

Supplementary Tables

Supplementary Table 1. Characteristics of patients for RNA sequencing

Patient characteristics	Total (N=36)
Age (years), Mean (SD)	70.4 (7.1)
Sex, N (%)	
Female	8 (22%)
Male	28 (78%)
Smoking, N (%)	
Former	27 (75%)
Never	9 (25%)
Tumor stage, N (%)	
Recurrent	4 (11%)
Stage IV	32 (89%)
Performance status, N (%)	
0-1	15 (42%)
2-3	21 (58%)
Histology, N (%)	
non-Squamous	25 (69%)
Squamous	11 (31%)
Driver mutation, N (%)	
WT	29 (81%)
EGFR	6 (17%)
ALK	1 (2.8%)
Tumor PD-L1 expression, N (%)	
0~49 %	9 (29%)
50~100 %	22 (71%)
Treatment line, N (%)	
1st line	12 (33%)
2~7 line	24 (67%)
PD-1 blocker, N (%)	
Nivolumab	20 (56%)
Pembrolizumab	16 (44%)
Blood test, Mean (SD)	

Albumin (g/dL)	3.40 (0.53)
LDH (U/L)	255 (93.8)
WBC (/μL)	7592 (3600)
Lymphocyte (/μL)	1438 (677)
Neutrophil (/μL)	5481 (3199)
Eosinophil (/μL)	173 (180)
Monocytes (/μL)	462 (212)
NLR	4.82 (3.67)

The clinical characteristics of patients for RNA sequencing were described. Continuous variables are shown as mean and standard deviation. Categorical variables are shown as sample numbers and percentages.

Supplementary Table 2. PFAA and metabolite concentrations before ICI therapy in patients for RNA sequencing

PFAA/metabolite (μM)	Mean (SD)
Glutamic Acid	51.8 (23.0)
Serine	101 (25.7)
Asparagine	40.3 (7.7)
Glycine	213.0 (66.7)
Glutamine	51.8 (23.0)
Histidine	65.7 (24.3)
Threonine	106.0 (30.6)
Alanine	302.0 (98.3)
Citrulline	29.9 (10.7)
Arginine	74.3 (18.0)
Proline	146.0 (54.3)
α-Amino Butyric Acid	16.6 (4.9)
Tyrosine	62.7 (14.1)
Valine	208.0 (50.7)
Methionine	21.1 (4.7)
Ornithine	65.0 (11.7)
Lysine	173.0 (45.7)
Isoleucine	65.7 (15.6)
Leucine	117.0 (31.2)

Phenylalanine	60.4 (12.2)
Tryptophan	45.9 (11.9)
3h-Kynurenine	0.06 (0.03)
3h-Anthranilic Acid	0.04 (0.02)
5h-Indol-3-Acetic Acid	0.06 (0.03)
5h-Tryptophan	0.00 (0.00)
Anthranilic Acid	0.02 (0.02)
Indol-3-Acetic Acid	2.06 (2.07)
Indol-3-Lactic Acid	0.81 (0.50)
Kynurenic Acid	0.05 (0.02)
Kynurenine	2.34 (0.68)
Picolinic Acid	0.05 (0.03)
Quinolinic Acid	0.67 (0.43)
Serotonin	0.14 (0.15)
Xanthurenic Acid	0.01 (0.01)
Neopterin	0.01 (0.01)
N'-Formyl-Kynurenine	0.02 (0.02)

Mean and standard deviation are shown.

Supplementary Table 3. Go enrichment of genes differentially expressed between the high- and low-risk groups

ID	Description	P	P.adj	gene ID
GO:0042110	T cell activation	0.000	<u>0.000</u>	AIF1/CD151/CEBPB/IL10/LGALS9/LILRB2/SFTPD/SLC11A1/SOX4/VSIG4/ZBTB16/BCL11B/BTLA/CD2/CD3D/CD3G/CD40LG/CD5/CD6/CD8A/CD8B/HES1/HHLA2/HSPH1/IL20RB/IL7R/LCK/LY9/RASGRP1/RHOH/RORA/THEMIS
GO:0030098	lymphocyte differentiation	0.000	<u>0.000</u>	IL10/LGALS9/LILRB2/PGLYRP1/SOX4/SPI1/ZBTB16/BCL11B/BLNK/CD2/CD3D/CD3G/CD40LG/CD8A/CR2/KZF3/IL7R/LCK/LY9/PCID2/RASGRP1/RHOH/RORA/THEMIS
GO:0140014	mitotic nuclear division	0.000	<u>0.001</u>	AURKB/BIRC5/CDC6/CDC45/CDT1/EPGN/HSPA1B/INSR/KIF18B/KIF4A/MKI67/NUSAP1/PKMYT1/PLK1/PSRC1/TPX2/UBE2C/MAP9/PCID2
GO:0050863	regulation of T cell activation	0.000	<u>0.002</u>	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/ZBTB16/BTLA/CD2/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL20RB/IL7R/LCK/RASGRP1
GO:0007088	regulation of mitotic nuclear division	0.000	<u>0.002</u>	AURKB/CDC6/CDC45/CDT1/EPGN/HSPA1B/INSR/MKI67/NUSAP1/PKMYT1/PLK1/UBE2C/MAP9/PCID2
GO:0051783	regulation of nuclear division	0.000	<u>0.002</u>	AURKB/CDC6/CDC45/CDT1/EPGN/FBXO43/HSPA1B/INSR/MKI67/NUSAP1/PKMYT1/PLK1/UBE2C/MAP9/PCID2
GO:1903037	regulation of leukocyte cell-cell adhesion	0.000	<u>0.004</u>	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/ZBTB16/BTLA/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL20RB/IL7R/LCK/RASGRP1
GO:0042098	T cell proliferation	0.000	<u>0.006</u>	AIF1/CD151/CEBPB/IL10/LGALS9/LILRB2/SFTPD/SLC11A1/VSIG4/CD40LG/CD6/HES1/HHLA2/IL20RB
GO:0000280	nuclear division	0.000	<u>0.006</u>	AURKB/BIRC5/CDC6/CDC45/CDT1/EPGN/FBXO43/HSPA1B/INSR/KIF18B/KIF4A/MKI67/MND1/NUSAP1/PKMYT1/PLK1/PSRC1/TOP2A/TPX2/UBE2C/MAP9/PCID2
GO:0030217	T cell differentiation	0.000	<u>0.007</u>	LGALS9/LILRB2/SOX4/ZBTB16/BCL11B/CD2/CD3D/CD3G/CD8A/IL7R/LCK/LY9/RASGRP1/RHOH/RORA/THEMIS
GO:0097421	liver regeneration	0.000	<u>0.007</u>	CEBPB/IL10/TYMS/CCND1/PTCH1/WDR35

GO:0046651	lymphocyte proliferation	0.000	0.007	AIF1/CD151/CEBPB/IL10/LGALS9/LILRB2/SFTPD/SLC11A1/VSIG4/CD40LG/CD6/CR2/HES1/HHLA2/IKZF3/IL20RB/IL7R
GO:0032943	mononuclear cell proliferation	0.000	0.007	AIF1/CD151/CEBPB/IL10/LGALS9/LILRB2/SFTPD/SLC11A1/VSIG4/CD40LG/CD6/CR2/HES1/HHLA2/IKZF3/IL20RB/IL7R
GO:0001754	eye photoreceptor cell differentiation	0.000	0.007	CABP4/MYO7A/ROM1/CCDC66/CEP290/PRKCI/RORB
GO:0007159	leukocyte cell-cell adhesion	0.000	0.008	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/ZBTB16/BTLA/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL20RB/IL7R/LCK/RASGRP1
GO:0007052	mitotic spindle organization	0.000	0.008	AURKB/BIRC5/HSPA1B/KIF4A/PLK1/PSRC1/SPC25/STMN1/TPX2/MAP9
GO:0050870	positive regulation of T cell activation	0.000	0.008	AIF1/LGALS9/LILRB2/ZBTB16/BTLA/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL7R/LCK/RASGRP1
GO:0030278	regulation of ossification	0.000	0.008	CEBPB/JAG1/LTF/OMD/ZBTB16/ADRB2/AXIN2/ID3/NOG/PTCH1/RORB/S1PR1/TOB2/TPH1
GO:0003007	heart morphogenesis	0.000	0.009	CPE/FOXC1/INSR/JAG1/MYBPC3/PKP2/SOX4/AXIN2/BBS7/CCDC4/0/EFNA1/HES1/NOG/PTCH1/S1PR1/TNNC1
GO:1902850	microtubule cytoskeleton organization involved in mitosis	0.000	0.009	AURKB/BIRC5/HSPA1B/KIF4A/NUSAP1/PLK1/PSRC1/SPC25/STMN1/TPX2/MAP9
GO:0042129	regulation of T cell proliferation	0.000	0.009	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/CD40LG/CD6/HES1/HHLA2/IL20RB
GO:0042462	eye photoreceptor cell development	0.000	0.009	CABP4/MYO7A/CCDC66/CEP290/PRKCI/RORB
GO:0048285	organelle fission	0.000	0.010	AURKB/BIRC5/CD6/CDCA5/CDT1/EPGN/FBXO34/HSPA1B/INSR/KIF18B/KIF4A/MKI67/MND1/NUSAP1/PKMYT1/PLK1/PSRC1/TOP2A/TPX2/UBE2C/MAP9/PCID2
GO:0051249	regulation of lymphocyte activation	0.000	0.010	AIF1/CEBPB/IL10/LGALS9/LILRB2/PGLYRP1/SFTPD/VSIG4/ZBTB16/BTLA/CD2/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IKZF3/IL20RB/IL7R/LCK/PCID2/RASGRP1
GO:0070661	leukocyte proliferation	0.000	0.010	AIF1/CD151/CEBPB/IL10/LGALS9/LILRB2/SFTPD/SLC11A1/VSIG4/CD40LG/CD6/CR2/HES1/HHLA2/IKZF3/IL20RB/IL7R
GO:0045931	positive regulation of mitotic cell cycle	0.000	0.010	AIF1/CDC6/CDCA5/CDK1/CDT1/EPGN/INSR/NUSAP1/UBE2C/CCND1/HES1/PCID2
GO:1902105	regulation of leukocyte differentiation	0.000	0.010	C1QC/CEBPB/LGALS9/LILRB2/LTF/NME1/PGLYRP1/PPARGC1B/ZBTB16/CD2/IKZF3/IL7R/PCID2/RASGRP1/ROR2/TOB2
GO:0003208	cardiac ventricle morphogenesis	0.000	0.010	CPE/FOXC1/JAG1/MYBPC3/PKP2/SOX4/NOG/TNNC1
GO:0031100	animal organ regeneration	0.000	0.010	ADM/CDK1/CEBPB/IL10/TYMS/CCND1/PTCH1/WDR35
GO:0007093	mitotic cell cycle checkpoint	0.000	0.011	AURKB/CDC6/CDK1/CDT1/CLSPN/E2F1/PLK1/SOX4/TOP2A/BRSK1/CCND1/PCID2
GO:1903039	positive regulation of leukocyte cell-cell adhesion	0.000	0.011	AIF1/LGALS9/LILRB2/ZBTB16/BTLA/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL7R/LCK/RASGRP1
GO:0090307	mitotic spindle assembly	0.000	0.011	AURKB/BIRC5/HSPA1B/KIF4A/PLK1/TPX2/MAP9
GO:0022407	regulation of cell-cell adhesion	0.000	0.012	AIF1/CEBPB/IL10/JAG1/LGALS9/LILRB2/SFTPD/VSIG4/ZBTB16/BTLA/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL20RB/IL7R/LCK/RASGRP1
GO:0051098	regulation of binding	0.000	0.013	APOE/AURKB/CDCA5/CDT1/E2F1/FOXC1/HJURP/IL10/NME1/P2RY1/PLK1/SLP1/STMN1/ADRB2/ENHO/HABP4/HES1/ID3/NOG
GO:0051384	response to glucocorticoid	0.000	0.013	AANAT/ADM/AIF1/ALPL/DDIT4/IL10/PPARGC1B/TYMS/ABCC2/CCND1/UCP3
GO:0022409	positive regulation of cell-cell adhesion	0.000	0.014	AIF1/IL10/LGALS9/LILRB2/ZBTB16/BTLA/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL7R/LCK/RASGRP1
GO:0042130	negative regulation of T cell proliferation	0.000	0.014	CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/IL20RB
GO:0051101	regulation of DNA binding	0.000	0.014	CDCA5/CDT1/E2F1/FOXC1/HJURP/NME1/ENHO/HABP4/HES1/ID3/C1QA/C1QB/C1QC/C2/EXO1/IL10/JAG1/KIR3DL1/LGALS9/SERPIN G1/SLC11A1/CD40LG/CD8A/CR2/IL20RB/IL7R/LTA/RASGRP1
GO:0002449	lymphocyte mediated immunity	0.000	0.016	AURKB/BIRC5/CD6/CDCA5/CDT1/HJURP/KIF18B/KIF4A/MKI67/NUSAP1/PLK1/PSRC1/SKA3/SPC25/TOP2A/AXIN2/PCID2
GO:0007059	chromosome segregation	0.000	0.016	C1QA/C1QB/C1QC/C2/CAMP/DEFA3/EXO1/LTF/PGLYRP1/SERPIN G1/SFTPD/SLC11A1/SLPI/VSIG4/BLNK/CR2/LTA/PRSS3
GO:0006959	humoral immune response	0.000	0.017	AIF1/AURKB/CDC6/CDCA5/CDK1/CDT1/E2F1/EPGN/HMGNS/IL10/INSR/NUSAP1/PSRC1/SOX4/UBE2C/CCND1/CXCR5/HES1/PCID2
GO:0045787	positive regulation of cell cycle	0.000	0.017	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/CD40LG/CD6/HES1/HHLA2/IKZF3/IL20RB
GO:0050670	regulation of lymphocyte proliferation	0.000	0.017	CABP4/MYO7A/ROM1/CCDC66/CEP290/PRKCI/RORB
GO:0046530	photoreceptor cell differentiation	0.000	0.017	AIF1/GCHFR/IL10/INSR/SLC1A3/RORA/SLC44A4/TPH1/WDR35
GO:0042136	neurotransmitter biosynthetic process	0.000	0.017	CPE/FOXC1/JAG1/MYBPC3/PKP2/SOX4/HES1/NOG/SALL4/TNNC1
GO:0003231	cardiac ventricle development	0.000	0.017	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/CD40LG/CD6/HES1/HHLA2/IKZF3/IL20RB
GO:0032944	regulation of mononuclear cell proliferation	0.000	0.017	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/CD40LG/CD6/HES1/HHLA2/IKZF3/IL20RB
GO:0000083	regulation of transcription involved in G1/S transition of mitotic cell cycle	0.000	0.017	CDC6/CDT1/E2F1/TYMS/GF11
GO:0031348	negative regulation of defense response	0.000	0.017	APOE/GPX1/IL10/IL1R2/LGALS9/NR1H3/PGLYRP1/SERPIN G1/VSI G4/WFDC1/ABCD2/CD200/IL20RB/RORA
GO:0032496	response to lipopolysaccharide	0.000	0.017	ADM/ALPL/CEBPB/DEFA3/IL10/LGALS9/LILRB2/LTF/NR1H3/SLC11A1/SLP1/TIMP4/ABCC2/CD6/GF11/LTA/WDR35
GO:0031570	DNA integrity checkpoint	0.000	0.017	CDC6/CDK1/CDT1/CLSPN/E2F1/PLK1/SOX4/TOP2A/BRSK1/CCND1

				/USP28
GO:0002437	inflammatory response to antigenic stimulus	0.000	<u>0.018</u>	GPX1/IL10/CD6/IL20RB/LTA/RASGRP1
GO:0042461	photoreceptor cell development	0.000	<u>0.019</u>	CABP4/MYO7A/CCDC66/CEP290/PRKCI/RORB
GO:0032102	negative regulation of response to external stimulus	0.000	<u>0.020</u>	AIF1/APOE/GPX1/IL10/IL1R2/LGALS9/LTF/NR1H3/PGLYRP1/SERP ING1/VSIG4/WFDC1/ABCD2/CACNB3/CD200/IL20RB/PLAT/RORA/ SEMA3A
GO:0000075	cell cycle checkpoint	0.000	<u>0.020</u>	AURKB/CDC6/CDK1/CDT1/CLSPN/E2F1/PLK1/SOX4/TOP2A/BRSK 1/CCND1/PCID2/USP28
GO:0002683	negative regulation of immune system process	0.000	<u>0.020</u>	C1QC/CEBPB/GPX1/IL10/LGALS9/LILRB2/LTF/NME1/NR1H3/PGL YRP1/SERPING1/SFTPD/VSIG4/ZBTB16/CD200/HES1/IL20RB/IL7R/ TOB2/UBASH3A
GO:0000819	sister chromatid segregation	0.000	<u>0.020</u>	AURKB/CDC6/CDC45/CDT1/KIF18B/KIF4A/NUSAP1/PLK1/PSRC1/ TOP2A/AXIN2/PCID2
GO:0031960	response to corticosteroid	0.000	<u>0.020</u>	AANAT/ADM/AIF1/ALPL/DDIT4/IL10/PPARGC1B/TYMS/ABCC2/C CND1/UCP3
GO:1903706	regulation of hemopoiesis	0.000	<u>0.023</u>	C1QC/CEBPB/FOXC1/HSPA1B/JAG1/LGALS9/LILRB2/LTF/NME1/P GLYRP1/PPARGC1B/SP1/ZBTB16/CD2/HES1/IKZF3/IL7R/PCID2/R ASGRP1/ROR2/TOB2
GO:0002237	response to molecule of bacterial origin	0.000	<u>0.023</u>	ADM/ALPL/CEBPB/DEFA3/IL10/LGALS9/LILRB2/LTF/NR1H3/SLC 11A1/SLPI/TIMP4/ABCC2/CD6/GF11/LTA/WDR35
GO:0070663	regulation of leukocyte proliferation	0.000	<u>0.024</u>	AIF1/CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/CD40LG/CD6/HE S1/HHLA2/IKZF3/IL20RB
GO:0050678	regulation of epithelial cell proliferation	0.000	<u>0.024</u>	APOE/ATOH8/EPGN/GLUL/GPX1/IL10/NME1/WFDC1/BCL11B/CC ND1/CDH13/HES1/IQGAP3/NOG/PLCG1/PTCH1/TACSTD2/WNT7A
GO:0072593	reactive oxygen species metabolic process	0.000	<u>0.025</u>	AIF1/DDIT4/GCHFR/GPX1/HBE1/HBG1/HP/IFI6/IL10/INSR/NQO2/S FTPD/ABCD2/RORA/WDR35
GO:0050806	positive regulation of synaptic transmission	0.000	<u>0.025</u>	APOE/GLUL/GRIN2C/LILRB2/SLC1A3/ADRB2/CACNB3/MPP2/NLG N2/ROR2/WNT7A
GO:0050728	negative regulation of inflammatory response	0.000	<u>0.025</u>	APOE/GPX1/IL10/IL1R2/NR1H3/PGLYRP1/WFDC1/ABCD2/CD200/I L20RB/RORA
GO:0051100	negative regulation of binding	0.000	<u>0.025</u>	AURKB/E2F1/IL10/P2RY1/SLPI/STMN1/ADRB2/ENHO/HABP4/ID3/ NOG
GO:0043368	positive T cell selection	0.000	<u>0.025</u>	BCL11B/CD3D/CD3G/LY9/THEMIS
GO:0048545	response to steroid hormone	0.000	<u>0.025</u>	AANAT/ADM/AIF1/ALPL/DDIT4/DEFA3/IL10/NR1H3/PPARGC1B/T YMS/ABCC2/CCND1/GPAM/LBH/PMEPA1/RORA/RORB/UCP3
GO:0000281	mitotic cytokinesis	0.000	<u>0.025</u>	CDT1/KIF4A/NUSAP1/PLK1/RHOC/STMN1/MAP9
GO:0035019	somatic stem cell population maintenance	0.000	<u>0.025</u>	SOX4/SP1/HES1/LBH/NOG/SALL4/WNT7A
GO:0042116	macrophage activation	0.000	<u>0.026</u>	AIF1/C1QA/IL10/NR1H3/SLC11A1/VSIG4/CD200/RORA
GO:0032945	negative regulation of mononuclear cell proliferation	0.000	<u>0.026</u>	CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/IL20RB
GO:0050672	negative regulation of lymphocyte proliferation	0.000	<u>0.026</u>	CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/IL20RB
GO:0045840	positive regulation of mitotic nuclear division	0.001	<u>0.026</u>	CDCA5/CDT1/EPGN/INSR/NUSAP1/UBE2C
GO:0060563	neuroepithelial cell differentiation	0.001	<u>0.026</u>	CEBPB/JAG1/MYO7A/SOX4/HES1/SLC4A7
GO:0070228	regulation of lymphocyte apoptotic process	0.001	<u>0.026</u>	AURKB/IL10/LGALS9/CD3G/EFNA1/IL7R
GO:0050867	positive regulation of cell activation	0.001	<u>0.032</u>	AIF1/IL10/LGALS9/LILRA5/LILRB2/ZBTB16/BTLA/CD2/CD40LG/C D5/CD6/HES1/HHLA2/HSPH1/IL7R/LCK/PCID2/RASGRP1
GO:0002460	adaptive immune response based on somatic recombination of immune receptors built from immunoglobulin superfamily domains	0.001	<u>0.032</u>	C1QA/C1QB/C1QC/C2/EXO1/IL10/JAG1/SERPING1/SLC11A1/CD40 LG/CD8A/CR2/IL20RB/IL7R/LTA/LY9/RORA
GO:0060236	regulation of mitotic spindle organization	0.001	<u>0.032</u>	HSPA1B/PLK1/PSRC1/TPX2/MAP9
GO:0090068	positive regulation of cell cycle process	0.001	<u>0.032</u>	AIF1/AURKB/CDC6/CDC45/CDK1/CDT1/E2F1/EPGN/INSR/NUSAP 1/SOX4/UBE2C/CCND1/CXCR5/PCID2
GO:0001819	positive regulation of cytokine production	0.001	<u>0.032</u>	AGPAT2/AIF1/CEBPB/HSPA1B/IL10/LGALS9/LILRA5/LILRB2/SLC 11A1/CD2/CD200/CD40LG/CD6/HHLA2/IL20RB/LTA/LY9/MCOLN2/ RASGRP1/RORA
GO:0000070	mitotic sister chromatid segregation	0.001	<u>0.032</u>	AURKB/CDC6/CDC45/CDT1/KIF18B/KIF4A/NUSAP1/PLK1/PSRC1/ PCID2
GO:0061640	cytoskeleton-dependent cytokinesis	0.001	<u>0.032</u>	AURKB/CDT1/KIF4A/NUSAP1/PLK1/RHOC/STMN1/MAP9
GO:0001503	ossification	0.001	<u>0.033</u>	ALPL/CEBPB/FOXC1/JAG1/LTF/OMD/PPARGC1B/ZBTB16/ADRB2/ AXIN2/ID3/NOG/PTCH1/ROR2/RORB/S1PR1/TOB2/TPH1
GO:0032649	regulation of interferon-gamma production	0.001	<u>0.033</u>	IL10/LGALS9/PGLYRP1/SLC11A1/CD2/IL20RB/LTA/RASGRP1
GO:0070664	negative regulation of leukocyte proliferation	0.001	<u>0.033</u>	CEBPB/IL10/LGALS9/LILRB2/SFTPD/VSIG4/IL20RB
GO:0042133	neurotransmitter metabolic process	0.001	<u>0.033</u>	AIF1/GCHFR/IL10/INSR/PHGDH/SLC1A3/RORA/SLC44A4/TPH1/W DR35

GO:0048732	gland development	0.001	<u>0.033</u>	CCNB2/CEBPB/FOXC1/GPX1/IL10/INSR/NME1/TYMS/BCL11B/CCDC40/CCND1/HES1/IQGAP3/LBH/NOG/PTCH1/SEMA3A/TPH1/WD R35
GO:0050673	epithelial cell proliferation	0.001	<u>0.033</u>	APOE/ATOH8/CEBPB/EPGN/GLUL/GPX1/IL10/NME1/WFDC1/BCL11B/CCND1/CDH13/HES1/IQGAP3/NOG/PLCG1/PTCH1/TACSTD2/WNT7A
GO:0051983	regulation of chromosome segregation	0.001	<u>0.036</u>	AURKB/CDC6/CDC45/CDT1/MKI67/PLK1/AXIN2/PCID2
GO:0033045	regulation of sister chromatid segregation	0.001	<u>0.036</u>	AURKB/CDC6/CDC45/CDT1/PLK1/AXIN2/PCID2
GO:0003206	cardiac chamber morphogenesis	0.001	<u>0.036</u>	CPE/FOXC1/JAG1/MYBPC3/PKP2/SOX4/HES1/NOG/TNNC1
GO:0032753	positive regulation of interleukin-4 production	0.001	<u>0.037</u>	CEBPB/LGALS9/CD40LG/IL20RB
GO:0051043	regulation of membrane protein ectodomain proteolysis	0.001	<u>0.037</u>	APOE/IL10/TIMP2/TIMP4
GO:1903708	positive regulation of hemopoiesis	0.001	<u>0.037</u>	FOXC1/HSPA1B/JAG1/LGALS9/LILRB2/PPARGC1B/ZBTB16/IL7R/PCID2/RASGRP1/ROR2
GO:0035315	hair cell differentiation	0.001	<u>0.039</u>	JAG1/MYO7A/HES1/SLC44A4/SLC4A7
GO:0044774	mitotic DNA integrity checkpoint	0.001	<u>0.040</u>	CDC6/CDK1/CLSPN/E2F1/SOX4/TOP2A/BRSK1/CCND1
GO:0098883	synapse pruning	0.001	<u>0.041</u>	C1QA/C1QB/C1QC
GO:0002861	regulation of inflammatory response to antigenic stimulus	0.001	<u>0.041</u>	GPX1/IL10/IL20RB/LTA
GO:0090224	regulation of spindle organization	0.001	<u>0.042</u>	HSPA1B/PLK1/PSRC1/TPX2/MAP9
GO:0034113	heterotypic cell-cell adhesion	0.001	<u>0.042</u>	IL10/LILRB2/PKP2/CD2/CD200/LCK
GO:0002696	positive regulation of leukocyte activation	0.001	<u>0.043</u>	AIF1/IL10/LGALS9/LILRB2/ZBTB16/BTLA/CD2/CD40LG/CD5/CD6/HES1/HHLA2/HSPH1/IL7R/LCK/PCID2/RASGRP1
GO:0060219	camera-type eye photoreceptor cell differentiation	0.001	<u>0.047</u>	CABP4/ROM1/CCDC66/RORB
GO:0045444	fat cell differentiation	0.001	<u>0.048</u>	CEBPB/E2F1/GPX1/JAG1/JDP2/ZBTB16/ADRB2/BBS7/CCND1/HES1/RORA/TPH1
GO:0002862	negative regulation of inflammatory response to antigenic stimulus	0.001	<u>0.050</u>	GPX1/IL10/IL20RB
GO:0007077	mitotic nuclear envelope disassembly	0.001	<u>0.050</u>	CCNB2/CDK1/PLK1
GO:2001198	regulation of dendritic cell differentiation	0.001	<u>0.050</u>	CEBPB/LGALS9/LILRB2

Go term enrichment results (P.adjust: BH method).

Supplementary Table 4. KEGG pathway enrichment of genes differentially expressed between the high- and low-risk groups

ID	Description	P	P.adj	geneID	group
hsa05150	Staphylococcus aureus infection	0.000	<u>0.001</u>	C1QA/C1QB/C1QC/C2/CAMP/DEFA3/FCGR3B/IL10	1
hsa04610	Complement and coagulation cascades	0.000	<u>0.003</u>	C1QA/C1QB/C1QC/C2/SERPINA1/SERPING1/VSIG4	1
hsa05133	Pertussis	0.000	<u>0.008</u>	C1QA/C1QB/C1QC/C2/IL10/SERPING1	1
hsa04110	Cell cycle	0.000	<u>0.014</u>	CCNB2/CDC6/CDK1/E2F1/E2F2/PKMYT1/PLK1	1
hsa05340	Primary immunodeficiency	0.000	<u>0.000</u>	BLNK/CD3D/CD40LG/CD8A/CD8B/IL7R/LCK/RFXAP	-1
hsa04640	Hematopoietic cell lineage	0.000	<u>0.001</u>	CD2/CD3D/CD3G/CD5/CD8A/CD8B/CR2/IL7R	-1
hsa04660	T cell receptor signaling pathway	0.000	<u>0.001</u>	CD3D/CD3G/CD40LG/CD8A/CD8B/LCK/PLCG1/RASGRP1	-1
hsa04064	NF-kappa B signaling pathway	0.001	<u>0.028</u>	BLNK/CD40LG/LCK/LTA/PLCG1/TRAF1	-1

KEGG pathway enrichment results (P.adjust: BH method). Group: 1: Upregulated in the high-risk group; -1:

Downregulated in the high-risk group.

Supplementary Figure Legends

Supplementary Figure 1. Detailed information about the influences of prior treatment and driver mutation on clinical responses.

(A) Comparison of overall survival among the subgroups stratified by treatment lines in patients with low (0-49%) and high (50-100%) PD-L1 expression levels. Each column in the upper graphs shows the overall survival time of individual patients in the 6 subgroups classified by treatment line and PD-L1 expression level. The lower table shows the Cox hazard ratios between the subgroups stratified by treatment lines in the low (0-49%) and high (50-100%) PD-L1 expression groups. (B) The detailed information on clinical characteristics (age, sex, histology, and type of mutations), clinical responses (anti-tumor response and OS) and treatments (molecular targeted or chemotherapeutic agents used in each treatment line) in NSCLC patients positive for driver gene mutations.

Supplementary Figure 2. Correlation of PFAAs and metabolites before ICI therapy and cancer prognosis (overall survival)

Kaplan-Meier analysis for overall survival in the groups stratified by the median concentration of 6 PFAAs and 3 metabolites, respectively. P value (log-rank test) and Cox hazard ratio (95% CI) are shown.

Supplementary Figure 3. Prognosis and response to ICI therapy in 36 patients for transcriptome analysis of PBMCs

(A) Kaplan-Meier estimates of overall survival in the high- (n = 6) and low-risk (n = 30) groups based on the multivariate model with PFAAs/metabolites in 36 patients included

in transcriptome analysis of PBMCs. P value (log-rank test) is shown. (B) The risk scores by the multivariate model with PFAAs/metabolites were compared using a Student's t-test between the subgroups classified by the anti-tumor responses (RECIST criteria).

Supplementary Figure 4. Function enrichment of genes differentially expressed between the high- and low-risk groups

(A) Dot plot of the top 10 GO terms from GO enrichment ($P < 0.05$). Size of dots represent recruited counts of genes; increased dot diameters indicate increased gene numbers. Red color, higher significance; blue color, lower significance. Details are shown in Supplementary Table 3. (B) Bar plot of top 8 pathways from KEGG pathway enrichment ($P < 0.05$). Red: upregulated pathways in the high-risk group; Blue: downregulated pathways in the high-risk group. Bar length shows significance ($-\log_{10}P$). Details are shown in Supplementary Table 4. (C) GSEA analysis of Reactome pathways enrichment ($P < 0.05$). NES = normalized enrichment score. Nominal p-value calculated by the permutation test in GSEA analysis.

Supplementary Figure 5. Function enrichment of amino acid metabolism-related genes differentially expressed between the high- and low-risk groups

Plot of differentially expressed AAMGs performed by KEGG pathway enrichment analysis. Red: upregulated pathways in the high-risk group; Blue: downregulated pathways in the high-risk group. Pathways showing difference in expression with significance ($P < 0.05$, method: BH). Bar length showing significance ($-\log_{10} P$).

Supplementary Figure 6. Identification of amino acid metabolism-related genes

associated with patient prognosis.

Kaplan-Meier estimates of overall survival in the subgroups stratified by RNA expression levels of AAMGs in PBMCs. Cutoff values between the high and low groups were set at the median of gene expression levels. P values (log-rank test) are shown.

Supplementary Figure 7. Potential mechanisms of amino-acid metabolism in anti-tumor immunity in cancer patients treated with ICI

The immune cells in the peripheral blood that circulated from the tumor microenvironment (TME) may reflect the composition, activity, and metabolic characteristics of immune cells within the TME. The multivariate model with PFAA/metabolite concentrations in the blood might be useful for inferring the amino acid metabolic characteristics of immune cells under the TME and systemic immune functions. Compared with the high-risk group, PBMCs in the low-risk group have characteristics similar to a "hot tumor" with a relatively high proportion of CD8⁺ T cells and M1 macrophages and show differential expression of genes related to amino acid metabolism, including *SLC11A1*, *PHGDH*, and *HAAO*. Once patients in the low-risk group are treated with PD-1 inhibitors, they block PD-1 receptors on T cells, which circulate and infiltrate into the TME. As a result, T cells are rejuvenated from a state of immune exhaustion, resulting in activation of a series of T cell-mediated immune response, which include enhancing the interaction between macrophages and T cells, releasing liquid factors, and subsequently promoting killing of cancer cells. Meanwhile, patients in the low-risk group had a higher concentration of PFAAs such as tryptophan and serine, which provide sufficient energy and material requirements for immune cells.