Supplementary Table 1. Immunomodulatory genes with differentially methylated positions on EPIC array following guadecitabine.
DMP: differentially methylated position, CD: cluster of differentiation, CTA: cancer testis antigen

Methylation response	Gene	DMP	Category
Hypermethylated	CD80	cg12978275	Immune checkpoint
	CD86	cg01436254 cg16331599 cg13617155 cg13069531	Immune checkpoint
	Wilms' tumour 1 (WT1)	cg22533573 cg06516124	CTA
	Melanoma-associated antigen A4 (MAGEA4)	cg24137136	CTA
	Synaptonemal complex protein 1 (SYCP1)	cg10440578	CTA
	Beta-2-microglobulin (B2M)	cg18696027	Antigen presentation
	Interferon gamma receptor 2 (IFNGR2)	cg17356733	Interferon pathway
Hypomethylated	CCCTC-Binding Factor Like (CTCFL)	cg25721806	CTA
	G antigen 2A (GAGE2A)	cg20503077	CTA
	Placenta-specific protein 1 (PLAC1)	cg17073891	CTA
	Synovial sarcoma X breakpoint 4 (SSX4)	cg26134482	CTA
	Synaptonemal complex protein 1 (SYCP1)	cg03964233	CTA
	A-kinase anchoring protein 3 (AKAP3)	cg07892051	CTA
	Paired-box 8 (PAX8)	cg06881093	CTA
	Preferentially expressed antigen of melanoma (PRAME)	cg22871485	CTA

Supplementary Table 2: Unbiased gene-set enrichment (GSEA) of gene transcription data
NES: Normalised Enrichment Score

Supplementary Table 2a: Baseline biopsy: Clinical benefit group *versus* non-clinical benefit group

Description	Set Size	Enrichment Score	NES	P value	Q values
HALLMARK_ALLOGRAFT_REJECTION	151	0.69788816	2.43557885	1.00E-10	1.63E-09
HALLMARK_INTERFERON_GAMMA_RESPONSE	187	0.62511124	2.22614765	1.00E-10	1.63E-09
HALLMARK_INTERFERON_ALPHA_RESPONSE	94	0.62508561	2.09187465	2.18E-07	2.37E-06
HALLMARK_INFLAMMATORY_RESPONSE	144	0.54622793	1.89281382	2.08E-06	1.36E-05
HALLMARK_IL6_JAK_STAT3_SIGNALING	74	0.56675501	1.83295926	0.00027006	0.00073436
HALLMARK_TNFA_SIGNALING_VIA_NFKB	176	0.51020743	1.80894753	4.79E-06	2.60E-05
HALLMARK_IL2_STAT5_SIGNALING	165	0.4947585	1.74065284	2.66E-05	9.65E-05
HALLMARK_KRAS_SIGNALING_UP	150	0.4997351	1.73884575	2.17E-05	8.87E-05
HALLMARK_OXIDATIVE_PHOSPHORYLATION	183	-0.3482923	-1.7022766	3.65E-05	0.0001084
HALLMARK_ADIPOGENESIS	179	-0.3591121	-1.7681903	3.01E-05	9.83E-05
HALLMARK_MYOGENESIS	127	-0.3978844	-1.8248259	1.87E-05	8.72E-05
HALLMARK_EPITHELIAL_MESENCHYMAL_TRANSITION	172	-0.4044718	-1.9651526	6.44E-07	5.26E-06
HALLMARK_ALLOGRAFT_REJECTION	151	-0.4277822	-2.0199805	1.14E-06	6.25E-06

Supplementary Table 2b: Baseline biopsy versus cycle 2 day 8 biopsy in responder group

Description	Set Size	Enrichment Score	NES	P value	Q values
HALLMARK_INTERFERON_GAMMA_RESPONSE	187	0.44618517	2.05493132	4.78E-07	7.80E-06
HALLMARK_KRAS_SIGNALING_UP	150	0.4579775	2.04523091	2.51E-06	2.73E-05
HALLMARK_ALLOGRAFT_REJECTION	151	0.45452851	2.04410514	7.91E-06	5.24E-05
HALLMARK_INTERFERON_ALPHA_RESPONSE	94	0.47994202	2.00335921	0.00010636	0.00043386
HALLMARK_COAGULATION	89	0.42793624	1.76399734	0.00294479	0.00800775
HALLMARK_MTORC1_SIGNALING	192	-0.3624494	-1.5380851	0.00206268	0.00611895
HALLMARK_G2M_CHECKPOINT	186	-0.3787977	-1.5948275	0.00139287	0.00454515
HALLMARK_ADIPOGENESIS	179	-0.3918795	-1.6476085	0.00091934	0.00333328
HALLMARK_E2F_TARGETS	195	-0.4295767	-1.8274382	1.12E-05	5.24E-05
HALLMARK_MYC_TARGETS_V1	194	-0.4389241	-1.8688391	9.87E-06	5.24E-05
HALLMARK_MYOGENESIS	127	-0.4937011	-1.9868303	9.77E-06	5.24E-05
HALLMARK_OXIDATIVE_PHOSPHORYLATION	183	-0.5593859	-2.3661623	1.00E-10	3.26E-09