Supplementary Table 1. Characteristic of melanoma patients treated with Ipilimumab.

Biographical and clinical data of patients enrolled in the study.

Variables	Italy n (%)	Sweden n (%)
Number of patients	115	29
Median age	61.3 (28-84)	67 (40-77)
SEX		
Male	63(54.8)	23(79)
Female	52(45.2)	6(21)
Primary melanoma site		
Cutaneous	86(74.8)	15(52)
Mucosal	6(5.2)	2(7)
Uveal	9(7.8)	0(0)
S.P.I.	6(5.2)	2(7)
Unclassified	8(7.0)	10(34)
Site of melanoma		
AJCC Stage		
IV	115(100)	29(100)
M1a	6(5.2)	4(14)
M1b	6(5.2)	5(17)
M1c	103 (89.6)	20(69)
CNS metastases at baseline	17 (32.1)	6 (21)
LDH level		
Elevate (>480)	36(31.3)	5 (20)
Normal	49(42.6)	2(20)
UNK	30(26.1)	2(20)
Prior Therapy		
N=0	44(38.2)	6(60)
N=1	63(54.9)	1(10)
N=2	8(6.9)	3(30)
BRAF Status		
Screened for BRAF mutation	115(100)	27(93)
Not evaluable	24(20.9)	
Wild type	45(39.1)	19(70)
Mutation	46(40)	10(30)
N-RAS mutated	6(5.2)1(1.9)	-

Supplementary Table 2. Variables used in multivariate analysis at time point w0. In total, 131 parameters were considered, including biological, clinical and immune variables.

Variables w0	Types
Site MELANOMA	/, back, foot, leg, neck, scalp, thorax, vulva
Kind of melanoma	cutaneous, mucosal, SPI(ignoto), uveal, vulva
Melanoma size mm	
Ulceration	NO ulcer, ulcer
Age	
Nr of ipi doses	
Concurrent medical systemic melanoma treatment (e.g DTIC in BMS-24). Describe	NO, PEMBROLIZUMAB
months passed between IPI infusion and current medical treatment	
months passed between the last treatment and IPI infusion	
Site metastatis (code)	
CNS metastases at start of ipi (yes/no)	NO, YES
SEX	F, M
LDH U/L (4W bf dose)	
WBC (4W bf dose)	
Neutrophils (4W bf dose)	
lymphocytes (4W bf dose)	
Monocyte (4W bf dose)	
eosinophil (4W bf dose)	
basophils (4W bf dose)	
Lymphocytes (%)	
Lymphocytes (events)	
CD3 %	
CD3 (events)	
CD4 %	
CD4 (events)	
CD8 %	
CD8 (events)	
CD4/CD8 %	
NKT %	
CD56 (events)	
CD56 bright %	
CD56 dim %	
CD56 bright/NK %	
CD56 dim/NK %	
bright/dim %	
CD56+ CD8+ %	
PD-1+ CD4+ %	
PD-1+ CD8+ %	
PD-1 CD56 bright %	
PD-1 CD56 dim %	

CD57+ CD4 % CD57+ CD8+ % CD57 bright % CD57 dim % CD57 bright/CD57 dim % CCR7+ CD8+ % CCR7 bright % CCR7 dim % CCR2+ CD3+ % CCR2 bright % CCR2 dim % CXCR2+ CD3+ % CXCR2 bright % CXCR2 dim % CD16 bright % CD16 dim % CD69+ CD3+ % CD69 bright % CD69 dim % NKG2C bright % NKG2C dim % NKG2A bright % NKG2A dim % NKG2D+CD3 % NKG2D bright % NKG2D dim % KIRS+ CD8+ % KIRS bright % KIRS dim % DNAM-1+CD3 % DNAM-1 bright % DNAM-1 dim % NKp30 bright % NKp30 dim % NKp46 bright % NKp46 dim % TIM3+ CD3+ % TIM3+ CD8+ % TIM3+ CD8+ PD-1+ % TIM3 bright % TIM3 dim % PD-1+ CD3+ MFI PD-1+ CD8+ MFI PD-1 CD56 bright MFI PD-1 CD56 dim MFI CCR7+ CD3+ MFI CCR7+ CD8+ MFI CCR7 bright MFI CCR7 dim MFI CCR2+ CD3+ MFI CCR2 bright MFI CCR2 dim MFI CXCR2+ CD3+ MFI	

CXCR2 bright MFI	
CXCR2 dim MFI	
CD16 bright MFI	
CD16 dim MFI	
CD69+ CD3+ MFI	
CD69 bright MFI	
CD69 dim MFI	
NKG2D+CD3 MFI	
NKG2D bright MFI	
NKG2D dim MFI	
KIRS+ CD8+ MFI	
KIRS bright MFI	
KIRS dim MFI	
DNAM-1+CD3 MFI	
DNAM-1 bright MFI	
DNAM-1 dim MFI	
NKp30 bright MFI	
NKp30 dim MFI	
NKp46 bright MFI	
NKp46 dim MFI	
TIM3+ CD3+ MFI	
TIM3+ CD8+ MFI	
TIM3 bright MFI	
TIM3 dim MFI	
IL-2	
IL-4	
IL-6	
IL-8	
IL-10	
VEGF	
INFg	
TNF	
IL-1a	
IL-1b	
MCP-1	
EGF	
IL-15	
IL-21	

Supplementary Table 3. Additional variables used in multivariate analysis at time point W1 and W2. In total, 134 variables were used for W1 and W2 model building.

Variables w1 and w2	Types
Side effect Cholitis	G1, G2, G3, NO
Skin itch	G1. G2, NO
COMMENTS	Low dosage cortison, middle dosage cortison

Supplementary Table 4. Additional variables used in multivariate analysis at time point W3. In total, 135 variables were used.

Variables w3	Types
RECIST	PD, PR, SD

Supplementary Table 5. Clinical response and overall survival after therapy with ipilimumab.

Clinical parameters used to define the tumor response to the therapy.

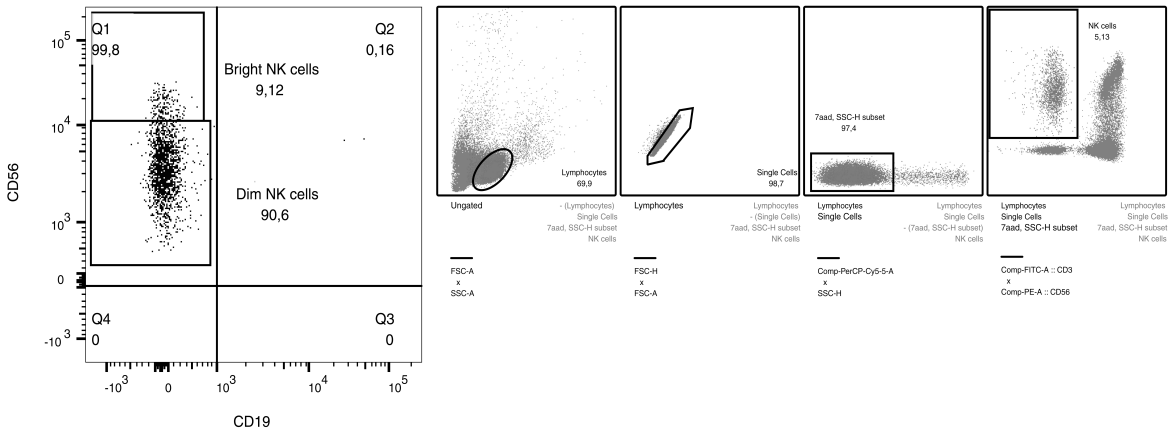
Best overall response:		
Complete response	3(2.6)	0
Partial response	10(8.7)	12(41)
Stable disease	24(20.9)	10(34)
Progression disease	78(67.8)	7(25)
Overall Survival (mo)		
Median OS	10,7	18
OS ≤6 mo (%)	38(33)	10(100)
6 < OS ≤12 mo (%)	36(31.3)	26(83)
12 < OS ≤24 mo (%)	37(32.2)	18(66)
OS > 24 mo (%)	4(3.5)	5(22)
Side effect to IPI		
Colitis	19(16.5)	2(7)
Skin itch	21(18.3)	7(24)
Other	6(5.2)	17(30)
No side effects	69(60)	15(52)

irRC,immune-related response criteria; OS, overall survival; mo, month; CI, confidence interval

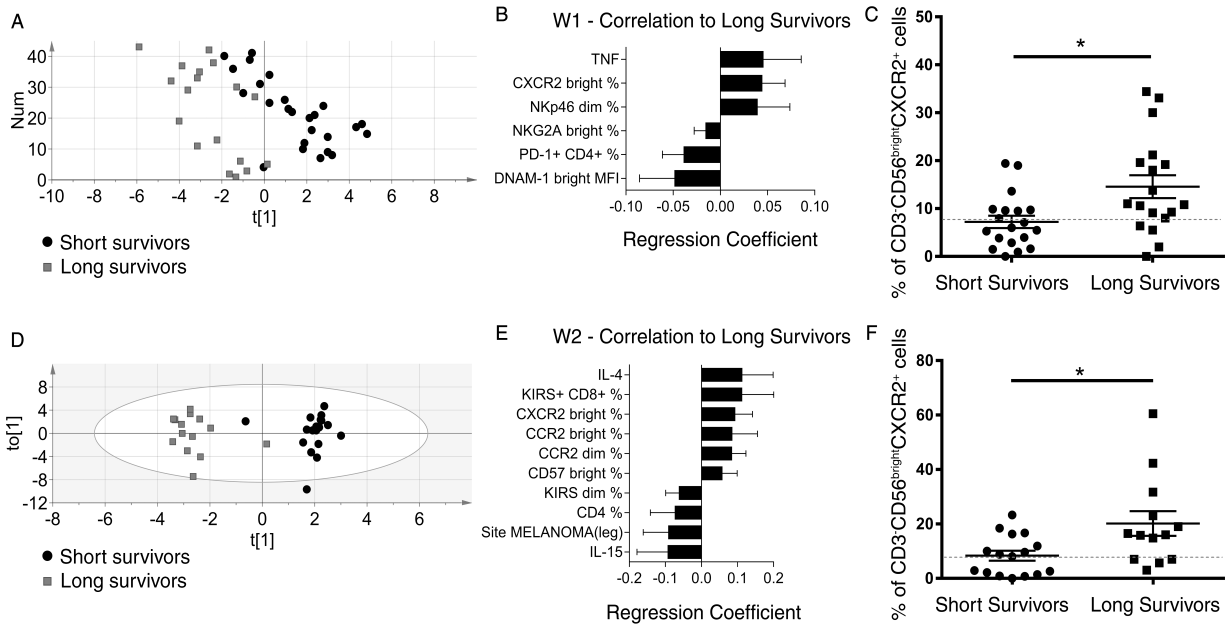
Supplementary Table 6. Results of Cox regression. For each predictive marker, we fitted a Cox model adjusted for age, sex, melanoma type, and the binary indicator of recist = "pd". We report the adjusted hazard ratio (hr) and a 95% asymptotic confidence interval (low, up) with the corresponding p-value; p_value_ph refers to the Shoenfeld's test for proportionality of hazards.

TIME W0	**hr**	**low**	**up**	**p**	**p_value_ph**
CD56_bright	0.6049	0.2689	1.3610	0.2244	0.2906
TIM3_bright	1.0210	0.9935	1.0493	0.1353	0.1059
TIM3_dim	0.9948	0.9781	1.0118	0.5465	0.9726
TIM3_bright_MFI	1.0006	1.0002	1.0009	0.0055	0.8461
TIM3_dim_MFI	1.0007	1.0001	1.0012	0.0180	0.7409
IL_15	1.2551	1.0995	1.4326	0.0008	0.6566
CD56_dim	0.9865	0.9567	1.0173	0.3870	0.1543
TIME W3	**hr**	**low**	**up**	**p**	**p_value_ph**
CD56_bright	0.6518	0.2661	1.5964	0.3490	0.0589
TIM3_bright	0.9892	0.9583	1.0210	0.5010	0.3554
TIM3_dim	0.9849	0.9635	1.0068	0.1764	0.4475
TIM3_bright_MFI	1.0005	0.9996	1.0014	0.2621	0.1601
TIM3_dim_MFI	1.0004	0.9992	1.0017	0.4895	0.2229
IL_15	1.1165	0.9917	1.2569	0.0683	0.5919
CD56_dim	0.9213	0.8598	0.9872	0.0201	0.7528

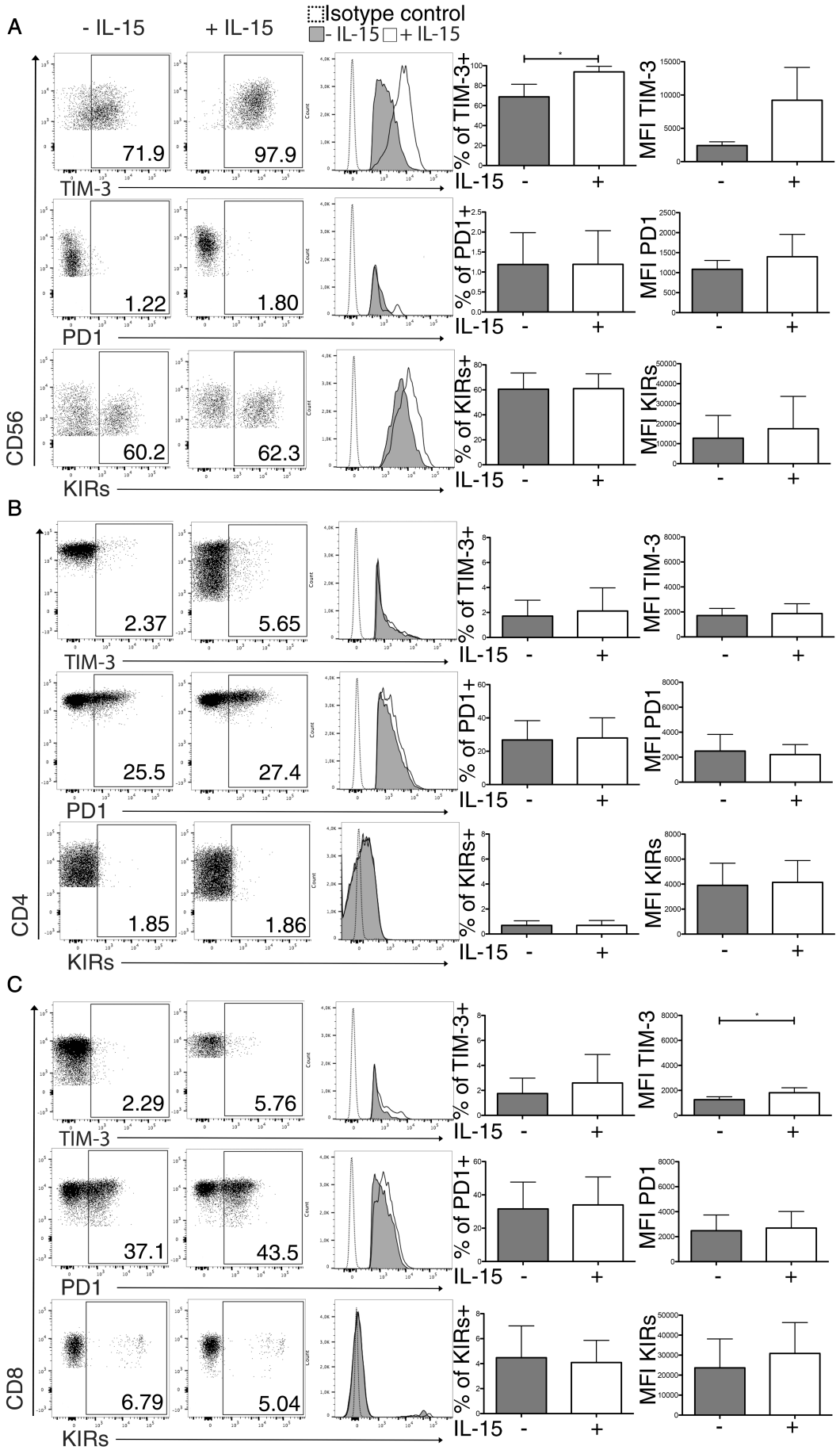
Supplementary Figure 1. Gating strategy for flow cytometer analysis. Cells were first gated for lymphocytes (SSC-A vs FSC-A) and singlets (FSC-H vs FSC-A). The lymphocyte gate is further analysed for their uptake of 7aad stain to determine live versus dead cells and their expression of CD3 and CD56, taking only the live cells. To exclude B cells contamination in the NK cell subset, we gate on $CD56^{+}$ $CD19^{-}$.



Supplementary Figure 2. Changes in NK cells phenotype at W1 and W2. Gray squares = long survivors, 12 months or more. Black circles = short survivors, < 12 months. Long and short survivors at W1 and W2 treatment**,** 17 long survivors, 21 short survivors **(A, D)**. Horizontal axis = predictive component, vertical axis = order of patients. Orange striped lines represent two confidence intervals of the model. Horizontal axis = predictive component. Vertical axis = Orthogonal component not related to difference between groups. **(A)** Withdrawal 1 only had one significant component, therefore +/- 2 confidence interval limit is displayed instead. 3 and 5 most significant variables correlated to long survival respectively at W1 **(B)** and W2 **(E)** treatment. Error bars = 95 % confidence intervals. Positive correlation to long survival means negative correlation to short survival, and vice versa. Frequency of CXCR2 on $CD56^{bright}$ cell subsets at W1 **(C)** and W2 **(F)** in peripheral blood of short (n. 21) and long (n.22) survivors. Statistical analyses were performed with Mann Whitney and Unpaired t test ***: p-value < 0.001; **: p-value < 0.01; *: p-value < 0.05.



Supplementary Figure 3. **Analysis of differences between Italian and Swedish long survivors.**Comparison of healthy donors and the two groups of long survivors for the significant markers. The statistical analysis does not evidence significative differences in expression **(A)** and frequency **(B)**, between Italian and Swedish long survivors. Supplementary Figure 4. In vitro effects of 10pg/ml IL-15 stimulation on NK and T cells phenotype. FACS assessment of the mean fluorescent intensities (MFI) and percentage of **(A)** NK cells ($CD3^{-}CD56^{+}$), **(B)** $CD4^{+}$ T cells ($CD3^{+}CD4^{+}$) and **(C)** $CD8^{+}$ T cells ($CD3^{+}CD8^{+}$) expressing TIM-3, PD-1 and KIRs at resting (no treatment) or after 120h of stimulation with IL-15 at 10pg/ml concentration. The data are presented as representative dot plots where the percentage of cells in each quadrant is indicated, and as representative histogram plots. Columns represent the statistical analysis from 3 independent experiments, *: p-value < 0.05 by Student's t test. Error bars, s.d.


A
- IL-15
+ IL-15
Isotype control
- IL-15 + IL-15
71.9
97.9
TIM-3
1.22
1.80
PD1
60.2
62.3
KIRs
CD56
% of TIM-3+
MFI TIM-3
% of PD1+
MFI PD1
% of KIRs+
MFI KIRs
IL-15 - +
B
2.37
5.65
TIM-3
25.5
27.4
PD1
1.85
1.86
KIRs
CD4
C
2.29
5.76
TIM-3
37.1
43.5
PD1
6.79
5.04
KIRs
CD8