First-in-Human Phase 1/1b Trial of the First-in-Class Bi-Steric mTORC1 Selective Inhibitor RMC-5552 in Patients with Advanced Solid Tumors

Schram AM[1], Naqash AR[2], Haura EB[3], Riess JW[4], Ulahannan SV[2], Ou SI[5], Capasso A[6], Munster PN[7], Cheng ML[7], Gustafson WC[8], Singh M[8], Bitman B[8], Friedman R[8], Penn R[8], Kar S[8], Wang Z[8], Tao L[8], Meyerowitz JG[8], Burris HA[9]

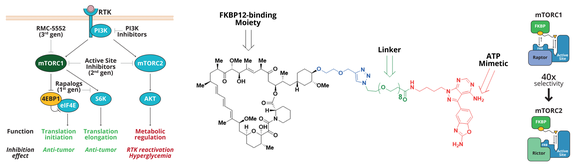
[1]Memorial Sloan Kettering Cancer Center, New York, NY; [2]Stephenson Cancer Center at the University of Oklahoma, Oklahoma City, OK; [3]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [4]UC Davis Comprehensive Cancer Center, Sacramento, CA; [5]Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA; [6]Livestrong Cancer Institutes, University of Texas at Austin, Austin, TX; [7]University of California San Francisco, San Francisco, CA; [8]Revolution Medicines, Redwood City, CA; [9]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN

RMC-5552 Background and Mechanism of Action

- Activation of the mTOR pathway plays a role in the oncogenesis and progression of many cancer types, and is frequently co-altered in RAS-driven tumors.[1]
- First-generation mTORC1-selective inhibitors were limited by incomplete inhibition of 4EBP1 phosphorylation, while second-generation pan-mTOR inhibitors had a low therapeutic index due to mTORC2-mediated toxicity such as hyperglycemia.[2,3]

RMC-5552 is a first-in-class bi-steric, third-generation mTOR inhibitor[1-3]

- Selectively recruited to mTORC1 via its FKBP12-binding moiety.
- Potently inhibits phosphorylation of the 4EBP1 tumor suppressor via a linked ATP-competitive moiety.
- Demonstrates key advantages over prior mTOR inhibitors in preclinical models.



Methods

- RMC-5552 is being investigated in an ongoing Phase I/Ib study (NCT04774952). Objectives include assessment of safety/tolerability, preliminary efficacy, pharmacokinetics, and defining the maximum tolerated and recommended Phase 2 doses.
- Patients received RMC-5552 as a weekly infusion. To address mucositis, a common toxicity in patients treated with mTOR inhibitors, patients prophylactically used dexamethasone mouthwash either alone or with tacrolimus mouthwash (TM).
- The cutoff date for all clinical data was 04 September 2023.

Results

1. Baseline Characteristics

	1.6 mg/3 mg (n=5)	6 mg (n=12)	8 mg* (n=16)	10 mg (n=8)	12 mg (n=8)	16 mg (n=4)	Overall (N=51)
Age, median (range), years	61 (56–62)	65 (53–77)	62 (56–74)	68 (44–76)	61 (41–80)	62 (48–67)	62 (41–80)
Male, n (%)	2 (40)	7 (58)	7 (44)	5 (63)	5 (83)	1 (25)	27 (53)
Cancer type, n (%)							
Head and neck	2 (40)	3 (25)	3 (19)	2 (25)	1 (17)	0	11 (22)
Colorectal	0	0	3 (19)	2 (25	1 (17)	1 (25)	7 (14)
Lung	0	0	3 (19)	1 (13)	2 (33)	0	6 (12)
Ovarian	1 (20)	3 (25)	1 (6)	0	0	1 (25)	6 (12)
Pancreatic	0	1 (8)	0	0	0	0	1 (2)
Other	2 (40)	5 (42)	6 (38)	3 (38)	2 (33)	2 (50)	20 (39)
ECOG PS, n (%)							
0	1 (20)	4 (33)	9 (56)	4 (50)	2 (33)	2 (50)	22 (43)
1	4 (80)	8 (67)	7 (44)	4 (50)	4 (67)	2 (50)	29 (57)
Number of prior cancer therapies, median (range)	5 (1–8)	4 (1–15)	3 (0–7)	3 (2–6)	3 (1–4)	6 (2–6)	3 (0–15)
Pathogenic mTOR pathway variant, local testing (%)	80	75	44	75	17	50	57

*Includes one subject who was dosed as part of the expansion phase prior to re-opening the escalation phase.

2. Incidence of Most Common TRAEs (≥15% Overall Population)

	1.6 mg/3 mg (n=5)		6 mg (n=12)		8 mg* (n=16)		10 mg (n=8)		12 mg (n=6)		16 mg (n=4)		Overall (N=51)	
	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3	All Grade	Grade ≥3
Number of subjects with any event, n (%)	5 (100)	2 (40)	11 (92)	4 (33)	14 (88)	5 (31)	7 (88)	3 (38)	5 (83)	3 (50)	3 (75)	3 (75)	45 (88)	20 (39)
Stomatitis/mucositis†	1 (20)	0	6 (50)	1 (8)	7 (44)	0	5 (63)	1 (13)	4 (67)	2 (33)#	3 (75)	1 (25)	26 (51)	5 (10)
Fatigue‡	1 (20)	0	5 (42)	1 (8)	7 (44)	0	4 (50)	1 (13)	3 (50)	0	2 (50)	0	22 (43)	2 (4)
Nausea	0	0	6 (50)	0	6 (50)	1 (6)	4 (50)	0	3 (50)	0	2 (50)	0	21 (41)	1 (2)
Decreased appetite	2 (40)	0	8 (67)	0	4 (25)	0	1 (13)	0	1 (17)	1 (17)	1 (25)	0	17 (33)	1 (2)
Vomiting	0	0	5 (42)	0	4 (25)	0	1 (13)	0	2 (33)	0	1 (25)	0	13 (26)	0
Rash§	0	0	4 (33)	1 (8)	3 (19)	1 (6)	1 (13)	0	1 (17)	0	1 (25)	0	10 (20)	2 (4)
Diarrhea	1 (20)	0	0	0	4 (25)	0	3 (38)	0	1 (17)	0	0	0	9 (18)	0
Anemia	1 (20)	1 (20)	1 (8)	0	5 (31)	3 (19)	0	0	0	0	1 (25)	1 (25)	8 (16)	5 (10)

A subject with multiple severity grades for a given AE was counted only once at the highest severity grade. Preferred terms were sorted by decreasing order of frequency. MedDRA version 23.0. *Includes one subject who was dosed as part of the expansion phase prior to re-opening the escalation phase; †Including the following preferred terms: mucosal inflammation, oral mucosal blistering, oral pain, stomatitis; ‡Including the following preferred terms: asthenia, fatigue, malaise; §Including following preferred terms: dermatitis allergic, erythema, rash, rash macular, rash maculo-papular, rash pustular; #All events of Grade 3 mucositis at 12 mg IV QW occurred in patients using dexamethasone mouthwash alone.

- TRAEs of hyperglycemia occurred in 4% of patients (both Grade 2) and were not dose limiting.
- The most common Grade 3 TRAE at dose levels ≥6 mg was mucositis/stomatitis, which was dose-dependent and limited tolerability in the absence of TM.
- No Grade 4 or 5 TRAEs were observed at any dose level.

3. AEs Leading to Dose Modifications

Number of Subjects with Event, n (%)	1.6 mg/3 mg (n=5)	6 mg (n=12)	8 mg* (n=16)	10 mg (n= 8)	12 mg (n=6)	16 mg (n=4)	Overall (N=51)
AEs leading to dose interruption	4 (80)	8 (67)	8 (50)	7 (88)	3 (50)	3 (75)	33 (65)
AEs leading to dose reduction	0	0	0	1 (13)	0	0	1 (2)
AEs leading to dose and schedule change	0	0	0	0	1 (17)	1 (25)	2 (4)
AEs leading to RMC-5552 discontinuation	0	1 (8)	2 (13)	0	0	0	3† (6)
TRAEs leading to dose interruption	2 (40)	5 (42)	4 (25)	4 (50)	3 (50)	2 (50)	20 (39)
TRAEs leading to dose reduction	0	0	0	1 (13)	0	0	1 (2)
TRAEs leading to dose and schedule change	0	0	0	0	1 (17)	1 (25)	2 (4)
TRAEs leading to RMC-5552 discontinuation	0	1 (8)	0	0	0	0	1 (2)

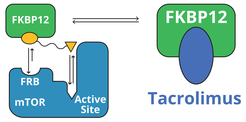
*Includes one subject who was dosed as part of the expansion phase prior to re-opening the escalation phase; †Grade 3 asthenia, Grade 3 rash maculo-papular, Grade 3 pneumonia aspiration.

- Mucositis limited tolerability at doses ≥8 mg IV QW in patients using dexamethasone mouthwash alone, and was the most common AE leading to dose interruption.

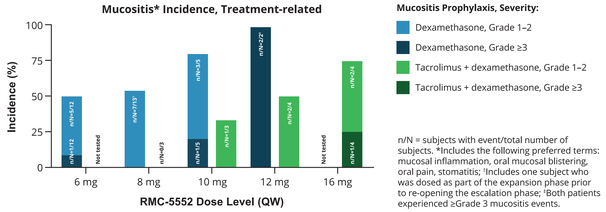
4. Tacrolimus Mouthwash: Potential Mucositis Mitigation Strategy

Rationale for use of TM as a mucositis mitigation measure:

- RMC-5552 binds to FKBP12 and the FKBP12-RMC-5552 complex is recruited to mTORC1.
- Tacrolimus may bind to FKBP12 in oral mucosa, thus occupying the RMC-5552 binding site to prevent RMC-5552 inhibition of mTORC1.



5. Incidence and Severity of Mucositis by Use of Tacrolimus Mouthwash



n/N = subjects with event/total number of subjects. *Includes the following preferred terms: mucosal inflammation, oral mucosal blistering, oral pain, stomatitis; †Includes one subject who was dosed as part of the expansion phase prior to re-opening the escalation phase; ‡Both patients experienced ≥Grade 3 mucositis events.

- Between 8–12 mg, the rate of treatment-related stomatitis/mucositis was 65% (15%, Grade 3) in patients treated without TM (n=20) versus 30% (no Grade 3) in patients treated with TM (n=10).
- TM prophylaxis enabled dose escalation beyond dose levels previously considered intolerable due to mucositis (10–12 mg).
- Unbound plasma exposures at 8–12 mg were within the range that induced significant anti-tumor activity in preclinical models.

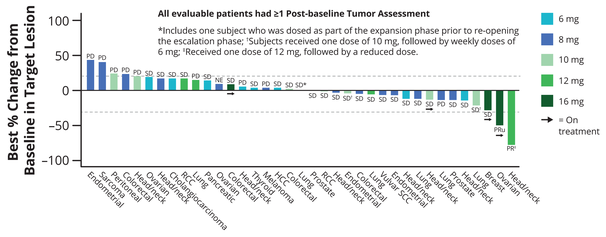
6. Dose-dependent Exposure Increase of RMC-5552 After Single or Repeat Dosing

Dose (mg)	Day	PK Parameters	
		C_{max} (nM)	AUC_0 (nMxh)
6	1	101 ± 34.2	**140** ± 48.7
	15	155 ± 43.0	**219** ± 87.1
8	1	148 ± 60.8	**213** ± 77.5
	15	332 ± 135	**460** ± 202
10	1	204 ± 64.0	**276** ± 87.1
	15	284 ± 161.5	**391** ± 231
12	1	264 ± 117	**345** ± 137
	15	391 ± 115	**579** ± 220
16	1	370 ± 51	**610** ± 141
	15*	529	1022

*Patient n=1.

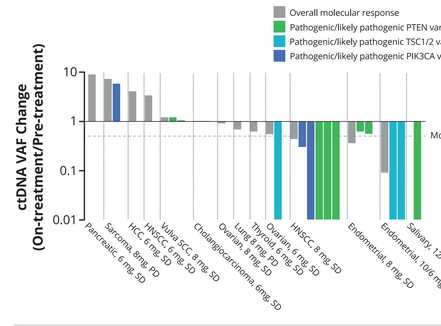
- Exposure on C1D15 was approximately 1.5–2x higher than C1D1 despite undetectable trough levels, across all dose levels.

7. Best Percent Change in Tumor Burden from Baseline Efficacy Evaluable Subjects Treated at ≥6 mg



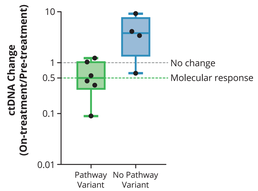
- The disease control rate was 68% among efficacy-evaluable patients treated at ≥6 mg (n=40).
- One patient with a salivary gland tumor harboring a PTEN mutation had a confirmed PR with 78% reduction and 16 months duration of response, and another patient with ovarian cancer had an unconfirmed PR on their first scan and is still on treatment.
- Since data cutoff date, one patient with breast cancer harboring a PTEN mutation had an unconfirmed PR at C5D1, and she remains on treatment as of October 9, 2023.

8. Clearance of Pathogenic mTOR Pathway Variants in ctDNA at Doses ≥6 mg



Change in mean VAF from C1D1 to C3D1 determined by Guardant Health molecular response algorithm. Molecular response is ≥50% reduction. Complete loss of allele is truncated at 0.01. *Not evaluable for overall molecular response.

9. Molecular Responses to RMC-5552 in Patients with an mTOR Pathway Variant



Patients with best response as SD per RECIST who received ≥6 mg RMC-5552. Pathway variant = harboring pathogenic PTEN, PIK3CA, or TSC1/2 variant at baseline.

Change in mean VAF from C1D1 to C3D1 determined by Guardant Health molecular response algorithm. Molecular response is ≥50% reduction.

Conclusions

- These early data indicate that RMC-5552 monotherapy is tolerated at doses predicted to have anti-tumor activity, and that selective inhibition of mTORC1 alleviates mTORC2-mediated toxicities, such as hyperglycemia.
- While PRs were observed in tumors with and without mTOR pathway-activating mutations, preliminary molecular response data suggest the potential for greater activity against tumors harboring these mutations.
- Dose optimization is ongoing, and mucositis prophylaxis has enabled further dose intensification for future combination studies with RAS(ON) inhibitors.

References: 1. Burnett GL, et al. J Med Chem. 2023;66:149–169; 2. Meng D, et al. Oncogene. 2023;42:2207–2217; 3. Lee BJ. et al. Nat Chem Biol. 2021;17:1065–1074.

Abbreviations: 4EBP1, eukaryotic translation initiation factor 4E-binding protein 1; AE, adverse event; AKT, protein kinase B; ATP, adenosine triphosphate; C, cycle; CaN, calcineurin; C_{max}, time to maximum concentration; ctDNA, circulating tumor DNA; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; eIF4E, eukaryotic translation initiation factor; FKBP, FK506 binding proteins; FKBP12, 12-kDa FK506-binding protein; FRB, FKBP rapamycin binding; HCC, hepatocellular carcinoma; IV, intravenous; MedDRA, Medical Dictionary for Regulatory Activities; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; PD, progressive disease; PK, pharmacokinetics; PR, partial response; PRu, unconfirmed partial response; PTEN, phosphatase and tensin homolog; QW, weekly; RAS, rat sarcoma; RECIST, Response Evaluation Criteria in Solid Tumors; RCC, renal cell carcinoma; RTK, receptor tyrosine kinase; S6K, ribosomal protein S6 kinase; SCC, squamous cell carcinoma; SD, stable disease; TM, tacrolimus mouthwash; TRAE, treatment-related adverse event; TSC1/2, tuberous sclerosis proteins 1 and 2; VAF, variant allele frequency.

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