Anti-tumor Activity and Tolerability of the SHP2 Inhibitor RMC-4630 as a Single Agent in Patients with RAS-Addicted Solid Cancers

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Disclosure Information

AACR Annual Meeting 2021 | April 10-15, 2021 | Virtual Meeting

Dr. Marianna Koczywas, MD

I have no financial relationships to disclose.

- and -

I will discuss the following off label use and/or investigational use in my presentation: ongoing and planned studies of RMC-4630

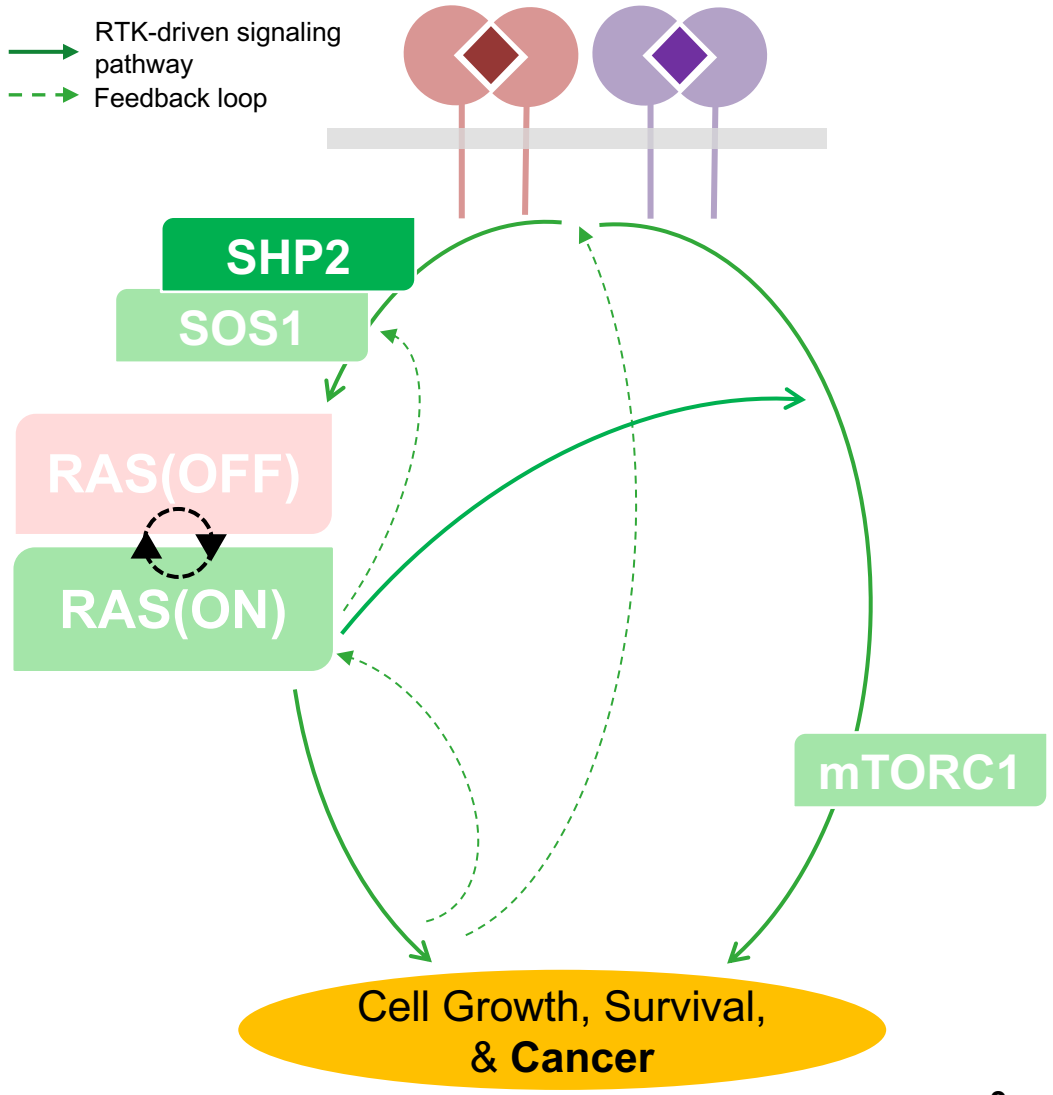
RMC-4630: Potent, Oral Inhibitor of SHP2 – Central Node in the RAS Signaling Pathway

Primary objective of single agent phase 1 study (RMC-4630-01) is to establish a recommended phase 2 dose and schedule (RP2DS) for:

- Phase 1b monotherapy expansion
- Guide RMC-4630 dosing as a combination partner to position RMC-4630 as a 'backbone' for RAS-addicted tumors

Preliminary reports from RMC-4630-01 have shown:

- Initial monotherapy activity in multiple cancers and genotypes
- Initial clinical evidence of enhanced immune infiltration in tumors



RMC-4630/SAR442720. Under 2018 partnership with Sanofi

RMC-4630-01: Study Design to Exploit Intermittent Target Inhibition

In preclinical models intermittent dosing of RMC-4630 resulted in:

- Plasma concentrations consistent with induction of tumor cell apoptosis
- Superior efficacy
- Improved tolerability

Key Eligibility Criteria

- Advanced solid tumor malignancy
- Received prior standard of care therapies
- ECOG 0-1
- No active brain metastases

Study Design

- 3-6 patients per cohort
- Dose expansions (below RP2D) per observed safety/PK/PD/efficacy data in up to 12 patients
- Treatment until disease progression, intolerance or withdrawal

Schedule	Dose§ Levels	All (N=106)	
QD Schedule	20 mg QD	12	49
	40 mg QD	13	
	60 mg QD	18	
	80 mg QD	6	
Intermittent Schedule D1D4	140 mg	8	31
	200 mg	18	
	240 mg	5	
Intermittent Schedule D1D2	200 mg*	10	26
	240 mg	11	
	280 mg	5	

*Recommended Phase 2 Dose and Schedule (RP2DS)
§Cycle length 28-days for all dose schedules

EDC data as of 20 Feb 2021

RP2DS Maximizes Dose Intensity Without Compromising Safety and Tolerability

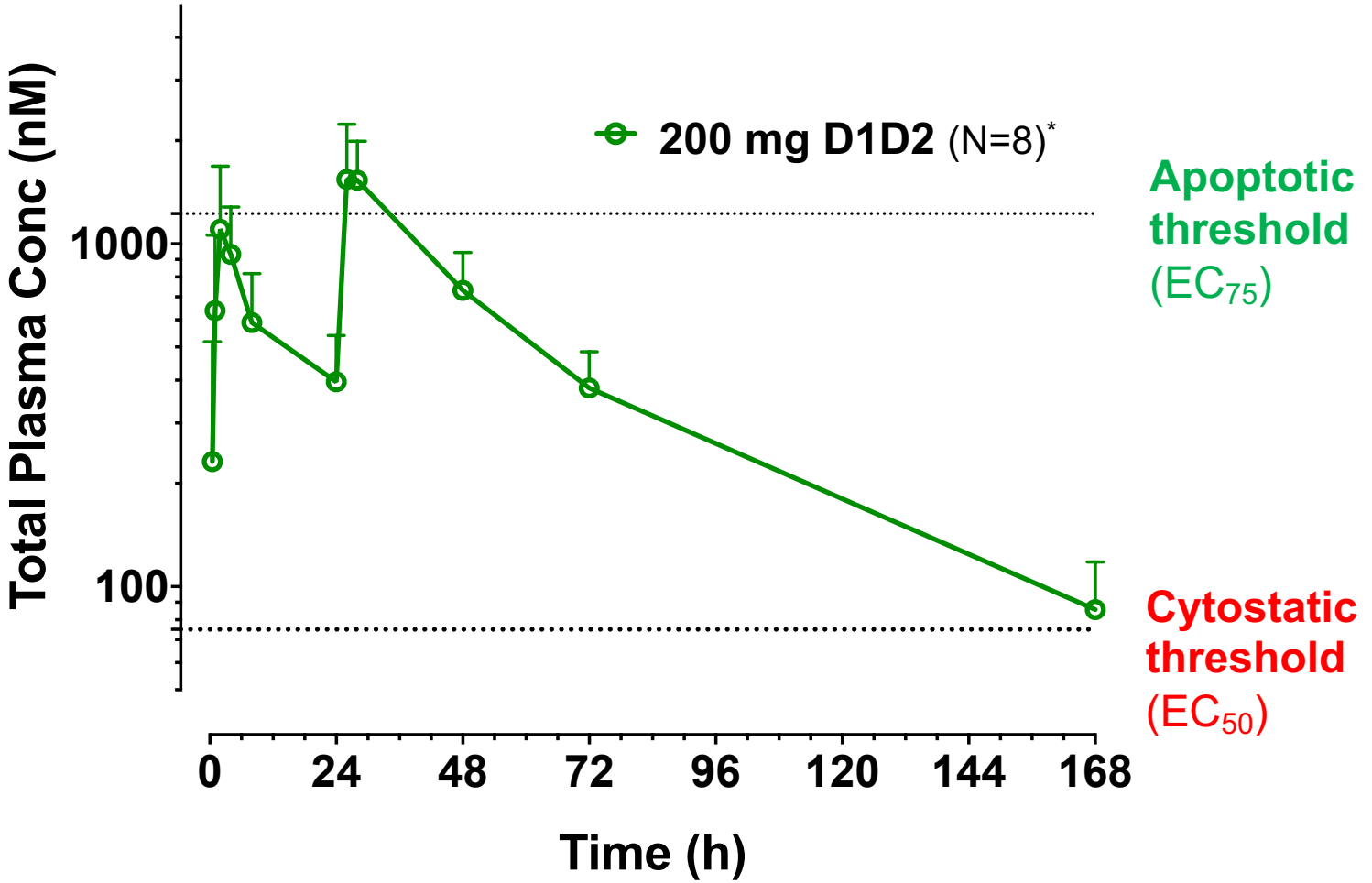
Related Adverse Events in >20% of Patients	Intermittent Schedule (D1D4) (N=31)		Intermittent Schedule (D1D2)			
			200 mg (RP2DS) (N=10)		All (N=26)§	
	Any Grade	Grade ≥3	**Any Grade**	**Grade ≥3**	Any Grade	Grade ≥3
Diarrhoea	13 (41.9%)	2 (6.5%)	**4 (40.0%)**	**0**	11 (42.3%)	1 (3.8%)
Edema*	9 (29.0%)	2 (6.5%)	**4 (40.0%)**	**0**	12 (46.2%)	0
Fatigue	12 (38.7%)	2 (6.5%)	**3 (30.0%)**	**0**	8 (30.8%)	0
Thrombocytopenia**	9 (29.0%)	3 (9.7%)	**4 (40.0%)**	**1 (10.0%)**	8 (30.8%)	3 (11.5%)
Anemia***	8 (25.8%)	3 (9.7%)	**2 (20.0%)**	**0**	7 (26.9%)	3 (11.5%)
Nausea	7 (22.6%)	2 (6.5%)	**1 (10.0%)**	**0**	2 (7.7%)	0
Decreased Appetite	3 (9.7%)	0	**3 (30.0%)**	**0**	5 (19.2%)	0
Myalgia	2 (6.5%)	0	**3 (30.0%)**	**0**	4 (15.4%)	0

Tolerability Parameters	Intermittent Schedule (D1D4) (N=31)	Intermittent Schedule (D1D2)	
		200 mg (RP2DS) (N=10)	All (N=26)§
Related Grade ≥3 AEs	17 (54.8%)	**2 (20.0%)**	11 (42.3%)
Grade 3	16 (51.6%)	**2 (20.0%)**	9 (34.6%)
Grade 4	1 (3.2%)	**0**	2 (7.7%)
AEs leading to dose interruption	18 (58.1%)	**5 (50.0%)**	17 (65.4%)
AEs leading to dose reductions	2 (6.5%)	**0**	2 (7.7%)
AEs leading to study drug discontinuation	4 (12.9%)	**0**	1 (3.8%)

Company-defined MedDRA Query (CMQ) includes eyelid edema, face edema, generalized edema, lip edema, edema, edema peripheral, periorbital edema, and peripheral swelling;
** Includes platelet count decrease; *** Includes hemoglobin decrease; §Includes dose levels 200 mg, 240 mg, and 280 mg D1D2

EDC data as of 20 Feb 2021

Target Exposure Predicted from Preclinical Models Exceeded at 200 mg D1D2 Dosing (RP2DS)

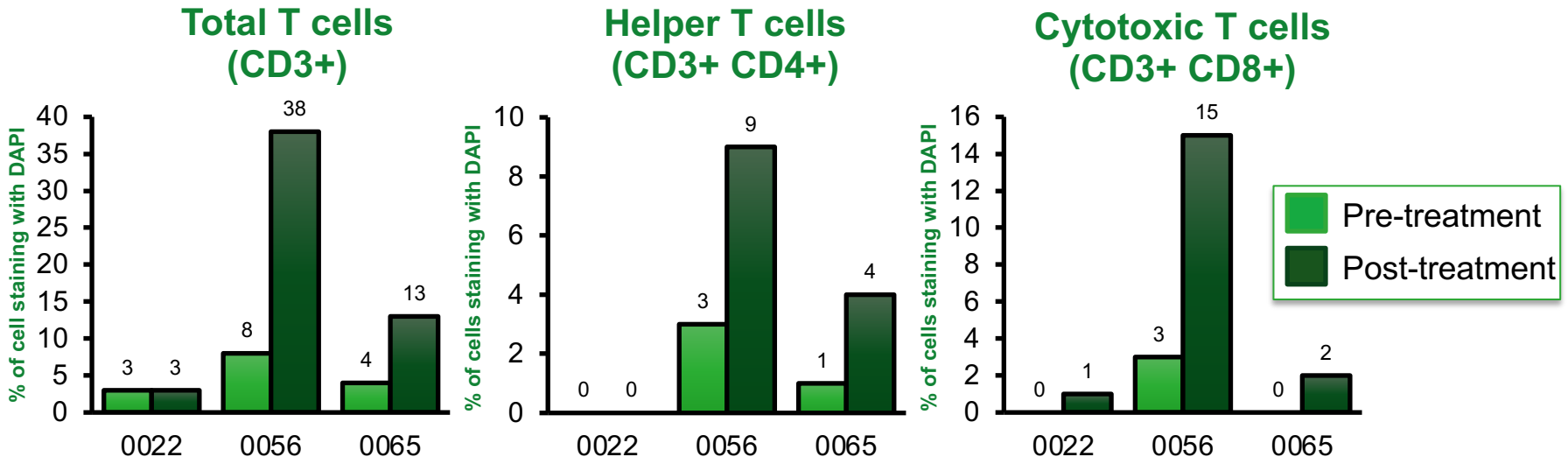


pERK EC_{75} and EC_{50} in NCI-H358 $KRAS^{G12C/WT}$ NSCLC Xenograft Model

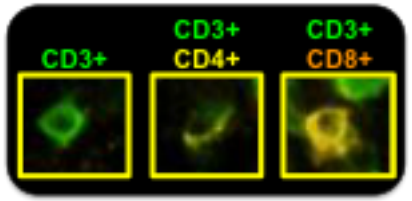
*PK for all patients in the 200 mg D1D2 dose escalation cohort where PK sampling timepoints are post-C1D1 and C1D2 dosing and C1D8 trough (~168 h)

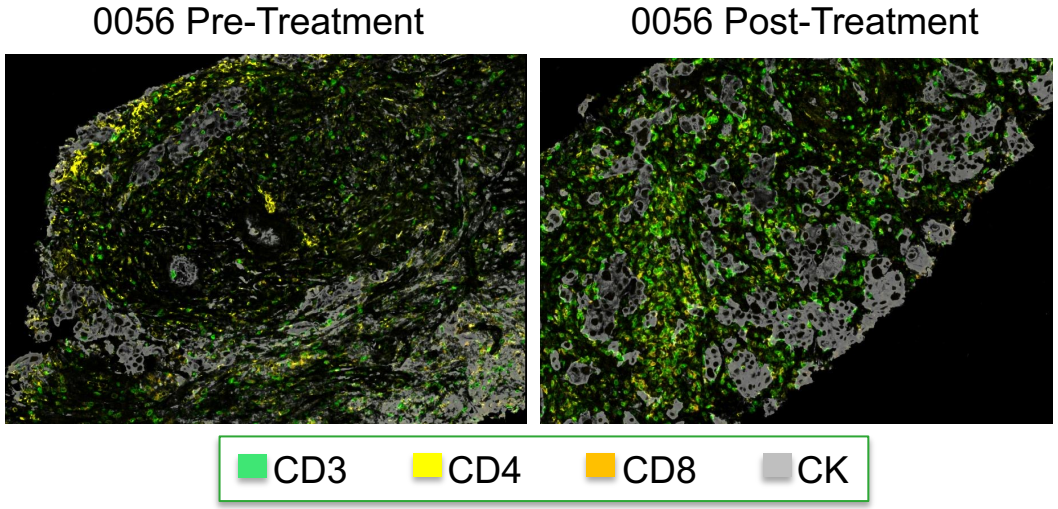
Preliminary Observations Suggest Increased T Cell Infiltration in Tumors on RMC-4630 Treatment

For More RMC-4630 PD Results, Visit LB050



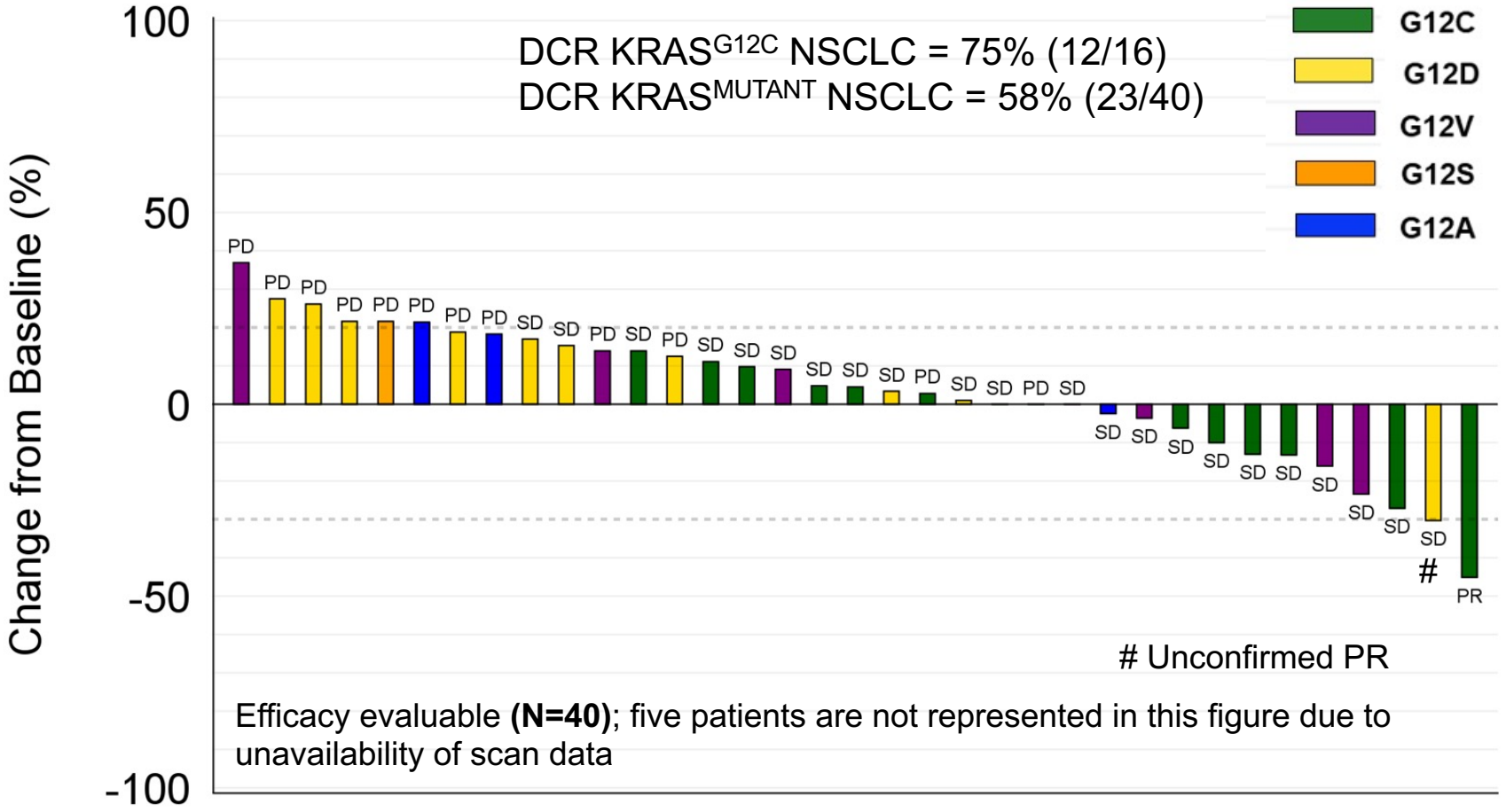
Pt. ID	Histotype	Mutations	Dose	Best Response
0022	SARCOMA	NF1:E73fs	40mg QD	PD
0056	NSCLC	KRAS:G12C	60mg QD	PR
0065	NSCLC	KRAS G12C	140mg D1D4	SD





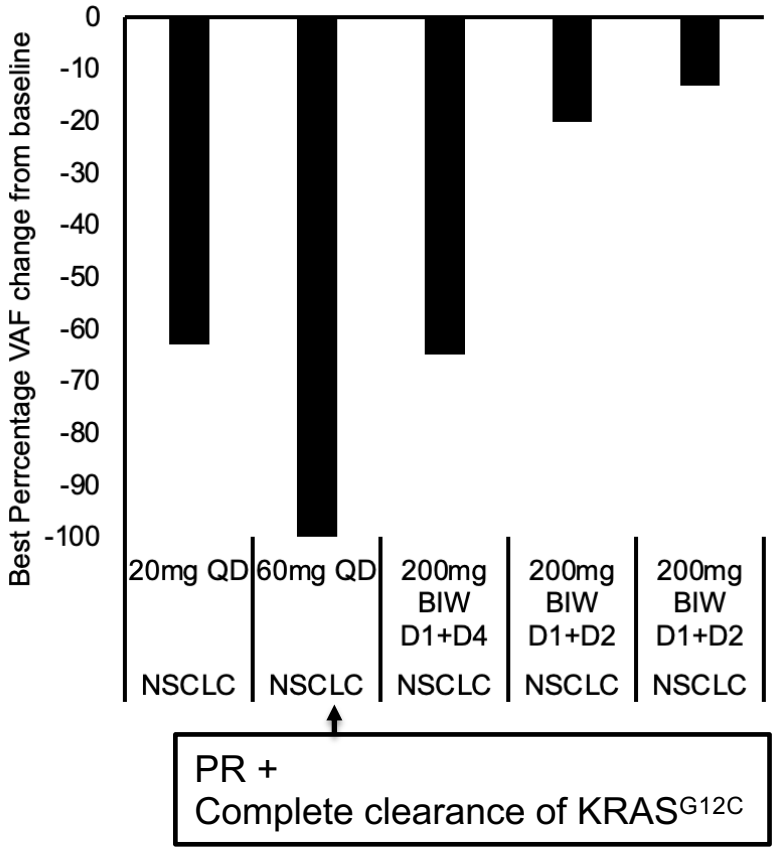
Single Agent RMC-4630 Results in Objective and Molecular Responses in KRAS^{MUTANT} NSCLC

For More RMC-4630 ctDNA Results, Visit LB054



NSCLC = Non-small cell lung cancer; DCR = Disease Control Rate (no PD at first response assessment); PD = Progressive Disease; SD = Stable Disease; PR = Partial Response; PD, SD and PR each per RECIST 1.1

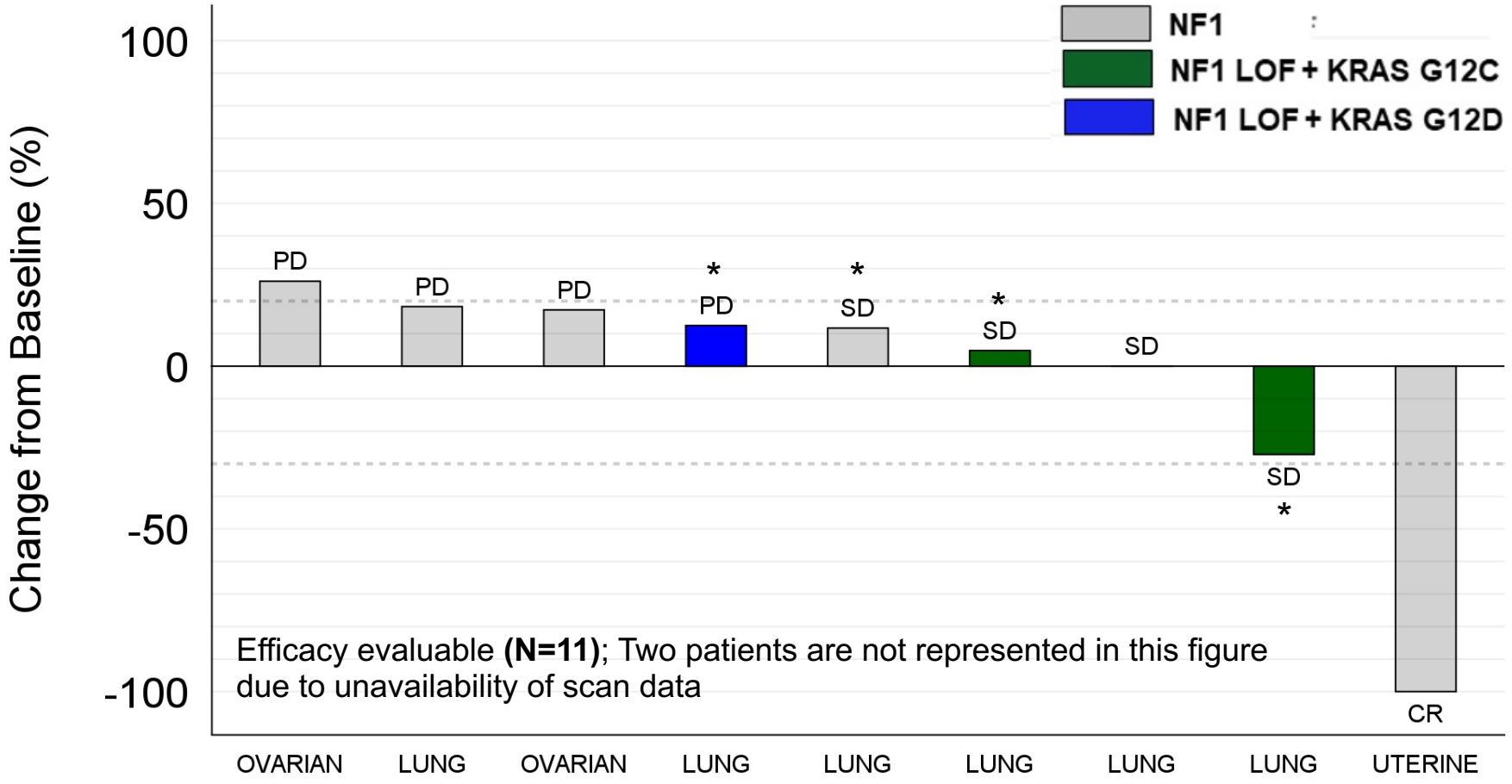
Best percentage change in variant allele frequency (VAF) in circulating tumor DNA* for all KRAS^{G12C} NSCLC



*Circulating tumor DNA detected using Guardant Health OMNI

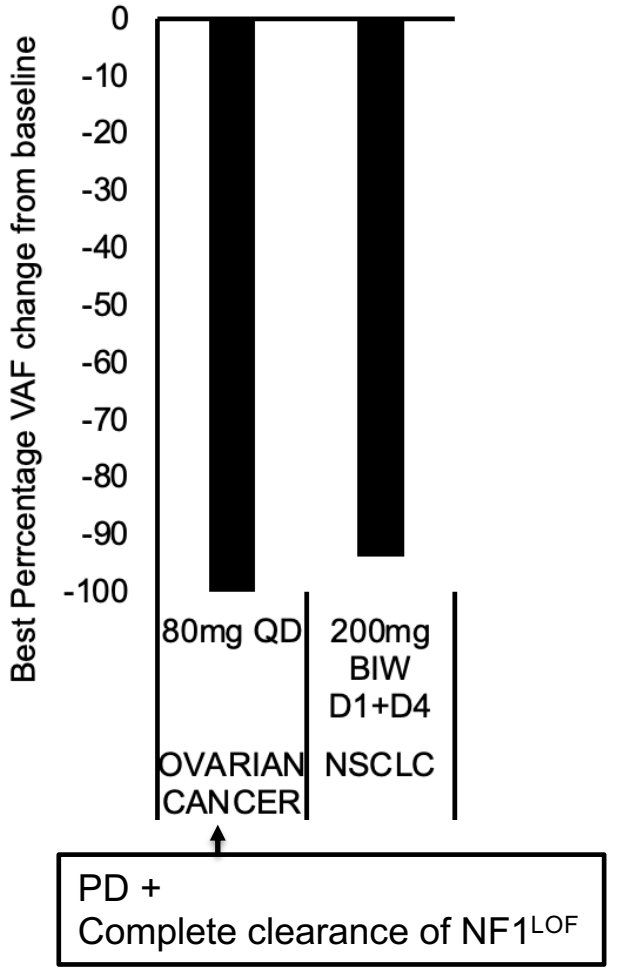
Single Agent RMC-4630 Results in a Complete Response in NF1^{LOF} Uterine Cancer

For More RMC-4630 ctDNA Results, Visit LB054



NF1^{LOF}: Loss, or significant reduction, in neurofibromin protein function is presumed from nature of mutation.
*Four patients had NF1^{LOF} mutations per retrospective ctDNA analysis and eligibility was based on historical genomic report

Best percentage change in variant allele frequency (VAF) in circulating tumor DNA§



§Circulating tumor DNA detected using Guardant Health OMNI

Central Clinical Thesis: RMC-4630 as Backbone for Rational, Mechanism-Based Combinations

RMC-4630 Combination Strategies[1]		Compound	Collaborator	
"Clamp" RAS Pathway	MEK inhibitors	cobimetinib (Cotellic®)	Roche	Ph 2[2]
	ERK inhibitors	LY-3214996	Netherlands Cancer Institute	
Mutant-Selective Inhibitors	$KRAS^{G12C}$ inhibitors	sotorasib / AMG 510	Amgen	Ph 1b
		TBA	AstraZeneca	
	RTK inhibitors	osimertinib (Tagrisso®)		Ph 1b[2]
Immune	Checkpoint inhibitors	pembrolizumab (Keytruda®)	Sanofi	Ph 1b

(1) Clinical development under Sanofi-RevMed collaboration agreement with individual studies sponsored by different companies
(2) Study sponsored by RVMD

Conclusions

- Intermittent dosing enables optimized plasma exposure at recommended phase 2 dose and schedule for RMC-4630
- Safety and tolerability profile is consistent with on-pathway inhibition
- Anti-tumor activity in RAS-addicted cancers was demonstrated by tumor regressions, PD effects, and molecular responses
- Positions RMC-4630 for further phase 2 development and as a potential backbone of RAS-directed therapies[1,2]

1: Revolution Medicines S-1 filing January 2020
2: Smith JA et al AACR 2020

Acknowledgements

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