A Phase 1 Study of MM-141, a Novel Tetravalent Monoclonal Antibody Targeting IGF-1R and ErbB3, in Relapsed or Refractory Solid Tumors

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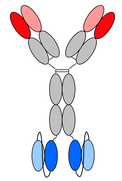
Abstract #420

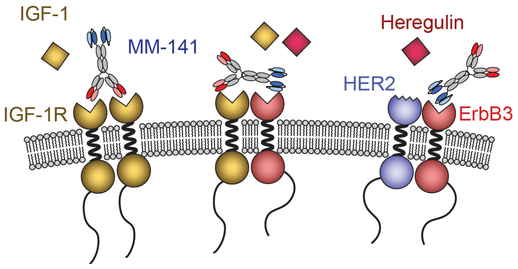
MM-141 Molecule Overview

Anti-IGF-1R IgG1 antibody (K_D=0.3nM)

genetically fused with

anti-ErbB3 antibody fragment (K_D=0.9nM)





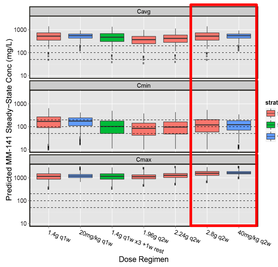
MM-141 inhibits PI3K/AKT/mTOR by:

- blocking growth factor induced signaling via IGF-1R and ErbB3
- degrading receptor complexes of IGF-1R and ErbB3 including their heterodimers with ErbB2 and IR

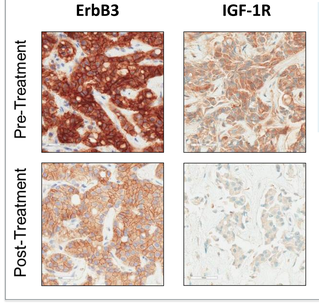
Pharmacokinetics and Pharmacodynamics Results

PK Parameters of MM-141 by dose level

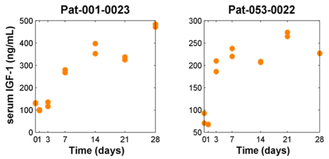
Nominal Dose	Statistics	C_{max}, mg/L	$t_{1/2}$, days	AUC_{0-t}, h·mg/L
40 mg/kg Q2W	Geometric Mean	951.2	5.2	82831.4
	Upper 95% CI	1124.5	6.9	499523.0
	Lower 95% CI	804.6	3.9	68939.2
	N	8	8	8



40 mg/kg Q2W achieves target steady state concentrations. Population PK modeling demonstrated no substantive differences between 40 mg/kg Q2W dosing and 2.8g Q2W. Fixed dosing will be used in future clinical trials.



-Receptor degradation observed between pre-treatment and on-treatment samples (MM-141 monotherapy, 20 mg/kg QW)
-Increase in total IGF serum levels observed during treatment supports effective receptor blockade

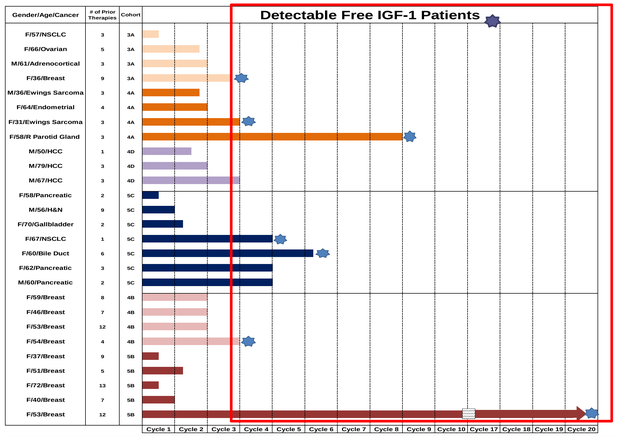


Results

Adverse Event (≥20% Occurrence)	Overall n = 42 (%)	Monotherapy n = 18 (%)	MM-141 + everolimus n = 13 (%)	MM-141 + nab-paclitaxel + gemcitabine n = 11 (%)
Vomiting	20 (47.6%)	10 (55.6%)	6 (46.2%)	4 (36.4%)
Headache	18 (42.9%)	6 (33.3%)	7 (53.8%)	5 (47.4%)
Nausea	18 (42.9%)	7 (38.9%)	3 (23.1%)	8 (72.7%)
Decreased Appetite	18 (42.9%)	8 (44.4%)	5 (38.5%)	5 (45.5%)
Anemia	16 (38.1%)	5 (27.8%)	3 (23.1%)	8 (72.7%)
Hypokalemia	16 (38.1%)	3 (16.7%)	6 (46.2%)	7 (63.6%)
Thrombocytopenia	15 (35.7%)	4 (22.2%)	2 (15.4%)	9 (81.8%)
Fatigue	14 (33.3%)	5 (27.8%)	5 (38.5%)	4 (36.4%)
Diarrhea	14 (33.3%)	2 (22.2%)	3 (23.1%)	7 (63.6%)
Infusion Related Reaction	12 (28.6%)	6 (33.3%)	4 (30.8%)	2 (18.2%)
Neutropenia	12 (28.6%)	3 (16.7%)	3 (23.1%)	6 (54.5%)
Weight Decrease	12 (28.6%)	4 (22.2%)	6 (46.2%)	2 (18.2%)
Dyspnea	10 (23.8%)	5 (27.8%)	2 (15.4%)	3 (27.3%)
Aspartate Aminotrasferase Increase	10 (23.8%)	4 (22.2%)	3 (23.1%)	3 (27.3%)
Abdominal Pain	9 (21.4%)	4 (22.2%)	2 (15.4%)	3 (27.3%)

Grade 3 or Higher Adverse Event (≥3% occurrence)	Overall n = 42 (%)	Monotherapy n = 18 (%)	MM-141 + everolimus n = 13 (%)	MM-141 + nab-paclitaxel + gemcitabine n = 11 (%)
Neutropenia	7 (16.7%)	0	3 (23.1%)	4 (36.4%)
Hypokalemia	6 (14.3%)	0	2 (15.4%)	4 (36.4%)
LFT Increase	5 (11.9%)	2 (11.1%)	3 (23.1%)	0
Pain	4 (9.5%)	1 (5.6%)	2 (15.4%)	1 (9.1%)
Fatigue	4 (9.5%)	1 (5.6%)	1 (7.7%)	2 (18.2%)
Thrombocytopenia	4 (9.5%)	0	1 (7.7%)	3 (27.3%)
Anemia	3 (7.1%)	0	1 (7.7%)	2 (18.2%)
Dyspnea	3 (7.1%)	2 (11.1%)	1 (7.7%)	0
Hypophosphatemia	3 (7.1%)	1 (5.6%)	2 (15.4%)	0
Infusion Related Reaction	2 (4.8%)	1 (5.6%)	1 (7.7%)	0
Neutrophil Count Decreased	2 (4.8%)	0	1 (7.7%)	1 (9.1%)
Infection	2 (4.8%)	1 (5.6%)	1 (7.7%)	0
Small Intestinal Obstruction	2 (4.8%)	2 (11.1%)	0	0

Treatment duration of patients from Phase 1 study of MM-141



Summary of Treatment Duration (Median in Weeks)

	Overall	Monotherapy	MM-141 + everolimus	MM-141 + nab-paclitaxel + gemcitabine
sFree IGF-1^{+} (*)	15.7 (n=21)	13 (n=8)	18.6 (n=8)	15.5 (n=5)
sFree IGF-1^{-} (*)	9.0 (n=17)	10.2 (n=6)	7.3 (n=5)	9.1 (n=6)
Entire Cohort	12.6 (n=42)	10.9 (n=18)	14.3 (n=13)	12 (n=11)

*Serum free IGF-1 ELISA assay

Study Design

Cohort: [n]	MM-141 (mg/kg) monotherapy	Cohort: ER/PR+ BrCa [n]	MM-141 (mg/kg) + everolimus (mg)	Cohort: Solid Tumors [n]	MM-141 (mg/kg) + nab-paclitaxel (mg/m²) + gemcitabine (mg/m²)
1A [3]	6 qw	1B	X	1C	X
2A [4]	12 qw	2B	X	2C	X
3A [4]	20 qw	3B	X	3C	X
4A [4]	40 q2w	4B [4]	20 q2w + 5	4C [4]	12 qw + 125 + 1000
4D [3]	20 qw in HCC	5B [9]	40 q2w + 5	5C [7]	20 qw + 125 + 1000

- "3 + 3" design, followed by expansion cohorts
- 4 week DLT evaluation period

NCT# 01733004

Objectives

- Determine the Maximum Tolerated Dose (MTD) or Recommended Phase 2 Dose (RP2D) of MM-141 as a single agent
- Determine the MTD or RP2D of MM-141 in combination with everolimus, and in combination with nab-paclitaxel and gemcitabine
- Determine the adverse event profile
- Determine the pharmacokinetics and immunogenicity parameters

Key Inclusion Criteria

- Cytologically or histologically confirmed advanced malignant solid tumor for which no curative therapy exists that has recurred or progressed following standard therapy
- Measurable disease according to RECIST v1.1
- No-insulin dependent or uncontrolled diabetes
- BMI between 18 and 32.5

Conclusions/Summary

- **MM-141 was well tolerated both as monotherapy and in combination with everolimus or nab-paclitaxel/gemcitabine in patients with relapsed /refractory solid tumors. Recommended dosing is 2.8g Q2W.**
- **MTD was not reached for MM-141 monotherapy or MM-141 + nab-paclitaxel/gemcitabine. Two DLT's were reported in cohort 5B (MM-141 with everolimus): a Grade 3 Neutropenia and a Grade 4 IRR.**
- **Pharmacodynamics markers of total IGF, ErbB3 and IGF-1 receptor levels demonstrate target engagement.**
- **Clinical results suggest that stratification based on pre-treatment serum levels of free IGF-1 may be associated with longer anti-tumor activity. This hypothesis is currently being tested in a randomized Phase 2 study combining MM-141 with nab-paclitaxel/gemcitabine in pancreatic cancer patients with elevated serum levels of free IGF-1.**