A Phase 1 study of the anti-ErbB3 antibody MM-121 in combination with weekly paclitaxel in patients with advanced gynecological and breast cancers

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Abstract

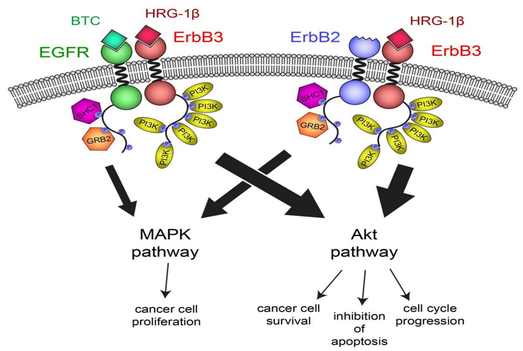
Background: MM-121 is a fully human monoclonal antibody targeting the epidermal growth factor receptor family member ErbB3. ErbB3 has been widely implicated in driving cancer growth and in the development of resistance to conventional chemotherapies and targeted agents across multiple malignancies. Single agent weekly paclitaxel is a standard regimen for patients with advanced gynecological and metastatic breast cancers. Here we present results from an ongoing Phase 1 study evaluating the combination of MM-121 and weekly paclitaxel.

Methods: A total of 28 patients with either platinum resistant ovarian cancer, metastatic endometrial cancer, primary peritoneal cancer, fallopian tube cancer (gynecological cancers) or Her2 Non Overexpressing Breast Cancer (HER2 neg. mBC), were treated in a dose escalation (10 pts) or expansion cohort (18 pts). Patients were treated until disease progression or intolerable toxicity. Response was assessed every eight (8) weeks according to RECIST 1.1. In the dose-expansion cohorts, pre- and post-treatment fresh tumor biopsies were obtained from 12 patients to assess ErbB3 signaling status and its potential as a predictive marker for MM-121 response.

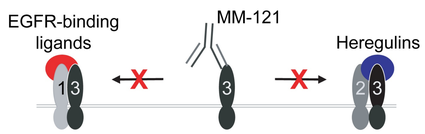
Results: To date, 28 patients have been treated with a median follow up of 7.4 months (range 0.8 – 17.7). The median age was 57 years (range 35 – 75), and patients had received a median of four (range 1 – 11) prior lines of therapy in the adjuvant or metastatic setting including chemotherapies as well as anti-hormonal therapies. Common (>20%) adverse events of any grade included fatigue (64%), peripheral neuropathy (57%), diarrhea (13%), rash (43%) and alopecia (39%). Grade 3/4 toxicities included fatigue (14%), peripheral neuropathy (7%), diarrhea (7%), neutropenia (14%), anemia (7%), mucosal inflammation (11%), and small intenstinal obstruction (11%). 23 (82%) patients were evaluable for response and the overall clinical benefit rate, defined as PR or SD lasting for >4 months, was 70%. 48% achieved a PR and 39% a confirmed PR with a median duration of response of 2.7 months (range1.7 – 15.1) and 22% had SD >4 months with a median duration of SD of 5.3 months (range 4.7-13.6). 9% of patients had PD at first assessment and 26% remain on study with a median on-study time of 13.5 months (range 5.3 – 17.7). Translational analyses exploiting tissue analysis in combination with in silico modeling are ongoing.

Conclusion: The combination of MM121 and paclitaxel showed activity in advanced gynecological and breast cancers.

MM-121 Molecule Overview



- Fully human IgG2 antibody; no ADCC mediated toxicities
- 0.8 nM monovalent affinity
- Recognizes ErbB3 and blocks ligand binding
- Prevents heterodimerization of ErbB3 with other receptors (EGFR, ErbB2, ErbB4, IGF1R, c-Met)
- Induces internalization and degradation of ErbB3



Inclusion Criteria, Key Objectives, and Study Design

Key inclusion criteria

- Cytological or histological confirmation of locally advanced/metastatic or recurrent epithelial ovarian cancer, fallopian tube cancer, primary peritoneal cancer or endometrial cancer with disease that is resistant or refractory to platinum agents as defined by GOG criteria, or;
- Cytological or histological confirmation of locally advanced /metastatic Her2 non-overexpressing breast cancer
- Measurable disease according to RECIST v1.1
- Expansion cohort patients must have unstained archival tumor tissue available and be eligible for and consent to a pre- and post treatment core needle biopsy

Objectives

- Evaluate the safety and tolerability of escalating doses of the MM-121 and paclitaxel combination and to characterize dose-limiting toxicities (DLTs) associated with this combination
- Characterize the efficacy of the combination of MM-121 and paclitaxel using objective response rate and clinical benefit rate at 16 weeks

Key Study Design Features

- Phase 1 standard "3+3" design followed by additional expansion cohorts
- MM-121 dosed weekly for 4 week cycles
- 4 week DLT evaluation period
- Patients scanned every 8 weeks
- Expansion cohorts explored alternated dosing regimens i.e. every other week dosing
- Archived tissue, pre-dose biopsy, and post-dose biopsy mandatory for all patients in expansion cohort for biomarker evaluation

Dosing Cohorts

Dose (mg/kg) IV*	# of Patients
Dose Escalation	
20/12	7
40/20	3
Expansion Cohort	
20/12	6
40/20	6
40 every other week	6
40/20 three weeks on, one week off	--
Total Patients	28

*Weekly dosing unless stated otherwise
Paclitaxel is administered weekly concurrently at 80 mg/ m^2 IV

Adverse Event Data

Summary of Adverse Events Seen in Greater than 20% of the Population

Adverse Event	Any Grade [n (%)]	At Least Grade 3 [n (%)]
Fatigue	18 (64)	4 (14)
Neuropathy peripheral	16 (57)	2 (7)
Diarrhoea	13 (48)	2 (7)
Nausea	12 (43)	0
Neutropenia	12 (43)	4 (14)
Rash	12 (43)	0
Alopecia	11 (39)	0
Epistaxis	10 (36)	0
Stomatitis	10 (36)	1 (4)
Abdominal pain	9 (32)	0
Anaemia	9 (32)	2 (7)
Oedema peripheral	9 (32)	0
Pruritus	7 (25)	0
Cough	6 (21)	0
Dyspepsia	6 (21)	0
Dyspnoea	6 (21)	1 (4)
Hypokalaemia	6 (21)	1 (4)
Hypomagnesaemia	6 (21)	0
Mucosal inflammation	6 (21)	3 (11)

Summary of All Grade 3 and 4 Adverse Events

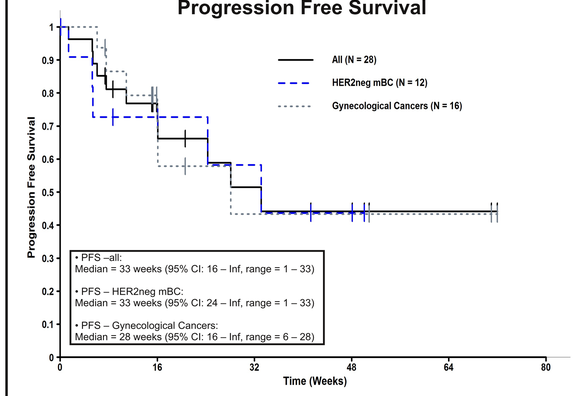
Adverse Event	Frequency of Grade 3/4 [n (%)]
Fatigue	4 (14)
Neutropenia	4 (14)
Mucosal inflammation	3 (11)
Small intestinal obstruction	3 (11)
Anaemia	2 (7)
Diarrhoea	2 (7)
Neuropathy peripheral	2 (7)
Abdominal pain upper	1 (4)
Ascites	1 (4)
Death	1 (4)
Dehydration	1 (4)
Dermatitis allergic	1 (4)
Disease progression	1 (4)
Dyspnoea	1 (4)
Gastritis	1 (4)
Hypokalaemia	1 (4)
Hyponatraemia	1 (4)
Intestinal obstruction	1 (4)
Intestinal perforation	1 (4)
Lymphopenia	1 (4)
Nail infection	1 (4)
Sepsis	1 (4)
Stomatitis	1 (4)
Syncope	1 (4)
Thrombosis	1 (4)
Urinary tract infection pseudomonal	1 (4)

Demographics

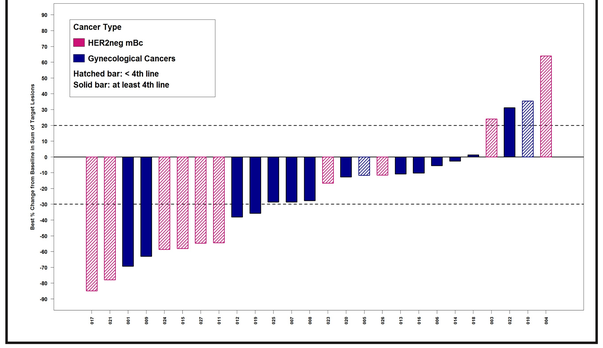
Median Age, [y (range)]	57 (35-75)
Gender [n (%)]	
Female	28 (100)
ECOG [n (%)]	
0	11 (39)
1	17 (61)
Diagnosis [n (%)]	
HER2neg metastatic breast cancers	12 (43)
metastatic gynecological cancers	16 (57)
Prior lines of chemotherapy [n (%)]	4 (1-11)
Prior taxane exposure [n (%)]	24 (86)

Results

Progression Free Survival



Best Response for Target Lesion by Patient



Summary

- Observed safety profile of the MM-121 combination with weekly paclitaxel appears comparable to expected toxicities with weekly paclitaxel monotherapy
- Disease control rate at 16 weeks was 70%
- Objective response rate was 39%
- Median PFS in overall study population was 33 weeks
- 22% of patients had SD >4 months with a median duration of SD of 5.3 months (range 4.7-13.6)
- 9% of patients had PD at first assessment
- No MTD reached in dose escalation phase of study
- The combination of MM121 and paclitaxel showed activity in advanced gynecologic cancers and breast cancers
- A phase 2 study in ovarian cancer patients of MM-121 in combination with paclitaxel is currently open to enrollment

For questions or comments, please email clinicalposters@merrimackpharma.com

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