Final results of a first-in-human study evaluating the safety, pharmacology and initial efficacy of MM-151, an oligoclonal anti-EGFR antibody in patients with refractory solid tumors

Abstract #170118

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Abstract

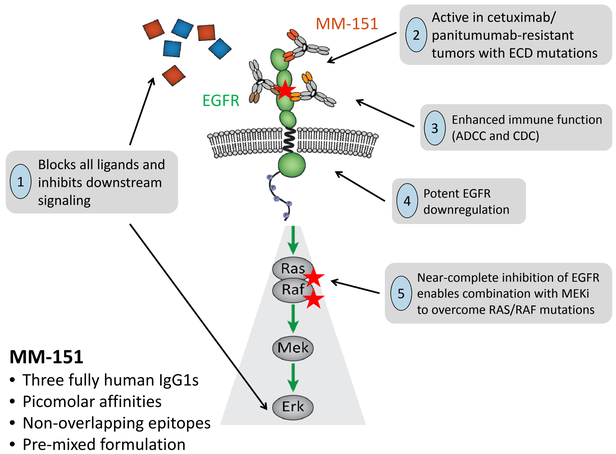
Background: MM-151 is a mixture of three IgG1 antibodies designed to bind simultaneously to non-overlapping EGFR epitopes and inhibit ligand-mediated signal amplification, downregulate EGFR expression, and enhance immune-effector activities (ADCC, CDC). A Phase 1 study was completed to assess safety, tolerability, pharmacology and preliminary clinical activity of MM-151 alone and in combination with irinotecan.

Methods: This study evaluated MM-151 when administered as a monotherapy and in combination with irinotecan. An expansion cohort was also enrolled to evaluate clinical activity in EGFR-refractory metastatic CRC patients (pts). Subset analyses and additional biomarker evaluations were performed in EGFR-driven indications.

Results: A total of 111 patients were treated (87 pts on monotherapy). The most common tumor types were CRC (45 [41%]), NSCLC (11 [10%]) and SCCHN (14 [13%]). Weekly dose selection was previously reported. Reported here are final safety and biomarker data. Most adverse events were CTCAE Grades 1 and 2. The most common Grade 3 (G3) or higher non-infusion related reaction (IRR) AEs included EGFR-pathway toxicities such as maculopapular rash (11 [9.9%]), hypomagnesemia (10 [9%]), general rash (8 [7.2%]) and diarrhea (8 [7.2%]). G3 IRRs occurred in 8/57 (14%) of pts enrolled at the non-optimized dosing guidelines vs. 1/57 (1.7%) of pts in the optimized dosing cohorts. Biomarker analyses revealed a complex set of resistance mechanisms. Notably, clinically meaningful treatment durations were achieved in patients presenting with multiple resistance markers, including RAS/RAF mutations. Within a CRC subset, 13/29 (45%) achieved SD or PR at 3 cycles of treatment and 5/29 (17%) achieved a PR, with highly durable responses and disease control.

Conclusions: Results to date demonstrate that MM-151 has an acceptable tolerability profile. Preliminary indications of objective clinical activity across both the EGFR-refractory and naïve populations suggest potential for broad effect. Biomarker profiling also suggests that MM-151 may overcome mechanisms of resistance. Further clinical evaluation is underway.

Mechanisms of Action



MM-151
- Three fully human IgG1s
- Picomolar affinities
- Non-overlapping epitopes
- Pre-mixed formulation

Key Eligibility Criteria

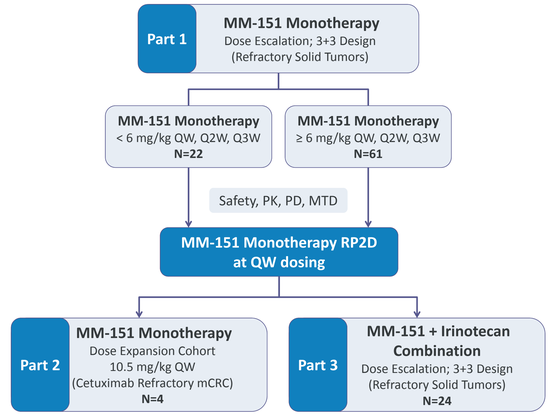
General
- ≥ 18 years of age
- Measurable disease per RECIST v1.1
- ECOG Performance Score of 0 or 1
- Adequate bone marrow reserves, renal, hepatic and cardiac function

Part 1
- Advanced solid tumor that is refractory to standard therapy
- Archival tumor tissue

Part 2
- Histologically confirmed KRAS wild-type CRC
- Documented response on cetuximab/panitumumab

Part 3
- EGFR-driven cancers, including CRC, HNSCC, NSCLC and TNBC

Study Design



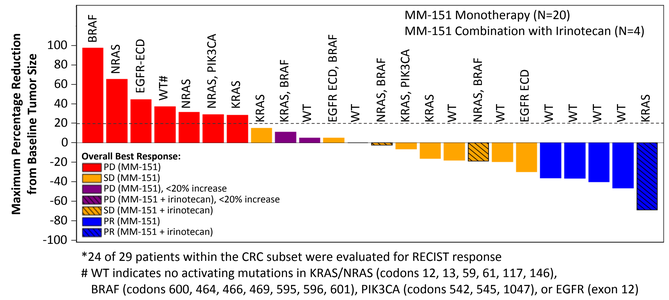
Patient Demographics

Characteristic	MM-151 Monotherapy (N=87)	MM-151 + Irinotecan (N=24)	Overall (N=111)
Gender, n (%)			
Male	39 (44.8)	14 (58.3)	53 (47.7)
Female	48 (55.2)	10 (41.7)	58 (52.3)
Age (years)			
Median	62	57.5	61
Range	30-85	39-85	30-85
Type of Cancer, n (%)			
Colorectal Cancer	38 (43.7)	7 (29.2)	45 (40.5)
Head and Neck Cancer	6 (6.9)	8 (33.3)	14 (12.6)
Non Small Cell Lung Cancer	9 (10.3)	2 (8.3)	11 (9.9)
Triple Negative Breast Cancer	2 (2.3)	1 (4.2)	3 (2.7)
Other Cancer Types	32 (36.8)	6 (25.0)	38 (34.2)
Time Since First Diagnosis (Months)			
Mean/SD	45.11 / 35.818	46.08 / 42.558	45.32 / 37.173
Median	32.66	39.38	33.61
Min/Max	2.8 / 233.7	8.2 / 226.2	2.8 / 233.7
Time Since Metastatic Diagnosis (Months)			
Mean/SD	31.58 / 25.010	27.78 / 23.032	30.78 / 24.546
Median	23.69	21.29	22.87
Min/Max	0.8 / 95.3	0.4 / 96.0	0.4 / 96.0

Preliminary Efficacy in Colorectal Cancer Patients

Subset analyses were performed for a cohort of colorectal cancer patients (N=29) who received the minimum efficacious dose of ≥ 6 mg/kg on QW or Q2W schedules.

Best response (per RECIST v1.1) versus genomic status

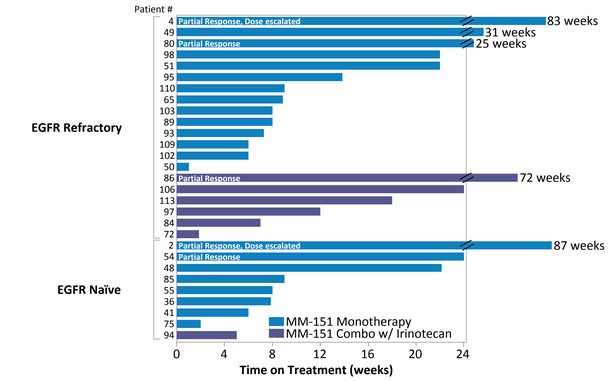


*24 of 29 patients within the CRC subset were evaluated for RECIST response
WT indicates no activating mutations in KRAS/NRAS (codons 12, 13, 59, 61, 117, 146), BRAF (codons 600, 464, 466, 469, 595, 596, 601), PIK3CA (codons 542, 545, 1047), or EGFR (exon 12)

- 13 of 24 patients (54%) had a reduction in target lesions
- Of the 15 patients who did not have early disease progression, 7 patients were wild-type, 4 KRAS mutant, 3 BRAF mutant, 2 NRAS mutant, and 2 EGFR ECD mutants (including co-occurring)

Time on Treatment for MM-151 Monotherapy and Irinotecan Combination

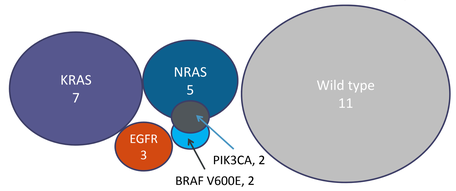
Overall median PFS was 4.0 months (CI 2.1- 5.4), with maximum PFS of 20.1 and 16.9 months on the MM-151 monotherapy and MM-151 + irinotecan combination cohorts, respectively.



Biomarker Studies

Genomic alterations were assessed in blood and tissue samples using next-generation sequencing assays performed by GuardantHealth (Guardant360) and OmniSeq (OmniSeq Comprehensive or OmniSeq PGM).

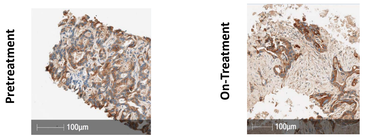
Pre-treatment somatic mutations in CRC efficacy cohort (N=28)



- Mutually exclusive activating mutations in KRAS/NRAS/BRAF were identified in 39% of CRC patients (11 of 28)
- Low occurrence of ***acquired*** KRAS/NRAS/BRAF mutations following treatment with MM-151 ± irinotecan was determined by an analysis of available, matched pre/post-treatment serum samples
  - Acquired mutation in 1 of 5 WT CRC patients
  - Acquired mutations in 2 of 19 WT patients (all indications)
- No CRC patients acquired an EGFR exon 12 mutation (N=8)

Summary of Exploratory Biomarker Analyses

- Heterogeneous mixtures of both low- and high-affinity EGFR ligands were measured in all pre-treatment serum (protein; N=20 CRC; N=35 all indications) and archival tissue (mRNA; N=20 CRC) samples.
  - High affinity ligands detected in pre-treatment biopsies within highly refractory CRC patients (N=4 of 4)
- EGFR downregulation was observed in matched pre/on-treatment tissue biopsies collected on the Part 2 CRC expansion (N=4).



- NK cell depletion was observed in blood samples from an unselected cohort of patients (N=4 of 4) following the first dose of MM-151 and is consistent with engagement of immune-effector activity (ADCC).
- No apparent trends in copy number variations were observed for EGFR, ErbB2, and MET in a comparison of pre-treatment and post-treatment samples (via Guardant360). Observed loss and acquisition of copy gain.

Adverse Events (all patients)

MM-151 Monotherapy (N=87)

Adverse Event *	Any Grade n (%)	Grade 3-4 n (%)
Infusion related reaction	61 (70.1)	11 (12.6)
Rash	39 (44.8)	7 (8.0)
Hypomagnesaemia	31 (35.6)	7 (8.0)
Fatigue	21 (24.1)	1 (1.1)
Diarrhoea	20 (23.0)	1 (1.1)
Dermatitis acneiform #	18 (20.7)	3 (3.4)
Rash maculo-papular	17 (19.5)	8 (9.2)
Dry skin	17 (19.5)	2 (2.3)
Pruritus	17 (19.5)	1 (1.1)
Nausea	14 (16.1)	0
Stomatitis #	12 (13.8)	1 (1.1)
Hypokalaemia	11 (12.6)	0
Weight decreased	9 (10.3)	0
Hypophosphataemia	9 (10.3)	4 (4.6)

MM-151 + Irinotecan (N=24)

Adverse Event *	Any Grade n (%)	Grade 3-4 n (%)
Diarrhoea #	19 (79.2)	4 (16.7)
Fatigue	16 (66.7)	0
Infusion related reaction	14 (58.3)	2 (8.3)
Rash maculo-papular	13 (54.2)	3 (12.5)
Nausea	11 (45.8)	1 (4.2)
Vomiting #	11 (45.8)	2 (8.3)
Decreased appetite	11 (45.8)	0
Hypomagnesaemia	10 (41.7)	3 (12.5)
Hypokalaemia	7 (29.2)	2 (8.3)
Alopecia	6 (25.0)	0
Mucosal inflammation	6 (25.0)	0
Dry skin	5 (20.8)	0
Stomatitis	5 (20.8)	0
Weight decreased	5 (20.8)	0
Anaemia	5 (20.8)	3 (12.5)
Neutropenia #	4 (16.7)	2 (8.3)
Rash	3 (12.5)	1 (4.2)
Dermatitis acneiform	3 (12.5)	1 (4.2)
Dysgeusia	3 (12.5)	0
Asthenia	3 (12.5)	0
Neutrophil count decreased	3 (12.5)	3 (12.5)

* Most common adverse events in ≥ 10% of patients in the MM-151 monotherapy or MM-151/irinotecan combination cohort
# contains a qualifying dose-limiting toxicity (DLT) event

- Toxicities in MM-151 monotherapy are similar to those observed with cetuximab. No MTD defined, however recommended dosing established.
- Combination treatment did not appear to exacerbate toxicities typical with irinotecan

Infusion Related Reactions by Infusion Schedule

Infusion Related Reaction (IRR)	Original[i] (N=37) n (%)	Modified 1[ii] (N=17) n (%)	Modified 2[iii] (N=57) n (%)
Any Grade	30 (81.1)	12 (70.6)	33 (57.9)
Grade 1	4 (10.8)	2 (11.8)	12 (21.1)
Grade 2	18 (48.6)	8 (47.1)	17 (29.8)
Grade 3	8 (21.6)	2 (11.8)	4 (7.0)
Grade 4	0	0	0
Grade 5	0	0	0

i. 90 minute infusion, steady rate, no premedication
ii. Premedications and steady rate increase (weight-based dosing)
iii. Premedications, two fixed priming doses (225 mg and 450 mg) followed by weight-based dosing at a staged rate increase

- Two classes of infusion related reactions were observed:
  - *Hypersensitivity* (onset within first ~15 minutes of infusion)
  - *Acute* (within 2 – 4 hours, coinciding with cytokine release)
- The most commonly reported IRR symptoms include rash, flushing and itching
- IRR frequency and severity were decreased following the introduction of the *Modified 2* infusion schedule

Conclusions

- MM-151 has demonstrated a comparable safety profile to approved EGFR inhibitors as a monotherapy and in combination with irinotecan
- Dosing schedule was established, including priming doses and premedication, followed by weight-based dosing at a staged rate increase
- Clinical validation of MM-151 mechanistic foundations observed in EGFR downregulation, expression of high affinity ligands across indications (including refractory mCRC) and activity in tumors expressing EGFR and downstream mutations (acquired and *de novo*)
- Decrease in measurable lesions observed in 54% of evaluable patients in CRC cohort were observed in both WT and mutant patients
- MM-151 demonstrates promising activity in highly refractory patient populations. Additional studies are planned within mCRC and other EGFR-driven indications as a monotherapy or in combination.

Acknowledgments

Merrimack Pharmaceuticals extends gratitude to our clinical investigators, collaborators, the study patients and their families for their participation in this first-in-human study.