

Supplementary Table S3. Comparison of baseline clinical factors in rapid progressors (PFS < 2 months) versus other progressors (PFS ≥ 2 months).

Factor	PFS < 2 months (n=22)	PFS ≥ 2 months (n=18)	<i>P value</i>
Age in years (median)	69 (34 – 96)	65 (49 – 91)	0.7984
Sex, male	16/22 (73%)	10/18 (56%)	0.3267
ECOG PS, ≥1	12/22 (55%)	7/18 (39%)	0.3596
Elevated LDH¹	11/22 (50%)	4/17 (24%)	0.1116
Tumour burden	128 (19-366)	47 (15-200)	0.0625
Number of mets	6.5 (2-17)	5 (1-12)	0.2913
Number of organ sites with mets	3 (1-7)	2 (1-4)	0.1655
Brain mets	9/22 (41%)	3/18 (17%)	0.1654
Liver mets	8/22 (36%)	3/18 (17%)	0.2863
Staging, M1C/M1D	16/22 (73%)	8/18 (44%)	0.1064
BRAF V600E mutation²	5/8 (63%)	0/1 (0%)	0.4444

ECOG PS - Eastern Clinical Oncology Group (ECOG) performance status; LDH – lactate dehydrogenase; Tumor burden - sum of diameters of large metastases according to RECIST criteria; mets – metastases; n – number; % - percentage.

¹ missing values: 1

² as a proportion of total BRAF mutations

Supplementary Table S4. Subsequent therapies received by patients who progressed on anti-PD-1-based therapies.

Subsequent Therapy	Progressed on anti-PD-1 (n=13)	Progressed on ipilimumab + anti-PD-1 (n=9)
Ipilimumab + anti-PD-1	9/13 (69%)	0/9 (0%)
Ipilimumab monotherapy	3/13 (23%)	0/9 (0%)
Chemotherapy	1/13 (8%)	2/9 (22%)
Targeted therapy	0/13 (0%)	7/9 (78%)

Supplementary Table S5. Comparison of baseline clinical factors in patients who are still alive versus those who have died at the data cut.

Factor	Alive (n=14)	Dead (n=26)	<i>P value</i>
Age in years (median)	77 (37 – 96)	65 (34 – 89)	0.1539
Sex, male	9/14 (65%)	17/26 (64%)	>0.9999
ECOG PS, ≥1	7/14 (50%)	12/26 (46%)	>0.9999
Elevated LDH¹	4/13 (31%)	11/26 (42%)	0.7281
Tumour burden	44 (15-366)	121 (15-242)	0.2741
Number of mets	5 (2-17)	7 (1-12)	0.4633
Number of organ sites with mets	2 (1-7)	3 (1-5)	0.4273
Brain mets	5/14 (36%)	7/26 (27%)	0.7201
Liver mets	1/14 (7%)	10/26 (38%)	0.0614
Staging, M1C/M1D	7/14 (75%)	17/26 (65%)	0.5001
BRAF V600E mutation²	2/5 (40%)	3/4 (75%)	0.5238

ECOG PS - Eastern Clinical Oncology Group (ECOG) performance status; LDH – lactate dehydrogenase; Tumor burden - sum of diameters of large metastases according to RECIST criteria; mets – metastases; n – number; % - percentage.

¹ missing values: 1

² as a proportion of total BRAF mutations

Supplementary Table S6. Comparison of baseline clinical factors in non-responders with low TILs versus intermediate/high TILs.

Factor	Low TILs (n=14)	Intermediate/High TILs (n=23)	<i>P value</i>
Age in years (median)	72 (49 – 96)	67 (34 – 87)	0.2192
Sex, male	10/14 (71%)	14/23 (61%)	0.7245
ECOG PS, ≥1	7/14 (50%)	10/23 (43%)	0.7447
Elevated LDH¹	5/14 (36%)	9/22 (41%)	>0.9999
Tumour burden	102 (19-202)	118 (15-366)	0.6111
Number of mets	7.5 (2-17)	5.5 (2-17)	0.8401
Number of organ sites with mets	2.5 (1-5)	3 (1-7)	0.9033
Brain mets	2/14 (14%)	8/23 (35%)	0.2603
Liver mets	6/14 (43%)	5/23 (22%)	0.2679
Staging, M1C/M1D	7/14 (50%)	15/23 (65%)	0.4933
BRAF V600E mutation²	1/3 (33%)	4/5 (80%)	0.4643

ECOG PS - Eastern Clinical Oncology Group (ECOG) performance status; LDH – lactate dehydrogenase;
Tumor burden - sum of diameters of large metastases according to RECIST criteria; mets –
metastases; n – number; % - percentage.

¹ missing values: 1

² as a proportion of total BRAF mutations

Supplementary Table S7. KEGG pathway analysis of differentially expressed genes.

NAME	SIZE	ES	NES	NOM p-val	FDR q-val
KEGG_HEMATOPOIETIC_CELL_LINEAGE	3	-0.82609	-1.50926	0.027896997	0.10045286
KEGG_PRIMARY_IMMUNODEFICIENCY	2	-0.83333	-1.35503	0.104803495	0.17845923
KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	2	-0.83333	-1.33643	0.092337914	0.16044548

Supplementary Table S8. Comparison of baseline clinical factors between non-responders in Cluster 1 and Cluster 2 based on unsupervised hierarchical clustering of 26 differentially expressed genes.

Factor	RNA cluster 1 (n=17)	RNA cluster 2 (n=20)	<i>P</i> value
Age in years (median)	61 (33 – 86)	70 (41 – 95)	0.1174
Sex, male	12/17 (71%)	12/20 (60%)	0.7307
ECOG PS, ≥1	5/17 (29%)	12/20 (60%)	0.0994
Elevated LDH¹	5/16 (31%)	9/20 (45%)	0.5007
Tumour burden²	118 (15 – 242)	90.5 (15 – 366)	0.5452
Number of mets²	5.5 (2 – 12)	7 (1 – 17)	0.7297
Number of organ sites with mets	3 (1-4)	2 (1-7)	0.5363
Brain mets	4/17 (24%)	6/20 (30%)	0.7246
Liver mets	5/17 (29%)	6/20 (30%)	>0.9999
Staging, M1C/M1D	11/17 (65%)	11/20 (55%)	0.7384
BRAF V600E mutation³	2/3 (67%)	3/5 (60%)	>0.9999
Received subsequent therapies	10/17 (59%)	11/20 (55%)	>0.9999

ECOG PS - Eastern Clinical Oncology Group (ECOG) performance status; LDH – lactate dehydrogenase; Tumor burden - sum of diameters of large metastases according to RECIST criteria; mets – metastases; n – number; % - percentage.

¹ missing values: 1

² missing values: RNA cluster 1 – 1; RNA cluster 2 – 4

³ as a proportion of total BRAF mutations

Supplementary Table S9. Comparison of baseline clinical factors between non-responders in Cluster A, Cluster B and Cluster C based on unsupervised hierarchical clustering of 36 genes, including druggable immune checkpoints.

Factor	RNA cluster A (n=6)	RNA cluster B (n=14)	RNA cluster C (n=17)	<i>P value</i>
Age in years (median)	68 (51 – 77)	63 (33 – 95)	68 (41 – 88)	0.8079
Sex, male	3/6 (50%)	9/14 (64%)	12/17 (71%)	0.7355
ECOG PS, ≥1	4/6 (67%)	4/14 (29%)	9/17 (53%)	0.2291
Elevated LDH ¹	2/6 (33%)	2/13 (15%)	10/17 (59%)	0.0541
Tumour burden ²	137 (15 – 166)	76 (15 – 242)	122 (19 – 366)	0.9026
Number of mets ²	8 (3 – 9)	5 (2 – 12)	6.5 (1 – 17)	0.6626
Number of organ sites with mets	2 (1-4)	3 (1-4)	3 (1-7)	0.4772
Brain mets	1/6 (17%)	3/14 (21%)	6/17 (35%)	0.6116
Liver mets	1/6 (17%)	3/14 (21%)	7/17 (41%)	0.3963
Staging, M1C/M1D	2/6 (33%)	8/14 (57%)	12/17 (71%)	0.27
BRAF V600E mutation ³	1/2 (50%)	1/2 (50%)	3/4 (75%)	>0.9999
Received subsequent therapies	3/6 (50%)	7/14 (50%)	11/17 (65%)	0.6709

ECOG PS - Eastern Clinical Oncology Group (ECOG) performance status; LDH – lactate dehydrogenase;
Tumor burden - sum of diameters of large metastases according to RECIST criteria; mets –
metastases; n – number; % - percentage.

¹ missing values: 1

² missing values: RNA cluster A – 1; RNA cluster B – 1; RNA cluster C – 1

³ as a proportion of total BRAF mutations