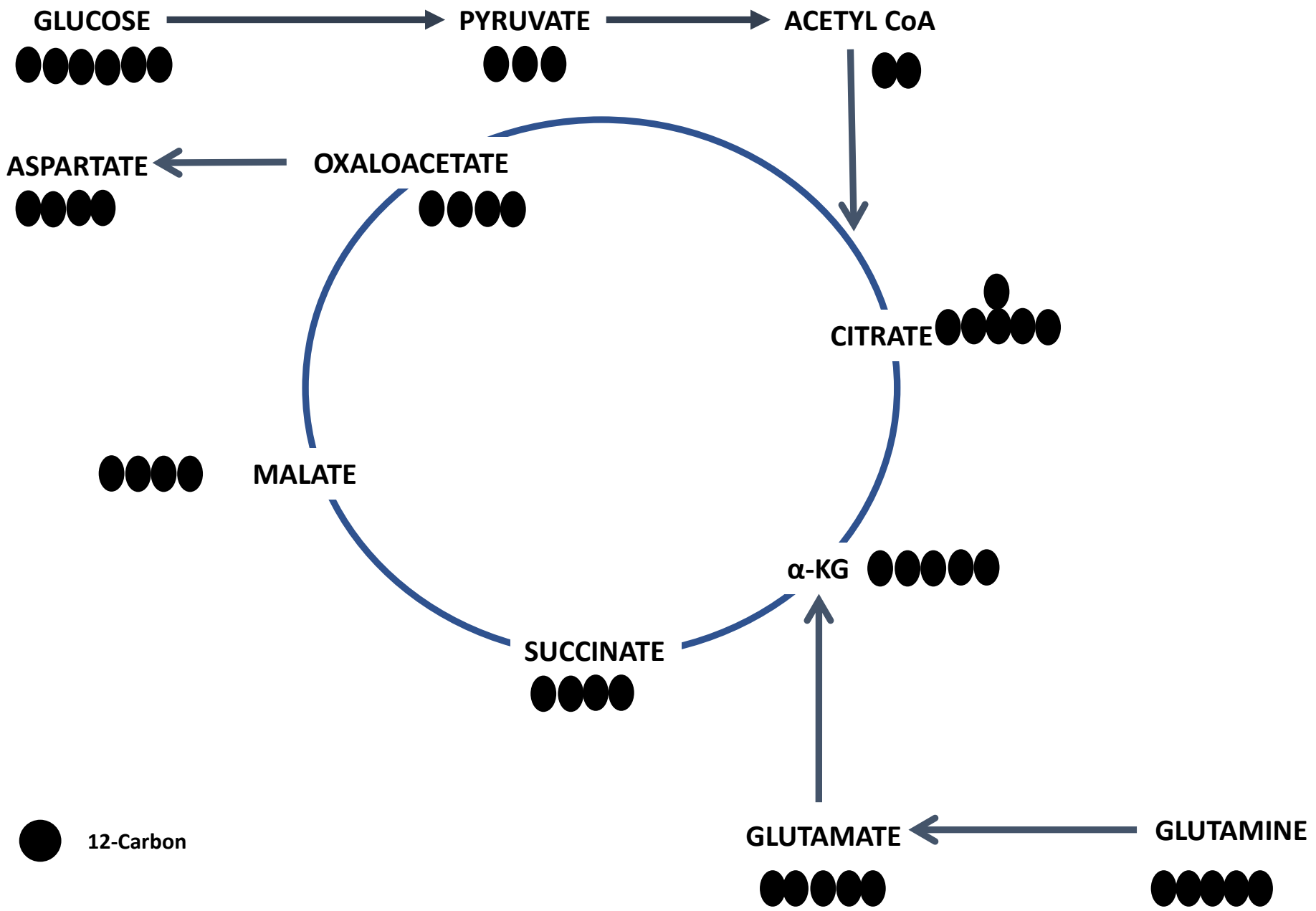
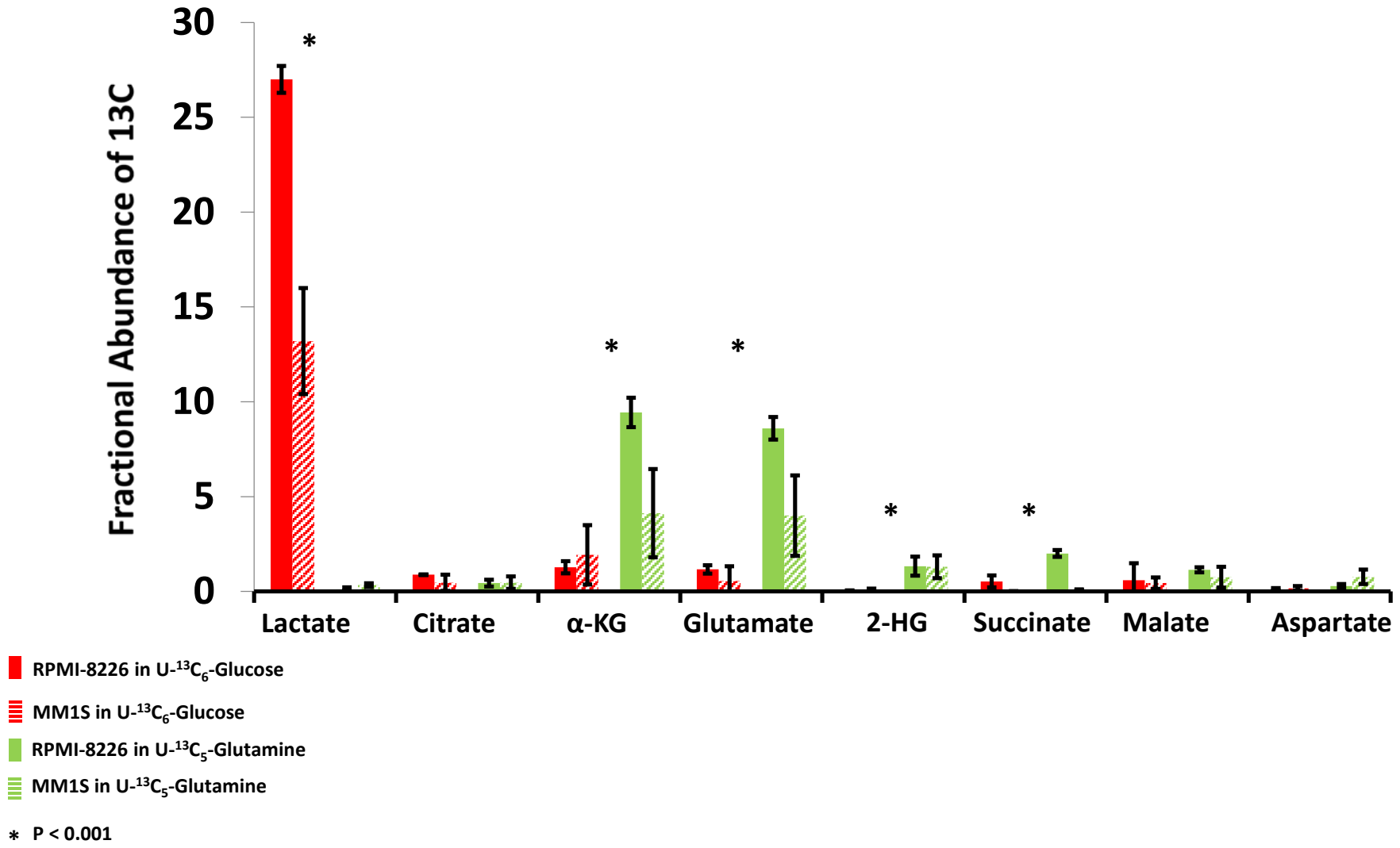
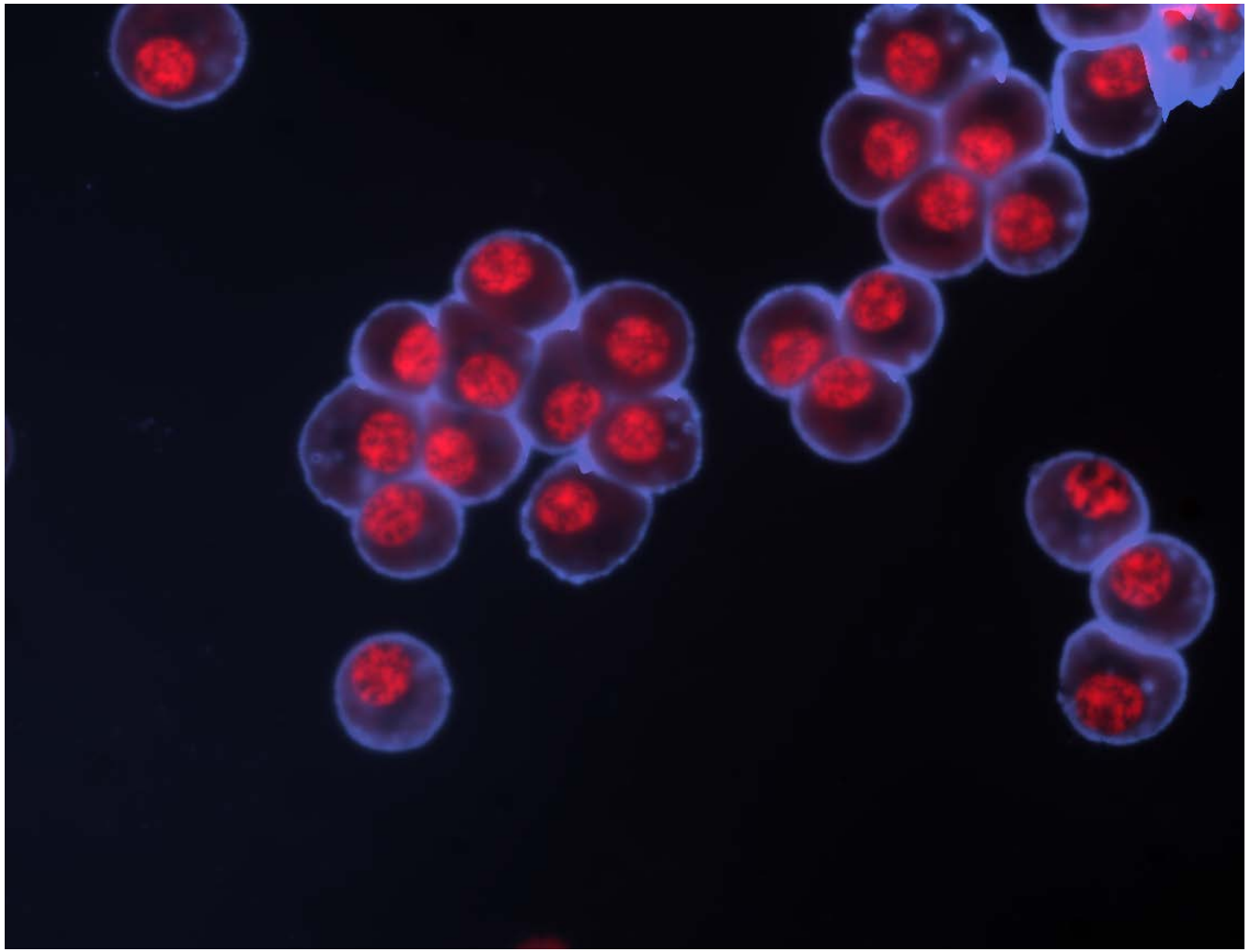


Supplement Figure 1: Schema of the TCA cycle and its various intermediates including anaplerotic pathways for glutamine and glucose. Each intermediate is represented by the number of carbon atoms (black filled circles) in their molecular structure.

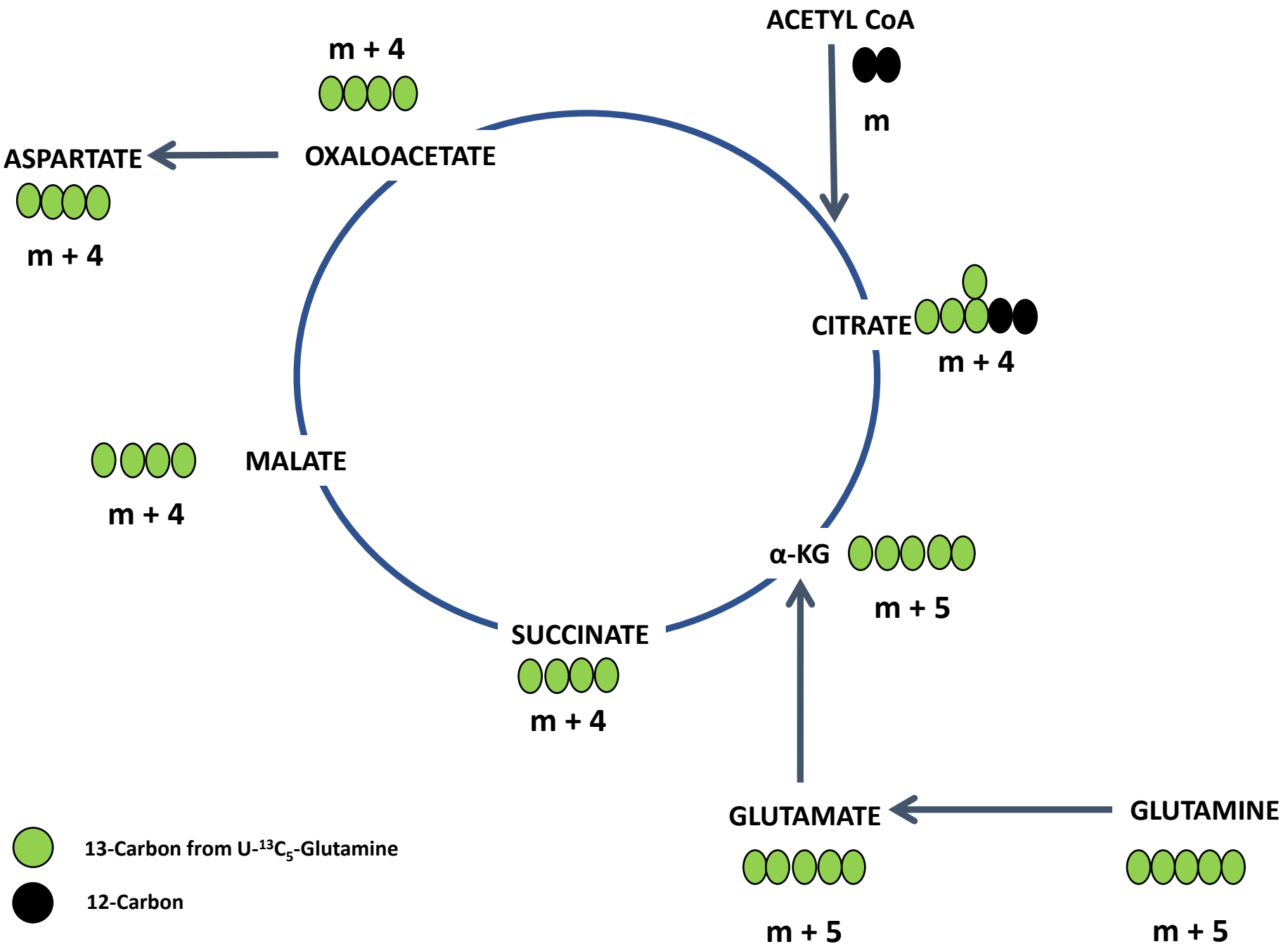


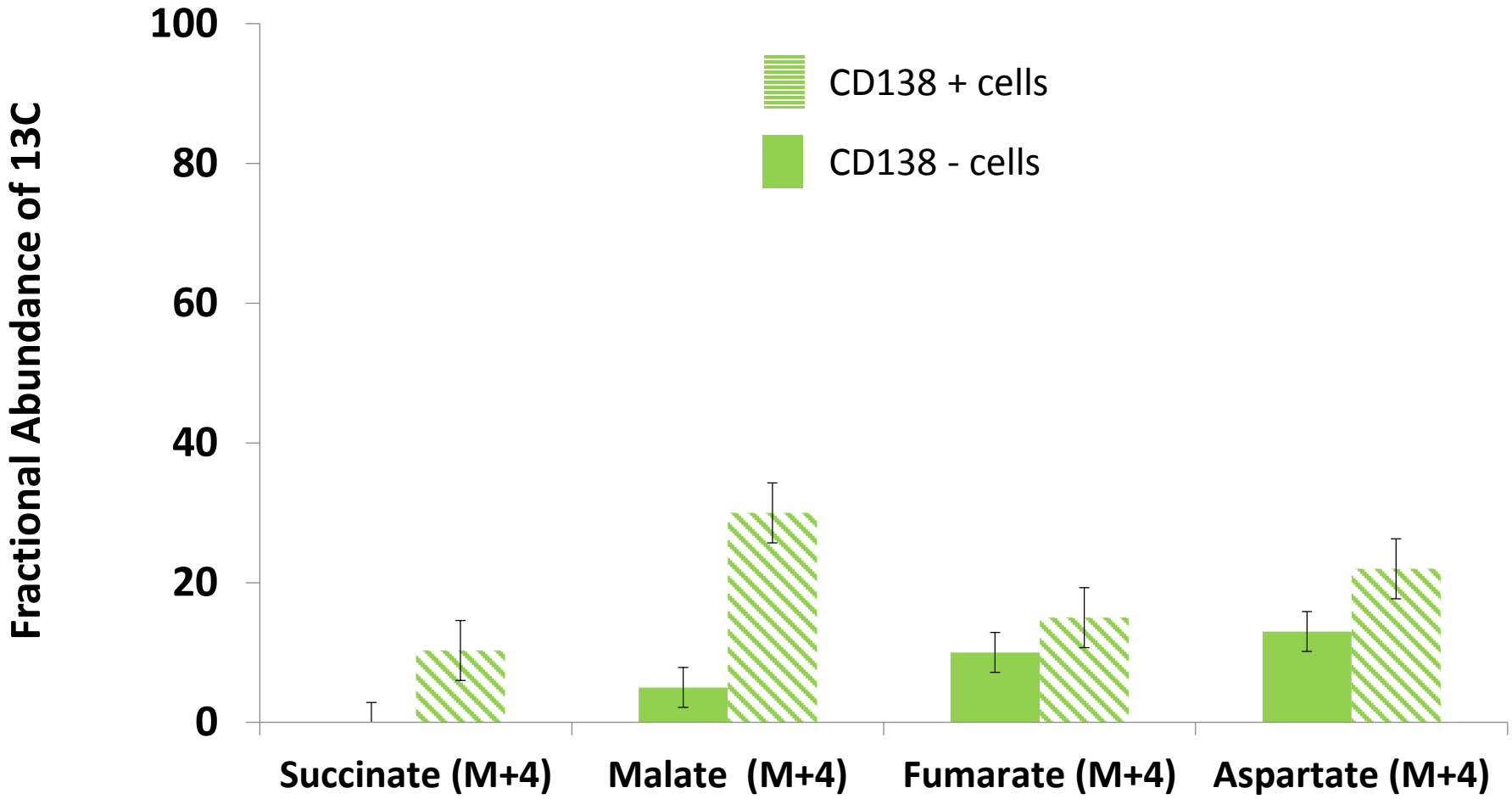
Supplement Figure 2: The distribution of the various isotopomers present in the spent media of HMCLs after 24 hours of incubation with either U-$^{13}C_6$-Glucose or U-$^{13}C_5$-Glutamine. From U-$^{13}C_6$-Glucose (red bars): (m+3) Lactate, (m+2) Citrate, (m+2) α-KG, (m+2) Glutamate, (m+2) 2-HG, (m+2) Succinate, (m+2) Malate and (m+2) Aspartate. From U-$^{13}C_5$-Glutamine (green bars): (m+3) Lactate, (m+4) Citrate, (m+5) α-KG, (m+5) Glutamate, (m+5) 2-HG, (m+4) Succinate, (m+4) Malate and (m+4) Aspartate.



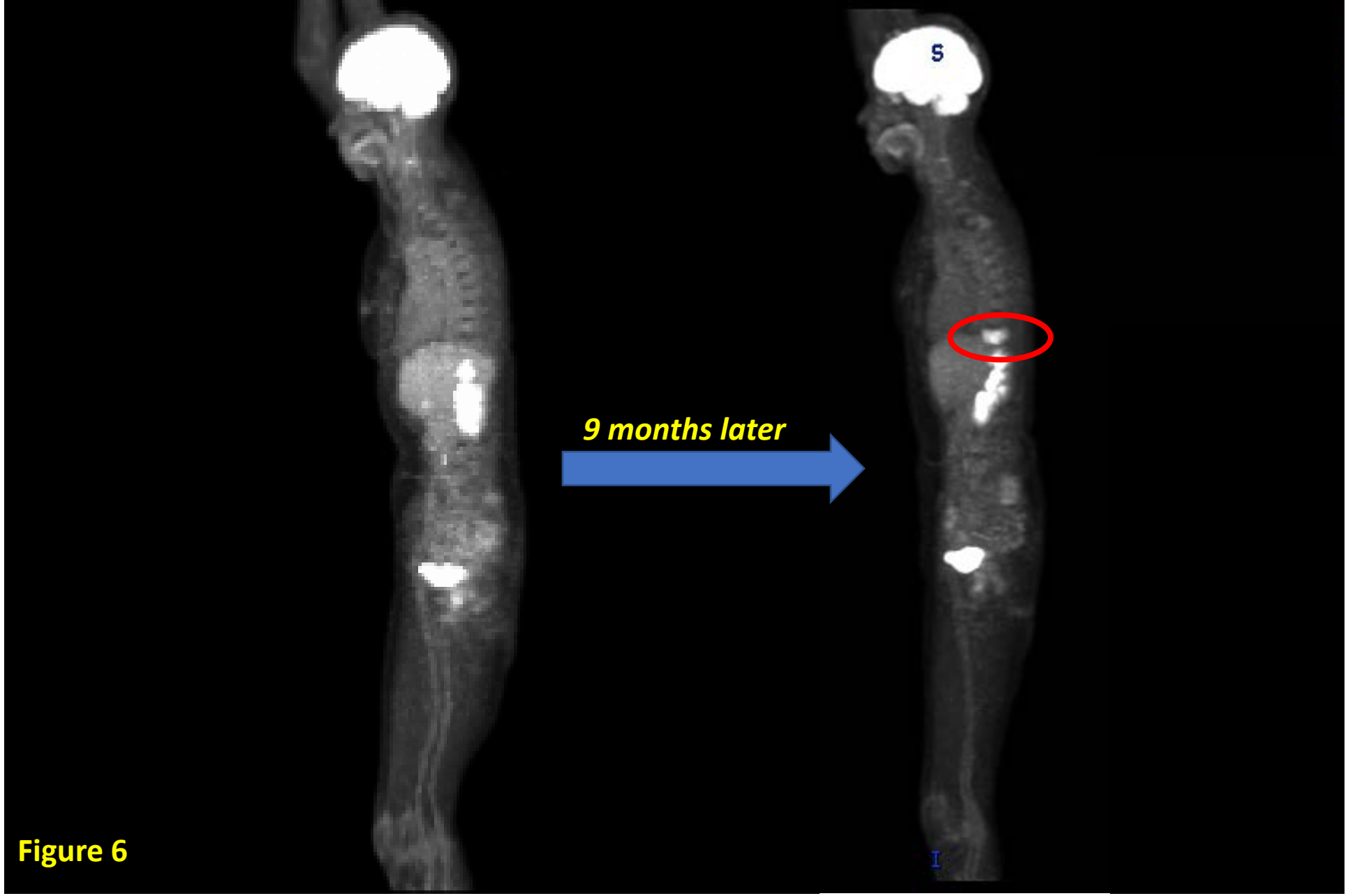
Supplement Figure 3: Sample picture of the light chain restriction of plasma cells to confirm clonality. Blue color staining of the membranes represents kappa restriction and green color staining (absent) represents lambda restriction.

Supplement Figure 4: Expected mass isotopomer distribution of the intermediates in the TCA cycle as a result of glutamine anaplerosis of U-$^{13}C_5$-Glutamine. Each intermediate is represented by the number of carbon atoms in their molecular structure with green circle representing ^{13}C and black circles representing ^{12}C.





Supplement Figure 5: Mass isotopomer distribution of the various TCA cycle intermediates as a result of *ex vivo* glutamine anaplerosis of U-$^{13}C_5$-Glutamine into CD138 positive and CD138 negative cells derived from the bone marrow aspirates of one of the patients with MM.



Supplement Figure 6: PET/CT images of a sample patient with SMM at diagnosis (left) and 9 months later at the time of progression to MM with a symptomatic lytic thoracic vertebrae bone lesion highlighted by the red circle (right).

Supplementary Table 1: Clinical characteristics of the four patients with newly diagnosed or relapsed MM whose bone marrow PCs underwent *ex vivo* SIRM evaluation

Clinical Characteristics	Patient #1	Patient #2	Patient #3	Patient #4
Stage of Disease	Relapsed	Relapsed	Newly Dx	Newly Dx
Age	70	71	64	55
Gender	Female	Male	Male	Female
BMPCs	95%	10%	40%	80%
FISH	Del 17p, t(4;14), +1q	Del 17p	Trisomies	+1q
S-Phase	0.7%	5.1%	1.2%	0.8%
Paraprotein Type	IgA Kappa	Kappa only	IgG Kappa	IgA Lambda
Hemoglobin	8.1 g/dL	13.3 g/dL	13.0 g/dL	10.7 g/dL
Calcium	9.8 mg/dL	9.1 mg/dL	9.3 mg/dL	10.2 mg/dL
Creatinine	0.9 mg/dL	1.5 mg/dL	1.1 mg/dL	0.8 mg/dL

Supplementary Table 2: Clinical characteristics of patients with MGUS and MM whose bone marrow plasma underwent assessment of TCA metabolite concentrations

	Age	Gender	BMPC (%)	Glutamate µM	2-HG µM	α-KG µM
MGUS #1	75	M	5	50	0.2	12
MGUS #2	44	M	0	91	0.2	8
MGUS #3	73	F	5	30	0.7	19
MGUS #4	53	F	0	105	0.2	11
MGUS #5	63	F	5	60	0.2	12
MM #1	53	M	5	96	0.4	8.1
MM #2	89	F	60	104	0.4	9.8
MM #3	70	M	10	62	0.5	5.1
MM #4	71	M	20	115	0.3	13
MM #5	52	M	15	73	0.3	8.2
MM #6	69	F	< 5	55	0.2	15.3
MM #7	86	M	10	27	0.2	7.8
MM #8	48	M	15	68	0.5	9.2
MM #9	78	M	10	21	0.3	6.2
MM#10	52	M	40	119	0.3	7.8
MM#11	70	M	25	47	0.3	8.3
MM#12	70	F	95	81	0.3	8.2
MM#13	74	F	40	87	1.2	12.4
MM#14	78	M	50	60	0.5	6.9
MM#15	77	M	95	128	0.2	11.6

Supplementary Table 3: Clinical characteristics of patients with SMM whose bone marrow supernatant underwent assessment of TCA metabolite concentrations

Patient #	Age	Gender	BMPC%	Glutamate µM	2-HG µM	α-KG µM	%PCs w/ c-Myc expression	TTP (months)	OS (months)
SMM #1	55	F	50%	28	0.4	5.5	20	7	63
SMM #2	68	F	15%	70	0.5	8.4	30	6	88#
SMM #3	38	M	20%	133	0.2	4.4	10	107*	126#
SMM #4	64	M	25%	127	1.4	6.1	30	7	118#
SMM #5	66	M	30%	199	1.7	9.3	50	12	103
SMM #6	57	M	15%	64	0.2	7.7	30	14	108#
SMM #7	57	M	10%	243	0.3	11.6	10	114*	138#
SMM #8	64	F	30%	158	0.3	5.6	10	69	151#
SMM #9	66	M	50%	58	0.5	6.6	50	9	107#
SMM #10	67	F	15%	86	0.6	9.6	10	12	13
SMM #11	30	F	30%	299	0.6	3.3	10	122*	144#
SMM #12	66	M	40%	61	0.5	7.0	30	2	47#
SMM #13	82	M	30%	32	0.3	6.7	20	11	48#
SMM #14	72	F	20%	48	0.3	8.4	50	5	59#
SMM #15	71	M	10%	39	0.3	5.7	10	62*	68#
SMM #16	54	F	15%	403	0.2	0.3	10	7	59
SMM #17	61	M	15%	42	0.3	5.0	40	57	96#
SMM #18	60	F	10%	74	0.3	8.0	30	68*	86#
SMM #19	79	M	50%	42	4.2	6.9	20	3	50#
SMM #20	60	F	20%	31	0.3	7.0	10	8	45
SMM #21	61	M	15%	36	0.4	6.3	40	60*	90#
SMM #22	67	F	40%	195	0.3	0.6	20	6	83
SMM #23	62	F	30%	76	0.3	7.2	10	58*	84#
SMM #24	80	F	50%	37	0.2	5.5	10	19	45
SMM #25	42	M	10%	61	0.2	4.9	10	51*	78#

*: Did not progress to MM at last follow up

#: Alive at last follow up

Supplementary Table 4: Clinical characteristics of patients with SMM whose peripheral blood plasma underwent assessment of TCA metabolite concentrations

Patient #	Age	Gender	BMPC%	Glutamate µM	2-HG µM	a-KG µM	TTP (months)	OS (months)
SMM #1	64	M	25%	216	0.88	0.61	7	118
SMM #2	70	M	20%	264	0.72	4.4	124*	150#
SMM #3	66	M	30%	445	0.79	0.27	12	103
SMM #4	58	M	20%	415	0.98	0.23	16	110
SMM #5	58	M	10%	472	0.65	11.60	66	177#
SMM #6	67	F	10%	420	0.49	0.93	96*	96
SMM #7	46	M	50%	480	0.71	0.30	2	64
SMM #8	66	M	50%	494	0.72	0.28	9	107
SMM #9	60	F	10%	478	0.61	0.19	68*	86#
SMM #10	73	F	50%	455	0.54	0.21	17	33
SMM #11	67	F	15%	404	0.82	0.25	12	13
SMM #12	61	M	15%	409	0.41	0.29	57	81
SMM #13	66	M	40%	108	0.74	6.42	2	46#
SMM #14	42	M	10%	366	0.94	0.25	51*	78#
SMM #15	82	M	30%	204	0.43	3.99	11	45#
SMM #16	72	F	20%	409	0.37	7.44	5	58#
SMM #17	53	M	20%	533	0.64	1.08	2	15
SMM #18	60	F	20%	409	0.83	0.22	8	45
SMM #19	53	F	15%	480	1.25	0.95	212*	242
SMM #20	56	F	30%	487	1.23	0.41	5	29
SMM #21	40	M	10%	552	0.49	4.63	93*	93#
SMM #22	53	M	40%	464	0.72	0.36	5	52
SMM #23	81	M	30%	323	4.63	1.32	2	4
SMM #24	61	M	15%	384	0.41	0.92	57*	81#
SMM #25	65	M	15%	450	0.63	1.33	136	168#

*: Did not progress to MM at last follow up

#: Alive at last follow up