Randomized Phase 2 Trial of Seribantumab in Combination with Erlotinib in Patients with EGFR Wild-type Non-Small Cell Lung Cancer

Poster #13960

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Introduction

- Seribantumab (MM-121) is a fully human IgG2 antibody that binds to ErbB3 and displaces the binding of the heregulin (HRG) ligand to the receptor (1)
- HRG-ErbB3 signaling mediates resistance to a broad range of targeted and cytotoxic therapies (1-3)
- Preclinical and clinical studies have suggested that heregulin is aberrantly overexpressed in non-small cell lung cancer (NSCLC) and contributes to resistance of EGFR-targeted therapies (1)
- Erlotinib is an EGFR tyrosine kinase inhibitor (TKI), which was initially approved for treatment of patients with NSCLC regardless of the EGFR mutation status, but later was shown to be most effective in patients with EGFR-mutant tumors
- We conducted a Phase 1/2 study assessing the combination of seribantumab plus erlotinib in patients with EGFR wild-type tumors who had not previously received prior EGFR TKI-targeted therapy (Group A), patients with EGFR activating mutations who had no prior EGFR TKI-targeted therapy (Group B), and patients whose tumors were resistant to EGFR-targeted therapies (Group C)
- Here, we report Phase 2 results of the largest group (Group A), consisting of patients with confirmed EGFR wild-type tumors and describe the potential predictive power of HRG expression

Objectives

Primary objectives

- To estimate progression-free survival (PFS) for patients treated with seribantumab plus erlotinib

Secondary objectives

- To determine the adverse event (AE) profile for seribantumab plus erlotinib
- To determine the pharmacokinetic (PK) parameters and immunogenicity of seribantumab in combination with erlotinib
- To obtain initial estimates of other key efficacy endpoints, including overall survival (OS), objective response rate (ORR), and clinical benefit rate (CBR)
- To gather clinical data on potentially predictive biomarkers to be measured in blood and tumor tissue

Study Design

This was a multicenter, open-label Phase 1/2 study (NCT00994123), which had 2 parts:

- The Phase 1 portion of the study aimed to identify the MTD of seribantumab plus erlotinib and to optimize the dosing schedule.
- The Phase 2 portion was an open-label randomized study of seribantumab plus erlotinib (experimental arm) versus erlotinib alone (control arm) in three populations of patients with advanced NSCLC.

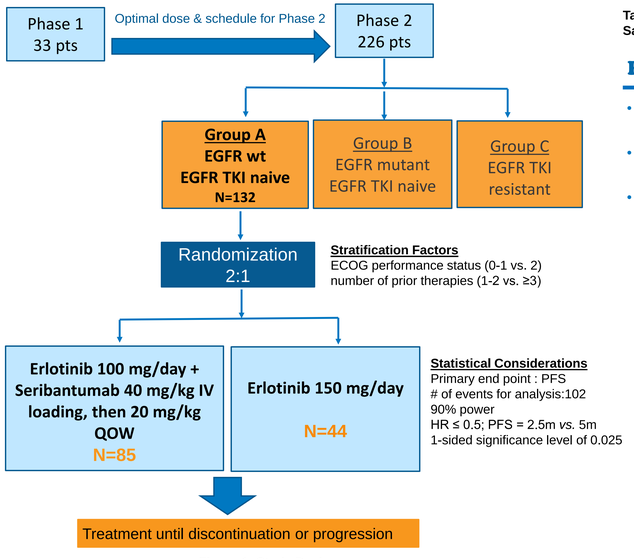

Figure 1: Study Design

Key Eligibility Criteria

- Confirmed locally advanced or metastatic NSCLC
- ≥ 18 years of age, ECOG performance status of 0-2
- Progression after ≥ 1 prior regimen
- No prior exposure to EGFR TKI such as gefitinib, erlotinib, or afatinib
- Patients must have had a lesion amenable to biopsy and been willing to undergo a pre-treatment biopsy, unless they underwent a biopsy within 2 months prior and had sufficient tumor tissue available for biomarker testing and had no intervening systemic treatment since this biopsy (palliative radiation was permitted)
- Adequate end-organ function

Patients Demographic and Clinical Characteristics

Patient Characteristics	All Patients N=129	Experimental Arm seribantumab 20 mg/kg QW + erlotinib 100 mg QD N=85	Control Arm erlotinib 150 mg QD N=44
Age, years			
Median (range)	64 (35-85)	65 (35-85)	64 (41-80)
Gender, n (%)			
Male	77	50 (58.8)	27 (61.4)
Female	52	35 (41.2)	17 (38.6)
Race, n (%)			
White	110	74 (87.1)	36 (81.8)
Asian	13	7 (8.2%)	6 (13.6)
Black/African American	5	3 (3.5)	2 (4.5)
American/Indian or Alaska native	1	1 (1.2)	0 (0)
Smoking history, n (%)			
Current Smoker	22	17 (20.0)	5 (11.4)
Former smoker	80	54 (63.5)	26 (59.1)
Never-smoker	24	12 (14.1)	12 (27.3)
History not known	3	2 (2.4)	1 (2.2)
Tumor Histology, n (%)			
Adenocarcinoma	92	57 (67.1)	35 (79.5)
Squamous Cell Carcinoma	26	22 (25.9)	4 (9.1)
Adenosquamous Carcinoma	3	1 (1.2)	2 (4.5)
Large Cell Carcinoma	2	1 (1.2)	1 (2.3)
Other or Unclassified Carcinoma	6	4 (4.8)	2 (4.5)
Brain Metastases			
n (%)	20	12 (14.1)	8 (18.2)

Table 1: Phase 2 Patient Demographics and Baseline Characteristics by Dose Level – Group A, Safety Population

Retrospective Biomarker Analyses for HRG

- 69/132 (54%) patients had tissue available and successful biomarker for HRG data obtained
- Positive HRG mRNA ISH (score ≥1) was correlated with improved PFS for seribantumab arm compared to control (HR < 1)
- There was no statistical difference between groups with RNA-ISH 1-2 and >2

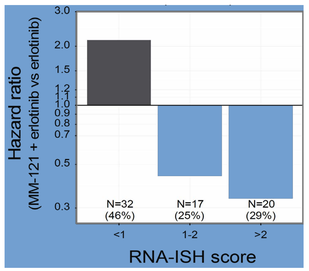

Figure 2: Local Progression Free Survival Hazard Ratio by HRG RNA-ISH Score in Pre-Treatment Biopsy Samples in Group A (EGFR wild-type)

HRG-positive Patients Had Inferior PFS and Appeared to Benefit from Addition of Seribantumab

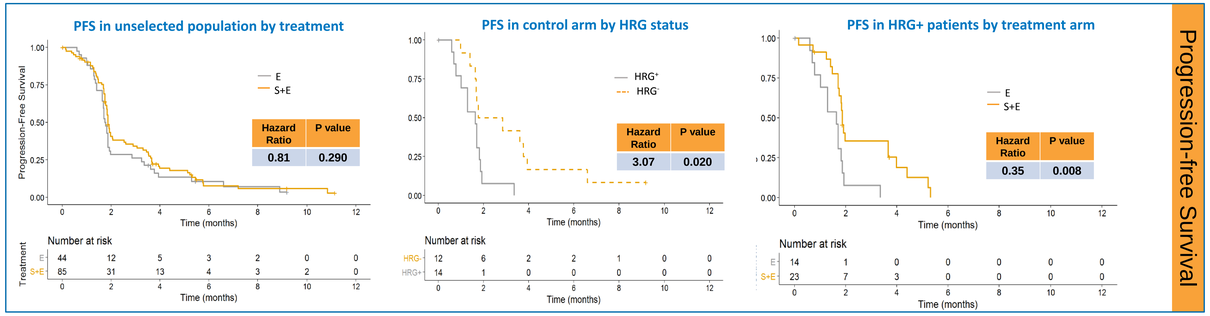

Figure 3: Progression- free Survival in NSCL Patients Enrolled in Group A
S+E = seribantumab + erlotinib (experimental) arm, E = erlotinib (control) arm
Hazard Ratio is defined for (S+E vs. E) or (HRG-positive vs. HRG-negative)

Clinical Response

Best overall response	NSCLC HRG+	
	S+E	E
Complete Response (CR)	1 (4.3%)	0 (0%)
Partial Response (PR)	0 (0%)	0 (0%)
Stable Disease (SD)	8 (34.8%)	1 (7.1%)
Progressive Disease (PD)	10 (43.5%)	10 (71.4%)
Not evaluable	4 (17.4%)	3 (21.4%)

Table 2: Response rates in the experimental and control arms for the HRG+ population

Safety

- A total of 129 (97%) patients were a part of the safety population, which included those who received at least a part of a seribantumab infusion or a dose of erlotinib.
- All patients experienced at least one treatment-emergent adverse event (TEAE)
- The most common TEAEs of any grade were diarrhea, rash, decreased appetite, fatigue, and nausea in both arms
- There were generally slightly higher incidences of low-grade toxicities in the experimental treatment arm compared to control
- Overall, there was no meaningful difference in the types TEAEs Grade 3 or higher of toxicities experienced between the two arms, except diarrhea, which was more frequently observed in the experimental arm *vs.* control arm

Preferred Term	Experimental Arm seribantumab 20 mg/kg QW + erlotinib 100 mg QD N=85 n (%)		Control Arm erlotinib 150 mg QD N=44 n (%)	
	All Grade	Grade ≥ 3	All Grade	Grade ≥ 3
At least 1 TEAE	85 (100)	49 (57.6)	44 (100)	25 (56.8)
Diarrhea	59 (69.4)	7 (8.2)	27 (61.4)	2 (4.5)
Rash	46 (54.1)	3 (3.5)	21 (47.7)	3 (6.8)
Decreased appetite	37 (43.5)	1 (3.3)	16 (36.4)	0 (0)
Fatigue	31 (36.5)	1 (1.2)	13 (29.5)	0 (0)
Nausea	29 (34.1)	1 (1.2)	14 (31.8)	0 (0)
Dry skin	28 (32.9)	1 (1.2)	11 (25.0)	0 (0)
Weight decreased	27 (31.8)	0 (0)	11 (25.0)	0 (0)
Dyspnea	22 (25.9)	9 (10.6)	9 (20.5)	6 (13.6)
Vomiting	19 (22.4)	2 (2.4)	11 (25.0)	1 (2.3)
Dermatitis acneiform	14 (16.5)	0 (0)	12 (27.3)	1 (2.3)
Stomatitis	20 (23.5)	0 (0)	5 (11.4)	0 (0)
Cough	16 (18.8)	0 (0)	6 (13.6)	0 (0)
Pruritis	10 (11.8)	1 (1.2)	10 (22.7)	1 (2.3)
Back pain	15 (17.6)	2 (2.4)	4 (9.1)	0 (0)
Dizziness	11 (12.9)	1 (1.2)	8 (18.2)	0 (0)
Constipation	10 (11.8)	0 (0)	7 (15.9)	0 (0)
Hypokalemia	14 (16.5)	4 (4.7)	3 (6.8)	0 (0)
Dysgeusia	14 (16.5)	0 (0)	1 (2.3)	0 (0)

Table 3: Treatment Emergent Adverse Events (≥15%) in the Phase 2 Safety Population of Group A by Preferred Term

Summary of Results and Discussion

- In the unselected patient population, seribantumab did not improve treatment outcomes when combined with erlotinib in patients with EGFR wild-type NSCLC
- Retrospective biomarker analysis suggests that HRG mRNA levels measured by ISH are predictive for seribantumab response
- The combination of seribantumab and erlotinib appeared to improve PFS in the predefined patient sub-group with high HRG mRNA levels assessed by RNA-ISH
- Although the biomarker population (n=69) was significantly smaller than the intent-to-treat population (n=129), decreasing the power of the biomarker analysis, this limitation was mitigated by the large effect size of the addition of seribantumab to erlotinib in the HRG-positive patient population
- The observed safety profile was consistent with the expected toxicities for seribantumab and appeared manageable
- The key limitation is that the experimental regimen was built upon an erlotinib backbone, and it is now better appreciated that erlotinib has little single agent activity in EGFR wild-type tumors. At the time this study was designed, erlotinib was approved as second-line therapy for all NSCLC tumors, including EGFR wild-type and squamous histology (4)

Conclusions

- Our data support the hypothesis that addition of seribantumab to standard therapy might provide clinical benefit to patients with HRG+ EGFR wild-type NSCLC
- Based on these data, a prospective, randomized, open-label, international, multicenter Phase 2 study of seribantumab, in combination with docetaxel, is underway in patients with HRG-positive advanced NSCLC adenocarcinoma (NCT02387216)

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