

Supplementary data: **β -catenin-mediated immune evasion pathway frequently operates in primary cutaneous melanomas**

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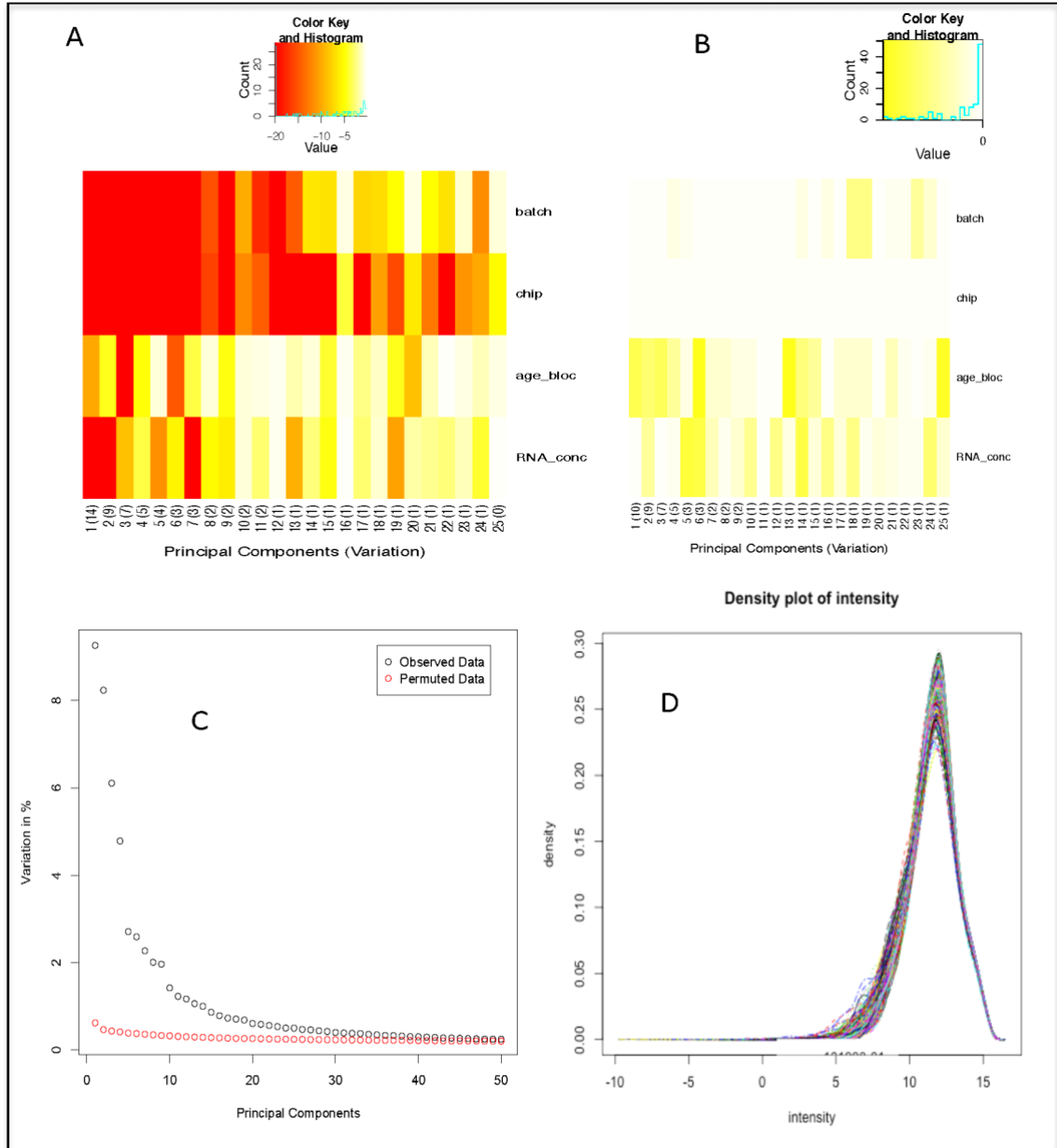


Figure S1. Leeds Melanoma Cohort (LMC) whole genome transcriptomic data quality control. **A.** Heatmap showing a strong correlation between the top 25 principal components of the whole transcriptome and technical variables batch, chip, age of the FPPE block and RNA concentration. Red color indicates highly significant correlation [$\log_{10}(\text{P value})$ down to -20]. **B.** After adjusting out the effect of the chip, no principal component correlated with technical variables. **C.** The proportion of variance explained by the top 50 principal components after chip adjustment remained much higher than that of permuted data (average of 1000

permutations), indicating that biological variation remained intact. **D.** Normalised density plots.

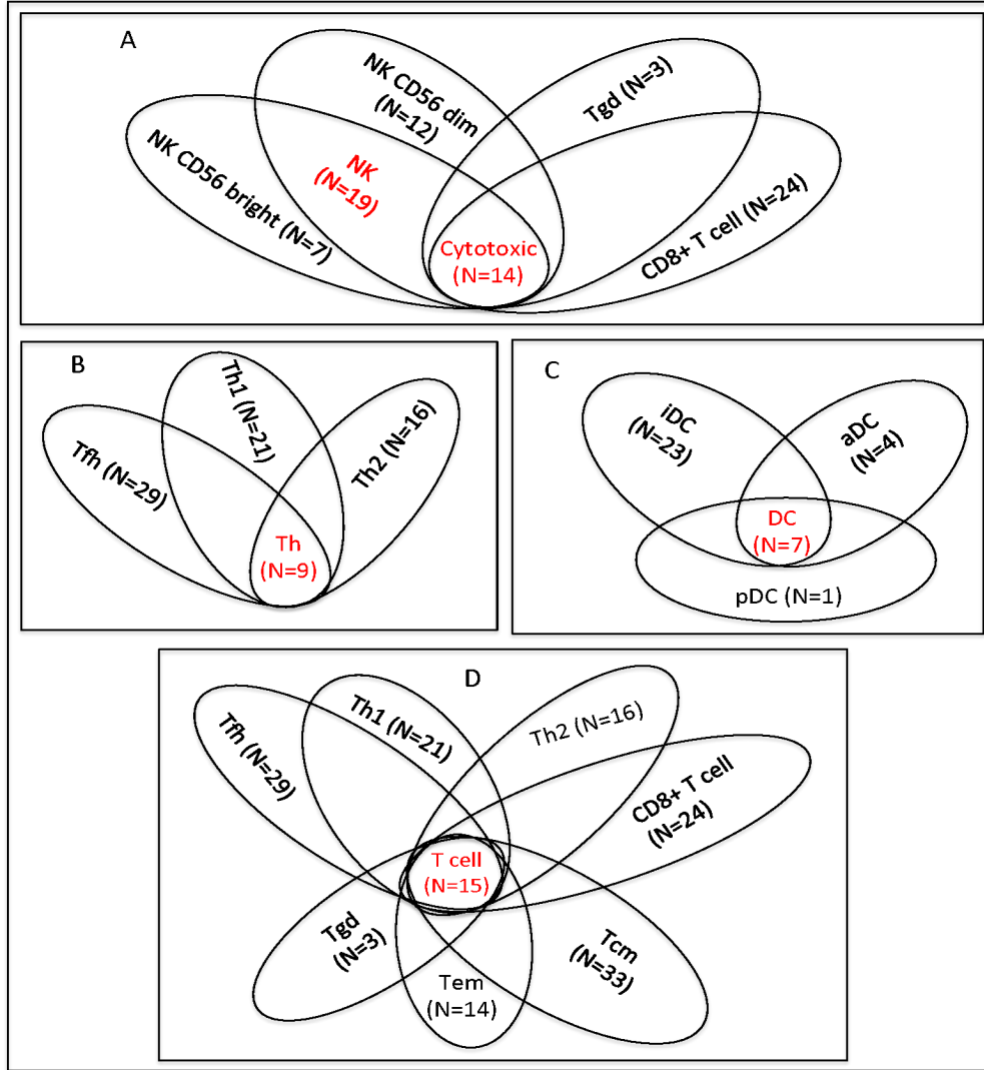


Figure S2. Schematic representation of overlapping immune cell subtypes defined in Bindea *et al* (1). Shown in brackets are the numbers of genes of each cell subtype after applying our filters (see also Table S2). **A.** Genes expressed by CD56^{dim} and CD56^{bright} Natural Killer cells were defined the broader NK (e.g. *BCL2*, *MRC2*, ...). Genes expressed by NK, gamma-delta T and CD8 + T-cells defined the cytotoxic cells (e.g. *KLRB1*, *KLRD1*, *GZMH*, *GZMA*, ...). **B.** Genes expressed by 3 types of helper T-cells defined the broader helper T-cell (Th). They included e.g. *ICOS*, *CD28*, *BATF*, ... **C.** Genes expressed by activated, immature and plasmacytoid DCs defined the broader DC subset (e.g. *CCL17*, *CCL22*, *CCL13*, *CD209*, ...). **D.** Genes expressed by various types of T and helper T-cells defined the broader T-cell (e.g. *LCK*, *CD3G*, *CD3D*, *CD3E*, *TRAT1*, ...).

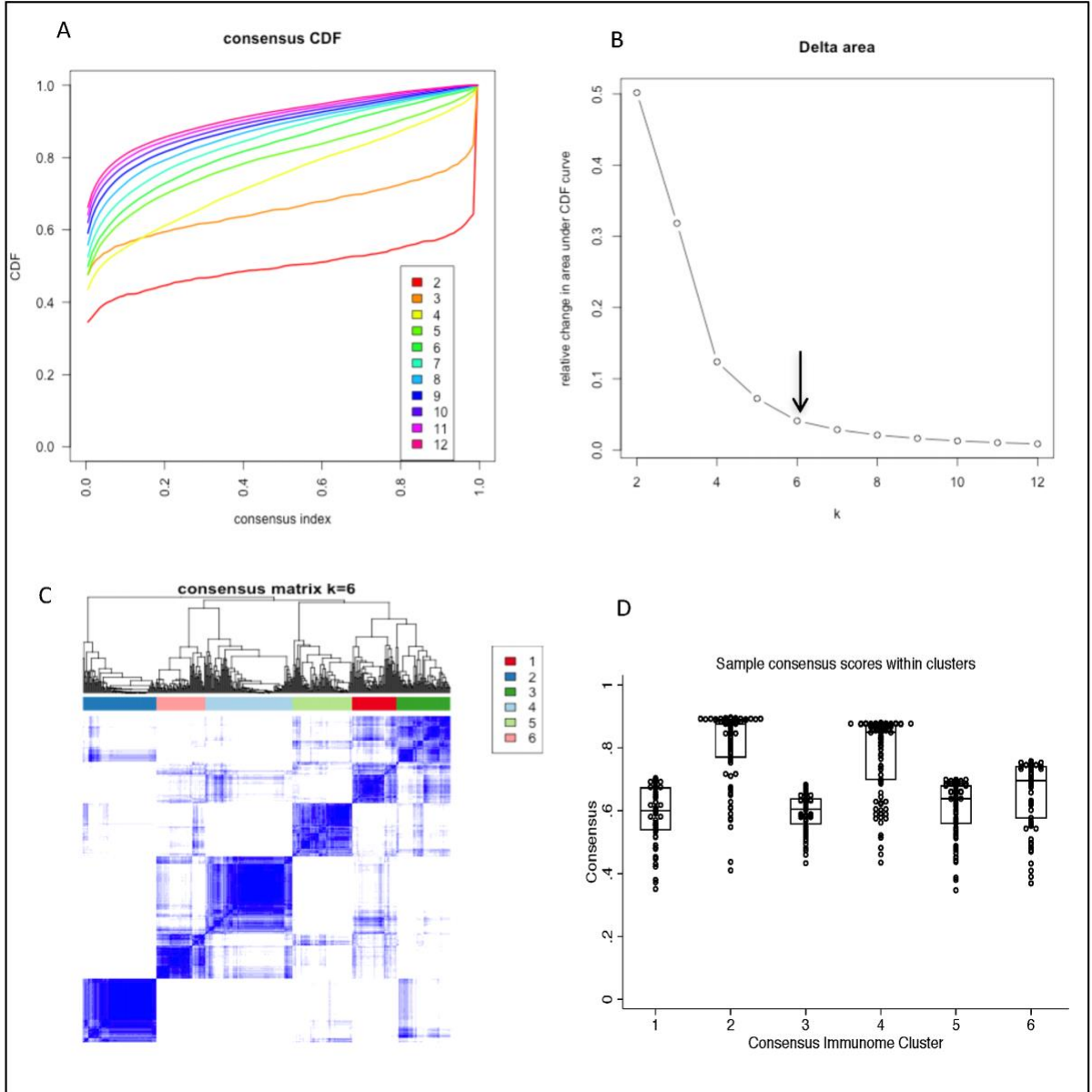


Figure S3. Consensus cluster analysis (2) conducted in 2/3 of LMC dataset. **A.** Cumulative density functions (CDF) of independent runs considering 2 to 12 clusters in 5000 data resampling. **B.** Relative change in area under the CDF with increasing number of tumor clusters (k). This area shows little variation after k=6 and we chose this number as optimal (shown by an arrow). **C.** Sample dendrogram with k=6. The diagram is symmetrical and blue color indicates high consensus (i.e. samples occurring in the same cluster with high frequency in the 5000 repeats) while white indicates no consensus (samples never classified together). **D.** Sample consensus scores within the 6 optimal clusters. Cluster 2 and 4 have the greatest consensus but all clusters have a median consensus > 0.63.

A

Gene Cluster G1			Gene Cluster G3			
<u>Macrophage</u>	<u>Immature Dendritic Cell</u>	<u>Mast Cell</u>	<u>Cytotoxic</u>	<u>T Cell</u>	<u>Activated and plasmacytoid DCs</u>	<u>NK CD56^(DIM) and NK cells</u>
SCG5		HDC	APOL3	SH2D1A		
PTGDS		MAOB	KLRD1	TRAT1	INDO	IL21R
CHIT1	CH25H	MS4A2	KLRB1	LCK	LAMP3	KIRD55
ME1	FABP4	SIGLEC6	KLRF1	PRKCQ	EBI3	KIR3DL3
ATG7	F13A1	GATA2	GNLY	GIMAP5	IL3RA (pDC)	KIR3DL2
GM2A	CD1B	TPSB2	GZMH	CD96		KIR2DL3
MARCO	CD1E	ADCYAP1	GZMA	CD2		KIR3DL1
CD68	CCL22	PTGS1	DUSP2	CD3E		GZMB
COLEC12	CCL13	BLNK	CTSW	CD3D		SPN (NK)
CLEC5A	CD1C	BCL11A	NKG7	CD3G		NC1R (NK)
	VASH1	SLC24A3		CD6		
	H53ST2	CALB2		SKAP1		
	CARD9	CTSG		ITM2A		
		TPSAB1				
		CPA3				
		SLC18A2				

Gene Cluster G2				Gene Cluster G4	
<u>CD8+ T cell</u>	<u>Central memory T cell</u>	<u>Th2</u>	<u>Eosinophil</u>	<u>NK CD56^(bright) cells</u>	
ZNF91	RPP38	PHEX	HES1	RRAD	
SF1	PHC3	WDHD1	LRP5L	MADD	
ZNF609	REPS1	NEIL3	RCOR3	MPPED1	
ZNF22	POLR2J2	ADCY1	ACACB	FOXJ1	
SFRS7	ST3GAL1	PTGIS	C9ORF156	PLA2G6	
SLC16A7	ATF7IP	CENPF	SYNJ1	XCL1	
ARHGAP8	KLF12	HELLS	KBTBD11		
C4ORF15	CEP68	AHI1	GALC		
KLF9	ATM	CDC25C	THBS4		
VAMP2	SNRPN		CAT		
MYST3	CREBZF		RRP12		
C12ORF47	TIMM8A		GPR44		
ZEB1	MLL		THBS1		
CDKN2AIP	INPP4B				
	PSPC1				
	PDXDC2				
	PCM1				

B

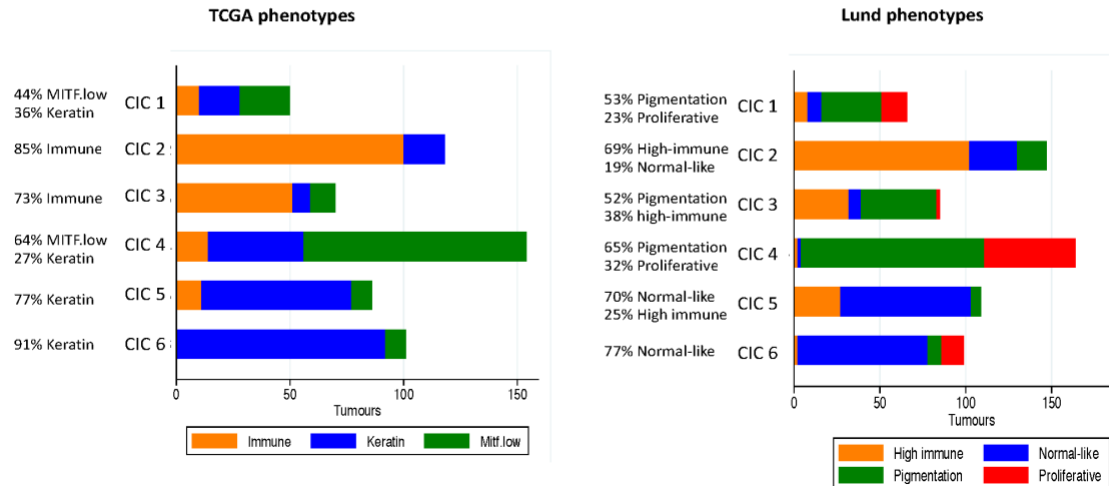


Figure S4. A. Overrepresentation in gene clusters G1-G4 of Figure 1A of the main txt. B.

Overlap between the 6 CICs in the LMC dataset (training and test sets pooled) and molecular phenotypes inferred using two published transcriptomic signatures developed using predominantly metastatic tumors (see references in the main text).

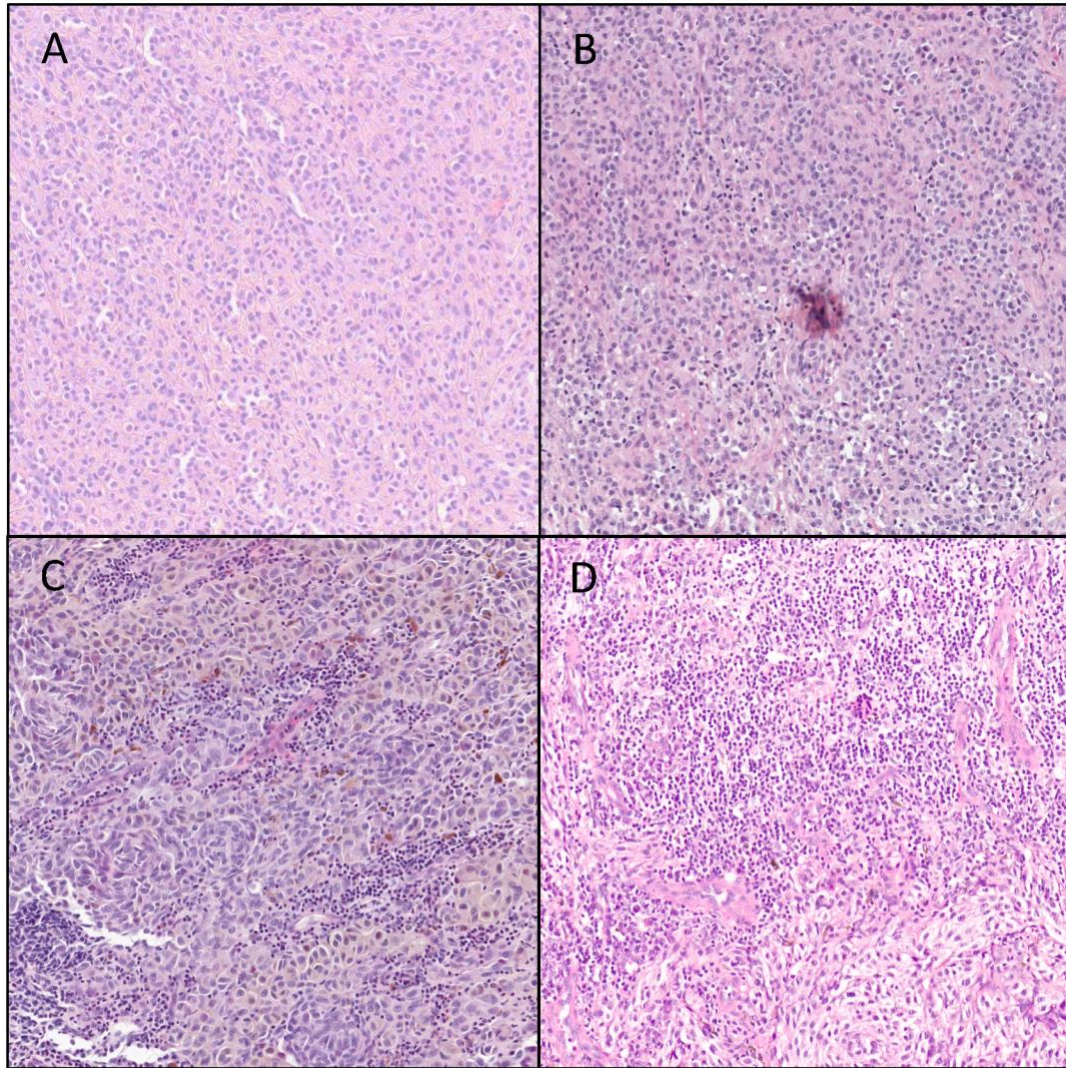


Figure S5. Representative images of H&E-stained primary melanomas from sectioned FFPE blocks in the LMC. Blocks were examined and annotated to identify an appropriate region for mRNA sampling for transcriptomic profiling. Retrospectively the H&Es were scored for the presence of tumour infiltrating lymphocytes (TILs) in the exact location corresponding to the sampled region of the block. Tumors were scored as containing (A) ‘no’ TILs; (B) ‘some’ TILs; (C) ‘moderate’ TILs and (D) ‘lots’ of TILs.

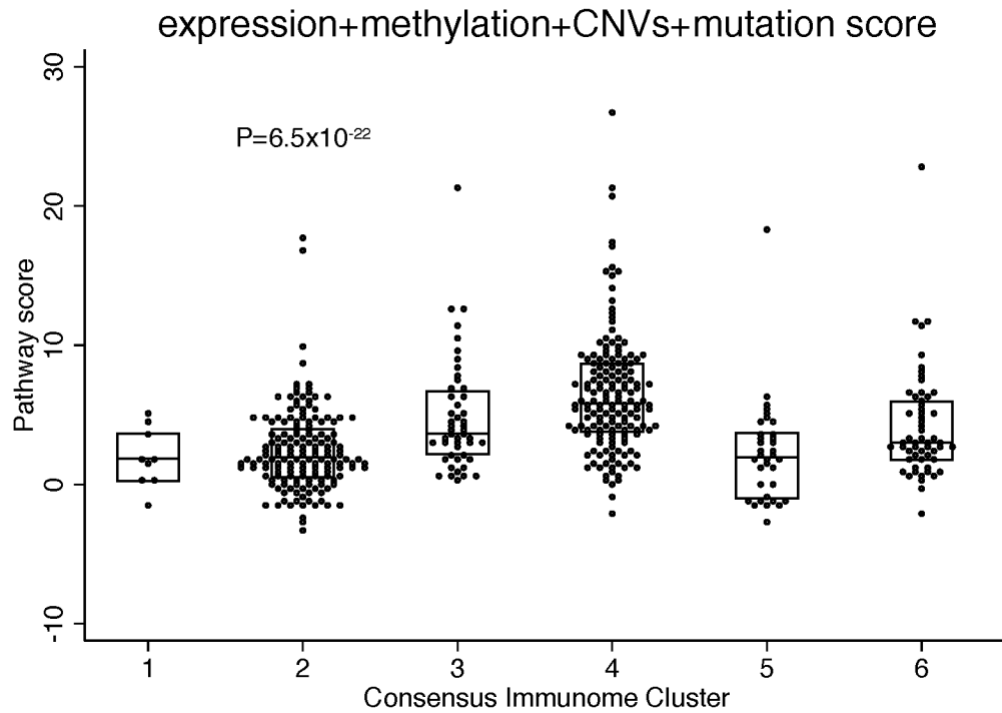


Figure S6. Distribution of β -catenin signaling pathway score across the 6 Consensus Immunome Clusters in TCGA skin melanoma dataset. The pathway scoring used gene expression, promoter methylation, driver mutations and copy number alterations for *CTNNB1*, *c-MYC*, *APC*, *APC2*, *SOX2*, *SOX11*, *TCF1*, *TCF12* and *VEGFA* (see Methods). The Pvalue is from a Kruskal-Wallis test.

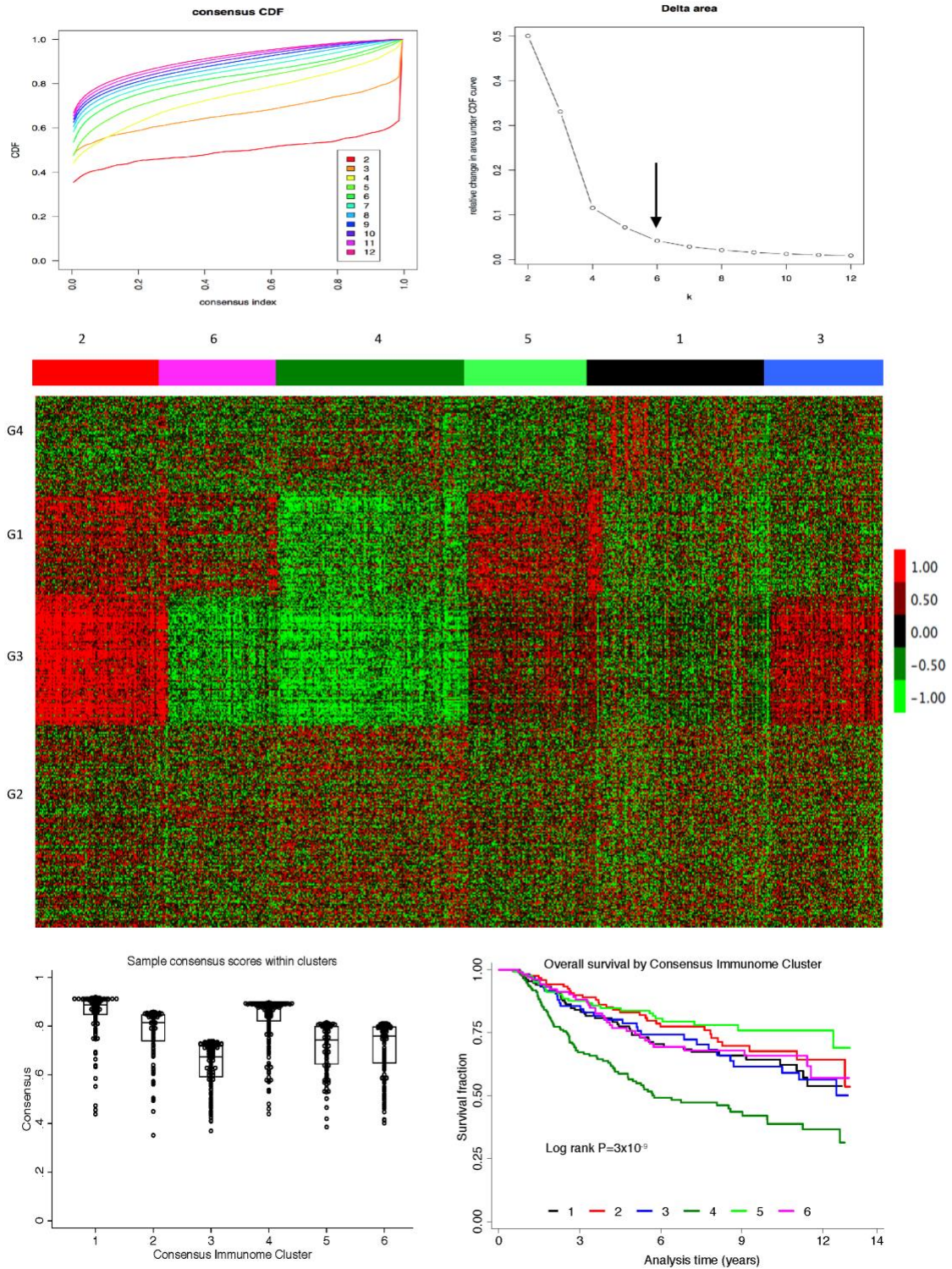


Figure S7. New consensus cluster analysis pooling the full LMC dataset and TCGA primaries. The consensus CDF, optimal number of clusters, heatmap and cluster association with survival are similar to those obtained in the original analysis based on 2/3 of LMC as training set.

Table S1. Sample histological characteristics in the training and test LMC data subsets

Characteristic	Number and percentage or median and range *		
	Training (N=465)	Test (N=238)	P
Male sex	216 (46.5%)	102 (42.9%)	0.37
Age at diagnosis (years)	58.4 (18.3, 81.2)	58.1 (20.3, 77.1)	0.54
Tumor site			
Limbs	195 (42.0%)	103 (43.3%)	0.64
Trunk	161 (34.7%)	72 (30.2%)	
Head/neck	51 (11.0%)	29 (12.2%)	
Other	57 (12.3%)	34 (14.3%)	
Died from melanoma	157 (33.8 %)	76 (31.9%)	0.63
Relapsed	167 (35.9%)	76 (31.9%)	0.29
Follow up time (years)	7.6 (0.8, 13.4)	7.5 (0.5, 13.6)	0.73
AJCC stage			
I	158 (34.3%)	75 (32.0%)	0.41
II	238 (51.6%)	117 (50.0%)	
III	65 (14.1%)	42 (18.0%)	
Ulcerated	154 (33.1%)	81 (34.0%)	0.81
Mitotic rate (count per mm ²)	3 (0, 83)	3 (0, 70)	0.78
Breslow thickness (mm)	2.3 (0.3, 20)	2.5 (0.7, 15)	0.87
Vascular invasion	51 (12.4%)	18 (8.4%)	0.13
<i>BRAF</i> -V600 mutation	183 (48.4%)	90 (44.1%)	0.32
<i>NRAS</i> mutation (codon 12,13 or 61)	93 (24.9%)	49 (24.5%)	0.92
TILs			
Brisk	55 (14.3%)	27 (16.0%)	0.42
Non-brisk	240 (62.5%)	101 (60.0%)	
Unclassified	41 (10.7%)	13 (7.7%)	
Absent	48 (12.5%)	28 (16.6%)	

* Missing data excluded in percentage calculation

& Rare site=non-exposed to the sun such as anal, perineal, penile, vulvar or oropharyngeal

Table S2: Melanoma immunome gene and cell list

GENE	PROBE	IMMUNE CELL	FUNCTION
ABCB4	ILMN_1767349	B-cells	adaptive
FCRL2	ILMN_1791329	B-cells	adaptive
SCN3A	ILMN_1657591	B-cells	adaptive
GLDC	ILMN_1806754	B-cells	adaptive
CD72	ILMN_1723004	B-cells	adaptive
QRSL1	ILMN_1733364	B-cells	adaptive
CR2	ILMN_2369666	B-cells	adaptive
SPIB	ILMN_2143314	B-cells	adaptive
COCH	ILMN_1711514	B-cells	adaptive
CD19	ILMN_1782704	B-cells	adaptive
MS4A1	ILMN_1697830	B-cells	adaptive
BACH2	ILMN_1659943	B-cells	adaptive
SLC15A2	ILMN_2211739	B-cells	adaptive
BLK	ILMN_1668277	B-cells	adaptive
OSBPL10	ILMN_1669497	B-cells	adaptive
BLNK	ILMN_2142935	B-cells	adaptive
TNFRSF17	ILMN_1768016	B-cells	adaptive
HLA-DQA1	ILMN_1808405	B-cells	adaptive
HLA-DOB	ILMN_1700428	B-cells	adaptive
GNG7	ILMN_1728107	B-cells	adaptive
PNOC	ILMN_1676003	B-cells	adaptive
DTNB	ILMN_1798819	B-cells	adaptive
CCR9	ILMN_1664316	B-cells	adaptive
TCL1A	ILMN_1788841	B-cells	adaptive
BCL11A	ILMN_1752899	B-cells	adaptive
GZMM	ILMN_1690561	CD8 T-cells	adaptive
VAMP2	ILMN_1713491	CD8 T-cells	adaptive
ZFP36L2	ILMN_2150258	CD8 T-cells	adaptive
MYST3	ILMN_2095840	CD8 T-cells	adaptive
ZNF22	ILMN_1798533	CD8 T-cells	adaptive
KLF9	ILMN_1778523	CD8 T-cells	adaptive
PRF1	ILMN_1740633	CD8 T-cells	adaptive
ZEB1	ILMN_1762231	CD8 T-cells	adaptive
ARHGAP8	ILMN_2297096	CD8 T-cells	adaptive
SFRS7	ILMN_1778836	CD8 T-cells	adaptive
ZNF91	ILMN_1802053	CD8 T-cells	adaptive
CD8A	ILMN_1760374	CD8 T-cells	adaptive
LIME1	ILMN_2183687	CD8 T-cells	adaptive
SF1	ILMN_1742808	CD8 T-cells	adaptive
CD8B	ILMN_1748601	CD8 T-cells	adaptive
SLC16A7	ILMN_1810053	CD8 T-cells	adaptive
FLT3LG	ILMN_2091412	CD8 T-cells	adaptive
ZNF609	ILMN_1799082	CD8 T-cells	adaptive
PF4	ILMN_1767037	CD8 T-cells	adaptive

TSC22D3	ILMN_2276952	CD8 T-cells	adaptive
PPP1R2	ILMN_1683044	CD8 T-cells	adaptive
C12orf47	ILMN_1798957	CD8 T-cells	adaptive
CDKN2AIP	ILMN_1773066	CD8 T-cells	adaptive
C4orf15	ILMN_2160124	CD8 T-cells	adaptive
GZMA	ILMN_1779324	Cytotoxic cells	adaptive
KLRD1	ILMN_1797988	Cytotoxic cells	adaptive
KLRB1	ILMN_2079655	Cytotoxic cells	adaptive
GNLY	ILMN_1790692	Cytotoxic cells	adaptive
CTSW	ILMN_1794364	Cytotoxic cells	adaptive
APBA2	ILMN_1723626	Cytotoxic cells	adaptive
KLRK1	ILMN_2222443	Cytotoxic cells	adaptive
DUSP2	ILMN_1712959	Cytotoxic cells	adaptive
APOL3	ILMN_1756862	Cytotoxic cells	adaptive
RORA	ILMN_2322499	Cytotoxic cells	adaptive
ZBTB16	ILMN_2305407	Cytotoxic cells	adaptive
GZMH	ILMN_1731233	Cytotoxic cells	adaptive
KLRF1	ILMN_2055781	Cytotoxic cells	adaptive
NKG7	ILMN_1682993	Cytotoxic cells	adaptive
FRYL	ILMN_1798467	T helper cells	adaptive
ATF2	ILMN_1748271	T helper cells	adaptive
ICOS	ILMN_1669927	T helper cells	adaptive
PPP2R5C	ILMN_1789283	T helper cells	adaptive
GOLGA8A	ILMN_1712469	T helper cells	adaptive
C13orf34	ILMN_1761486	T helper cells	adaptive
LRBA	ILMN_1652160	T helper cells	adaptive
BATF	ILMN_1668822	T helper cells	adaptive
CD28	ILMN_1749362	T helper cells	adaptive
ITM2A	ILMN_2076600	T-cells	adaptive
BCL11B	ILMN_1665761	T-cells	adaptive
PRKCQ	ILMN_1733421	T-cells	adaptive
GIMAP5	ILMN_1769383	T-cells	adaptive
CD6	ILMN_1746565	T-cells	adaptive
CD3E	ILMN_1739794	T-cells	adaptive
CD2	ILMN_1695025	T-cells	adaptive
NCALD	ILMN_2343097	T-cells	adaptive
CD3D	ILMN_2325837	T-cells	adaptive
LCK	ILMN_2377109	T-cells	adaptive
CD3G	ILMN_1717197	T-cells	adaptive
TRAT1	ILMN_1684943	T-cells	adaptive
SKAP1	ILMN_1751400	T-cells	adaptive
CD96	ILMN_2415786	T-cells	adaptive
SH2D1A	ILMN_1705892	T-cells	adaptive
NFATC3	ILMN_2360028	Tcm	adaptive
FOXP1	ILMN_1738179	Tcm	adaptive
DOCK9	ILMN_1773413	Tcm	adaptive

TRAF3IP3	ILMN_1780397	Tcm	adaptive
FYB	ILMN_1796537	Tcm	adaptive
TIMM8A	ILMN_1722239	Tcm	adaptive
AQP3	ILMN_1651574	Tcm	adaptive
RPP38	ILMN_1680386	Tcm	adaptive
NEFL	ILMN_1659086	Tcm	adaptive
REPS1	ILMN_2222768	Tcm	adaptive
CASP8	ILMN_1673757	Tcm	adaptive
CEP68	ILMN_1808500	Tcm	adaptive
ATF7IP	ILMN_1716435	Tcm	adaptive
USP9Y	ILMN_2056795	Tcm	adaptive
CLUAP1	ILMN_2242491	Tcm	adaptive
POLR2J2	ILMN_3241970	Tcm	adaptive
HNRPH1	ILMN_2101920	Tcm	adaptive
MLL	ILMN_1668683	Tcm	adaptive
KLF12	ILMN_1762801	Tcm	adaptive
PDXDC2	ILMN_3251217	Tcm	adaptive
PHC3	ILMN_2179873	Tcm	adaptive
CDC14A	ILMN_1655983	Tcm	adaptive
PCM1	ILMN_2042595	Tcm	adaptive
INPP4B	ILMN_2198878	Tcm	adaptive
CYorf15B	ILMN_1756506	Tcm	adaptive
PSPC1	ILMN_1724490	Tcm	adaptive
CREBZF	ILMN_1784847	Tcm	adaptive
SNRPN	ILMN_1656537	Tcm	adaptive
CYLD	ILMN_2287941	Tcm	adaptive
ST3GAL1	ILMN_1683313	Tcm	adaptive
ATM	ILMN_1779214	Tcm	adaptive
PCNX	ILMN_1740010	Tcm	adaptive
TXK	ILMN_1741143	Tcm	adaptive
TBCD	ILMN_1795400	Tem	adaptive
TBC1D5	ILMN_1767433	Tem	adaptive
VIL2	ILMN_1795937	Tem	adaptive
EWSR1	ILMN_1697735	Tem	adaptive
GDPD5	ILMN_1701643	Tem	adaptive
NFATC4	ILMN_1796018	Tem	adaptive
PRKY	ILMN_1772163	Tem	adaptive
AKT3	ILMN_2325610	Tem	adaptive
LTK	ILMN_1679290	Tem	adaptive
C7orf54	ILMN_1655961	Tem	adaptive
CCR2	ILMN_2376431	Tem	adaptive
FLI1	ILMN_1665738	Tem	adaptive
MEFV	ILMN_2115752	Tem	adaptive
DDX17	ILMN_1675124	Tem	adaptive
ZNF764	ILMN_1727938	TFH	adaptive
C18orf1	ILMN_2351795	TFH	adaptive

SIRPG	ILMN_1771801	TFH	adaptive
KCNK5	ILMN_1766918	TFH	adaptive
THADA	ILMN_1706818	TFH	adaptive
PVALB	ILMN_2069224	TFH	adaptive
POMT1	ILMN_1743663	TFH	adaptive
CXCL13	ILMN_1718552	TFH	adaptive
B3GAT1	ILMN_1761093	TFH	adaptive
SMAD1	ILMN_1705392	TFH	adaptive
CHGB	ILMN_1765966	TFH	adaptive
PDCD1	ILMN_1806725	TFH	adaptive
SLC7A10	ILMN_1681087	TFH	adaptive
HEY1	ILMN_1788203	TFH	adaptive
TSHR	ILMN_1746712	TFH	adaptive
MYO7A	ILMN_1811719	TFH	adaptive
MYO6	ILMN_1727080	TFH	adaptive
MAF	ILMN_1719543	TFH	adaptive
CHI3L2	ILMN_2326273	TFH	adaptive
PASK	ILMN_1667022	TFH	adaptive
STK39	ILMN_1791328	TFH	adaptive
KIAA1324	ILMN_1771482	TFH	adaptive
MKL2	ILMN_1690807	TFH	adaptive
BLR1	ILMN_1699669	TFH	adaptive
PTPN13	ILMN_2374683	TFH	adaptive
ST8SIA1	ILMN_2048011	TFH	adaptive
TOX	ILMN_1788886	TFH	adaptive
SH3TC1	ILMN_1756595	TFH	adaptive
ICA1	ILMN_1814787	TFH	adaptive
CD160	ILMN_1742001	Tgd	adaptive
C1orf61	ILMN_1759652	Tgd	adaptive
TARP	ILMN_1723944	Tgd	adaptive
CSF2	ILMN_1661861	Th1 cells	adaptive
CMAH	ILMN_1704084	Th1 cells	adaptive
HBEGF	ILMN_2121408	Th1 cells	adaptive
DGKI	ILMN_1718266	Th1 cells	adaptive
CTLA4	ILMN_2261627	Th1 cells	adaptive
GGT1	ILMN_2368585	Th1 cells	adaptive
LRP8	ILMN_1677765	Th1 cells	adaptive
APBB2	ILMN_3251699	Th1 cells	adaptive
CD38	ILMN_2233783	Th1 cells	adaptive
IL22	ILMN_1735208	Th1 cells	adaptive
LTA	ILMN_1795464	Th1 cells	adaptive
EGFL6	ILMN_2057479	Th1 cells	adaptive
ATP9A	ILMN_2089073	Th1 cells	adaptive
LRRN3	ILMN_2048591	Th1 cells	adaptive
CD70	ILMN_1760247	Th1 cells	adaptive
SYNGR3	ILMN_1786379	Th1 cells	adaptive

IL12RB2	ILMN_1761921	Th1 cells	adaptive
APOD	ILMN_1780170	Th1 cells	adaptive
ZBTB32	ILMN_1732981	Th1 cells	adaptive
IFNG	ILMN_2207291	Th1 cells	adaptive
DUSP5	ILMN_1656501	Th1 cells	adaptive
IL17RA	ILMN_1728724	Th17 cells	adaptive
IL17A	ILMN_1774983	Th17 cells	adaptive
RORC	ILMN_1734366	Th17 cells	adaptive
MB	ILMN_1666109	Th2 cells	adaptive
CDC25C	ILMN_1725260	Th2 cells	adaptive
MICAL2	ILMN_1785141	Th2 cells	adaptive
ADCY1	ILMN_2120555	Th2 cells	adaptive
GATA3	ILMN_2406656	Th2 cells	adaptive
WDHD1	ILMN_2377150	Th2 cells	adaptive
PTGIS	ILMN_1667692	Th2 cells	adaptive
CXCR6	ILMN_1674640	Th2 cells	adaptive
LAIR2	ILMN_1807491	Th2 cells	adaptive
AHI1	ILMN_1791006	Th2 cells	adaptive
CENPF	ILMN_1664516	Th2 cells	adaptive
HELLS	ILMN_1783610	Th2 cells	adaptive
NEIL3	ILMN_1757697	Th2 cells	adaptive
PHEX	ILMN_1668242	Th2 cells	adaptive
ANK1	ILMN_2317186	Th2 cells	adaptive
IL26	ILMN_2123182	Th2 cells	adaptive
FOXP3	ILMN_1768049	TReg	adaptive
CCL1	ILMN_2086965	aDC	innate
LAMP3	ILMN_2170813	aDC	innate
INDO	ILMN_1656310	aDC	innate
EBI3	ILMN_1802653	aDC	innate
CD209	ILMN_1676372	DC	innate
CCL13	ILMN_1783593	DC	innate
HSD11B1	ILMN_1811370	DC	innate
NPR1	ILMN_1779897	DC	innate
CCL17	ILMN_1710186	DC	innate
CCL22	ILMN_2160476	DC	innate
PPFIBP2	ILMN_1675656	DC	innate
TKTL1	ILMN_1674009	Eosinophils	innate
ACACB	ILMN_1763852	Eosinophils	innate
IL5RA	ILMN_1756455	Eosinophils	innate
CAT	ILMN_1651705	Eosinophils	innate
EPN2	ILMN_1815519	Eosinophils	innate
THBS4	ILMN_1736078	Eosinophils	innate
SYNJ1	ILMN_1701991	Eosinophils	innate
THBS1	ILMN_1686116	Eosinophils	innate
IGSF2	ILMN_1799278	Eosinophils	innate
LRP5L	ILMN_1718633	Eosinophils	innate

HRH4	ILMN_1810424	Eosinophils	innate
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RNASE2	ILMN_1730628	Eosinophils	innate
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EMR1	ILMN_1780601	Eosinophils	innate
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KBTBD11	ILMN_1784630	Eosinophils	innate
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HES1	ILMN_1710284	Eosinophils	innate
CCR3	ILMN_1763322	Eosinophils	innate
FZD2	ILMN_1653711	iDC	innate
SYT17	ILMN_1657760	iDC	innate
SLC26A6	ILMN_1785252	iDC	innate
PPARG	ILMN_1800225	iDC	innate
FABP4	ILMN_1773006	iDC	innate
CD1C	ILMN_1654210	iDC	innate
TM7SF4	ILMN_1793730	iDC	innate
CSF1R	ILMN_1686623	iDC	innate
HS3ST2	ILMN_1712475	iDC	innate
MS4A6A	ILMN_1797731	iDC	innate
GUCA1A	ILMN_1662086	iDC	innate
TACSTD2	ILMN_1739001	iDC	innate
CLEC10A	ILMN_2415303	iDC	innate
CD1A	ILMN_1723520	iDC	innate
ABCG2	ILMN_1789641	iDC	innate
GSTT1	ILMN_1730054	iDC	innate
CD1B	ILMN_1726230	iDC	innate
VASH1	ILMN_1796216	iDC	innate
CARD9	ILMN_1712532	iDC	innate
CD1E	ILMN_2335754	iDC	innate
MMP12	ILMN_1768035	iDC	innate
F13A1	ILMN_1717163	iDC	innate
CH25H	ILMN_1741021	iDC	innate
GPC4	ILMN_1789502	Macrophages	innate
CD163	ILMN_2379599	Macrophages	innate
MSR1	ILMN_1694400	Macrophages	innate
CCL7	ILMN_1683456	Macrophages	innate
CXCL5	ILMN_2171384	Macrophages	innate
CHIT1	ILMN_3249477	Macrophages	innate
SULT1C2	ILMN_2415329	Macrophages	innate
BCAT1	ILMN_1766169	Macrophages	innate

COL8A2	ILMN_1674050	Macrophages	innate
GM2A	ILMN_2221046	Macrophages	innate
COLEC12	ILMN_1679049	Macrophages	innate
DNASE2B	ILMN_1789130	Macrophages	innate
MARCO	ILMN_1731503	Macrophages	innate
ATG7	ILMN_1790978	Macrophages	innate
SCG5	ILMN_2065773	Macrophages	innate
KAL1	ILMN_1750373	Macrophages	innate
SGMS1	ILMN_1740505	Macrophages	innate
CHI3L1	ILMN_3307868	Macrophages	innate
CD84	ILMN_1698367	Macrophages	innate
CYBB	ILMN_1682312	Macrophages	innate
MS4A4A	ILMN_2370336	Macrophages	innate
CLEC5A	ILMN_1780465	Macrophages	innate
CD68	ILMN_2359907	Macrophages	innate
ME1	ILMN_1736042	Macrophages	innate
FN1	ILMN_2366463	Macrophages	innate
PTGDS	ILMN_1664464	Macrophages	innate
CEACAM8	ILMN_1806056	Mast cells	innate
SLC18A2	ILMN_2070003	Mast cells	innate
CTSG	ILMN_1680424	Mast cells	innate
CMA1	ILMN_1770772	Mast cells	innate
SIGLEC6	ILMN_2299095	Mast cells	innate
TPSB2	ILMN_3243238	Mast cells	innate
HDC	ILMN_1792323	Mast cells	innate
MAOB	ILMN_1727360	Mast cells	innate
SLC24A3	ILMN_1663519	Mast cells	innate
NR0B1	ILMN_1800160	Mast cells	innate
GATA2	ILMN_2102670	Mast cells	innate
TAL1	ILMN_1748450	Mast cells	innate
ADCYAP1	ILMN_1763344	Mast cells	innate
CALB2	ILMN_1748840	Mast cells	innate
CPA3	ILMN_1766551	Mast cells	innate
TPSAB1	ILMN_2169801	Mast cells	innate
MPO	ILMN_1705183	Mast cells	innate
SCG2	ILMN_1703178	Mast cells	innate
ABCC4	ILMN_2194009	Mast cells	innate
HPGD	ILMN_2166457	Mast cells	innate
PRG2	ILMN_1729314	Mast cells	innate
MS4A2	ILMN_1806721	Mast cells	innate
LOC339524	ILMN_1699320	Mast cells	innate
PTGS1	ILMN_1665100	Mast cells	innate
SLC22A4	ILMN_2050911	Neutrophils	innate
CEACAM3	ILMN_1743570	Neutrophils	innate
MGAM	ILMN_1714643	Neutrophils	innate
TNFRSF10C	ILMN_1672114	Neutrophils	innate

SIGLEC5	ILMN_1652381	Neutrophils	innate
LILRB2	ILMN_2312340	Neutrophils	innate
PDE4B	ILMN_1782922	Neutrophils	innate
ALPL	ILMN_1701603	Neutrophils	innate
CD93	ILMN_1704730	Neutrophils	innate
IL8RB	ILMN_1680397	Neutrophils	innate
HPSE	ILMN_2092850	Neutrophils	innate
S100A12	ILMN_1748915	Neutrophils	innate
VNN3	ILMN_1804935	Neutrophils	innate
DYSF	ILMN_1810420	Neutrophils	innate
HIST1H2BC	ILMN_1680937	Neutrophils	innate
FPR1	ILMN_2092118	Neutrophils	innate
BST1	ILMN_1770161	Neutrophils	innate
G0S2	ILMN_1691846	Neutrophils	innate
CRISPLD2	ILMN_1790689	Neutrophils	innate
CREB5	ILMN_1731714	Neutrophils	innate
FCAR	ILMN_2279367	Neutrophils	innate
KCNJ15	ILMN_1675756	Neutrophils	innate
CYP4F3	ILMN_3251260	Neutrophils	innate
SLC25A37	ILMN_1715969	Neutrophils	innate
FCGR3B	ILMN_2134453	Neutrophils	innate
CSF3R	ILMN_2371280	Neutrophils	innate
MADD	ILMN_1743583	NK CD56bright cells	innate
XCL1	ILMN_1718792	NK CD56bright cells	innate
PLA2G6	ILMN_1697654	NK CD56bright cells	innate
MPPED1	ILMN_1801778	NK CD56bright cells	innate
FOXJ1	ILMN_1802190	NK CD56bright cells	innate
RRAD	ILMN_2186137	NK CD56bright cells	innate
GTF3C1	ILMN_1789839	NK CD56dim cells	innate
GZMB	ILMN_2109489	NK CD56dim cells	innate
KIR3DL2	ILMN_2190842	NK CD56dim cells	innate
KIR3DL1	ILMN_2131828	NK CD56dim cells	innate
KIR2DS1	ILMN_2166812	NK CD56dim cells	innate
SPON2	ILMN_1676099	NK CD56dim cells	innate
KIR2DL3	ILMN_1667232	NK CD56dim cells	innate
KIR3DL3	ILMN_2082593	NK CD56dim cells	innate
IL21R	ILMN_1661687	NK CD56dim cells	innate
KIR3DS1	ILMN_3242156	NK CD56dim cells	innate
FLJ20699	ILMN_1692464	NK CD56dim cells	innate
KIR2DS5	ILMN_1691803	NK CD56dim cells	innate
TBXA2R	ILMN_1744251	NK cells	innate
PSMD4	ILMN_3307799	NK cells	innate
TINAGL1	ILMN_1807169	NK cells	innate
FZR1	ILMN_1753207	NK cells	innate
ADARB1	ILMN_1679797	NK cells	innate
LDB3	ILMN_2305599	NK cells	innate

PDLIM4	ILMN_1663976	NK cells	innate
SLC30A5	ILMN_1709728	NK cells	innate
BCL2	ILMN_1801119	NK cells	innate
IGFBP5	ILMN_1750324	NK cells	innate
MRC2	ILMN_1783946	NK cells	innate
FUT5	ILMN_1773310	NK cells	innate
NCR1	ILMN_1750761	NK cells	innate
PRX	ILMN_1786648	NK cells	innate
MCM3AP	ILMN_1784766	NK cells	innate
SMEK1	ILMN_1654998	NK cells	innate
MAPRE3	ILMN_1734290	NK cells	innate
SPN	ILMN_1801040	NK cells	innate
FGF18	ILMN_1693483	NK cells	innate
IL3RA	ILMN_1747344	pDC	innate

Table S3. Association between the 6 CICs and Tumor infiltrating lymphocytes (TILs) measured by a single observer (S O'S) in pooled LMC dataset

TILs	CIC 1	CIC 2	CIC 3	CIC 4	CIC 5	CIC 6	P*	P**	P***	P****
Measured in whole tumor (%)										
Brisk	11.1	22.6	22.5	3.6	3.0	2.2	3×10^{-10}	1.5×10^{-6}	6×10^{-7}	3.6×10^{-6}
Non-brisk	85.7	73.7	76.1	67.7	82.1	88.9				
No TILs	3.2	3.7	1.4	14.3	8.1	9.9				
Measured in tumor core sampled for mRNA extraction										
Lots	4.8	19.3	6.5	1.4	6.0	3.8	9×10^{-14}	2.5×10^{-5}	2.6×10^{-13}	0.01
Moderate	12.9	21.8	14.3	8.8	23.8	10.1				
Some	38.7	39.5	36.4	26.3	46.4	51.9				
None/Barely perceptible	43.6	19.4	42.9	63.5	23.5	34.2				

* Comparison of all 6 CICs; ** Comparison of all CICs except CIC 4; ***CIC 2 vs. CIC 4; **** CIC 3 vs CIC 4.

Table S4. Prognostic effect of CICs in multivariable analysis including Breslow thickness and ulceration in the LMC

Characteristic	CIC 4 vs. CIC 2		CIC 4 vs. all others	
	HR (95% CI) ^	P	HR (95% CI) ^	P
-	3.0 (1.92, 4.53)	8.1x10 ⁻⁷	2.5 (1.88, 3.29)	1.8x10 ⁻¹⁰
Age, sex, tumor site	2.5 (1.59, 3.81)	5.7x10 ⁻⁵	2.1 (1.58, 2.79)	3.2x10 ⁻⁷
Age, sex, site, mitotic rate, ulceration, Breslow thickness	2.0 (1.19, 3.31)	0.008	1.7 (1.25, 2.44)	0.001
Age, sex, site, mitotic rate, ulceration, Breslow thickness, vascular invasion	1.9 (1.11, 3.19)	0.02	1.6 (1.11, 2.39)	0.01
Age, sex, site, mitotic rate, ulceration, Breslow thickness, vascular invasion, mutation status §	1.7 (0.95, 3.04)	0.08	1.6 (1.09, 2.28)	0.02
<i>CD8A</i> **	3.6 (1.75, 7.37)	5x10 ⁻⁴	2.5 (1.79, 3.44)	5x10 ⁻⁸
<i>CD8B</i> **	2.3 (1.18, 4.36)	8.1x10 ⁻⁷	2.2 (1.60, 2.97)	8.2x10 ⁻⁷

^ Hazard ratio and 95% confidence interval for melanoma specific survival (MSS)

§ *BRAF-V600* and *NRAS* (codon 12, 13 or 61) mutation status. Although the difference between CIC 2 and CIC4 in this model with 10 variables is not significant (P=0.08), the hazard ration remains strong at 1.7.

** In these bivariate models, the CICs retain a significant prognostic value while neither *CD8A* nor *CD8B* are significant.

Table S5. Consensus Immunome Cluster for paired primary/metastatic samples

Patient	Primary Immunome cluster	Metastasis Immunome cluster	Metastasis site ^{&}
1	High Immune CIC2	Low Immune/ β -catenin High CIC4	Nodal
2	High Immune CIC2	High Immune CIC2*	Nodal
3	Intermediate Immune/Keratin Rich CIC5	High Immune CIC2*	Nodal
4	Intermediate Immune/Keratin Rich CIC5	Low Immune/ β -catenin High CIC4	Bone/Subcutaneous
5	Intermediate Immune/Keratin Poor CIC3	Low Immune/ β -catenin Low CIC1	Nodal
6	Low Immune/Keratin Rich CIC6	High Immune CIC2*	Nodal
7	Low Immune/ β -catenin High CIC4	Low Immune/ β -catenin High CIC4	Nodal
8	Low Immune/ β -catenin High CIC4	Intermediate Immune/Keratin Rich CIC5**	Subcutaneous
9	Low Immune/Keratin Rich CIC6	Low Immune/Keratin Rich CIC6	Skin/subcutaneous

[&] No visceral metastases were available. Generally speaking the immune status of the metastases was poorer than the primary tumor (participant 1,4,5) or similar (participant 2, 7 and 9). In four metastases, the Immunome profile was suggestive of local tumor environment/contamination. In 3 nodal metastases (participant 2, 3 and 6) marked *, the immunome profile was suggestive of contamination of the tumor sample by nodal lymphocytes and in 1 marked ** there was evidence for a keratin signature in a skin metastasis.

Table S6. Fold change between CIC2 (baseline) and CIC4 for β -catenin signaling components (P value from Mann-Whitney test)

Gene	LMC		TCGA	
	Fold change	P	Fold change	P
<i>CTNNB1</i>	1.59	4×10^{-15}	1.26	6×10^{-4}
<i>SOX2</i>	1.56	0.001	2.1	0.006
<i>SOX11</i>	1.84	3×10^{-7}	2.1	0.001
<i>c-MYC</i>	1.61	2×10^{-12}	1.6	3×10^{-8}
<i>TCF12</i>	1.13	0.001	1.4	5×10^{-6}
<i>TCF1</i>	1.03	0.38	1.1	0.02
<i>APC2</i>	1.70	4×10^{-6}	2.1	2×10^{-7}
<i>VEGFA</i>	1.36	5×10^{-6}	1.8	10^{-8}
<i>APC</i>	1.37	2×10^{-8}	1.3	4×10^{-4}
<i>DKK2</i>	0.57	3×10^{-10}	0.54	3×10^{-4}
<i>DKK3</i>	0.67	3×10^{-6}	0.70	0.02