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Supplemental Material to:

Reshma Rangwala, Claire Chang, Janice Hu, Kenneth Algazy, Tracey Evans, Leslie Fecher, Lynn Schuchter, Drew A Torigian, Jeffrey Panossian, Andrea Troxel, Kay-See Tan, Dan F Hetjian, Angela Demichele, David Vaughn, Maryann Redlinger, Abass Alavi, Jonathon Kaiser, Laura Pontiggia, Lisa E Davis, Peter J O'Dwyer, and Ravi K Amaravadi

Combined MTOR and autophagy inhibition: Phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma

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Table S1. HCQ dose cohorts

HCQ/mg day Dose Cohort	N	HCQ Schedule
200	11	200 mg daily
400	3	200 mg twice daily
800	9	400 mg twice daily
1200	15	600 mg twice daily

Table S2. Melanoma patient characteristics	
Age , median (range)	60 (51-80)
Gender, N (%)	
Male	14 (74%)
Female	5 (26%)
ECOG PS, N (%)	
0	13 (68%)
1	6 (32%)
Stage, N (%)	
M1a/M1b	21%
M1c	69%
LDH, N (%)	
LDH < ULN	47%
LDH>ULN	53%
Brain mets, N (%)	
	5 (26%)
BRAF mutation status, N (%)	
BRAF mutant	16% (2 V600E, 1K601E)
BRAF WT	84%
Prior therapies	
Number, median (range)	1 (0-5)
Prior ipilumumab, N (%)	2 (11%)
Prior BRAF inhibitor, N (%)	2 (11%)

Table S3. Dose escalation and dose limiting toxicities				
HCQ dose cohort (mg/day)	**HCQ dosing**	**N**	**Dose-limiting toxicity (N)**	**Other serious adverse events (N)**
200	200 mg po qd	11	Grade 4 thrombocytopenia and bleeding (1)	None
400	200 mg po bid	3	None	Grade 4 pulmonary tumor abscess
800	400 mg po bid	9	None	Grade 5 pneumonia and sepsis (1) Grade 3 perirectal abscess (1)
1200	600 mg po bid	15	None	Grade 3 anal fissure (1)

Table S4. Evidence of progressive melanoma at study entry in HCQ 1200 mg/day patients				
Patient*	Representative lesions	Prior scan**, cm	Baseline scan, cm	Evidence of progressive disease at study entry?
1	Left adrenal mass	absent	3.1	Yes
	Right adrenal mass	0.5	1.3	
2	RML Lung	0.7	1.2	Yes
	RUL Lung	1.3	2.1	
	Left inguinal LN	2.1	2.9	
	cutaneous nodule	2	2.8	
3	Liver #1	2.1	2.5	Yes
	Liver #2	3	3.3	
	Number of liver lesions		increased	
4	cutaneous nodule	absent	1.7	Yes
	Left hilar LN	asbent	1.5	
5	Liver #1	0.7	1.7	Yes
	Number of liver lesions		increased	
6	LLL Lung #1	2	3	Yes
	LLL Lung #2	3.6	4.3	
	Number of lung lesions		increased	
	Liver #1	7.2	9.6	
	Number of liver lesions		increased	
	Left inguinal LN	6.5	7.7	
7	LUL lung #1	0.8	1.5	Yes
	LUL lung #2	0.8	2.1	
	Left axillary LN	1.9	2.8	
8	gall bladder	5.9	6.3	Yes
	spleen #1	7.1	7.4	
	spleen #2	3.5	2.8	
9	Number of liver lesions	0	5	Yes
10	Number of lung lesions	6	8	Yes
	RLL Lung #1	1	2.5	
11	Number of liver lesions	not specified	15	Yes
	Right adrenal mass	absent	1.5	
	pancreatic mass	absent	2.2	
	portocaval LN	absent	5	
12	RML Lung	0.9	1.3	Yes
	subcarinal LN	1.8	2.8	
	Left axillary LN	1.7	1.9	
	Left hilar LN	absent	1.6	
	Spleen #1	3	3.4	
	Spleen #2	2.8	3.2	
	Left adrenal	5.6	6.2	
	gastric mass	2	3.1	
13	Right axillary LN	2.6	3.7	Yes
	Left axillary LN	2.5	3.3	

* Patients with advanced melanoma treated with temsirolimus and 1200 mg/day of hydroxychloroquine.
**CT or PET/CT scan obtained immediately prior to baseline scan (between 2 weeks and 6 months prior to baseline).
Abbreviations: RML, right middle lobe; RUL, right upper lobe; LN, lymph node; LLL, left lower lobe; LUL, left upper lobe

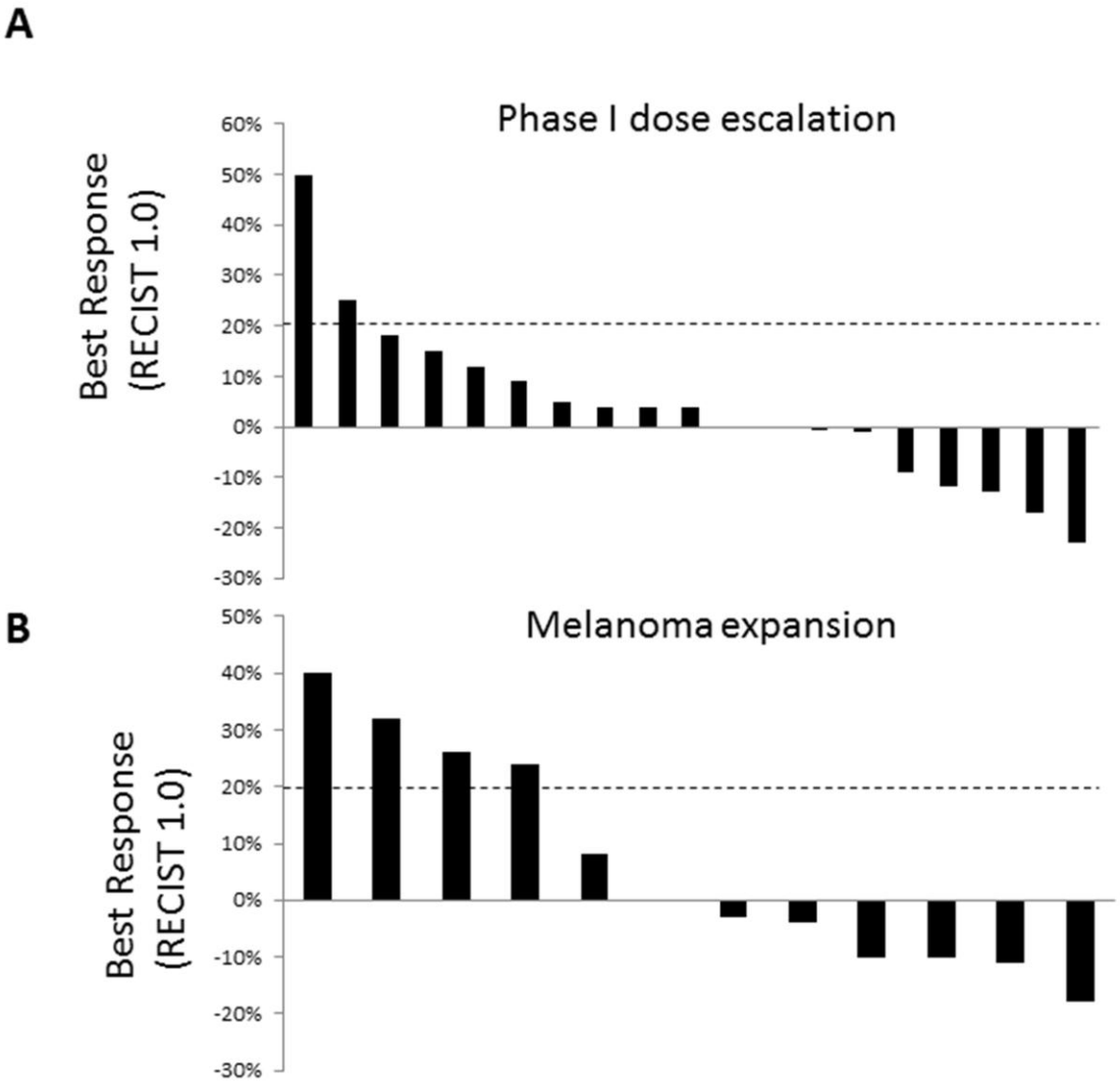

Figure S1. Waterfall plots of best response by sum of target lesions at nadir in patients treated with temsirolimus and hydroxychloroquine. Each bar represents an individual patient. (**A**) Dose escalation cohort. (**B**) Melanoma expansion cohort. Dotted line, threshold for progressive disease.

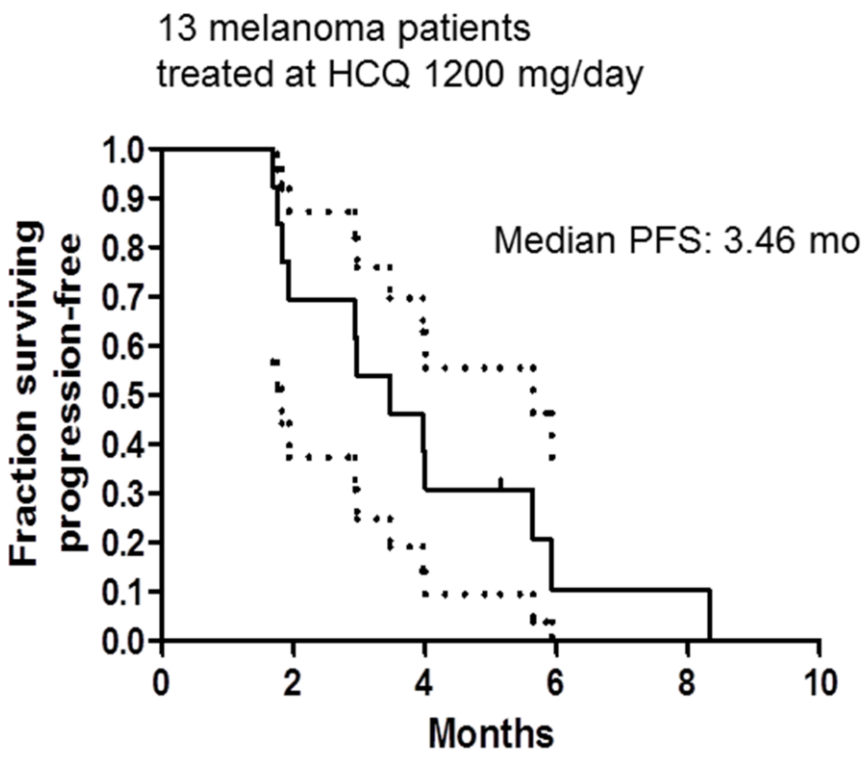

Figure S2. Kaplan Meier survival analysis of progression-free survival in 13 melanoma patients treated with temsirolimus and HCQ 1200 mg/day. Dotted lines, 95% confidence intervals.