Article:
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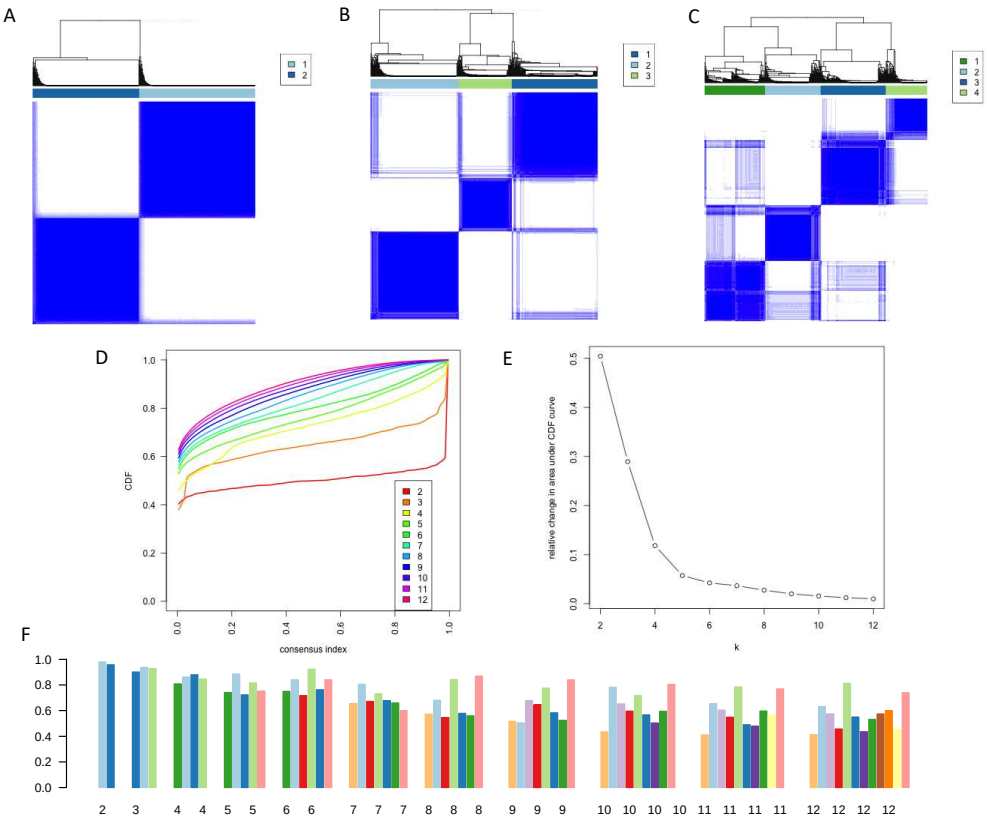
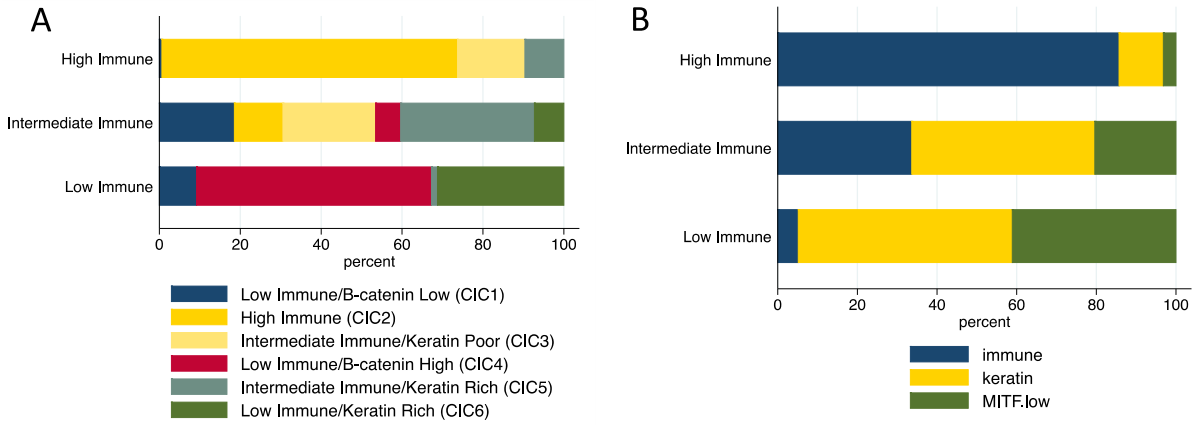


Figure S1 **Graphical representation of consensus clustering results**

(A) Sample dendrogram and heatmap with the number of clusters (k) equals 2; (B) k=3; (C) k=4. Each heatmap is symmetrical and blue color indicates high consensus (i.e. samples occurring in the same cluster with high frequency in the 5000 iterations), white colour indicates no consensus (samples always classified in different clusters). (D) Cumulative density functions (CDF) of independent runs with k=2 to 12 clusters in 5000 data resampling. (E) Relative change in area under the CDF with increasing k. (F) Cluster consesus plot, comparing the values of each cluster consensus for all ks.



C

TCGA_classes				
	Haz. Ratio	P	[95% Conf. Interval]	
Immune	-	-	-	-
Keratin	0.98	0.916	0.66	1.44
MTF low	1.97	0.001	1.34	2.90
3 Immune Subgroups				
	Haz. Ratio	P	[95% Conf. Interval]	
High immune	-	-	-	-
Intermediate Immune	1.57	0.046	1.01	2.43
Low Immune	2.10	0.001	1.37	3.23

Figure S2 **Comparison between the three immune subgroups and 2 published signatures**

(A) Intersection of the 3 new immune subgroups with the previously published 6 consensus immunome clusters (CICs) (Nsengimana et al., 2018): The High Immune Subgroup was predominantly composed of CIC2 plus some tumours of CIC3 and CIC5, all of which were described as having either high or intermediate immune infiltrates (Nsengimana et al., 2018). The Low Immune Subgroup was predominantly composed of CIC4 and CIC6, both of which were described as having low immune infiltration. Overall, there was a large concordance between the two signatures, as indicated by a Cramer V=0.72 (Cramer V is large when it is greater than 0.5). (B) Intersection of the 3 new immune subgroups with the TCGA classes in LMC. Although the High Immune subgroup overlapped well with the Immune phenotype of TCGA signature (85.7% agreement), the Intermediate and the Low immune groups did correspond to one of the other TCGA groupings. The overall agreement between the two signatures is moderate with Cramer's V=0.47 (Cramer V is moderate when it is comprised between 0.3 and 0.5). (C) Table representing the association with MSS and the three TCGA classes in LMC and the 3 new immune subgroups.

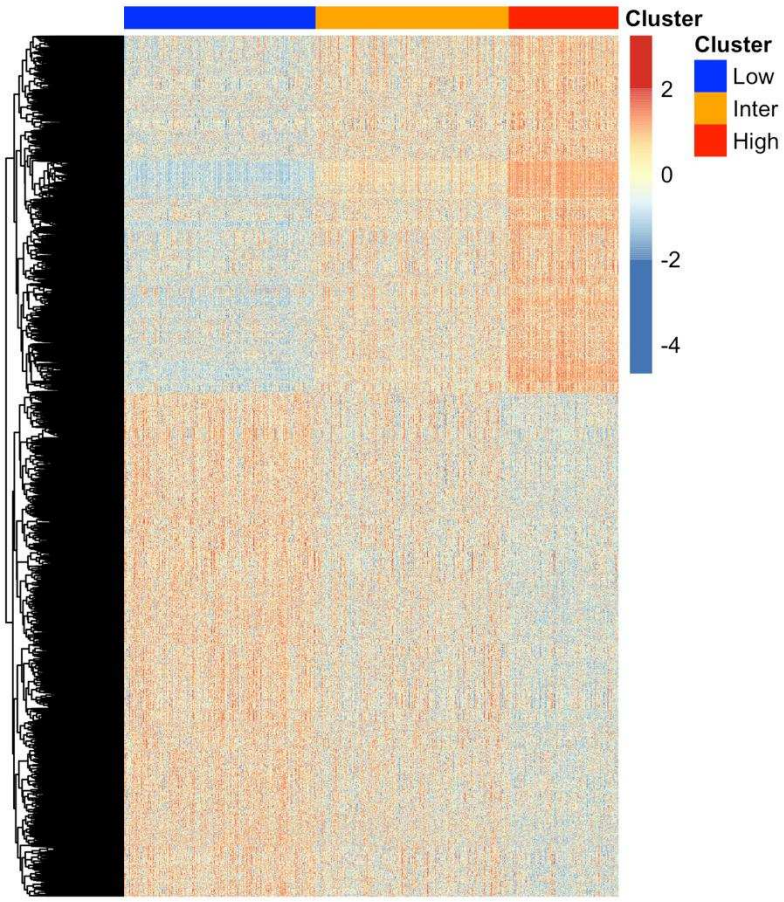


Figure S3 **Whole transcriptomic differential expression among the three immune subgroups represented on a heatmap (Kruskal Wallis and Bonferroni correction were used).** Columns represent samples, rows represent genes. Genes were hierarchically clustered while samples were maintained in their respective groups.

A

Gene name	Ever smokers (mean of log2 gene expression)	Never smokers (mean of log2 gene expression)	Ever vs never smokers (Fold change)	P	Non smokers (mean of log2 gene expression)	Still smokers (mean of log2 gene expression)	Non vs still smokers (Fold change)	P
GPR15 (whole data)	8.0	7.9	**1.07**	**0.12**	7.9	8.3	**1.32**	**0.01**
***GPR15* (High Immune)**	8.5	8.1	**1.32**	**0.02**	8.1	9.0	**1.9**	**0.002**

B

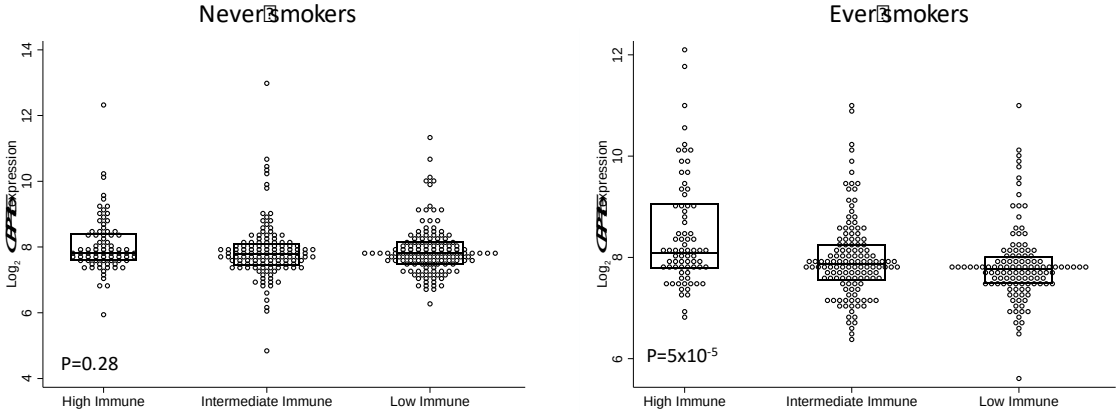


Figure S4 **Association between smoking (ever/never and non/still) and *GPR15* expression in the whole dataset, High Immune Subgroup and across the three immune subgroups.**

(A) Differential expression of *GRP15* between ever *vs* never smokers and non *vs* still smokers in the whole dataset and the High Immune Subgroup alone, using Mann Whitney U test. (B) *GPR15* expression across the immune subgroups in never smokers and ever smokers (Kruskal-Wallis test).

Table S1 Melanoma Specific Survival (MSS) for each of the immune cell scores in LMC and overall survival (OS) in TCGA, using univariable Cox proportional hazard model. Significant results after multiple-testing correction by Bonferroni method are in shown bold.

	LMC (primaries)				TCGA (metastases)			
Cell type	HR	P	95% CI low	95% CI up	HR	P	95% CI low	95% CI up
Activated_B_cells	**0.60**	**$1.18x10^{-5}$**	**0.37**	**0.83**	**0.63**	**$2.79x10^{-6}$**	**0.44**	**0.82**
Central_memory_CD4	**0.54**	**$7.31x10^{-6}$**	**0.27**	**0.81**	**0.52**	**$5.46x10^{-5}$**	**0.21**	**0.84**
Central_memory_CD8	0.72	$9.58x10^{-3}$	0.47	0.97	**0.55**	**$4.33x10^{-7}$**	**0.33**	**0.78**
Cytotoxic_cells	**0.72**	**$3.35x10^{-4}$**	**0.54**	**0.90**	**0.65**	**$1.91x10^{-6}$**	**0.47**	**0.83**
DC	**0.51**	**$4.27x10^{-6}$**	**0.23**	**0.80**	**0.53**	**$1.81x10^{-6}$**	**0.28**	**0.79**
Effector_memory_CD8	**0.63**	**$2.97x10^{-4}$**	**0.38**	**0.88**	**0.54**	**$1.49x10^{-8}$**	**0.33**	**0.75**
Eosinophil	1.39	$2.13x10^{-2}$	1.11	1.67	0.72	$5.97x10^{-2}$	0.38	1.06
iDC	0.88	$2.87x10^{-1}$	0.63	1.12	**0.56**	**$1.85x10^{-6}$**	**0.32**	**0.80**
Immature_B_cells	**0.66**	**$7.16x10^{-4}$**	**0.41**	**0.90**	**0.61**	**$1.12x10^{-5}$**	**0.40**	**0.83**
Macrophages	0.71	$1.20x10^{-2}$	0.44	0.98	**0.68**	**$2.24x10^{-3}$**	**0.44**	**0.93**
Mast_cells	**0.51**	**$3.90x10^{-5}$**	**0.19**	**0.83**	0.56	$3.50x10^{-3}$	0.18	0.95
MDSC	**0.64**	**$9.27x10^{-5}$**	**0.41**	**0.86**	**0.62**	**$1.58x10^{-5}$**	**0.40**	**0.84**
Memory_B_cells	1.03	$8.11x10^{-1}$	0.79	1.27	**0.65**	**$2.06x10^{-3}$**	**0.37**	**0.92**
Monocytes	0.94	$5.74x10^{-1}$	0.72	1.16	**0.65**	**$7.30x10^{-5}$**	**0.44**	**0.86**
Neutrophils	0.68	$4.18x10^{-3}$	0.41	0.94	**0.49**	**$4.83x10^{-7}$**	**0.22**	**0.77**
NK	**0.68**	**$2.39x10^{-4}$**	**0.47**	**0.89**	**0.64**	**$4.16x10^{-5}$**	**0.43**	**0.85**
NK56_bright	**0.71**	**$8.60x10^{-4}$**	**0.50**	**0.91**	**0.55**	**$4.08x10^{-7}$**	**0.32**	**0.78**
NK56_dim	0.78	$3.39x10^{-2}$	0.54	1.01	**1.66**	**$1.14x10^{-3}$**	**1.36**	**1.97**
NKT	**0.67**	**$2.43x10^{-4}$**	**0.46**	**0.88**	**0.48**	**$3.04x10^{-6}$**	**0.16**	**0.79**
pDC	0.91	$2.09x10^{-1}$	0.76	1.06	**0.77**	**$1.13x10^{-3}$**	**0.62**	**0.93**
T_cells	**0.55**	**$4.58x10^{-6}$**	**0.29**	**0.81**	**0.55**	**$2.36x10^{-7}$**	**0.32**	**0.78**
TFH	**0.69**	**$4.00x10^{-4}$**	**0.49**	**0.90**	**0.65**	**$3.78x10^{-6}$**	**0.47**	**0.83**
TGD	**0.68**	**$1.19x10^{-3}$**	**0.45**	**0.91**	**0.64**	**$3.66x10^{-6}$**	**0.46**	**0.83**
Th1	**0.57**	**$4.55x10^{-6}$**	**0.33**	**0.81**	**0.58**	**$1.35x10^{-7}$**	**0.37**	**0.78**
Th17	0.82	$2.45x10^{-1}$	0.47	1.16	0.44	$2.87x10^{-3}$	-0.10	0.98
Th2	**0.51**	**$6.17x10^{-8}$**	**0.27**	**0.75**	**0.56**	**$6.08x10^{-8}$**	**0.35**	**0.77**
Treg	**0.59**	**$8.19x10^{-5}$**	**0.32**	**0.85**	**0.54**	**$5.92x10^{-7}$**	**0.31**	**0.78**

Table S2 Associations of clinico-pathological characteristics with the three immune subgroups in LMC (N=703). Chi squared test was used for categorical variables while Mann Whitney U test (2 groups) or Kruskall Wallis test (>2 groups) were used for continuous variables. TILs categories are defined as: absent: no lymphocytes infiltrated melanoma, brisk: lymphocytes present in the tumor or infiltrating the entire base of the tumor, non-brisk: lymphocytes are observed in one or more foci of tumor.

Characteristic	Low Immune	Intermediate Immune	High Immune	P-value (N)
Number of participants (703)	272	275	156	
Melanoma death (%)	36.02	28.74	18.75	0.001 (666)
Age at diagnosis (median, years)	58.3	55.7	59.9	0.6 (703)
Site of melanoma				0.02 (702)
Limbs (%)	38.60	45.62	44.23	
Head (%)	11.03	10.95	12.82	
Trunk (%)	31.62	33.94	34.62	
Rare (i.e. sun protected) (%)	18.75	9.49	8.33	
Sex (% males)	43.01	44.73	50.00	0.4 (703)
***BRAF*-mutated (%)**	40.47	50.42	51.16	0.06 (582)
***NRAS*-mutated (%)**	29.77	24.36	16.80	0.03 (574)
Ulcerated (%)	36.03	33.45	28.85	0.32 (703)
Breslow thickness (median, mm)	2.43	2.3	2.02	0.004 (692)
Mitotic rate (median, count/mm^2)	4	3	2.5	0.0002 (596)
AJCC stage (%)				0.17 (695)
I	29.74	34.44	38.46	
II	51.30	52.59	48.08	
III	18.96	12.96	13.46	
TILs (%) (clinic dermatopathologists)				4.0×10^{-7} (553)
Brisk	8.46	13.18	27.27	
Non-brisk	62.19	65.00	55.30	
Unclassified	7.46	10.00	12.88	
No TILs	21.89	11.82	4.55	
TILs (%) – (single observer, S O'S)				3.62×10^{-8} (601)
Brisk	3.98	9.83	22.70	
Non-brisk	84.07	84.62	73.76	
No TILs	11.95	5.56	3.55	
Smoking (% ever smoked)	47.2	51.56	48.68	0.6 (658)
Season-adjusted serum vitamin D at recruitment (winter median, nmol/L)	40.1	41.2	36.07	0.2 (549)

Table S3 Differences in immune cell scores tested between ever, never smokers in the High Immune Subgroup, using Mann U Whitney test. Negative Z score indicates higher score in ever smokers. None of the immune cells showed a significant difference by smoking status.

Cell Type	Z score	P value
pDC	**-1.80**	**0.07**
NK56_bright	**1.60**	0.11
Cytotoxic_cells	**1.52**	0.13
TFH	**1.23**	0.22
Mast_cells	**-1.04**	0.30
Th2	**-0.98**	0.33
NKT	**0.90**	0.37
DC	**-0.87**	0.38
Memory_B_cells	**-0.87**	0.39
Th17	**0.78**	0.43
Central_memory_CD8	**-0.72**	0.47
TGD	**0.63**	0.53
Monocytes	**-0.62**	0.53
Neutrophils	**0.61**	0.54
Effector_memory_CD8	**0.54**	0.59
Macrophages	**0.52**	0.60
NK	**0.52**	0.61
T_cells	**-0.37**	0.71
Activated_B_cells	**0.36**	0.72
Central_memory_CD4	**-0.31**	0.76
Th1	**0.28**	0.78
iDC	**-0.28**	0.78
MDSC	**-0.22**	0.82
Eosinophil	**-0.13**	0.89
Treg	**0.09**	0.93
NK56_dim	**0.04**	0.97
Immature_B_cells	**-0.01**	0.99

Table S4 Association between ever/never smoking with histological features of the tumors. The Chi square test was used for categorical variables while Mann Whitney U test (2 groups) or Kruskall Wallis test (>2 groups) were used for continuous variables.

Characteristic	Ever smokers	Never Smokers	P-value (N)
Number of participants (152)	74	78	
Ulcerated (%)	34	26	0.27 (152)
Breslow thickness (median, mm)	2.2	1.95	0.51 (149)
Mitotic rate (median, count/mm^2)	3.5	2	0.08 (129)
TILs (%) (clinic			0.1 (128)
dermatopathologists)	23	32.8	
Brisk	65.6	46.3	
Non-brisk	9.8	13.4	
Unclassified	1.6	7.5	
No TILs			
TILs (%) – (single observer, S O'S)			0.7(139)
Brisk	20.6	25.3	
Non-brisk	76.5	70.4	
No TILs	2.9	4.2	