

Populations	Metformin Only						Pre vs. Post-treatment (p-value)
	Pre-treatment samples (N=7)			Post-treatment samples (N=9)			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
<b>AMPK<sup>+</sup> cells</b>	28 ± 19	29	51- 4	43 ± 16	41	76 - 26	0.886
<b>Tumour cells</b>	18 ± 7	17	31- 1	26 ± 18	22	58 - 2	0.468
AMPK <sup>+</sup>	55 ± 33	7	88 - 12	69 ± 17	67	97- 49	0.688
PDL1 <sup>+</sup>	30 ± 30	22	86- 4	17 ± 15	12	43- 0	0.375
<b>PDL1<sup>-</sup> Tim3<sup>+</sup></b>	7 ± 4	9	12.0- 1	7 ± 4	6	15- 2	0.938
<b>Leukocytes</b>	25 ± 10	25	39- 10	18 ± 10	16	37- 5	0.375
AMPK <sup>+</sup>	36 ± 31	25	71- 2	44 ± 24	38	82- 14	0.688
PDL1 <sup>+</sup>	16 ± 31	5	86- 0	2 ± 2	2	5.0- 0	0.156
Helper T cells	7 ± 3	8	12.0- 3	6 ± 4	6	14 - 2	0.578
Cytotoxic T cells	2 ± 3	1	8.0- 0	2 ± 1	1	4.0 - 0	0.578
Regulatory T cells	1 ± 1	1	2.0- 0	1 ± 1	0	2.0 - 0	0.938
CD4 <sup>+</sup> T cells							
Naïve	3 ± 2	3.00	7.0 - 1.0	1 ± 1	1.00	5.0 - 0	0.219
Central Memory	3 ± 2	3.00	7.0- 1	3 ± 4	2	12.0- 1	0.938
Effector	1 ± 0	1	2.0- 0	0 ± 0	0.00	1.0- 0	0.031
Effector Memory	1 ± 1	0.00	2.0 - 0	1 ± 1	1.00	2.0 - 0	0.844
CD8 <sup>+</sup> T cells							
Naïve	1 ± 2	1.00	5.0- 0	0 ± 0	0.00	1.0- 0	0.375
Central Memory	1 ± 1	1.00	3.0- 0	1 ± 1	1.00	3.0- 0	0.375
Effector	0	0.00	0	0	0.00	0	0.188
Effector Memory	0	0.00	0	0	0.00	0	0.563
Exhausted T cells	0	0.00	0	0	0.00	0	0.188
NK cells	0	0.00	1.0 - 0	0	0.00	1.0 - 0	0.469

**Table S2.** Immune cell populations in patients treated with metformin only as determined by ChipCytometry analysis. Data for AMPK<sup>+</sup>, tumor and PDL1<sup>-</sup>Tim3<sup>+</sup> cell populations and leukocyte cell populations are expressed as percent of all cells. Data for leukocyte cell populations are represented as percent of leukocytes (CD45<sup>+</sup>). Data for CD4<sup>+</sup> T cell populations are represented as percent of CD4<sup>+</sup> T cells, and CD8<sup>+</sup> T cells populations as percent of CD8<sup>+</sup> T cells.

Populations	Metformin + Nivolumab						Pre vs. Post-treatment (p-value)
	Pre-treatment samples (N=7)			Post-treatment samples (N=7)			
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	
<b>AMPK<sup>+</sup> cells</b>	37 ± 17	4	58 - 11	44 ± 21	49	67 - 8	0.688
<b>Tumor cells</b>	34 ± 11	31	47 - 14	24 ± 20	21	59 - 0	0.219
AMPK <sup>+</sup>	64 ± 28	7	90 - 17	70 ± 0.35	0.85	0.92 - 0	0.688
PDL1 <sup>+</sup>	9 ± 9	6	21 - 1	14 ± 18	10	47 - 0	0.688
<b>PDL1<sup>-</sup> Tim3<sup>+</sup></b>	10 ± 7	8	25 - 4	14 ± 7	12	28 - 7	0.031
<b>Leukocytes</b>	12 ± 5	11	19 - 6	23 ± 14	17	44 - 11	0.031
AMPK <sup>+</sup>	34 ± 16	39	49 - 5	48 ± 21	50	80 - 19	0.563
PDL1 <sup>+</sup>	4 ± 6	2	15 - 1	6 ± 4	5	11.0 - 0	0.438
Helper T cells	5 ± 1	5	7.0 - 4	10 ± 8	7	21 - 3	0.156
Cytotoxic T cells	1 ± 1	1	2.0 - 0	1 ± 1	1	4.0 - 0	0.156
Regulatory T cells	1 ± 0	0	1.0 - 0	1 ± 1	1	3.0 - 0	0.688
CD4 <sup>+</sup> T cells							
Naïve	1 ± 1	1.00	3.0 - 0	3.0 ± 3	2.00	10.0 - 0	0.313
Central Memory	3 ± 1	3.00	4.0 - 2	5 ± 4	3	11.0 - 0	0.313
Effector	0 ± 0	0	1.0 - 0	1 ± 1	1.00	2.0 - 0	0.063
Effector Memory	0 ± 0	1.00	1.0 - 0	1 ± 1	0.00	3.0 - 0	0.563
CD8 <sup>+</sup> T cells							
Naïve	0 ± 0	0.00	1.0 - 0	0 ± 0	0.00	1.0 - 0	0.688
Central Memory	1 ± 0	0.00	1.0 - 0	1 ± 1	1.00	3.0 - 0	0.313
Effector	0	0.00	0	0	0.00	0	0.25
Effector Memory	0	0.00	0	0	0.00	0	0.125
Exhausted T cells	0	0.00	1.0-0	0	0.00	0	0.625
NK cells	0	0.00	1.0 - 0	0 ± 1	0.00	2.0 - 0	0.625

**Table S3.** Immune cell populations in patients treated with metformin plus nivolumab as determined by ChipCytometry analysis. Data for AMPK<sup>+</sup>, tumor and PDL1<sup>-</sup> Tim3<sup>+</sup> cell populations and leukocytes cell populations are expressed as percent of all cells. Data for leukocyte cell populations are represented as percent of leukocytes (CD45<sup>+</sup>). Data for CD4<sup>+</sup> T cell populations are represented as percent of CD4<sup>+</sup> T cells, and CD8<sup>+</sup> T cells populations as percent of CD8<sup>+</sup> T cells.

Populations	Pre-treatment (N=17)			C1D1 (N=17)			C1D15 (N=17)			ETO			Pre-treatment versus C1D1 (p value)	Pre-treatment versus C1D15 (p value)	Pre-treatment versus EOT (p value)
	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range	Mean ± SD	Median	Range			
<b>CD3<sup>+</sup> cells</b>	43 ± 18	47	75 - 11	45 ± 20	49	79 - 13	41 ± 15	43	64 - 19	36 ± 20	40	76 - 9	0.0608	0.7393	0.4052
CD4 <sup>+</sup> T cells	61 ± 12	62	86 - 38	57 ± 10	59	73 - 36	59 ± 8	61	69 - 38	61 ± 11	6	76 - 46	0.3406	0.1709	0.2525
<i>Naïve</i>	28 ± 22	22	97 - 9	28 ± 21	21	94 - 9	26 ± 22	20	96 - 8	30 ± 19	25	65 - 10	0.6178	0.4036	0.9138
<i>Central Memory</i>	49 ± 20	5	83 - 1	48 ± 20	47	81 - 3	54 ± 19	52	86 - 21	51 ± 17	51	84 - 30	0.3505	0.294	0.3161
<i>Effector</i>	2 ± 3	1	11.0 - 0	2 ± 3	1	12.0 - 0	2 ± 2	1	9.0 - 0	1 ± 1	0	4.0 - 0	0.2133	0.0316	0.8371
<i>Effector Memory</i>	22 ± 17	23	55.0 - 0	22 ± 17	20	52 - 0	21 ± 16	21	46 - 0	17 ± 17	13	43 - 0	0.6897	0.2733	0.6605
CD137 <sup>+</sup> CD4 <sup>+</sup> T cells	2 ± 1	2	3.0 - 0	2 ± 1	1.00	4.0 - 1	2 ± 1	2	4.0 - 1	3 ± 1	3	5.0 - 1	0.5668	0.3684	0.0562
CD8 <sup>+</sup> T cells	31 ± 11	28	51 - 18	28 ± 10	28.00	51 - 14	28 ± 9	26	52 - 16	22 ± 7	22	32 - 9	0.0789	0.2506	0.1189
<i>Naïve</i>	38 ± 19	37	75 - 5	34 ± 21	28.00	82 - 4	29 ± 18	2	70 - 4	33 ± 18	30	66 - 11	0.3251	0.0812	0.0475
<i>Central Memory</i>	21 ± 18	16	64 - 0	22 ± 18	18.00	71 - 0	20 ± 16	13	51 - 0	28 ± 20	25	68 - 6	0.9569	0.4758	0.4601
<i>Effector</i>	23 ± 18	19	57 - 2	23 ± 19	17.00	63 - 2	21 ± 16	15	52 - 3	16 ± 12	13	44 - 3	0.192	0.203	0.1853
<i>Effector Memory</i>	18 ± 13	17	50 - 0	21 ± 15	23.00	61 - 2	23 ± 20	21	76 - 1	24 ± 22	18	69 - 2	0.1529	0.6184	0.0973
CD137 <sup>+</sup> CD8 <sup>+</sup> T cells	2 ± 1	2	3.0 - 1	2 ± 1	2.00	4.0 - 1	2 ± 2	2	8.0 - 1	2 ± 2	2	9.0 - 0	0.7625	0.6122	0.4642

**Table S4.** Immune cell populations in PBMCs of patients treated with metformin then metformin plus nivolumab at various time points. Data for CD3<sup>+</sup> cell populations are represented as percent of all cells. Data for CD4<sup>+</sup> and CD8<sup>+</sup> T cell populations are represented as percent of CD3<sup>+</sup> T cells.

Immune Marker, mean ( $\pm$ SD)	Pre-treatment comparisons		Post-treatment comparisons		Difference Post - Pre	
	Progressive Disease (PD) (n= 12)	Stable Disease (SD) (n =2)	Progressive Disease (PD) (n= 14)	Stable Disease (SD) (n =2)	Progressive Disease (PD) (n= 11)	Stable Disease (SD) (n =2)
AMPK <sup>+</sup> cells	0.333(0.175)	0.259(0.285)	0.447(0.186)	0.334(0.108)	0.107 (0.312)	0.075 (0.177)
Tumor cells	0.283(0.119)	0.132(0.038)	0.261(0.193)	0.173(0.066)	-0.028 (0.2)	0.042 (0.028)
PDL1 <sup>+</sup> Tim3 <sup>+</sup>	0.085(0.058)	0.086(0.051)	0.098(0.067)	0.104(0.058)	0.038 (0.066)	0.018 (0.007)
Leukocytes	0.177(0.108)	0.221(0.082)	0.203(0.119)	0.206(0.115)	0.052 (0.171)	-0.014 (0.198)
Helper T cells	0.064(0.027)	0.06(0.04)	0.074(0.062)	0.096(0.063)	0.022 (0.073)	0.036 (0.104)
Cytotoxic T cells	0.017(0.022)	0.008(0)	0.014(0.012)	0.02(0.009)	-0.002 (0.026)	0.012 (0.009)
Regulatory T cells	0.008(0.006)	0.003(0.003)	0.007(0.008)	0.013(0.001)	0 (0.012)	0.009 (0.004)
Naïve CD4 <sup>+</sup> T cells	0.021(0.011)	0.034(0.044)	0.021(0.027)	0.019(0.002)	0.005 (0.034)	-0.015 (0.043)
Central Memory CD4 <sup>+</sup> T cells	0.031(0.016)	0.017(0.013)	0.038(0.036)	0.069(0.068)	0.014 (0.039)	0.052 (0.055)
Effector CD4 <sup>+</sup> T cells	0.005(0.004)	0.006(0.008)	0.005(0.006)	0.003(0.004)	-0.001 (0.006)	-0.003 (0.005)
Effector Memory CD4 <sup>+</sup> T cells	0.007(0.006)	0.003(0.001)	0.01(0.011)	0.005(0)	0.004 (0.011)	0.002 (0.001)
Naïve CD8 <sup>+</sup> T cells	0.009(0.014)	0.005(0.003)	0.004(0.003)	0.006(0.002)	-0.005 (0.015)	0.001 (0.001)
Central Memory CD8 <sup>+</sup> T cells	0.008(0.008)	0.003(0.003)	0.009(0.01)	0.015(0.011)	0.003 (0.013)	0.012 (0.008)
Effector CD8 <sup>+</sup> T cells	0(0)	0(0)	0(0.001)	0(0)	0 (0)	0 (0)
Effector Memory CD8 <sup>+</sup> T cells	0(0)	0(0)	0(0.001)	0(0)	0 (0.001)	0 (0)
Exhausted T cells	0.001(0.002)	0.001(0.001)	0.001(0.001)	0.002(0.003)	0 (0.001)	0.001 (0.002)
NK cells	0.002(0.003)	0.006(0.008)	0.003(0.006)	0.008(0.006)	0.001 (0.007)	0.002 (0.002)
AMPK <sup>+</sup> tumor cells	0.608(0.277)	0.499(0.535)	0.714(0.276)	0.579(0.129)	0.106 (0.452)	0.08 (0.405)
PDL1 <sup>+</sup> tumor cells	0.159(0.148)	0.451(0.582)	0.153(0.167)	0.162(0.069)	-0.055 (0.108)	-0.289 (0.65)
AMPK <sup>+</sup> leukocytes	0.344(0.228)	0.39(0.446)	0.478(0.231)	0.349(0.038)	0.145 (0.364)	-0.041 (0.408)
PDL1 <sup>+</sup> leukocytes	0.045(0.047)	0.431(0.61)	0.039(0.036)	0.031(0.024)	-0.013 (0.05)	-0.4 (0.585)

**Table S5.** Clinical correlates for tissues of patients treated with metformin or metformin plus nivolumab

Immune Marker, mean (±SD)	Pre-treatment comparisons		C1D1 comparisons		C1D15 comparisons		EOT comparisons		Difference C1D15- Pre Screening	
	Progressive Disease (PD) (n=15)	Stable Disease (SD) (n=2)	Progressive Disease (PD) (n=15)	Stable Disease (SD) (n=2)	Progressive Disease (PD) (n=13)	Stable Disease (SD) (n=2)	Progressive Disease (PD) (n=9)	Stable Disease (SD) (n=2)	Progressive Disease (PD) (n=13)	Stable Disease (SD) (n=2)
CD3 <sup>+</sup> cells (% of all cells)	0.427(0.192)	0.46(0.132)	0.44(0.21)	0.557(0.123)	0.418(0.162)	0.384(0.049)	0.344(0.218)	0.427(0.044)	0.011 (0.139)	-0.076 (0.059)
CD4 <sup>+</sup> cells (%of CD3 cells)	0.61(0.123)	0.584(0.058)	0.566(0.094)	0.62(0.159)	0.589(0.074)	0.6(0.128)	0.596(0.106)	0.664(0.135)	-0.018 (0.108)	0.016 (0.05)
Central Memory CD4 <sup>+</sup> T cells (%CD4)	0.464(0.191)	0.648(0.258)	0.464(0.19)	0.633(0.255)	0.521(0.174)	0.639(0.315)	0.484(0.142)	0.639(0.279)	0.054 (0.098)	-0.009 (0.041)
Naïve CD4 <sup>+</sup> T cells (%CD4)	0.287(0.228)	0.211(0.073)	0.283(0.227)	0.252(0.129)	0.272(0.229)	0.21(0.178)	0.311(0.199)	0.272(0.181)	-0.032 (0.062)	0 (0.075)
Effector CD4 <sup>+</sup> T cells (%CD4)	0.018(0.027)	0.021(0.027)	0.017(0.029)	0.017(0.018)	0.017(0.025)	0.02(0.022)	0.01(0.012)	0.013(0.015)	0.006 (0.024)	-0.001 (0.004)
Effector Memory CD4 <sup>+</sup> T cells (%CD4)	0.232(0.176)	0.121(0.158)	0.239(0.172)	0.089(0.119)	0.22(0.166)	0.133(0.113)	0.196(0.174)	0.071(0.089)	0.001 (0.057)	0.012 (0.032)
CD137 <sup>+</sup> CD4 <sup>+</sup> T cells (%CD4)	0.017(0.007)	0.015(0.009)	0.016(0.008)	0.026(0.001)	0.018(0.006)	0.028(0.017)	0.03(0.014)	0.015(0.007)	0.001 (0.011)	0.013 (0.006)
CD8 <sup>+</sup> cells (%CD3 cells)	0.297(0.111)	0.405(0.116)	0.273(0.099)	0.323(0.132)	0.275(0.092)	0.311(0.087)	0.214(0.072)	0.255(0.095)	-0.033 (0.091)	-0.095 (0.021)
Central Memory CD8 <sup>+</sup> T cells (%CD8 cells)	0.211(0.176)	0.24(0.235)	0.219(0.192)	0.212(0.179)	0.201(0.158)	0.196(0.198)	0.286(0.204)	0.23(0.234)	0.014 (0.072)	-0.044 (0.026)
Naïve CD8 <sup>+</sup> T cells (%CD8 cells)	0.39(0.191)	0.272(0.169)	0.348(0.223)	0.26(0.033)	0.302(0.195)	0.194(0.005)	0.352(0.185)	0.232(0.135)	-0.118 (0.195)	-0.078 (0.116)
Effector CD8 <sup>+</sup> T cells (%CD8 cells)	0.22(0.168)	0.318(0.281)	0.217(0.193)	0.307(0.194)	0.198(0.166)	0.283(0.194)	0.132(0.086)	0.27(0.238)	-0.01 (0.063)	-0.036 (0.062)
Effector Memory CD8 <sup>+</sup> T cells (%CD8 cells)	0.178(0.139)	0.171(0.122)	0.21(0.165)	0.221(0.017)	0.217(0.21)	0.329(0.008)	0.23(0.244)	0.27(0.131)	0.033 (0.206)	0.158 (0.081)
CD137 <sup>+</sup> CD8 <sup>+</sup> T cells (%CD8 cells)	0.016(0.005)	0.015(0.007)	0.015(0.009)	0.023(0.01)	0.016(0.008)	0.051(0.048)	0.023(0.024)	0.025(0.004)	0 (0.005)	0.036 (0.029)

**Table S6.** Clinical correlates for PBMS of patients treated with metformin then metformin plus nivolumab