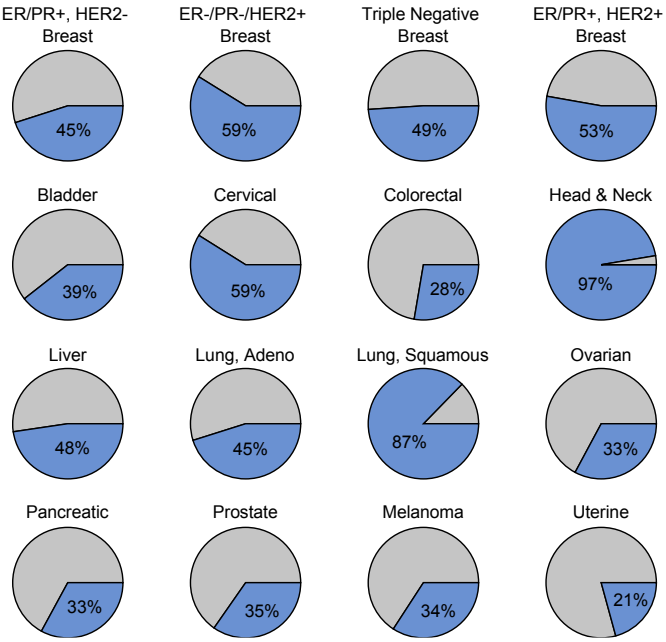
not inhibit tumor growth, only when paclitaxel was combined with MM-121 tumor shrinkage was observed (Figure 3B).

Figure 3: (A) A549 NSCLC xenograft model treated with 300µg q3d MM-121, 20 mg/kg paclitaxel and the combination of MM-121 + paclitaxel q3d
(B) A549 NSCLC xenograft model treated with 20 mg/kg up to day 29 with Paclitaxel followed by paclitaxel + MM-121



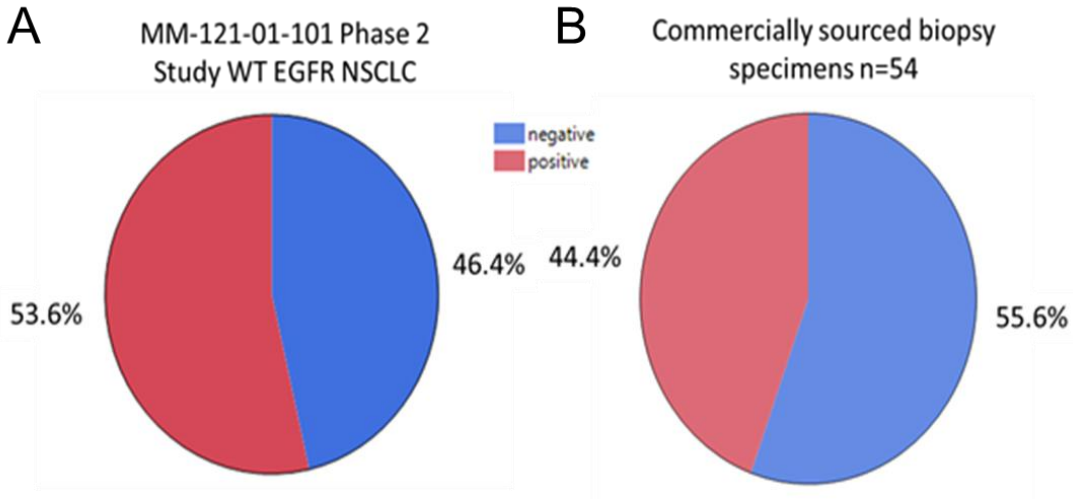
Previous randomized phase 2 clinical trials of MM-121 in breast and ovarian cancer provided a threshold level of HRG expression measured by quantitative RT-PCR above which increased PFS was observed upon the addition of MM-121 to standard-of-care therapy. This RT-PCR data threshold was applied to the Cancer Genome Atlas (TCGA) dataset to determine the prevalence of HRG expression above this threshold in a wide variety of solid tumors (Figure 4). Based on this analysis, 87% of the squamous cell carcinoma samples were above the defined threshold. Squamous cell carcinoma is one of the indications with the highest prevalence of HRG expression among all solid tumor types. 45% of the adenocarcinoma samples had HRG mRNA levels above this threshold (Figure 4). Overall, these data suggest that NSCLC is one indication in which HRG-driven ErbB3 signaling is particularly prevalent.

Figure 4: HRG mRNA expression levels across different indications based on the TCGA data set



In addition, HRG expression was assessed using an RNA in situ hybridization (RNA-ISH) assay in pre-treatment core needle biopsies obtained from patients enrolled in the MM-121-01-101 study of MM-121 in EGFR wild-type NSCLC. Overall 54% of the samples scored 1+ or higher (Figure 5A). Furthermore, we expanded our analysis and analyzed an additional 53 archival lesions and biopsies that were procured from Cureline (Figure 5B). Comparable to the findings in the MM-121-01-101 lung study, the prevalence of HRG mRNA by RNA-ISH with a score of ≥1+ was found to be 44%, again supporting development of MM-121 in NSCLC.

Figure 5: HRG mRNA expression across NSCLC tissue samples



1.3.2 Clinical Experience of MM-121 in Humans

MM-121 has been studied in eight previous clinical trials under IND #100605 with a total of 700 patients being exposed to MM-121 alone or in combination with other anti-cancer therapies. The

first trial was a phase 1 open label, dose escalation study using a modified "3 + 3" design. Six cohorts of patients were enrolled (n=25), at doses of 3.2, 6, 10, 15 and 20 mg/kg and a 40 mg/kg loading dose followed by 20 mg/kg weekly maintenance dosing, and an expansion cohort of patients was enrolled at 20 mg/kg with a 40 mg/kg loading dose. At the close of the study, 43 patients were exposed to MM-121. A Maximum Tolerated Dose (MTD) was not identified, and the highest dose tested was 40 mg/kg loading dose followed by 20 mg/kg on a weekly dosing schedule.

Several other MM-121 trials were initiated in varying indications and chemotherapy combinations. Investigators should refer to the MM-121 Investigator's Brochure for more information regarding ongoing and previous trials of MM-121. Previous experiences in NSCLC and safety of MM-121 in combination with chemotherapy are described in more detail below.

1.3.2.1 Previous Experience of MM-121 in NSCLC

MM-121 was tested in combination with erlotinib in a phase 1/2 study in NSCLC. Following a 3+3 dose escalation design in the phase 1 portion of the trial and selection of a phase 2 dose (as presented at the American Society of Clinical Oncology (ASCO)) (Sequist et al., 2012) patients were assigned to three different treatment groups. Group A enrolled 129 NSCLC patients whose tumors are wild-type for EGFR and who have progressed after at least one prior line of standard chemotherapy that did not contain an EGFR TKI. Patients were randomized 2:1 to receive MM-121 every other week at a dose of 20 mg/kg IV in combination with daily 100 mg erlotinib p.o. (N=85) or to receive daily 150 mg erlotinib p.o. alone (N=44). The primary efficacy objective of achieving a 50% reduction in hazard ratio in the MM-121 group vs. the erlotinib group alone was not reached. A total of 95 out of the 129 patients were documented as having a PFS event, resulting in a hazard ratio of 0.816 [95%CI: 0.552-1.207]. Overall, the median PFS of the experimental arm was 1.9 months versus 1.8 months on the control arm.

A preplanned biomarker analysis using fresh tissue biopsies obtained from all patients enrolled into group A of the study showed that patients who had HRG positive tumors had a poor outcome on the erlotinib only arm, and seemed to benefit from the addition of MM-121 to erlotinib. These data are described in detail in Section 1.4.

1.3.3 Potential Toxicities with MM-121

The safety profile of MM-121 has been robustly studied across nine previously conducted clinical trials, conducted as a monotherapy and in combination with various targeted and cytotoxic therapies.

Findings from trials of MM-121 in human subjects are comprised of safety data from 962 patients that have been enrolled into MM-121 studies under the IND #100605, including 700 patients that have been exposed to MM-121 alone (n=43) or in combination with other anti-cancer therapies (n=657). Treatment-emergent adverse events (TEAEs) were reported in 98.9% of patients, regardless of relationship to study treatment. More than half the patient population reported TEAEs in the following systems organ class: gastrointestinal disorders (88.9% treatment, 74.8% control), general disorders and administration site conditions (78.7% treatment, 72.1% control), skin and subcutaneous tissue disorders (75.9% treatment, 64.1% control), metabolism and nutrition disorders (59.3% treatment, 45.0% control), respiratory, thoracic and mediastinal disorders (57.4% treatment, 45.4% control), nervous system disorders (57.1% treatment, 54.2%) control), and infections and infestations (53.4% treatment, 46.9% control),

As of July 2014, the most frequently occurring (>20% of patients) treatment emergent adverse events across all patients exposed to MM-121 as single agent or in combination therapies included: diarrhea (70.3%), fatigue (51.9%), nausea (45.4%), rash (32.9%), decreased appetite (29.7%), alopecia (26.4%), anemia (24.9%), vomiting (24.9%), hypokalemia (22.6%), stomatitis (22.3%), and peripheral neuropathy (20.1%).

A breakdown of safety data by study is presented in the Investigator Brochure, including a separate study of MM-121 in combination with a PI3K-inihibitor, XL147, which was conducted by a different Sponsor. Toxicities observed with combinations relevant to this study are further summarized below.

1.3.3.1 Previous Safety Experience of MM-121 in Combination with Taxanes

MM-121 was administered in combination with paclitaxel in a Phase 1 dose escalation study with no MTD observed and a randomized phase 2 trial in platinum-refractory or resistant advanced/metastatic ovarian cancer. Patients on the treatment arm were given MM-121 weekly at a loading dose of 40 mg/kg IV followed a week later by weekly doses of 20 mg/kg IV. Paclitaxel was administered at 80 mg/m^2 IV weekly for all patients regardless of assignment. Of the 220 patients enrolled on the study, 134 patients (95.7%) on the treatment arm reported at least one TEAE that was considered related to treatment, mostly due to diarrhea (63.6% treatment, 28.8% control), nausea (36.4% treatment, 36.3% control), fatigue (35.7% treatment, 33.8% control), and alopecia (33.6% treatment, 30.0% control).

Grade 3 or higher TEAEs that were considered related to treatment were reported in 51/140 patients (36.4%) on the treatment arm and in 24/80 patients (30.0%) on the control arm. The most frequently reported grade 3 or higher TEAEs that were assessed as related to treatment on the treatment arm included anemia, occurring in 8 patients (5.7%) versus 4 patients (5.0%) on the control arm, and diarrhea, occurring in 8 patients (5.7%) versus 2 patients (2.5%) on the control arm.

MM-121 was also combined with cabazitaxel in an open-label phase 1 cohort of 11 advanced solid tumor patients who had received multiple lines of prior chemotherapy. In this dose escalation study, MM-121 was administered at either 12 mg/kg weekly with a loading dose of 20 mg/kg, or at 20 mg/kg weekly with a loading dose of 40 mg/kg. Cabazitaxel was administered at a dose of either 20 mg/m^2 or 25 mg/m^2 Q3W. Of the 11 patients, 100% reported at least one TEAE of any grade that was considered related to the study combination treatment, primarily diarrhea (11 patients, 100%), fatigue (5 patients, 45.5%), hypophosphatemia (5 patients, 45.5%), and nausea (5 patients, 45.5%). Of the grade 3 TEAEs reported, two instances each of fatigue, febrile neutropenia, hypophosphatemia, neutropenia, and thrombocytopenia were assessed by the investigator(s) to be related to the treatment regimen, as well as one instance of decreased white blood cell count. Additionally, two grade 4 events of neutropenia and thrombocytopenia were assessed as related to study treatment regimen.

No MTD was identified for the combination of MM-121 and cabazitaxel with the highest tested combination dose being 40/20 mg/kg weekly for MM-121 (loading dose followed by maintenance dose) and 25 mg/m^2 for cabazitaxel once every three weeks.

1.3.3.2 Safety Review of MM-121 and Docetaxel Combination

While extensive data supports the safety of the combination of MM-121 with taxanes, there was no data available for the safety of the combination of MM-121 and docetaxel, specifically, at the beginning of the current study, MM-121-01-02-09. As such, a safety data assessment took place

in accordance with the guidelines outlined in Section 5.4. Enrollment into the docetaxel backbone was paused 21Apr2016 after the twelfth patient was randomized to docetaxel or MM-121 plus docetaxel and completed one full cycle of treatment, and the emerging safety data on both arms was reviewed by investigators, medical monitors and representatives from the sponsor.

At the time of the safety review, 8 patients had been randomized to receive MM-121 plus docetaxel (median number of cycles started = 4.5, range = 1-11) and 4 patients randomized to receive docetaxel alone (median number of cycles started = 1.5, range = 1-2). The reviewed data included patient demographics, medical history, extent of drug exposure, dose modifications, and all adverse and serious adverse events recorded. One patient randomized to docetaxel alone withdrew consent after the first dose of docetaxel and so no safety data was available for this patient.

Of the 12 patients reviewed, 7 patients (87.5%) on the treatment arm reported at least one TEAE that was considered possibly, probably, or definitely related to treatment by the Investigator(s) (or relatedness either not reported or reported as unknown) compared to 3 patients (75.0%) on the control arm. The related TEAEs reported for >20% of patients on the treatment arm included: fatigue (75.0% treatment, 25.0% control), weight decrease (50.0% treatment, 0.0% control), diarrhea (37.5% treatment, 25.0% control), neutropenia (37.5% treatment, 50.0% control), nausea (37.5% treatment, 25.0% control), alopecia (37.5% treatment, 25.0% control), dehydration (25.0% treatment, 25.0% control), neutrophil count decrease (25.0% treatment, 0.0% control), stomatitis (25.0% treatment, 0.0% control), anemia (25.0% treatment, 0.0% control), and vomiting (25.0% treatment, 0.0% control).

Grade 3 or higher TEAEs that were considered possibly, probably, or definitely related to treatment by the Investigator(s) (or with relatedness either not reported or reported as unknown) were reported in 6/8 patients (75.0%) on the treatment arm and in 2/4 patients (50.0%) on the control arm. The reported grade 3 or higher TEAEs that were assessed as related to treatment on the treatment arm were neutropenia (37.5% treatment, 50% control), decreased neutrophil count (25.0% treatment, 0% control), leukopenia (12.5% treatment, 25.0% control), anemia (12.5% treatment, 0% control), fatigue (12.5% treatment, 0% control), GI hemorrhage (12.5% treatment, 0% control), and pneumonia (12.5% treatment, 0% control).

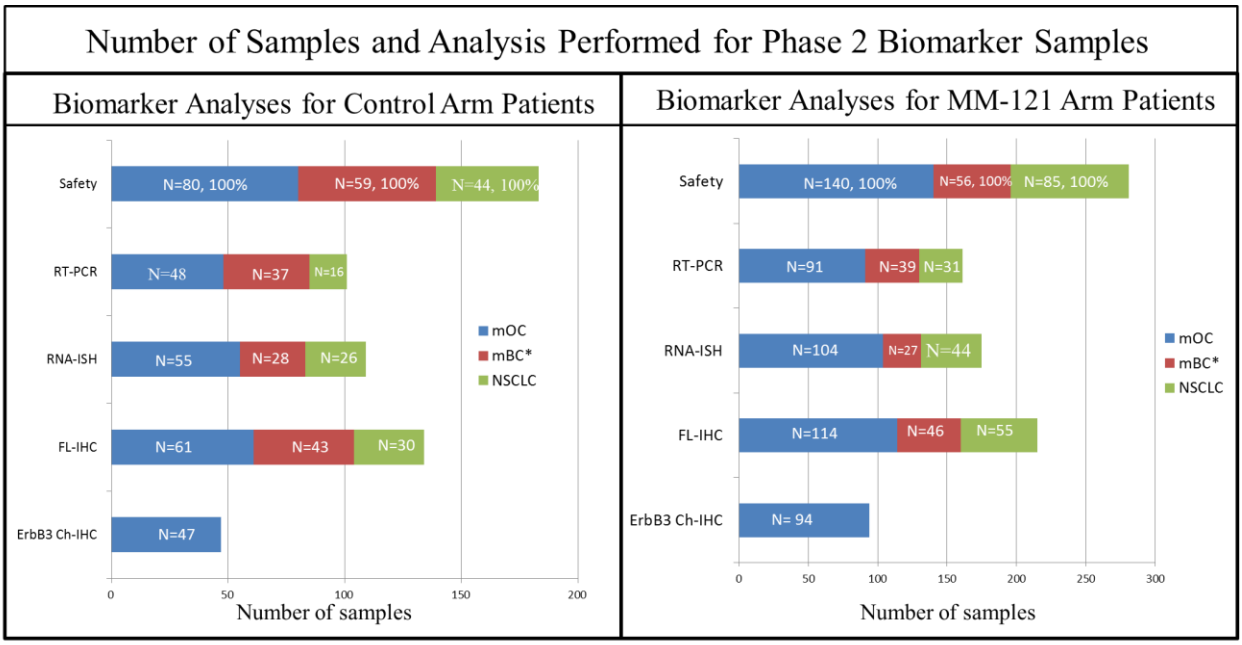
There were no adverse events that led to study drug discontinuation or death in patients exposed to MM-121 plus docetaxel. On 02May2016 the safety review team decided that enrollment to docetaxel alone or MM-121 + docetaxel can continue at the current dose level without modifications as outlined in the study protocol.

1.4 Study Rationale

Across the three randomized studies conducted with MM-121 in metastatic hormone receptor positive, HER2 negative breast cancer (mBC), platinum resistant ovarian cancer (mOC) and NSCLC that has progressed following a platinum based front-line therapy for metastatic or locally advanced disease, a consistent finding emerged: high mRNA levels of HRG appeared to be predictive of poor outcome when patients received only the standard of care treatment (exemestane (mBC), paclitaxel (mOC) or erlotinib (NSCLC)) (Figure 7). However, the data also showed that the addition of MM-121 to exemestane, paclitaxel and erlotinib significantly improved progression-free survival in patients who had HRG positive tumors (Figure 8). These data have been presented at ASCO (Higgins et al., 2014; Liu et al., 2014; Sequist et al., 2014), and Table 1 provides a summary for the findings in the overall study population and the HRG

positive subgroups. A summary of the number of the samples and the types of assays performed on the biomarker samples received are presented in Figure 6.

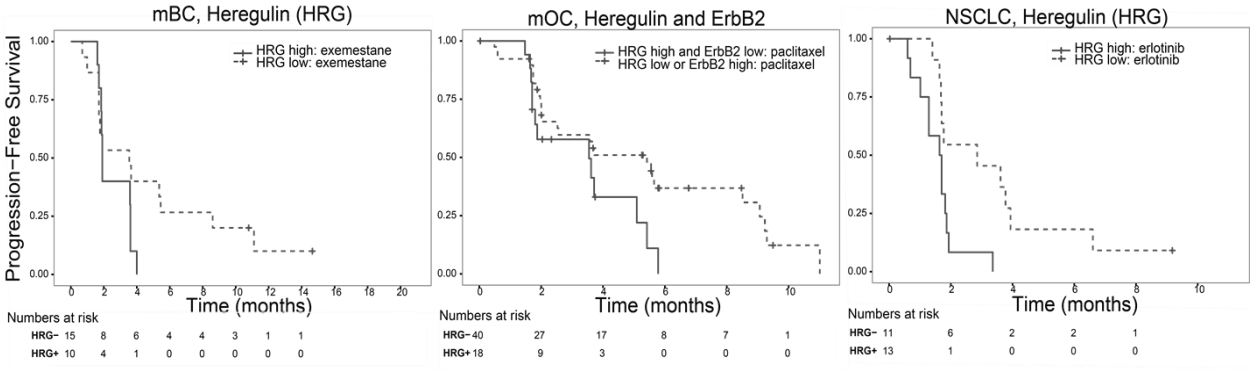
Figure 6: Number of biomarker samples collected and the analysis performed for the three randomized Phase 2 studies of MM-121



* Biomarker data for the mBC population are derived from archived tissue vs. fresh tissue obtained from the mOC and NSCLC patients

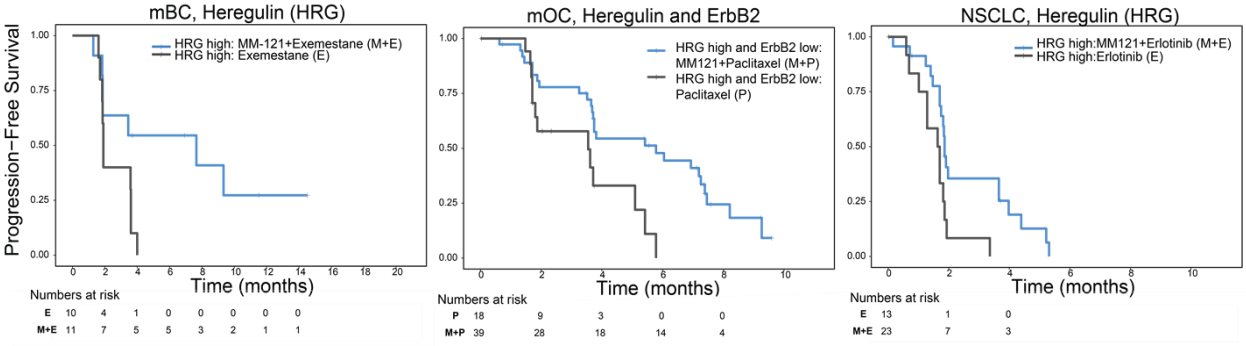
The results from these pre-planned retrospective analyses were consistent with the hypothesis that blockade of HRG-induced ErbB3 signaling by MM-121 can restore sensitivity to standard of care agents impacted by HRG. However, prospective selection of the relevant patient population is needed to validate these findings. A comprehensive review of the results from the completed MM-121 phase 2 studies further suggested that the effect of the MM-121-mediated blockade of HRG signaling is particularly effective in the context of therapeutic backbones that have substantial baseline efficacy. As such, erlotinib was not found to be an optimal combination partner as its activity in 2nd line NSCLC is fairly limited. Given the strong impact HRG signaling has on the efficacy of chemotherapies and the high prevalence of patients who have HRG positive tumors within NSCLC, we hypothesize that the combination of MM-121 with chemotherapy will deliver substantial clinical benefit to patients with NSCLC who have HRG positive tumors.

Figure 7: Positive HRG mRNA levels identify a subgroup of patients with an increased risk of progression on standard-of-care therapies



HRG mRNA was measured from fresh tumor biopsies using RNA in-situ hybridization (ISH) in the mOC and NSCLC studies and HRG positive was defined as staining positive (noted as "high" in the figure) and HRG negative (noted as "low" in the figure) as staining negative. In the mBC study HRG was measured using quantitative RT-PCR from archived tissue and HRG positive was defined as negative delta CT > -5. HER2 expression was measured using quantitative immunohistochemistry in mOC and HER2 low was defined as < 125892 receptors per cell which corresponds to an estimate of HER2 2+ using conventional HercepTest™. The three Kaplan-Maier plots show Risk of Progression estimates for patients with either high or low HRG mRNA levels in NSCLC (erlotinib), mOC (paclitaxel), and mBC (exemestane).

Figure 8: Treatment effect of MM-121 in patients with HRG positive tumors



The addition of MM-121 consistently extended progression-free survival in patients with positive HRG mRNA levels (solid lines all graphs). Patients with mOC were also selected for low HER2 expression. Patients in the mBC and NSCLC study were HER2 low in accordance with inclusion criteria (mBC) or disease biology (NSCLC).

Table 1: Summary statistics for experimental treatment vs. control PFS in HRG positive subgroup

Study group	N	Prev[a]	MM-121 treatment arm vs. control arm in HRG positive subgroup			MM-121 Arm		Comparator Arm	
						Events	PFS time (months)	Events	PFS time (months)
			HR	95%CI	P	n (%)	Median	n (%)	median
mBC (exemestane +/- MM-121)	*21*	*37%*	***0.32***	*0.11-0.97*	***0.044***	*7 (63.6)*	***7.7***	*10 (100)*	***1.9***
mOC (paclitaxel +/- MM-121)[b]	57	38%	**0.37**	0.18-0.79	**0.009**	26 (66.7)	**5.8**	13 (72.2)	**3.5**
NSCLC (erlotinib +/- MM-121)	36	54%	**0.37**	0.17-0.82	**0.014**	20 (87.0)	**1.9**	12 (92.3)	**1.7**

[a] Prev = Prevalence of HRG positive subpopulation calculated from overall study population
[b] In mOC the biomarker predicting benefit was a combination of HER2low and HRG positive

1.4.1 Previous Experience in Heregulin Negative Patients

In contrast to the data from the previous three randomized phase 2 studies indicating that heregulin positive patients perform poorly on control treatments, patients whose tumors are negative for heregulin were consistently shown across the three trials to perform relatively well on control treatments. The data further suggested that in mOC and NSCLC, patients with HRG negative tumors performed better on control than on the experimental arm. The statistics of the three phase 2 studies summarized in Table 2 suggest that further development of MM-121 should focus on patients with HRG positive tumors.

Table 2: Summary statistics for experimental treatment vs. control PFS in HRG negative subgroup

Study Group	MM-121 treatment arm vs. control arm in HRGlow			HRGlow MM-121 Arm		HRGlow Control Arm	
				Events	PFS time (months)	Events	PFS time (months)
	HR	95%CI	P	n (%)	median	n (%)	median
mBC (exemestane +/- MM-121)	1.06	0.51-2.19	0.87	17 (81.0)	2.4	13 (86.7)	3.5
mOC (paclitaxel +/- MM-121)*	1.54	0.98-2.44	0.062	65 (90.3)	3.5	27 (67.5)	5.4
NSCLC (erlotinib +/- MM-121)	2.43	1.07-5.55	0.034	19 (95.0)	1.6	10 (90.0)	2.9

[a] In mOC the biomarker predicting benefit was a combination of HER2low and HRGhigh

1.4.2 Rationale for MM-121 Dose Selection in Combination with Docetaxel

Pharmacokinetic (PK) analyses from previous studies support using a fixed dosing regimen for MM-121. As such, MM-121 will be administered at a fixed dose of 3000 mg on day 1 of each 21-day cycle in sync with the chemotherapy regimens administered in this study.

Pharmacokinetics of MM-121 were evaluated using population pharmacokinetic analysis from 499 patients, comprising 4925 data points from the combined Phase 1 and Phase 2 studies. The pharmacokinetic data of MM-121 was described using a two-compartment model, with estimated parameters provided in Table 3. Covariate selection evaluated potential relationships between baseline covariates (sex, race, age, weight, intended-dose, and study/indication) with volume of distribution and clearance. The results indicated significant relationships between weight, sex,

and clearance, with the final parameter estimates provided in Table 3. In particular, the model assumed a proportional relationship between the log of clearance (CL) and weight, and obtained an estimated proportionality constant of 0.203. In the presence of the relationship between weight and clearance, no significant relationship between volume and weight were observed.

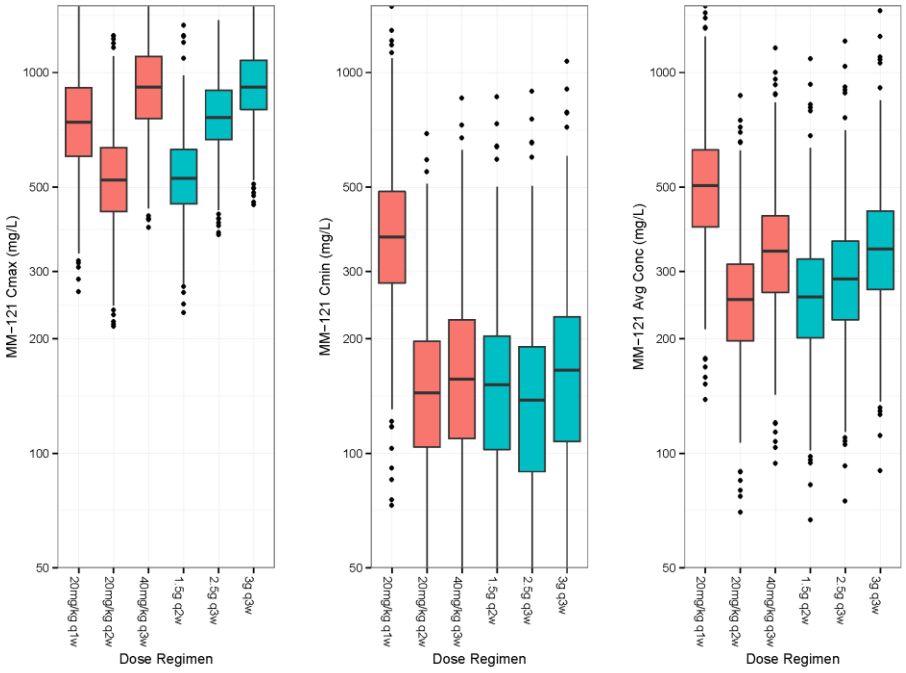
To evaluate the benefit of weight-based dosing, a simulation study was conducted by comparing pharmacokinetics with weight-based and fixed dose regimens. Post-hoc estimates of PK parameters from each of the 499 patients were used in the simulation. The simulated dose for the fixed dosing regimen was chosen by rounding up to the closest 500 mg dose unit. The simulation results showed comparable variability between both fixed-dosing and weight-based dosing regimens, suggesting no benefits of the reduced PK variability with weight-based dosing (Figure 9). For example, a weight-based dosing of 20 mg/kg Q2W and a corresponding fixed dose of 1.5 g Q2W have comparable maximum, minimum, and average steady-state concentration levels and variability. The result can be explained because estimated proportionality between log of CL and weight is 0.203, and therefore, a weight-based regimen (which assumed a proportionally constant of one between log of CL and weight) would tend to overdose higher-weight patients.

To evaluate the optimization of MM-121 dosing regimens for improved compliance and simplicity, a simulation study was conducted by comparing the simulation pharmacokinetics (averaged and minimum concentration) by different dose intervals. The results showed the potential to optimize the dosing frequency to once every 3 weeks. A dose regimen of 3000 mg Q3W is predicted to have: 1) a comparable maximum concentration (C_{max}) to 40 mg/kg Q3W, a dose level previously used as a loading dose for weight-based and weekly MM-121 dosing regimens; 2) a comparable minimum concentration (C_{min}) to 20 mg/kg Q2W which was the dose used in the previous MM-121 study in NSCLC in combination with 100 mg erlotinib; and 3) an average steady-state concentration that is in between 20 mg/kg Q2W and 20 mg/kg Q1W which is the previously studied regular dose for MM-121 following the 40 mg/kg loading dose in combination with chemotherapy. Therefore, this simulation study suggests that a MM-121 dose regimen of 3000 mg Q3W has a potential to improve compliance while maintaining the pharmacokinetic levels within the bounds of the exposures observed from previously studied MM-121 doses (40mg/kg + 20 mg/kg Q1W and 20mg/kg Q2W). In addition, no MTD was identified when MM-121 was combined with standard doses of pemetrexed, paclitaxel or cabazitaxel. In these studies, MM-121 was given together with full doses of the chemotherapy agents at 40 mg/kg as a loading dose followed by weekly doses of 20 mg/kg. The loading dose of 40 mg/kg equals 3000 mg in an average patient weighing 75kg. As such, the cumulative MM-121 dose proposed for this study, 3000 mg MM-121 Q3W as a fixed dose, does not exceed previously tested dose regimens.

Table 3: Final parameter estimates from population PK analysis of MM-121

Parameters	(Estimated) Values
Number of patients	499
Fixed effects	
CL (L/wk)	3.15
V (L)	3.23
Q (L/wk)	2.92
V2 (L)	2.68
Random effects	
Omega CL (%)	36%
Cov CL and V (%)	27%
Omega V (%)	37%
Sigma	
Additive	25.18
Proportional	0.23
Covariate selection	
WT-CL	0.203
SEX-CL	0.255
WT-V	0.002

Figure 9: Simulated MM-121 Pharmacokinetics (Average concentration) by weight-based and fixed dosing regimens and by dose and intervals.



2 Objectives

2.1 Primary Objective

The primary objective of this study is to determine whether the combination of MM-121 plus docetaxel is more effective than docetaxel alone based on investigator assessed Progression-Free

Survival (PFS) according to RECIST 1.1 in HRG positive patients (defined as HRG ISH score of ≥1+).

2.2 Secondary Objectives

The secondary objectives of this study are as follows:

- To determine whether the combination of MM-121 plus docetaxel is more effective than docetaxel alone in HRG positive patients (defined as HRG ISH score of ≥ 1+) for the following clinical outcome parameters:
  - Overall Survival (OS)
  - Objective Response Rate (ORR) based on RECISTv1.1
  - Time to Progression (TTP)
- To describe the safety profile of MM-121 in combination with docetaxel
- To characterize the pharmacokinetic (PK) profile of MM-121 when given in combination with docetaxel and of docetaxel when given in combination with MM-121

2.3 Exploratory Objectives

The exploratory objective of this study is:

- To evaluate if mechanistically linked exploratory biomarkers from tumor tissue or blood samples correlate with clinical outcomes.

3 Study Design

3.1 Overview of Study Design

This study is a randomized, open-label, international, multi-center, phase 2 study in patients with locally advanced or metastatic NSCLC histologically classified as adenocarcinoma that has progressed following one or two lines of systemic therapy for locally advanced and/or metastatic disease, of which one must have been a platinum containing regimen. The purpose of the study is to assess in patients with HRG positive tumors if the addition of MM-121 to docetaxel is more effective than docetaxel alone in prolonging progression-free survival.

Following signing the pre-screening informed consent form, all patients will provide a tissue sample (which meets the requirements for collection and processing as outlined in the study lab manual) to the designated central lab facility for HRG testing. If adequate archived tissue is not available, patients may undergo a procedure (e.g. fine needle aspiration (FNA), core needle biopsy (CNB), thoracentesis, or excisional biopsy) to obtain adequate tissue required to perform HRG testing. For these procedures, investigators are asked to choose an easily accessible tumor lesion to minimize any possible risk associated with the collection of the tissue. As a general guideline, if the selected procedural location has an established serious complication rate of >2% at the institution completing the procedure, this is considered a high risk procedure and should be avoided. Upon receipt of a tissue sample at the central lab, the investigational site will be informed of the results within 7 days. Patients with a positive HRG status, defined as HRG ISH score of ≥1+, will sign the full study consent form and will continue with screening procedures. Patients with tumors that show no staining for HRG (ISH score = 0) will not continue any further procedures for this study and will be considered screen failures. Minimal medical history for HRG negative patients will be collected.

In order to obtain fresh tissue from all patients enrolled, all patients that receive a positive HRG result for eligibility based on testing of archived samples will also be required to undergo a fresh

research biopsy (e.g. FNA, CNB, thoracentesis, or excisional biopsy) prior to first dose. It is important that no systemic therapy is administered between collection of this tissue and dosing on this study. An additional sample will not be requested from patients who underwent a fresh biopsy for eligibility testing.

After all screening procedures and determination of eligibility for treatment randomization (including HRG positive ISH result) have been completed, eligible patients will be randomized in a 2:1 ratio (experimental arm versus comparator arm) using an Interactive Web Response System (IWRS). Randomization will be stratified based on number of prior systemic therapies for locally advanced and/or metastatic disease (1 or 2) and prior anti-PD-1 or anti-PD-L1 will be capped at approximately 30% per group.

Patients will be randomized to Arm A or Arm B:

Arm A (Experimental Arm):

- MM-121: fixed dose of 3000 mg IV on day 1 of each 21-day cycle
- Docetaxel: 75 mg/m2 IV on day 1 of each 21-day cycle

Arm B (Comparator Arm):

- Docetaxel: 75 mg/m2 IV on day 1 of each 21-day cycle

Treatment must start within 7 days following randomization. Patients are expected to be treated until investigator assessed progressive disease or unacceptable toxicity. Tumor assessments will be measured and recorded by the local radiologist every 6 weeks (+/- 1 week) using the RECIST guidelines (version 1.1). All patients that come off treatment for reasons other than progressive disease will have a scan at the time of the End of Treatment visit. After patients come off treatment, survival information and information about subsequent therapies will be collected until death or study closure, whichever occurs first. After a minimum of 61 PFS events in the per protocol population have been reported, the final analysis will be performed.

In prior studies, MM-121 has been administered in combination with taxanes (paclitaxel and cabazitaxel) at the standard doses with no MTD reached. However, no data was available for the combination of MM-121 and docetaxel prior to starting the current study. Therefore, enrollment into this backbone was paused after the twelfth patient was randomized to docetaxel or MM-121 + docetaxel and completed one full cycle of treatment, and the emerging safety data on both arms was reviewed by investigators, medical monitors and representatives from the sponsor in accordance with Section 5.4. The safety review team decided that enrollment to docetaxel alone or MM-121 + docetaxel can continue at the current dose level without modifications as outlined in the study protocol. The DMC will continue to monitor safety data over the course of the study in accordance with the DMC Charter.

4 Study Population

The target population for this study is patients who are candidates to receive single agent docetaxel therapy for locally advanced or metastatic non-small cell lung cancer (NSCLC) that is histologically classified as adenocarcinoma. Such patients have received one or two lines of systemic therapy for locally advanced and/or metastatic disease, and shall have tumors that are positive for heregulin (HRG) mRNA as assessed by central testing. The investigator or his/her designee must ensure that all patients meet the following inclusion and exclusion criteria before being enrolled in the study:

4.1 Inclusion Criteria

To be eligible for participation in the study, patients must meet the following criteria. Patients who are HRG negative do not need to complete screening procedures beyond HRG assessment:

a) Patients with cytologically or histologically documented NSCLC classified as adenocarcinoma that is presenting as either:
   - Stage IV (metastatic disease) or
   - Stage IIIB disease not amenable to surgery with curative intent or
   - Recurrent or progressive disease following multimodal therapy (chemotherapy, radiation therapy, surgical resection or definitive chemoradiation therapy for locally advanced or metastatic disease)

b) Disease progression or evidence of recurrent disease during or after the last systemic therapy as documented by radiographic assessment
c) Received one prior platinum-based regimen for management of primary or recurrent disease
d) Received nivolumab, pembrolizumab or other anti-PD-1 or anti-PD-L1 therapy, where available and clinically indicated
e) Clinically eligible for treatment with docetaxel once every three weeks per the investigator's judgment
f) Must have at least one lesion amenable to collection of tissue
g) A positive in-situ hybridization (ISH) test for heregulin with a score of ≥1+, as determined by centralized testing
h) ECOG performance status (PS) of 0 or 1
i) Screening ECG without clinically significant abnormalities
j) Women of childbearing potential, as well as fertile men and their partners, must be willing to abstain from sexual intercourse or to use an effective form of contraception (an effective form of contraception is an oral contraceptive or a double barrier method or as defined by country-specific guidelines) during the study and for 6 months, in females and males, following the last dose of study drug(s), or greater, as in accordance with the label requirements or institutional guidelines for docetaxel
k) ≥ 18 years of age
l) Able to provide informed consent, or have a legal representative able and willing to do so
m) Patients who have experienced a venous thromboembolic event within 60 days of signing the main consent form should have been treated with anti-coagulants for at least 7 days prior to beginning treatment and for the duration of treatment on this study

4.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from randomization:

a) Known Anaplastic Lymphoma Kinase (ALK) gene rearrangement
b) Presence of exon 19 deletion or exon 21 (L858R) substitution of the EGFR gene
c) Pregnant or lactating
d) Prior radiation therapy to >25% of bone marrow-bearing areas
e) Received >2 prior lines of systemic anti-cancer drug regimens for locally advanced and/or metastatic disease
   - Any type of maintenance therapy, e.g. pemetrexed maintenance following first line treatment with cisplatin and pemetrexed, is not considered a separate line of therapy

f) Prior treatment with an anti-ErbB3 antibody
g) Prior treatment with docetaxel for advanced/ metastatic disease
h) Received other recent antitumor therapy including:
    - Investigational therapy administered within the 28 days or 5 half-lives, whichever is shorter, prior to the first scheduled day of dosing in this study
    - Radiation or other standard systemic therapy within 14 days prior to the first scheduled dose in this study, including, in addition (if necessary), the timeframe for resolution of any actual or anticipated toxicities from such radiation
i) CTCAE grade 3 or higher peripheral neuropathy
j) Presence of an unexplained fever > 38.5°C during screening visits that does not resolve prior to the first day of dosing. If the fever and active infection have resolved prior to randomization, the patient will be eligible. At the discretion of the investigator, patients with tumor fever may be enrolled.
k) Clinically active CNS metastasis
l) Use of strong CYP3A4 inhibitors
m) Any other active malignancy requiring systemic therapy
n) Known hypersensitivity to any of the components of MM-121 or previous CTCAE Grade 3 or higher hypersensitivity reactions to fully human monoclonal antibodies
o) History of severe hypersensitivity reactions to docetaxel
p) Known hypersensitivity to polysorbate (Tween) 80 or arginine
q) Inadequate bone marrow reserve as evidenced by:
    - ANC < 1,500/µl or
    - Platelet count < 100,000/µl or
    - Hemoglobin < 9 g/dL (5.59 mmol/L)
r) Serum/plasma creatinine > 1.5 x ULN for patients receiving docetaxel
s) Inadequate hepatic function as evidenced by:
    - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) > 1.5 x ULN concomitant with Alkaline phosphatase (AP) > 2.5 x ULN
    - Serum/plasma total bilirubin > ULN
t) Clinically significant cardiac disease, including: symptomatic congestive heart failure, unstable angina, acute myocardial infarction within 12 months of planned first dose, or unstable cardiac arrhythmia requiring therapy (including torsades de pointes)
u) Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals; or active human immunodeficiency virus (HIV) infection, active hepatitis B infection or active hepatitis C infection
v) Patients who are not appropriate candidates for participation in this clinical study for any other reason as deemed by the investigator

4.3 Assessing Heregulin Status in NSCLC Specimens

This study will only enroll patients with HRG positive tumors (defined as tumors with a HRG ISH score of ≥1+). Patients presenting with HRG negative tumors (HRG ISH score of 0) will not undergo any additional study procedures and will be considered screen failures. A patient's tumor HRG status will be assessed at a central CLIA certified lab using a qualified in situ hybridization (ISH) assay.

4.3.1 Description of HRG RNA-ISH Assay

RNA-ISH is a test in which oligonucleotide target probes are hybridized to the RNA in formalin-fixed, paraffin-embedded (FFPE) tissue samples. The signal on the target RNA molecule is detected by using a chromogenic substrate reaction. This approach enables mRNA molecules to be visualized and scored by pathologists in a manner similar to a standard immunohistochemistry (IHC) assay.

4.3.2 Implementation of HRG RNA-ISH Testing

The HRG RNA-ISH assay can be used to measure mRNA expression on tissue slides obtained from formalin-fixed paraffin embedded excision samples, core biopsies, fine needle aspirates or thoracenteses; therefore, any of these methods of collection is acceptable for testing. Specimens will be submitted directly by clinical sites to the designated CLIA certified central lab according to the collection, processing and shipment instructions outlined within the study lab manual.

The central lab will process the samples and provide the stained slides to a trained pathologist to assess tumor content and percentage of tumor cells expressing HRG mRNA. The pathologist will assign scores of 0, 1+, or 2+ based on HRG mRNA staining. Samples scored at ≥ 1+ will be considered HRG positive, and samples scored at 0 will be considered HRG negative. This result will be communicated back to the investigative site within 7 days of sample receipt at the central lab.

4.4 Patient Discontinuation

A patient may withdraw from the study at any time and for any reason. It is intended that patients will be treated until investigator-determined progressive disease (radiologic or clinical deterioration) or unacceptable toxicity. Some possible reasons for withdrawal from treatment include, but are not limited to the following:

- Progressive neoplastic disease per RECIST v1.1
- Clinical deterioration
- Adverse event, including treatment being withheld for 21 consecutive days without resolution of toxicities to grade 1 or baseline value
- Protocol violation / non-compliance
- Withdrawal of consent
- Investigator or Sponsor decision
- Patient is lost to follow-up

When a patient is discontinued from treatment for any reason, they are to undergo the assessments in the End of Treatment visit within 4 weeks of the last dose. All patients who discontinue treatment as a result of an adverse event must be followed until resolution or stabilization of the adverse event. At the time a patient withdraws from study treatment, an attempt should be made to determine the reason(s) for discontinuation. The patient will continue to be followed for survival information every 2 months after completion of the End of Treatment visit. All patients that come off treatment for reasons other than progressive disease per RECIST 1.1, should undergo a scan to assess disease status at the End of Treatment visit.

If a patient does not return to the clinic for the end of treatment visit or is not reached for overall survival follow-up, at least 3 documented attempts, including one via certified mail, should be made to contact the patient. If the patient does not respond to these requests, the date of death should be captured from public records.

5 Study Treatment

5.1 Method of Assigning Patients to Treatment Groups

If a patient is determined to be HRG positive, investigators will determine if the patient meets all other eligibility criteria. Once all study enrollment criteria have been fulfilled, patients will be randomized 2:1 to the treatment or comparator arm using an Interactive Web Response System (IWRS). Randomization will be stratified based on the number of prior systemic therapies for locally advanced and/or metastatic disease (1 or 2) and prior anti-PD-1 or anti-PD-L1 will be capped at approximately 30% per group.

5.2 MM-121

5.2.1 MM-121 Formulation, Packaging, and Labeling

MM-121 is supplied for IV administration as a sterile, colorless liquid at 25 mg/mL. It is packaged in sterile, single-use, clear borosilicate Type 1 glass vials that are closed with a coated rubber stopper and flip-off cap with flange.

Multiple vials of MM-121 will be packaged in a cardboard container. The individual vials, as well as the outside of the cardboard container, will be labeled in accordance with regulatory requirements and in compliance with country-specific guidelines. Additional details are provided in the study pharmacy binder.

5.2.2 MM-121 Product Storage and Stability

MM-121 Drug Product must be stored refrigerated (2-8°C) with protection from light. Light protection is not required during preparation or infusion. MM-121 must not be frozen.

Based on available stability data, the concentrate for solution for injection is stable for at least 36 months when stored according to conditions specified in the clinical supply label. Continued stability data are being generated, and longer stability may be available during the course of the study. The date of expiration will be noted on the drug label, or via other pharmacy notifications as required by local regulation. MM-121 should not be used beyond the date of expiration.

5.2.3 MM-121 Dosage, Preparation, and Administration

MM-121 should be administered as an IV infusion once every 3 weeks at a fixed dose of 3000 mg.

Administration of MM-121 will require multiple vials, all of which should come from the same lot number. MM-121 should be brought to room temperature prior to mixing with saline. Vials of MM-121 should not be shaken. The appropriate quantity of study drug will be removed from the vial, diluted with 0.9% normal saline to a final volume of 250 ml and administered over 60 minutes (±15 minutes) for all infusions in the absence of infusion reactions, using a low protein binding 0.20 or 0.22 micrometer in-line filter. The line should be flushed before and after the study drug infusion. Study drug should not be administered as a bolus or a push.

MM-121 should be administered immediately following the administration of docetaxel.

5.2.4 Management of Infusion Reactions to MM-121

Like other IV infusions, MM-121 administration may be associated with infusion related reactions (IRRs). Infusion related reactions will be defined according to the National Cancer Institute CTCAE (Version 4.03) definition of an allergic reaction/infusion reaction and anaphylaxis. In past clinical studies, IRRs with MM-121 have been rare with < 1% of patients

reporting an IRR, of which all were Grade 1 or 2. Study site policies or the following treatment guidelines shall be used for the management of infusion reactions.

Grade 1

- Slow infusion rate by 50%
- Monitor patient every 15 minutes for worsening of condition

Grade 2

- Stop infusion
- Administer diphenhydramine hydrochloride 50 mg IV, acetaminophen 500-650 mg orally or IV, and oxygen
- Resume infusion at 50% of the prior rate once infusion reaction has resolved
- Monitor patient every 15 minutes for worsening of condition
- For all subsequent infusions, pre-medicate with dexamethasone 10 mg orally or IV

Grade 3

- Stop infusion and disconnect infusion tubing from patient
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, bronchodilators for bronchospasm, and other medications or oxygen as medically necessary
- No further treatment with MM-121 will be permitted

Grade 4

- Stop the infusion and disconnect infusion tubing from patient
- Administer epinephrine, bronchodilators or oxygen as indicated for bronchospasm
- Administer diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV
- Consider hospital admission for observation
- No further treatment with MM-121 will be permitted

For patients who experience a Grade 1 or Grade 2 infusion reaction, at the discretion of the investigator, future infusions may be administered at a reduced rate (over 90 minutes).

For patients who experience a second Grade 1 or 2 infusion reaction, administer dexamethasone 10 mg IV. All subsequent infusions should be pre-medicated with diphenhydramine hydrochloride 50 mg IV, dexamethasone 10 mg IV, and acetaminophen 500-650 mg orally.

For patients who experience a Grade 3 or 4 infusion reaction, an anti-MM-121 antibody titer will be taken as close to the onset of the infusion reaction as possible for any patient experiencing an infusion reaction to MM-121. Anti-MM-121 antibody titer should also be obtained at the resolution of the event and 28 days (+/- 2 days) following the event.

5.2.5 Management of Toxicity Related to MM-121

In the event that a patient experiences a toxicity ≥ Grade 3 that is not an IRR and is possibly, probably or definitively related to MM-121 treatment, and not related to docetaxel it is at the investigator's discretion to hold dosing or to discontinue treatment. Prior to reducing the holding or discontinuing treatment, the investigator must notify the sponsor and Medical Monitor.

In the event that MM-121 treatment has been held for 21 consecutive days, the patient should be discontinued. No dose reductions for MM-121 are permitted.

5.2.5.1 Potential Toxicities with the Combination of MM-121 and Docetaxel

In addition to the established toxicities of docetaxel, it is expected that the addition of MM-121 to docetaxel may lead to an increased frequency of low grade diarrhea, rash, alopecia, stomatitis, hypokalemia and hypomagnesaemia. A slight increase in grade 3 diarrhea and/or hypokalemia may be observed, as well, in the combination setting. In previous studies, these events were generally well controlled with symptomatic treatments per institutional standards.

Pulmonary embolisms, which exist as an identified risk for chemotherapies such as docetaxel (Karavasilis et al., 2014; Kellokumpu-Lehtinen et al., 2012; Matulonis et al., 2008; Reck et al., 2014) have also been described as an adverse event of special interest (AESI) for ErbB-pathway related inhibitors, including MM-121 when administered in combination with paclitaxel. Increased frequencies were observed in combination of MM-121 with paclitaxel in two completed randomized studies in neo-adjuvant breast cancer (4 (3.1%) on the treatment arm vs. 0 (0%) on the control arm) and platinum-resistant ovarian cancer (6 (4.3%) on the treatment arm vs. 1 (1.3%) on the control arm). There was no general increase in venous thromboembolic events reported for these two studies. As such, pulmonary embolisms may be observed at a higher frequency with the combination of MM-121 and docetaxel. No increases in the frequency of pulmonary embolisms were observed in randomized studies with MM-121 in combination with erlotinib in NSCLC and in combination with exemestane in metastatic breast cancer. Patients who have experienced a venous thromboembolic event within 60 days of signing the main consent form for this study should be treated with anti-coagulants for at least 7 days prior to beginning treatment and remain on treatment for their participation on this study.

5.3 Docetaxel

Docetaxel (trade name: Taxotere®) is an antineoplastic agent belonging to the taxoid family that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. It stabilizes microtubules and as a result, interferes with the normal breakdown of microtubules during cell division. It is indicated for patients with breast cancer, non-small cell lung cancer (NSCLC) and prostate cancer.

For managing patients receiving docetaxel, investigators can use institutional guidelines, the docetaxel package insert or the following which has been obtained from the Taxotere® US package insert (Hospira, 2012):

5.3.1 Docetaxel Formulation, Packaging, Labeling, and Storage

Please refer to the docetaxel package insert located in the pharmacy binder for specific information on the docetaxel formulation.

Docetaxel will be supplied by the Sponsor and labeled for investigational use only according to local regulations. Docetaxel will be supplied as a USP infusion solution at 80 mg/8 mL or 80 mg/4 mL in a multi-use vial.

Docetaxel should be stored at room temperature (20 to 25°C). It should be retained in the original package to protect from light. It does not need to be protected from light during infusion.

5.3.2 Docetaxel Dosage, Preparation, and Administration

The approved dose of docetaxel in the second-line treatment of NSCLC is 75 mg/m^2 intravenously over 60 minutes once every 3 weeks. Docetaxel should be administered prior to MM-121 dosing.

Preparation, administration, and storage of docetaxel should be per the docetaxel package insert or SmPC.

5.3.3 Docetaxel Dose Modifications

Docetaxel should not be administered to patients with bilirubin > ULN, or to patients with AST and/or ALT > 1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Values for these indicators of liver function should be obtained prior to each treatment with docetaxel.

Docetaxel should also not be administered to patients with neutrophil counts < 1500 cells/mm^3. Frequent blood cell counts should be performed on all patients receiving docetaxel to monitor the occurrence of neutropenia.

Patients who experience either febrile neutropenia, ANC <500 cells/mm^3 for more than one week, severe or cumulative cutaneous reactions, or other Grade 3-4 non-hematological toxicities should have treatment withheld until resolution of the toxicity and then resume at 55 mg/m^2 or following your institutional guidelines. If treatment is held, at the discretion of the Investigator, and the time required for recovery from toxicity is more than 21 days, a patient's continuation on study should be discussed between the investigator and sponsor regarding risks and benefits of continued treatment. If the patient continues to experience these toxicities after the dose is reduced, no further treatment is allowed. The MM-121 dose should remain at the same dose level. Patients who develop > Grade 3 peripheral neuropathy should have docetaxel treatment discontinued entirely.

All patients randomized on the docetaxel-containing chemotherapy backbone should receive docetaxel at a dose of 75 mg/m^2 on cycle 1, week 1. However, if it is in the best interest of the patient, the dose may be reduced to 55 mg/m^2 for subsequent cycles at the investigator's discretion to improve tolerability.

5.3.4 Pre-treatment Regimen for Docetaxel

Due to the commonly experienced side effects of docetaxel, pre-treatment is suggested for all patients receiving this agent. Per the docetaxel package insert, all patients should be pre-medicated with oral corticosteroids such as dexamethasone (e.g. 8 mg twice daily) for 3 days, starting 1 day prior to docetaxel administration. For patients requiring dexamethasone pre-medication as a result of an MM-121 IRR, the patient should receive a total of 10 mg dexamethasone at the timepoints for pre-medication outlined in Section 5.2.4.

If institutional guidelines on docetaxel pre-medication differ, please follow institutional guidelines.

5.3.5 Potential Toxicities with Docetaxel

In the package insert, the warnings for docetaxel include toxic deaths, hypersensitivity reactions, hematologic effects, hepatic impairment and fluid retention.

The incidence of treatment-related mortality associated with docetaxel administration is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with NSCLC with a history of prior treatment with platinum-based chemotherapy who receive docetaxel as a single agent at a dose of 100 mg/m^2; however it is not planned that doses of 100 mg/m^2 will be assessed in this study.

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Docetaxel should not be administered to patients who have a history of severe hypersensitivity reactions to docetaxel or other drugs formulated with polysorbate 80.

Neutropenia (<2000 neutrophils/mm^3) occurs in virtually all patients given 60 – 100 mg/m^2 of docetaxel and grade 4 neutropenia (<500 cells/mm^3) occurs in 85% of patients given 100 mg/m^2 and 75% of patients given 60 mg/m^2.

Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity and toxic death. Patients with isolated elevations of transaminase >1.5 x ULN also had a higher rate of grade 4 febrile neutropenia but did not have an increased incidence of toxic death.

The most common adverse reactions across all docetaxel indications as outlined in the package insert include: infections, neutropenia, anemia, febrile neutropenia, nail disorders, fluid retention, asthenia, pain, nausea, diarrhea, vomiting, mucositis, alopecia, skin reactions, and myalgia.

In a clinical study of 92 patients, severe fluid retention occurred in 6.5% of patients that were pre-medicated and was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention due to ascites.

In a clinical trial of 176 NSCLC patients receiving docetaxel as a monotherapy in a second-line treatment, neutropenia was experienced by 84% patients, and 65% of those were grade 3 or 4 events. Other commonly experienced adverse events include anemia (91%), leukopenia (84%), alopecia (56%), fatigue (53%), pulmonary disorders (41%), infection (34%), nausea (34%), stomatitis (26%), diarrhea (23%), and vomiting (22%).

In studies of docetaxel in combination with an EGFR inhibitor, similar toxicities to docetaxel alone were observed. In a phase 1 dose-escalation trial of docetaxel combined with afatinib, 31 patients were enrolled to receive the combination at varying dose levels. Nine patients (29%) experienced a dose-limiting toxicity (DLT) of diarrhea (n=3) or febrile neutropenia (n=6). All patients experienced at least one adverse event, and the most frequently reported events were diarrhea (74%), neutropenia (65%), and rash (39%). Grade 3 and 4 adverse events were most hematological (Marshall et al., 2013).

Like other IV infusions, docetaxel administration may be associated with infusion reactions which should be treated per the US package insert, SmPC or per institutional guidelines.

5.4 Guidelines for Safety Review of MM-121 and Docetaxel Combination

After the twelfth patient was randomized to receive either MM-121 + docetaxel or docetaxel alone and completed a full cycle of therapy (i.e. 21 days after the patient's first dose of study drug administration), randomization to the docetaxel containing study arms was paused to permit a review of safety information related to the combination of MM-121 + docetaxel. Any patients currently in screening for the arm continued with screening and randomization; however, no new patients were presented the study for consideration until the data review had occurred.

The Sponsor compiled available safety data and convened a panel of investigators, study medical monitors and sponsor representatives to review the data. Data that were reviewed and considered included emerging safety and other relevant data from all patients receiving docetaxel on the study (experimental and comparator arm). Investigator and sponsor assessment of the overall

safety of the MM-121 + docetaxel combination carefully took into account the commonly experienced toxicities associated with docetaxel, as outlined in Section 5.3.5., and the currently available information on docetaxel. Attention was paid to the following adverse events before making a decision on the tolerability of the combination:

- Any MM-121 related (denoted as 'probably' or 'definitely' by the investigator) grade 3-4 non-hematologic toxicity which is determined to be not related to docetaxel by the investigator.
- Grade 3 or higher fatigue/asthenia lasting > 2 weeks in duration
- Grade 3 or higher vomiting or diarrhea lasting >72 hours despite confirmed treatment with an optimal anti-emetic or anti-diarrheal regimen
- Grade 3 hyperglycemia, hypomagnesaemia and hypokalemia lasting ≥7 days despite confirmed maximal medical management

After the safety review was completed, the safety review panel concluded that no critical safety findings were observed and that enrollment to the study may continue as planned without dose modifications. Documentation of this meeting is maintained in the study files and is available upon request. A summary of the safety of MM-121 plus docetaxel is in Section 1.3.3.2.

5.5 Rules for Dose Omissions and Modified Treatment Schedules

It is intended that MM-121 and docetaxel dosing occur on the same day. For cycles 1 through 6, if the dose of one or both study drugs is being held or delayed for up to 21 days, administration of both drugs should be held until the patient can be given both drugs. In this case, the date of dosing will be considered the start of the new cycle and the next cycle should begin 21 days after the dose was administered. In the event that dosing has been held for 21 consecutive days and the investigator does not wish to continue dosing at the current dose or at a reduced dose, the patient should be discontinued.

For cycles 7 and beyond, docetaxel treatment can be withheld at the discretion of the investigator if deemed necessary for the patient to recover from cumulative chemotherapy toxicities, in line with institutional guidelines. During any break from docetaxel dosing, MM-121 dosing should continue every three weeks and all procedures outlined in the schedule of assessments should be completed. As soon as the patient condition allows, dosing of docetaxel should be re-started on the next planned date of MM-121 treatment.

5.6 Concomitant and Prohibited Therapies

All intercurrent medical conditions and complications of the underlying malignancy will be treated at the discretion of the investigator according to acceptable local standards of medical care. Patients should receive analgesics, antiemetics, antibiotics, anti-pyretics, GCSF, peg-GCSF, and blood products as necessary. All concomitant medications, including transfusions of blood products, will be recorded on the appropriate page of the case report form. Concomitant therapy (non-investigational products) includes any prescription medication, over-the-counter preparation, herbal therapy, or radiotherapy used by a patient between the 28 days preceding randomization and the study treatment discontinuation visit. After the End of Treatment Visit, only anti-cancer therapies will be collected.

The following therapies are not permitted while on study treatment:

- Other anti-neoplastic therapy, including cytotoxics, targeted agents, endocrine therapy or other antibodies (patients who have been on GnRH analogues for more than 90 days prior to study entry may continue on these while on study)
- Radiotherapy (patients who require a short course of palliative radiotherapy may continue on the study treatment after discussion between the investigator and sponsor)
- Any other investigational therapy
- The use of strong CYP3A4 inhibitors is prohibited. If it becomes necessary to use any of these medications, it may permitted on a case by case basis requiring approval by the Sponsor prior to initiation of treatment

5.7 Accountability of Study Drug

The investigator and investigational site staff are responsible for maintaining an accurate inventory and accounting of study drug. A record of all vials of study drug received and administered will be maintained on an investigational drug inventory form provided by the Sponsor or an equivalent drug inventory form. The following information will be recorded:

- Date and quantity of study drug received
- Date and quantity of study drug dispensed from the pharmacy per patient
- Date and quantity of study drug administered to each patient
- Date and quantity of study drug destroyed (if prepared and dispensed, but not administered for any reason, the study drug may not be returned to inventory)
- Date and quantity of study drug returned to sponsor, if applicable

Each shipment of study drug will contain an invoice describing the amount of drug shipped to the investigational site. The information on the invoice will be verified against the actual amount of drug received, after which the investigator or the investigator's designee will place the invoice in the investigator's file.

The sponsor's monitor will reconcile the information on the investigational drug inventory form with the actual amount of study drug remaining at each site on a routine basis. At the conclusion of the study, the monitor will either package and ship all unused vials of study drug back to Sponsor for destruction or document the destruction, in accordance with local regulations and institutional policy. Following use, empty vials of study drug may be destroyed according to local regulatory and environmental requirements. A record of any such destruction will be placed in the investigator's file.

6 Schedule of Assessments

6.1 Schedule of Assessments: Treatment Group

Procedure	Screening Visit	Cycle 1[7]			Cycle 2[7]			Additional Cycles[7]			Every 6w after 1st dose[10]	End of Treatment (EoT)[16]	Every 2 mo. after EoT
		Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3			
Informed consent[0]	X												
HRG Testing	X[11]												
Medical history	X[1]												
Demographics	X[1]												
Vital signs	X[2]	X	X		X			X				X	
ECOG PS	X[2]	X	X		X			X				X	
CBC	X[2]	X	X		X			X				X	
Serum chemistry	X[2]	X	X		X			X				X	
Tumor Biopsy[13]	X												
Coagulation profile	X[2]	X	X		X			X				X	
Pregnancy test	X[2]											X	
ECG	X[1,3]	X[20]			X[20]			X[20]				X	
Archived tumor, if available	X[1]												
Serum for MM-121 PK		X[5]	X		X [6]			X [6]					
Serum for Ig[8,14]		X			X			X				X	
Serum for biomarkers[15]		X			X			X				X	
Plasma for docetaxel PK					X[17]								
Concomitant meds	X[1]	X	X		X			X				X	
MM-121 dosing		X			X			X					
Docetaxel dosing		X			X			X					
SAE/AE assessment and reporting[18]	X- *continuous monitoring*												
Hospitalization reporting[19]		X			X			X				X	
Disease evaluation[9]	X[1]										X	X[4]	
Overall Survival Reporting[12]													X

0. There are two informed consent forms on this study. Patients should sign the Pre-Screening Consent Form prior to submitting any type of tissue for HRG testing, including fresh tissue. Following receipt of HRG results and prior to any other study procedures, HRG+ patients should sign the full study consent form before continuing with screening.
1. Procedures to be completed within 28 days of first dose of study drug

2. Procedures to be completed within 7 days of first dose of study drug
3. Two independent readings at least 5 minutes apart
4. All patients that come of treatment for reasons other than progressive disease will have a scan at the time of the End of Treatment visit
5. MM-121 PK (**for experimental arm patients only**): pre-dose and immediately after the end of the MM-121 infusion (+15 mins);
6. MM-121 PK (**for experimental arm patients only**): pre-dose
7. All procedures should occur ±3 calendar days from scheduled date of visit
8. Immunogenicity samples should be collected for **experimental arm patients only** prior to dosing**.**
9. Disease evaluation per RECIST version 1.1.
10. Evaluations may be performed ± 1 week from the scheduled date of visit
11. HRG testing will be performed during screening (pre-treatment) to confirm heregulin levels for enrollment.
12. Should patients refuse or drop out of survival follow-up, attempts should be made to obtain any death information available via public records.
13. Research tumor biopsies will be performed for all HRG+ patients that did not undergo a fresh biopsy for eligibility testing. The research biopsy must be performed prior to first dose and no systemic therapy should be received between collection of this tissue and dosing on this study.
14. In the event a patient experiences an infusion reaction at any point in the study, an anti-MM-121 antibody assay will be taken within 24 hours of the event, in addition to the scheduled time-points. For patients who experience a Grade 3 or 4 infusion reaction to MM-121, an anti-MM-121 antibody titer will be taken as close to the onset of the infusion reaction as possible, at the resolution of the event and 28 days (+/- 2 days) following the event.
15. Serum for biomarkers should be collected prior to docetaxel dosing on week 1 of each cycle for all patients.
16. End of treatment visit should be completed within 4 weeks of the last dose of study drug.
17. Plasma for evaluation of docetaxel PK will be collected for 15 patients randomized to each of the following treatments: MM-121 + docetaxel or docetaxel alone. For Cycle 2 Week1 only, plasma should be collected at the following timepoints relative to the start of the docetaxel infusion: pre-infusion, post-infusion, 3 hours post start of infusion and 7 hours post-start of infusion. The window for each collection timepoint is (+ 15mins)
18. All adverse and serious adverse events should be collected and reported from the time of informed consent through the first survival follow-up. Adverse and serious adverse event collection and reporting for patients in both the Experimental and Control Arms should proceed as outlined in Section 9.1.3.
19. All patient hospitalizations and/or hospital visits should be collected, whether or not associated with an adverse event.
20. One reading prior to the start of the docetaxel infusion.

6.2 Screening and Baseline Visit

All procedures for screening and baseline are outlined in Section 6.1. The window for screening procedures begins after receipt of heregulin results. For further descriptions of the clinical and laboratory assessments required, please refer to Section 7 and Section 8 respectively.

6.2.1 RNA-ISH Heregulin Testing

All patients must submit a tissue sample to the central lab for RNA-ISH testing of heregulin levels following signing the pre-screening informed consent form, as this will determine patient eligibility for treatment randomization and subsequent screening procedures. Tissue samples may be submitted from either: 1) archived tissue from previously completed standard of care tissue acquisition or 2) fresh tissue from a core needle biopsy (CNB), fine needle aspiration (FNA), thoracentesis or excisional biopsy. If collection of fresh tissue is required in order to provide adequate tissue for testing, attempts should be made to acquire tissue from a tumor in a non-significant risk location, as determined by the investigator. As a general guideline, if the selected procedural location has an established serious complication rate of >2% at the institution completing the procedure, this is considered a high risk procedure and should be avoided. Samples obtained from a primary tumor, metastatic site or pleural effusion are acceptable. Upon receipt at the central lab, samples will be processed and analyzed at a central facility where they are scored by an independent pathologist as specified in the lab manual with a turnaround time of no longer than 7 days from date of receipt by the central lab. Pre-screening can take place at any time, including while the patient is receiving other systemic therapy. Any patient who scores positive (a score of ≥1+) for HRG mRNA will be eligible for the study and should sign the full study consent form before continuing with screening procedures.

6.2.2 Heregulin Negative Patients

Any patient whose tissue is negative (score of 0) for heregulin as determined by the RNA-ISH test will be considered a screen failure. Minimal medical history for HRG negative patients will be collected as required on the sample requisition form in the Laboratory Manual.

6.3 On-Study Visits

Patients who are confirmed to meet all inclusion and exclusion criteria will be randomized via an IWRS. Randomization must occur within 7 days of first dose (cycle 1 day 1).

All on-study procedures and assessments are outlined in Section 6.1. During the treatment period, a window of ±3 days will apply to all visits, unless otherwise stated.

6.4 End of Treatment Visit

When it is decided that a patient will stop receiving treatment on this study, an End of Treatment visit must be completed within 4 weeks of last dose of study drug. All End of Treatment procedures and assessments are outlined in Section 6.1.

6.5 Survival Follow-up

Survival data will be collected via telephone or clinic visits every 2 months (±10 days) from the date of last treatment until death, loss to follow-up, withdrawal of consent, or study termination by the Sponsor. During the first survival follow-up, any adverse events should be collected. In addition, any new anti-cancer therapies and procedures should be collected and documented during every survival follow-up. All survival information will be captured using the electronic

data capture (EDC) system. Should patients refuse or drop out of survival follow-up, attempts should be made to obtain any death information via public records whenever possible.

7 Clinical Procedures and Assessments

All following clinical procedures should be performed in accordance with the schedule of assessments outline in Section 6.1.

7.1 Medical History and Demographics

Demographic information including age, date of birth, race, ethnicity and gender will be collected.

A medical history will be collected including all pertinent prior medical conditions, surgeries or other medical procedures, allergies, and concomitant medications.

7.2 Adverse Event and Hospitalization Assessment Reporting

Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings. Adverse events should be reported throughout the course of the study, until the first survival follow-up (2 months from the date of last treatment), and followed through to resolution as detailed in Section 9.

In addition, information on patient hospitalizations and/or unscheduled hospital visits should also be collected in the eCRF, whether or not associated with an adverse event.

7.3 Vital Signs

Vital signs should include height (screening only), weight, resting blood pressure, pulse, respiratory rate, and temperature.

7.4 Performance Status Assessment

The Eastern Cooperative Oncology Group (ECOG) performance status (PS) will be obtained by the PI or his/her designee by questioning the patient about their functional capabilities.

7.5 Electrocardiogram (ECG)

A 12-lead electrocardiogram (ECG) will include a description of the cardiac rate, rhythm, interval durations, and an overall impression. QTc should be calculated using the Frederica method (QTcF).

7.6 Disease Evaluation

Tumor response will be evaluated by the local radiologist according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Eisenhauer et al., 2009) to establish disease progression by CT or MRI. In addition, other radiographic or scintigraphic procedures (such as radionuclide bone scans), as deemed appropriate by the investigator, will be performed to assess sites of neoplastic involvement. The same method of assessment must be used throughout the study. Please refer to image acquisition guidelines for the requirements for image collection and scanner qualification. Investigators should choose target and non-target lesions in accordance with RECIST v1.1 guidelines. Follow-up measurements and overall response should also be in accordance with these guidelines. To be assigned a status of confirmed partial response (PR) or

complete response (CR), changes in tumor measurements must be confirmed by repeated assessments that should be performed ≥30 days after the criteria for response are first met.

Disease should be assessed every 6 weeks (±1 week) from randomization regardless of treatment schedule. In cases where there is a suspicion of disease progression prior to the next scheduled scan, an unscheduled assessment should take place. All patients that come off treatment for reasons other than progressive disease will have a scan at the time of the End of Treatment visit.

8 Laboratory Procedures and Assessments

8.1 Complete Blood Count (CBC)

The CBC will include the following: hemoglobin, hematocrit, platelet count, RBC, WBC with differential (neutrophils, lymphocytes, monocytes, eosinophils, basophils and other cells).

8.2 Coagulation Profile

A coagulation profile will include activated partial thromboplastin time (aPTT), prothrombin time (PT), and an international normalized ratio (INR).

8.3 Serum Chemistry

Serum chemistry will include electrolytes (sodium, potassium, and chloride), BUN, serum creatinine, glucose, bilirubin, AST, ALT, alkaline phosphatase, LDH, uric acid, total protein, albumin, calcium, magnesium and phosphate.

8.4 Urine or Serum Pregnancy Test

A urine or serum pregnancy test will be obtained during Screening and the End of Treatment visit for all females of childbearing potential. Exempt female patients will include those who have undergone a bilateral oophorectomy or hysterectomy, or those who are menopausal (defined as absence of a menstrual cycle for at least 12 consecutive months). The reason for exemption should be recorded in the medical history.

8.5 Pharmacokinetic Testing

8.5.1 MM-121 PK samples

For patients on the experimental arm (Arm A), blood samples will be collected to determine the levels of monoclonal antibodies that comprise MM-121. The serum PK analysis will be performed pre- and post-dose on Cycle 1, Week 1, and pre-dose for all subsequent MM-121 infusions, as well as during the Cycle 1, Week 2 clinic visit, as outlined in Table 4. Approximately 5 mL of blood will be collected. The real time of blood collection must be documented in the respective eCRF. A laboratory manual will be provided with instructions for collecting, processing, and shipping the samples.

For patients on Arm A (experimental arm), PK samples should be collected at the following time-points relative **to the MM-121 infusion**:

Table 4: MM-121 PK Collection Time points for Arm A Patients

MM-121 PK Sample	Pre-infusion	Post-infusion
Cycle 1, Week 1	X	X
Cycle 1, Week 2	X*	
Cycle X, Week 1	X	

*No C1W2 infusion; sample should be collected at any point during C1W2 clinic visit

8.5.2 Docetaxel PK samples

To determine the levels of docetaxel, blood samples will be collected for 15 patients randomized to each of the following treatments: MM-121 + docetaxel, or docetaxel alone. For Cycle 2, Week1 only, plasma should be collected at the following time points relative to the start of the docetaxel infusion: pre-infusion, post-infusion, 3 hours post-start of infusion, and 7 hours post-start of infusion. Approximately 5 mL of blood will be collected. The real time of blood collection must be documented in the respective eCRF. A laboratory manual will be provided with instructions for collecting, processing, and shipping the samples.

8.6 Anti-MM-121 Immunogenicity

Serum samples will be collected to determine the presence of an immunologic reaction to MM-121 (i.e. human anti-human antibodies; HAHA). A laboratory manual will be provided with instructions for collecting, processing, and shipping these samples.

8.7 Biomarker Samples

Biomarker data will be explored from collected tissue and serum samples to assess potential associations with tumor response. To help further understand the biological phenotype of heregulin-positive NSCLC, these samples will be used to assess the mRNA and/or protein for clinically relevant biomarkers for NSCLC, including the PD-1 receptor, ErbB receptors, cMET, IGF-1R, and FGF receptor tyrosine kinases and their respective ligands (PD-L1, ErbB ligands, HGF, IGFs and FGFs). Efficacy outcomes considered for pre-specified mechanistic biomarker analysis will include OS, PFS, and ORR.

8.7.1 Tumor Biopsy

As described in Section 6.3, if archived tissue is available, it may be submitted in lieu of a fresh tissue sample for HRG testing. If this tissue is not available, patients can undergo a fresh tissue biopsy (core needle biopsy, fine needle aspiration, thoracentesis or excision biopsy) to determine eligibility and are also asked to submit a second pass core needle biopsy or second fine needle aspirate for research purposes if possible.

In order to obtain fresh tissue from all patients enrolled, all patients that receive HRG results for eligibility based on testing of archived samples will also be required to undergo a fresh research biopsy (either FNA, core needle, thoracentesis or excision biopsy) prior to first dose. It is important that no systemic therapy is administered between collection of this tissue and dosing on this study. An additional sample will not be requested from patients who underwent a fresh biopsy for eligibility testing.

Directions for processing and shipping the tissue sample for heregulin testing can be found in the laboratory manual.

8.7.2 Archived Tumor Samples

If available, formalin-fixed paraffin embedded tumor samples (either a tumor block or freshly cut slides) obtained at the time of primary disease diagnosis will be collected to compare biomarker expression at the time of disease diagnosis to expression in the sample submitted for HRG testing. This sample is in addition to the sample submitted for HRG testing. Directions and requirements for processing and shipping the archived tumor samples can be found in the laboratory manual.

8.7.3 Serum Samples

Serum samples will be collected at time points described in Section 6.1. The samples will be used to conduct exploratory studies to further characterize and correlate possible biomarkers that may help to predict or evaluate response to MM-121 in NSCLC patients. In the event that there is remaining sample available after conducting these analyses, it will be used by the Sponsor for future analysis of biomarkers that may be mechanistically linked to MM-121 activity. At the time of informed consent, patients will be able to refuse storage of these remaining samples. Directions for processing and shipping the samples can be found in the laboratory manual.

9 Adverse Event and Hospitalization Reporting

9.1 Definitions

9.1.1 Adverse Events

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign, including abnormal laboratory findings, symptoms, or diseases temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires in-patient hospitalization or prolongation of existing hospitalization (Exception: hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered an adverse event. NOTE: Complications that occur during hospitalization are adverse events and if a complication prolongs hospitalization, then the event is serious);
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

While the term “severe” is often used to describe the intensity (severity) of an event, the event itself may be of relatively minor significance (such as a severe headache). This is not the same as “serious”, which is based on a patient/event outcome or action criteria usually associated with events that pose a risk to a patient’s life or functioning.

9.1.2.1 Progressive Disease

Because of the natural history of non-small cell lung cancer, the vast majority of patients will progress on treatment due to their underlying condition, resulting in hospitalization, appropriate medical care or death. Therefore progression of underlying malignancy will not be recorded and nor uniquely captured as an adverse event or serious adverse event. In the event however that the investigator is unsure whether or not an symptom/AE is a associated with progression of the underlying malignancy, the symptom/AE should be recorded and captured as a serious adverse event if it meets the appropriate seriousness criteria, following SAE reporting procedures outlined in Section 9.3Assessing and Documenting Adverse Events and Hospitalizations

Adverse event assessment will begin in conjunction with informed consent. All adverse events occurring after signing informed consent should be captured on the adverse event page of the eCRF. All serious adverse events are to be reported as outlined in Section 9.3. Investigators should complete all routine and standard of care assessments to evaluate for toxicity and symptoms of drug-induced adverse events. This may include, but is not limited to, verbal reports from the patient and/or caregiver, physical examination and laboratory findings.

For heregulin negative patients, all adverse events, whether serious or not, will be described in the source documents and the adverse event page of the eCRF. All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur through the date of receipt of the HRG report, must be reported if they are related to any study procedure (i.e. tumor biopsy).

For heregulin positive patients, all adverse events, whether serious or not, will be described in the source documents and the adverse event page of the eCRF. All new events, as well as those that worsen in intensity or frequency relative to baseline, which occur through the first survival follow-up clinic visit or telephone call (2 months from the date of the last study treatment) must be reported. However, new adverse events felt by the investigator to be related to study treatment, must be reported any time the investigator becomes aware of such an event, even if this occurrence is after the first survival follow-up. All adverse events should be followed until resolution, or until the patient discontinues from the overall survival follow-up portion of the study.

Laboratory, vital signs or ECG abnormalities are to be recorded as Adverse Events only if they are medically relevant: symptomatic, requiring corrective treatment, leading to discontinuation and/or fulfilling a seriousness criterion.

Information to be reported in the description of each adverse event includes:

- A medical diagnosis of the event (if a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded)
- The date of onset of the event
- The date of resolution of the event
- A determination of whether the event is serious or not
- A determination of relatedness to the study drug
- Action taken with study drug: none; change in the study drug administration (e.g., temporary interruption in dosing); drug treatment required; non-drug treatment required; diagnostic or concomitant procedure performed; patient discontinued from the study (complete Treatment Termination case report form)

- Outcome: resolved without sequelae; resolved with sequelae; event ongoing; subject died (notify the Sponsor immediately, and complete the Serious Adverse Event page and the Subject Death page)

9.1.3 Hospitalizations

Information on patient hospitalizations and/or unscheduled hospital visits should be collected in the eCRF, whether or not associated with an adverse event.

9.2 Reporting Serious Adverse Events

Serious adverse events (SAE) will not be reported for patients who only sign the pre-screening consent form unless the serious event is directly related to any study procedure (i.e. tumor biopsy). Serious adverse event reporting will begin in conjunction with the date of informed consent. All fatal or life-threatening adverse events must be immediately reported to the Sponsor or CRO's medical team by telephone or e-mail. Within 24 hours of the event, the Serious Adverse Event Form must be faxed to the Drug Safety Manager whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known. De-identified source documentation of all examinations, diagnostic procedures, etc. which were completed with respect to the event should be included with the SAE form. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers (as assigned at the time of study enrollment) are properly mentioned on any copy of source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.

In case of accidental or intentional overdose of study drug (MM-121 or docetaxel), even if asymptomatic or not fulfilling a seriousness criterion, the overdose is to be reported to the Sponsor or Medical Monitor immediately (within 1 working day) using the AE and SAE forms. Overdose of study drug will be defined as ≥3300 mg of MM-121, and ≥133% of planned dose of docetaxel.

All other serious adverse events must be reported to the Drug Safety Manager within 24 hours by phone, e-mail or fax. Details are outlined in the study procedure manuals. The Serious Adverse Event Form must also be faxed to the Drug Safety Manager within 24 hours of the event whether full information regarding the event is known or not. Additional follow-up by the investigator will be required if complete information is not known.

The Medical Monitor shall be contacted as deemed necessary by the site. Current contact information shall be maintained at the site within the regulatory binder.

All serious adverse events (SAEs) will be evaluated by the Medical Monitor. If meeting the requirements for expedited reporting, the Sponsor will report the adverse event to all regulatory authorities with jurisdiction over ongoing trials with the study drug and to all other investigators involved in clinical trials with the study drug. The investigator is responsible for reporting all SAEs to the appropriate IRB/EC.

9.3 Determining the Severity and Relatedness of an Event

9.3.1 Grading the Severity of an Adverse Event

Each adverse event will be graded according to the NCI CTCAE V 4.03, which may be found at http://ctep.cancer.gov/reporting/ctc.html. For events not listed in the CTCAE, severity will be

designated as mild, moderate, severe, or life-threatening, or fatal which correspond to Grades 1, 2, 3, 4, and 5, respectively on the NCI CTCAE, with the following definitions:

- **Mild/Grade 1:** an event not resulting in disability or incapacity and which resolves without intervention;
- **Moderate/Grade 2:** an event not resulting in disability or incapacity but which requires intervention;
- **Severe/Grade 3:** an event resulting in temporary disability or incapacity and which requires intervention;
- **Life-threatening/Grade 4:** an event in which the patient was at risk of death at the time of the event
- **Fatal/Grade 5:** an event that results in the death of the patient

9.3.2 Relatedness to Study Drug

The investigator must attempt to determine if there exists reasonable possibility that an adverse event is related to the use of one or more study drugs, according to the following guidelines:

- **Unrelated:** This category is applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and/or the clinically plausible temporal sequence is inconsistent with the onset of the event and the administration of the study drug and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLY, PROBABLY, DEFINITELY RELATED or UNKNOWN.
- **Unlikely:** The event is clearly due to causes distinct from the use of the study drug, such as a documented pre-existing condition, the effect of a concomitant medication a new condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug
- **Possible:** The event follows a reasonable temporal sequence from administration of the study drug AND the event follows a known pathological response pattern to the study drug BUT the event could have been produced by an intercurrent medical condition which, based on the pathophysiology of the condition, and the pharmacology of the study drug, would be unlikely related to the use of the study drug or the event could be the effect of a concomitant medication
- **Probable:** The event follows a reasonable temporal sequence from administration of the study drug and the event follows a known response pattern to the study drug AND the event cannot have been reasonably explained by an intercurrent medical condition or the event cannot be the effect of a concomitant medication
- **Definite**: The event follows a reasonable temporal sequence from administration of the study drug, the event follows a known response pattern to the study drug and based on the known pharmacology of the study drug, the event is clearly related to the effect of the study drug
- **Unknown:** Based on the evidence available, causality cannot be ascribed

9.3.3 Reporting and Follow-up of Pregnancy

Patients who become pregnant while on study must immediately discontinue study treatment, and the pregnancy must be immediately reported to the Medical Monitor. Pregnancies occurring up to 6 months after the completion of the study medication must also be reported to the Sponsor.

The investigator should inform the patient of the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy.

In the event of a pregnancy occurring in the partner of a male patient participating in the study, the pregnant partner should be requested to report the pregnancy to the investigator, who in turn should report it to the Sponsor. The partner should also be informed of the risks of continuing with the pregnancy, and the possible effects on the fetus.

10 Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and completed prior to database lock. The SAP may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint and/or its analysis will also be reflected in a protocol amendment.

10.1 General Considerations

Categorical variables will be summarized by frequency distributions (number and percentage of patients) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, maximum). Testing will be conducted using a one-sided 0.025/two-sided 0.05 significance level unless stated otherwise. Descriptive statistics will be displayed in abbreviated treatment identifiers instead of MM-121+docetaxel, docetaxel alone, and overall.

10.2 Statistical Hypothesis and Determination of Sample Size

The primary hypothesis is to test for differences in progression-free survival (PFS) distributions.

A stratified log-rank test will be used to analyze PFS differences with the stratification factor in the model including: number of prior systemic therapies for locally advanced and/or metastatic disease (1 or 2). Statistical significance will be determined by using a one-sided type I error of 0.15. A stratified Cox proportional hazards model will be used to estimate the hazard ratio.

Approximately 61 PFS events are required to have at least 80% power to detect a 2 month improvement in median PFS over 3 months as compared between patients receiving the combination of MM-121 plus docetaxel versus docetaxel alone (i.e., hazard ratio ≤ 0.60), using a one-sided, stratified log-rank test at a significance level of 0.15 with patients randomized in a 2:1 ratio. Assuming an enrollment approximately 15 months in length, the required number of 61 PFS events is estimated to be achieved at approximately 18 months.

10.3 Analysis Populations

Due to the adjusted entry criteria, patients randomized prior to this amendment will be maintained as evaluable for the primary efficacy analysis where applicable. A thorough review of all patient level data will be performed on those already randomized. Those patients meeting the new entry criteria will be eligible to be part of the primary efficacy analysis and may contribute to the total sample size of 80 patients enrolled under Version 4.0 of the protocol, as long as no major protocol violations exist which would exclude them from the per protocol population. Major protocol violations include those not meeting the new entry criteria, those with no baseline measurable lesions, and those patients that never received at least 1 dose of study drug. The total number of patients randomized will not exceed the number needed to randomize

80 patients who qualify for the per protocol population of Version 4.0. It is estimated to be in the range of 110-150 patients.

Patients that meet eligibility criteria but have existing major protocol violations which would exclude them from the per protocol population will be analyzed as part of a sensitivity analysis by pooling them with the per protocol population.

Any patient randomized and not meeting the new entry criteria will be pooled with all other patients and analyzed as part of a sensitivity analysis population.

All patients previously randomized under previous protocols will be used either as part of the primary efficacy analysis in the per protocol population or in some form of sensitivity analysis. All patients dosed will contribute to the safety population.

Patients that have signed informed consent, are identified as HRG positive based on centralized tissue analysis, and have successfully completed study entry criteria will be delineated into the following analysis populations:

- **Intent-to-Treat (ITT) population**: This population includes randomized patients. Patients will be analyzed in the randomized group.
- **Per Protocol (PP)**: This population includes randomized and dosed patients. The PP population is the primary efficacy population and will only include patients that meet all inclusion/exclusion criteria as defined in Protocol Version 4.0 and that are confirmed HRG positive based on centralized analysis of tissue collected after progression on the most recent line of therapy (pre-treatment tissue sample). The PP will exclude those patients with major protocol violations, which will be defined in the SAP in more detail and assessed in an unbiased ongoing manner. Primary considerations for exclusion will be those patients with no measurable baseline tumor, non-evaluated baseline non-target tumor assessments, and incomplete tumor evaluations. Not all circumstances will result in exclusion, however a continual review of patient data will be performed to address data inconsistencies by the medical director, statistician, and clinical trial manager. Data will be reviewed without knowledge of progression/non-progression.
- **Safety (SAF) population**: The safety population includes patients receiving at least one dose of study medication. Patients will be analyzed by the treatment received and not by the treatment to which they were randomized. All safety analyses will be performed on this population.
- **PK population**: All treated patients with at least one PK assessment.

10.4 Disposition, Demographics, and Baseline Characteristics

Disposition of patients will be summarized, including those screened, treated, and discontinued. Reason for discontinuation will be summarized. Demographic and baseline characteristics will be summarized. Medical history and prior medications will be tabulated.

10.5 Efficacy Analysis

10.5.1 Primary Efficacy Analysis

Progression-Free Survival (PFS) based on investigator assessment is the primary endpoint of the study. PFS is defined as the time from randomization to the first documented radiographical progression of disease using RECIST 1.1, or death from any cause, whichever comes first. Details of censorship will be thoroughly explained in the SAP. The primary efficacy will be performed on the per protocol (PP) population using a stratified log-rank test. The Kaplan-Meier

method will be used to estimate median PFS and 70% CI for each treatment group. A stratified Cox proportional hazards model will be used to estimate the hazard ratio and the corresponding 70% confidence intervals. Stratification factor include: number of prior systemic therapies for locally advanced and/or metastatic disease (1 or 2).

10.5.2 Secondary Efficacy Analysis

Overall Survival (OS) is defined as the time from the date of randomization to the date of death from any cause. The OS analysis will be performed using a stratified log-rank test. The Kaplan-Meier method will be used to estimate median OS for each treatment group. A stratified Cox proportional hazard model will be used to obtain an estimate hazard ratio and corresponding 95% confidence intervals. OS will be analyzed using the same population and log-rank test as the PFS primary efficacy analysis. Kaplan-Meier curves displaying median OS and stratified Cox proportional hazard models will be performed similarly as PFS. Various sensitivity analyses will be performed on PFS and OS which will be described in the SAP. OS will also be analyzed as an unstratified log-rank test for the primary and all sensitivity analysis as well. Other analyses include a PFS sensitivity analysis performed by declaring all censors as events and testing with a stratified log-rank. Sensitivity analysis will include various patient populations such as per protocol patients with all patients previously randomized, per protocol new amendment patients only, etc.

Objective Response Rate (ORR) is defined as the proportion of patients with a RECIST v1.1 response recorded from randomization until disease progression characterized as either a Complete Response (CR) or Partial Response (PR) relative to the total number of evaluable patients. Frequency and percent will be as descriptive statistics while a Cochran-Mantel-Haenszel (CMH) test stratified by stratification factor will be tested. A chi-square test without stratification will also be presented. Frequency and percent along with 95% CI will be calculated.

Time to Progression (TTP) is defined as the time from the date of randomization to the date of objective tumor progression. Those patients without objective tumor progression will be censored at the date of last tumor assessment documenting no objective progression. Patients who died prior to first scan will be censored on the date of death.

10.5.3 Subgroup Analyses

PFS and OS will be reported for each level of stratification factor and baseline covariate to check the homogeneity of treatment effect across levels of factors as defined in the statistical analysis plan. Median values for each level of factor will be computed using Kaplan-Meier estimates. Cox proportional hazards model will be used to calculate hazard ratios and 95% CIs. Forest plots will be generated to display hazard ratio treatment differences across subgroups which will be defined in the SAP.

10.5.4 Safety Analyses

Safety analyses (adverse events and laboratory analyses) will be performed using the safety population. Adverse events will be coded using the latest MedDRA dictionary. Severity of adverse events will be graded according to the NCI CTCAE version 4.03. The docetaxel safety run-in analysis will include all patients randomized during this portion of the study.

Treatment-emergent adverse events (TEAEs) are defined as any event that occurred after the first dose of study drug and was not present prior to study drug administration or worsened in severity

after study drug administration. TEAEs will be collected through the end of treatment visit. Frequency and percent summaries will be presented for treatment-emergent adverse events (TEAE) defined as adverse events that occur or worsen in severity following the first dose of MM-121 or docetaxel. Additional tabulations include serious adverse events (SAE), TEAE-related to MM-121 or docetaxel and TEAE grade ≥ 3, and discontinuation due to TEAE. Adverse events will be summarized by System Organ Class and preferred term. All adverse event data will be listed by patient.

Maximum and minimum decrease in continuous laboratory data will be reported. Bar graphs depicting treatment arms will be reported. Frequency and percent of abnormal laboratory values (L/ULN, 2*L/ULN) will be assessed. Shift to most severe toxicity grade will be summarized.

Vital signs and ECG will be tabulated for the change from baseline by time point. Additional analyses may be performed as described in detail within the SAP.

10.5.5 Biomarker Analyses

Biomarker data will be explored from collected tissue and serum samples to assess potential associations with tumor response. These samples will be used to assess additional clinically relevant biomarkers, including but not limited to expression levels of the ErbB3 receptor, cMET, IGF-1R, and FGF receptor tyrosine kinases and will include assessment of their respective ligands (e.g. HGF, FGF-2, IGF-1, and IGF-2 mRNA or protein). PFS, ORR, and OS may be considered for exploratory biomarker analysis. Kaplan Meier methods for displaying graphs and Cox proportional models will be used when estimating hazard ratios with 95% confidence intervals. Biomarker analyses will be further detailed in the SAP.

10.5.6 Pharmacokinetic Analyses

Serum concentrations will be used to determine PK parameters for MM-121 and docetaxel as appropriate using population pharmacokinetic analysis. The resulting PK parameters will be associated with efficacy and safety endpoints as appropriate. Details will be provided in a separate population PK analysis plan.

10.6 Data Monitoring Committee

A regular review of safety data will be conducted by an independent Data Monitoring Committee (DMC) as outlined in the DMC charter. The DMC will consist of oncology and statistical experts, independent of the Sponsor. The charter of the DMC and the statistical analysis plan will be documented separately.

11 Study Administration

11.1 Pre-Study Documentation

Prior to initiating the trial, the investigator will provide the Sponsor or designee with the following documents:

- A signed FDA Form 1572
- A current (i.e. updated no more than 24 months prior) curriculum vitae for the Principal Investigator and each sub-investigator listed on the FDA Form 1572 that is signed and dated.
- A copy of the current medical license for the investigator and each sub-investigator.

- A letter from the IRB/EC stipulating approval of the protocol, the informed consent document, and any other material provided to potential trial participants with information about the trial (e.g. advertisements)
- The current IRB/EC membership list for the reviewing IRB/EC, or the multiple project assurance number from the U.S. Federal Wide Assurance program where applicable
- A signed Investigator Protocol Agreement
- A completed financial disclosure form for the investigator and all sub-investigators
- A current laboratory certification for the local reference laboratory and curriculum vitae of the laboratory director
- A list of current laboratory normal values for the reference laboratory

11.2 Source Documents

The investigator will maintain records separate from the case report forms in the form of clinic charts, medical records, original laboratory, radiology and pathology reports, pharmacy records, etc. The investigator will document in the clinic chart or medical record the date on which the patient signed informed consent prior to the patient's participation in the trial. Source documents must completely reflect the nature and extent of the patient's medical care, and must be available for source document verification against entries in the case report forms when the Sponsor's monitor visits the investigational site. Source documents regarding procedures such as scans and laboratory evaluations performed as part of the standard of care prior to enrollment in the study can be used to fulfill certain screening and baseline assessments. All information obtained from source documents will be kept in strict confidentiality. Source data sent to the Sponsor or the Sponsor's representative as supporting documentation for serious adverse events will be de-identified to preserve confidentiality.

11.3 Trial Ethics

The study will be performed according to the principles of the Declaration of Helsinki, the International Conference on Harmonization Guidance on Good Clinical Practice and the requirements of the US FDA and/or local regulatory authorities regarding the conduct of human clinical trials.

11.4 Patient Informed Consent

No study related procedures will be performed until a patient or a patient's legal representative has given written informed consent. The Sponsor will provide to the investigator a sample informed consent document that includes all the requirements for informed consent according the ICH GCP, U.S. FDA guidelines (21 CFR 50) and/or local regulatory guidelines. However, it is up to the investigator to provide a final informed consent that may include additional elements required by the investigator's institution. Changes to the Sponsor's sample informed consent should receive approval from the Sponsor or the Sponsor's representative prior to use in the study. The informed consent document must clearly describe the potential risks and benefits of the trial, and each prospective participant must be given adequate time to discuss the trial with the investigator or site staff and to decide whether or not to participate. Each patient who agrees to participate in the trial and who signs the informed consent form will be given a copy of the signed, dated and witnessed document. The provision of informed consent must be documented in the medical record.

11.5 Investigational Review Board Approval

The trial will not be initiated until there is approval of the protocol, informed consent document and any other material used to inform the patient about the nature of the trial by the local IRB or EC. The IRB or EC should be duly constituted according to local regulatory requirements. Approval must be in the form of a letter signed by the Chairperson of the IRB/EC or the Chairperson's designee, must be on IRB/EC stationary and must include the protocol by name and/or by designated number. If an investigator is a member of the IRB/EC, the approval letter must stipulate that the Investigator did not participate in the final vote, although the investigator may participate in the discussion of the trial. The investigator will also inform the IRB/EC of any SAE that the Sponsor reports to regulatory authorities, will report on the progress of the trial at least yearly (or more frequently if required by local regulation or guidance) and will provide to the IRB/EC a final summary of the results of the trial at the conclusion of the trial.

11.6 Monitoring

Overall study monitoring will be conducted through a combination of on-site visit and centralized monitoring. A risk-based, data-driven monitoring approach will be used to verify data for this trial which will also include a centralized review of data for quality, trends, consistency and general safety review. A clinical monitor will make regularly scheduled trips to the investigational site to review the progress of the trial, study data and site processes. At each visit, the monitor will review various aspects of the trial including, but not limited to: screening and enrollment logs; compliance with the protocol and study manual and with the principles of Good Clinical Practice; completion of case report forms; source data verification; study drug accountability and storage; facilities and staff.

The actual frequency of monitoring trips will depend on the enrollment rate and performance at each site. The investigator will allow Merrimack Pharmaceuticals, and/or its representatives or designees, access to all pertinent medical records, as required by federal regulations, in order to allow for the verification of data gathered in the CRFs and for the review of the data collection process.

During scheduled monitoring visits, the investigator and the investigational site staff must be available to meet with the study monitor in order to discuss the progress of the trial, make necessary corrections to case report form entries, respond to data clarification requests and respond to any other trial-related inquiries of the monitor. In addition to on-site monitoring visits, the Sponsor and/or representatives will also be routinely reviewing data. Any queries identified through this review will be managed within the systems established for query resolution and tracking. Inquiries related to study conduct which require further information or action will be discussed within the study team for appropriate and documented escalation plans. It is expected that response to data clarification requests and other trial-related inquiries will occur throughout the course of the study through regular communication with the site monitor, the Sponsor or representatives, and review/entry of data into the electronic study database.

At any time during the course of the study, representatives of the FDA and/or local regulatory agencies may review the conduct or results of the study at the investigational site. The investigator must promptly inform Merrimack Pharmaceuticals of any audit requests by health authorities, and will provide Merrimack Pharmaceuticals with the results of any such audits and with copies of any regulatory documents related to such audits.

In accordance with HIPAA and associated privacy regulations, a patient's authorization to use personal identifiable health information may be required from each patient before commencement of research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose and for what duration.

11.7 Confidentiality

It is the responsibility of the investigator to ensure that the confidentiality of all patients participating in the trial and all of their medical information is maintained. Case report forms and other documents submitted to the Sponsor must never contain the name of a trial patient. All patients in the trial will be identified by a unique identifier which will be used on all CRF's and any other material submitted to the Sponsor. All case report forms and any identifying information must be kept in a secure location with access limited to the study staff directly participating in the trial.

11.7.1 Confidentiality of Biomarker Samples

Blood and tissue samples collected as part of the biomarker analysis will be identified only by a number assigned to the patient at the study site; this number will be used in lieu of the patient's name in order to protect the patient's identity. The samples will be stored at a facility designated by the Sponsor. Other than the patient's unique identifying number, no additional patient information will be stored with these samples. Samples will be kept until they are used completely for the specified biomarker analyses, or, in the event there is remaining tissue or blood sample available, such specimens will be stored indefinitely. At the time of informed consent, patients will be able to refuse indefinite storage of these remaining samples. If indefinite storage is refused, any remaining samples will be destroyed following the completion of the study. Similarly, patients may withdraw approval at any time by submitting a written request to the study site investigator. Upon receipt of this withdraw of consent, no further analyses will be completed and the patient's remaining samples will be destroyed, however, data already collected will not be removed from the study dataset.

Any samples that a patient consents to be stored indefinitely may be used by the Sponsor for future oncological translational work, as directed by the findings of the exploratory biomarker evaluation and the results of the initial tissue biomarker evaluation. The results from these exploratory analyses may not necessarily be shared with the investigators or the participating subjects.

11.8 Protocol Amendments

The protocol will only be amended with the consent of the Sponsor and the IRB/EC. Changes to the protocol must be in the form of a written amendment; changes other than those of a simple administrative nature (e.g., a new telephone number for a medical monitor) must be submitted by the investigator to the local IRB/EC and such amendments will only be implemented after approval of the requisite IRB/EC. All amendments will also be submitted to the FDA and/or local regulatory authorities by the Sponsor.

Protocol changes to eliminate an immediate hazard to a trial patient may be implemented by the investigator immediately. The investigator must then immediately inform their IRB/EC and the Sponsor will immediately notify applicable regulatory authorities.

11.9 Records Retention

The investigator will retain the records of the clinical trial (including, but not necessarily limited to, CRFs, source documents, informed consent forms, drug accountability records, IRB/EC correspondence, Sponsor correspondence, etc.) for 2 years following the date that the last marketing application for the study drug is approved (or per local regulatory requirements), or if no marketing application is filed, or if such an application is not approved, for 2 years after the formal discontinuation of clinical development of the study drug. The Sponsor or designee will notify investigators when retention of study records is no longer required. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary.

Study records must be retained as per the GCP guidelines and local regulatory requirements, including, but not limited to, case report forms, signed informed consents, correspondence with the IRB/EC, study drug dispensing and inventory records, source documents (clinic charts, medical records, laboratory results, radiographic reports) and screening/enrollment logs.

Should the investigator relocate or retire the responsibility for maintaining the study records may be transferred to another investigator. The Sponsor must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage. If no other individual at the site is willing to assume this responsibility, the Sponsor will assume responsibility for maintaining the study records.

11.10 Study Termination

The Sponsor reserves the right to terminate the study at any site and at any time. Reasons for study termination may include, but are not limited to, the following

- Investigator non-compliance with the protocol, GCP or regulatory requirements
- Insufficient enrollment
- Safety concerns
- Drug supply or manufacturing issues
- The Sponsor’s decision to modify or discontinue the development of MM-121
- A request to discontinue the study by the FDA and/or local regulatory authorities

The Sponsor will promptly inform all investigators and the FDA and/or local regulatory authorities if the study is suspended or terminated for any reason. The investigator will promptly notify the IRB/EC if the study is suspended or terminated.

12 Investigator Signature Page

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study as outlined herein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the drug and the study. I will identify study personnel conducting study specific procedures and appropriately document their training and/or delegated responsibilities. I understand that the study may be terminated or enrollment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the patients in the study.

I agree to conduct this study in full accordance with all applicable regulations and Good Clinical Practice (GCP).

Signature of Investigator

Date

Print Name of Investigator

Signature of Sponsor

08/MAR 2017

Date

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