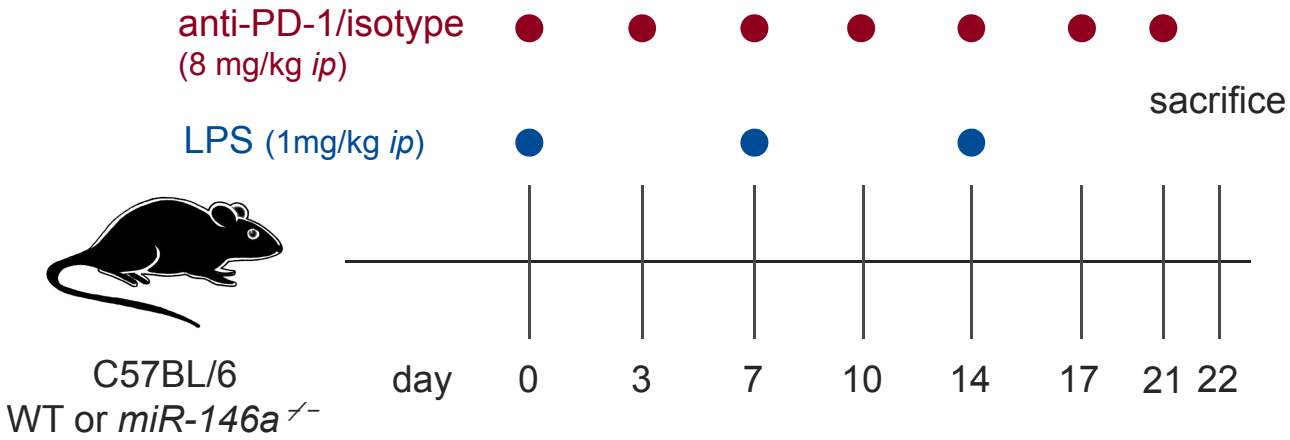
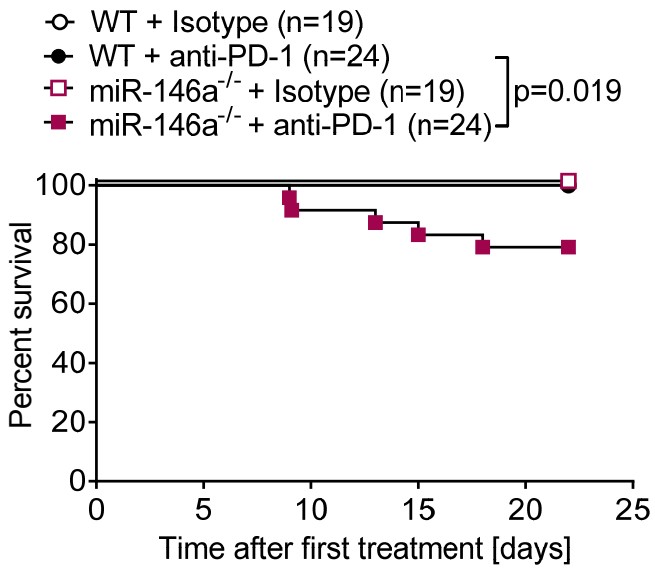
Suppl. Figure 1

A

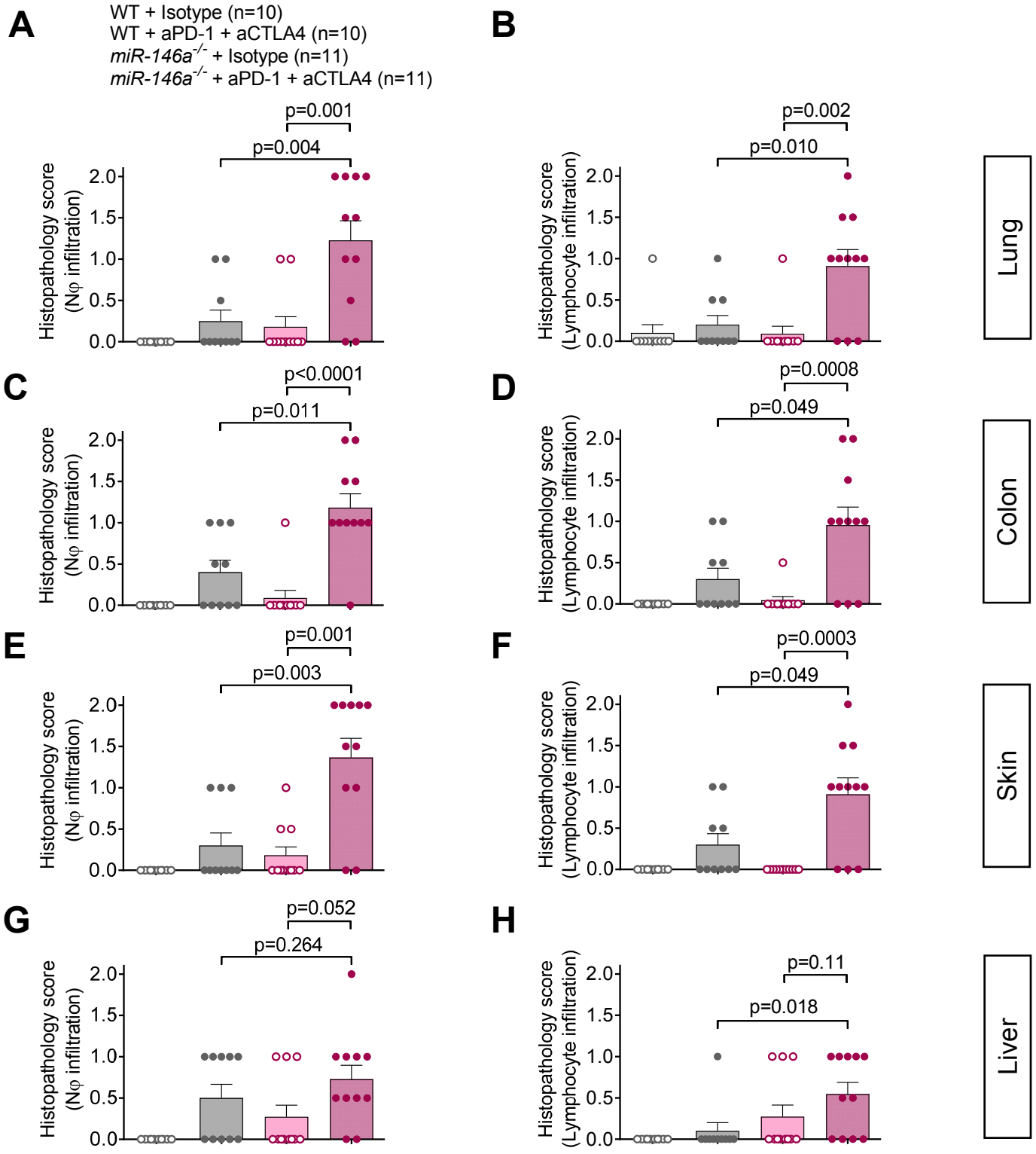


B



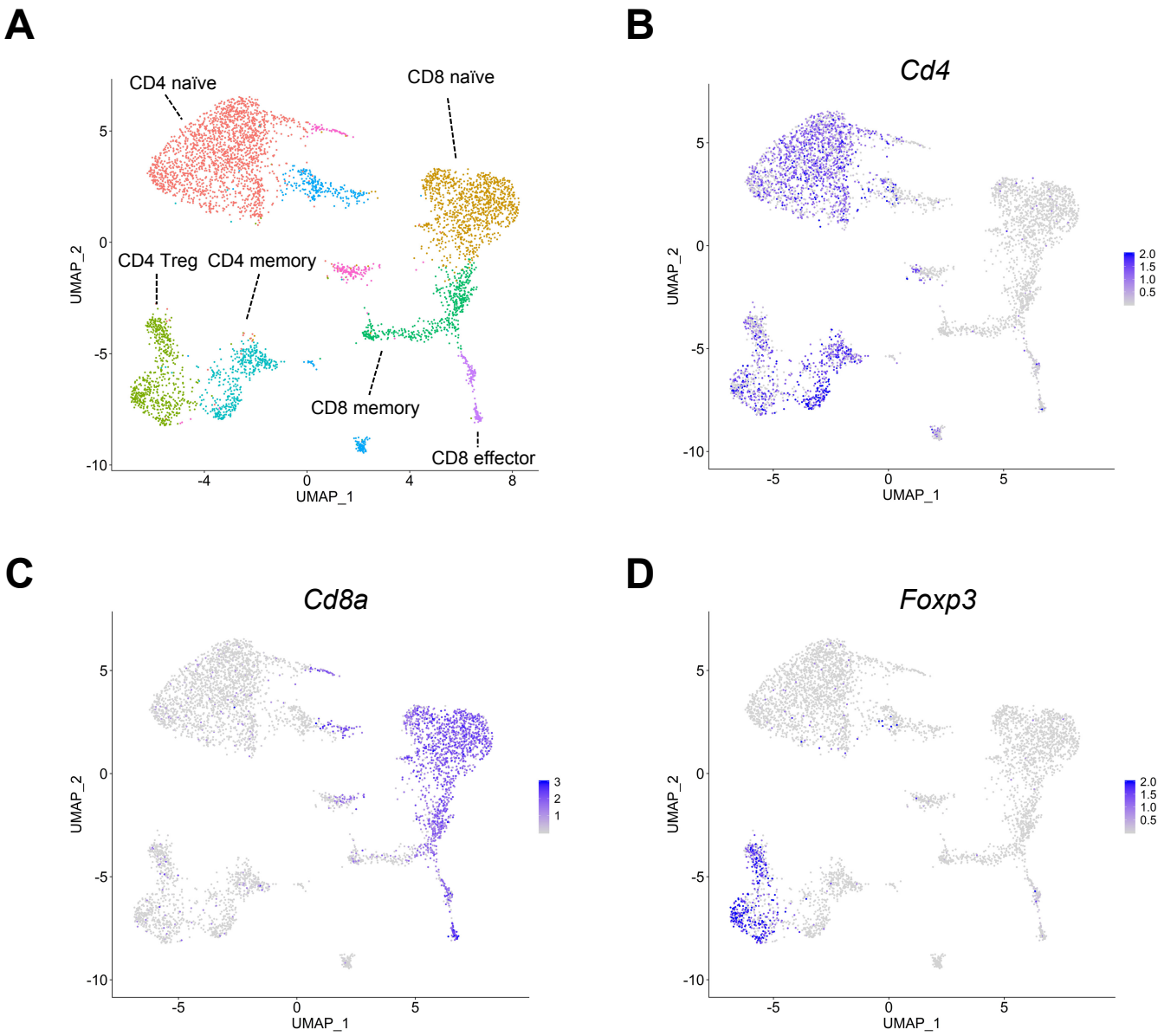
Suppl. Figure 1: Decreased survival of *miR-146a*$^{-/-}$ mice in a mouse model for immune-related adverse events (irAEs). A. In order to induce irAEs, C57BL/6 mice were injected intraperitoneally (*ip*) with 8 mg/kg anti-PD-1 antibody (clone J43) on days 0, 3, 7, 10, 14, 17 and 21 and with 1 mg/kg LPS *ip* on days 0, 7 and 14. Control mice received Armenian hamster isotype control antibody and LPS according to the same dose and schedule. Mice were sacrificed on day 22 and organs were isolated for downstream analysis. B. Kaplan-Meier curves depicting survival of irAE mice until the day of sacrifice. Data were pooled from four independent experiments. Statistics were calculated by log-rank (Mantel-Cox) test.

Suppl. Figure 2



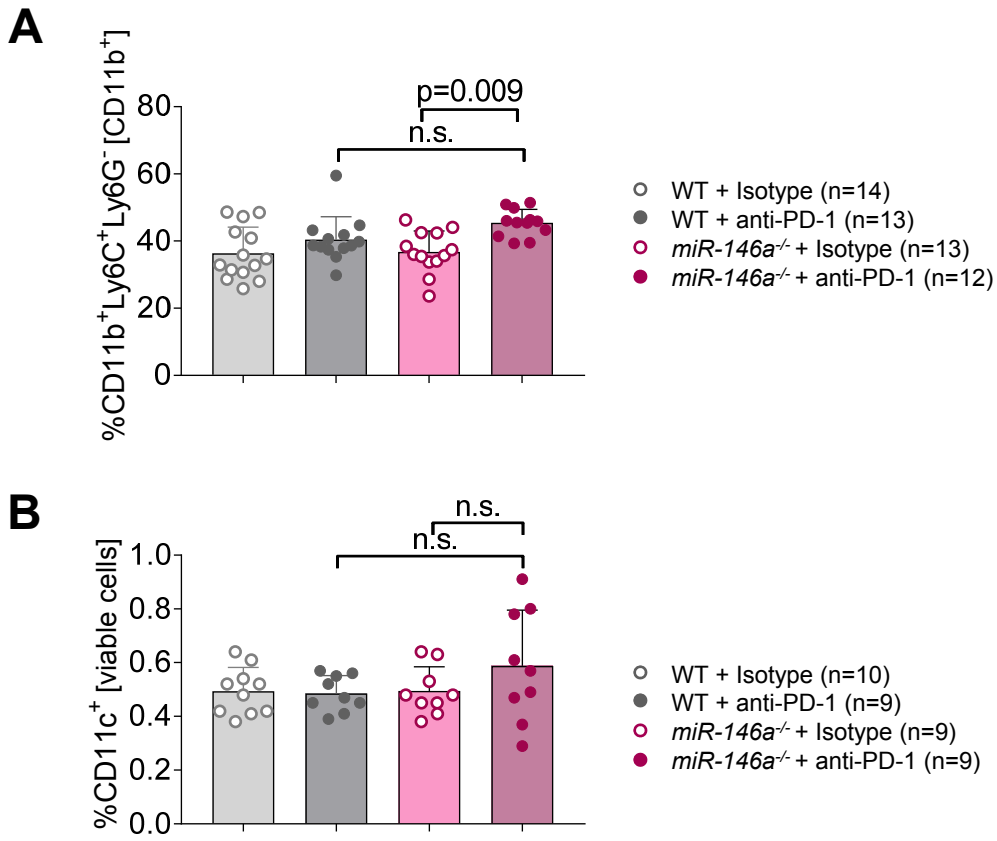
Suppl. Figure 2: *MiR-146a* deficiency increases irAE severity in mice treated with anti-PD-1 and anti-CTLA-4 combination therapy. Wildtype (WT) or *miR-146a*$^{-/-}$ BM chimeric mice (n=10-11 per group) were treated with anti-PD-1 + anti-CTLA-4 or the respective isotype control antibodies for two weeks as described. The lungs (A,B), colon (C,D), skin (E,F) and liver (G,H) were isolated on day 15 after the first ICI treatment for histopathological assessment. IrAE grading was performed by an experienced pathologist blinded to the treatment groups. 0=absent, 1=mild, 2=massive neutrophil/lymphocyte infiltration. Data were pooled from two independent experiments. Statistical significance was analysed by Kruskal-Wallis test followed by two-stage linear step-up procedure of Benjamini, Krieger and Yekutieli .

Suppl. Figure 3



Suppl. Figure 3: Identification of *miR-146a*$^{-/-}$ and WT T cell clusters by scRNA-seq. WT or *miR-146a*$^{-/-}$ mice (n=2 per group) were treated with low dose LPS and anti-PD-1/isotype control antibody for three weeks before capturing of MACS purified splenic T cells for scRNA-seq using 10x v3.1 Next GEM chemistry. Data were processed, visualized and analysed using the Seurat pipeline v3.0. A. Uniform Manifold Approximation and Projection (UMAP) plot of all cells shows distinct T cell clusters. B-D. Examples of feature plots showing expression of characteristic T cell subset markers including *Cd4* (B), *Cd8a* (C) and *Foxp3* (D) are depicted.

Suppl. Figure 4



Suppl. Figure 4: *MiR-146a* deficiency does not affect monocyte and dendritic cell proportions in the spleen. Wildtype (WT) or *miR-146a*$^{-/-}$ mice (n=9-10 per group) were treated with LPS and anti-PD-1/isotype control antibody as indicated and splenocytes assessed by flow cytometry on day 22. Proportions of CD11b^{+}Ly6C^{+}Ly6G^{-} monocytes (A) and CD11c^{+} dendritic cells (B) were analyzed. Statistical significance was analysed by one-way ANOVA followed by Tukey's post-hoc test. Pooled data from 2-3 independent *in vivo* experiments are shown.

Suppl. Table 1: Characteristics of patients included in the rs2910164 SNP analysis

Patient characteristics		rs2910164 genotype		
		GG (n=102)	GC (n=54)	CC (n=11)
Median age in years (range)		66 (27-85)	67.5 (29-85)	68 (56-82)
Male/female		66% / 34%	61% / 39%	73% / 27%
Disease	malignant melanoma	51 (50.0%)	28 (51.9%)	7 (63.6%)
	adenocarcinoma of the lung	22 (21.6%)	14 (25.9%)	4 (36.4%)
	squamous cell carcinoma of the lung	12 (11.8%)	6 (11.1%)	0 (0%)
	other lung cancer[A]	6 (5.9%)	2 (3.7%)	0 (0%)
	other[B]	11 (10.8%)	4 (7.4%)	0 (0%)
ECOG status	0	79 (77.5%)	38 (70.4%)	11 (100%)
	1	18 (17.6%)	14 (25.9%)	0 (0%)
	2	5 (4.9%)	2 (3.7%)	0 (0%)
Prior line(s) of therapy	0	45 (44.1%)	25 (46.3%)	7 (63.6%)
	1	29 (28.4%)	15 (27.8%)	2 (18.2%)
	2	18 (17.6%)	9 (16.7%)	2 (18.2%)
	3+	10 (9.9%)	5 (9.3%)	0 (0%)
Prior immune checkpoint inhibitor therapy		8 (7.8%)	8 (14.8%)	1 (9.1%)
Prior interferon therapy		11 (10.8%)	9 (16.7%)	1 (9.1%)
Prior tyrosine kinase inhibitor therapy		9 (8.9%)	3 (5.6%)	0 (0%)
Radiotherapy	before treatment	44 (43.1%)	13 (24.1%)	4 (36.4%)
	during treatment	15 (14.7%)	6 (11.1%)	4 (36.4%)
	whole brain radiotherapy	6 (5.9%)	6 (11.1%)	0 (0%)
	stereotactic neurosurgery	16 (15.7%)	13 (24.1%)	0 (0%)
Immune checkpoint inhibitor	Nivolumab	42 (41.2%)	20 (37.0%)	4 (36.4%)
	median no. of cycles (range)	13.0 (1-27)	17.5 (1-27)	9.5 (7-20)
	Pembrolizumab	54 (52.9%)	31 (57.4%)	6 (54.5%)
	median no. of cycles (range)	15.0 (1-20)	12.0 (3-19)	7.0 (3-19)
	PD-L1 inhibitor[C]	6 (5.9%)	3 (5.6%)	1 (9.1%)
	median no. of cycles (range)	16.5 (4-19)	14.0 (4-15)	1
Corticosteroids for treatment of side effects	none	79 (77.5%)	45 (77.8%)	4 (36.3%)
	low dose (< 1 mg/kg/day)	7 (6.9%)	4 (7.4%)	2 (18.2%)
	high dose (≥ 1 mg/kg/day)	16 (15.7%)	8 (14.8%)	5 (45.5%)

Treatment schedule: Atezolizumab 1200mg absolute repeated on d22 or 800mg absolute repeated on d15; Durvalumab 1500mg absolute repeated on d29; Nivolumab 3 mg/kg repeated on d15, Pembrolizumab 2 mg/kg or 200mg absolute repeated on d22.

[A] poorly differentiated NSCLC (4), SCLC (1), LCLC (1), atypical carcinoid (1), Adenosquamous carcinoma (1)

[B] Other: head-neck cancer (4), renal cancer (3), ileocaecal junction adenocarcinoma (1), anaplastic thyroid cancer (1), colorectal cancer (1), DLBCL (1), epitheloid pleural mesothelioma (1), follicular lymphoma (1), TCC of the bladder, parotid carcinoma (1)

[C] Atezolizumab (7), Avelumab (2), Durvalumab (1)

No., number.

Suppl. Table 2: Allele and genotype frequencies of *MIR146A* rs2910164 in patients treated with an immune checkpoint inhibitor

Genotype/allele	absolute number (%)		OR	95% CI	p-value
	CTCAE grade 0-2 (n=128)	**CTCAE grade 3-4** (n=39)			
G allele	206 (80.5)	52 (66.7)	1.000		0.014
C allele	50 (19.5)	26 (33.3)	2.060	1.173-3.618	
GG	82 (64.1)	20 (51.3)	1.000		0.007 / 0.683
GC	42 (32.8)	12 (30.8)	1.171	0.523-2.624	0.022
CC	4 (3.1)	7 (17.9)	7.175	1.913-26.917	
GC or GG	124 (96.9)	32 (82.1)	1.000		0.004
CC	4 (3.1)	7 (17.9)	6.781	1.870-24.597	

Suppl. Table 3: Frequencies of organ-specific irAEs in the different rs2910164 genotype groups

	rs2910164 genotype											
	GG (n=102)				GC (n=54)				CC (n=11)			
CTCAE grade	1	2	3	4	1	2	3	4	1	2	3	4
Gastrointestinal disorders	3 (2.9%)	3 (2.9%)	2 (2.0%)	0	4 (7.4%)	2 (3.7%)	1 (1.9%)	0	2 (18.2%)	0	1 (9.1%)	1 (9.1%)
Skin and subcutaneous tissue disorders	22 (21.6%)	9 (8.8%)	4 (3.9%)	0	8 (14.8%)	5 (9.3%)	2 (3.7%)	0	1 (9.1%)	1 (9.1%)	1 (9.1%)	0
Hypophysitis	0	0	2 (2.0%)	0	0	0	1 (1.9%)	0	0	0	0	0
Thyroid gland disorders	7 (6.9%)	14 (13.7%)	0	0	1 (1.9%)	3 (5.6%)	1 (1.9%)	0	0	1 (9.1%)	0	0
Pancreatitis	1 (1.0%)	0	1 (1.0%)	2 (2.0%)	0	1 (1.9%)	1 (1.9%)	0	0	0	1 (9.1%)	0
Musculoskeletal and connective tissue disorders	3 (2.9%)	6 (5.9%)	2 (2.0%)	0	2 (3.7%)	3 (5.6%)	1 (1.9%)	0	2 (18.2%)	1 (9.1%)	1 (9.1%)	0
Eye disorders	3 (2.9%)	1 (1.0%)	0	0	0	1 (1.9%)	0	0	0	0	0	0
Hepatobiliary disorders	4 (3.9%)	3 (2.9%)	3 (2.9%)	1 (1.0%)	2 (3.7%)	1 (1.9%)	4 (7.4%)	0	0	0	1 (9.1%)	1 (9.1%)
salivary and lacrimal gland disorders	4 (3.9%)	0	0	0	1 (1.9%)	2 (3.7%)	0	0	0	0	0	0
Respiratory disorders	3 (2.9%)	6 (5.9%)	1 (1.0%)	0	3 (5.6%)	0	1 (1.9%)	0	0	0	0	0
Renal disorders	0	1 (1.0%)	0	0	0	0	1 (1.9%)	0	0	0	0	0
Blood and lymphatic system disorders	1 (1.0%)	2 (2.0%)	3 (2.9%)	1 (1.0%)	1 (1.9%)	1 (1.9%)	0	0	1 (9.1%)	1 (9.1%)	1 (9.1%)	0
Allergic reaction	2 (2.0%)	3 (2.9%)	0	0	0	1 (1.9%)	0	1 (1.9%)	0	0	0	0
Other	4 (3.9%)	0	0	0	0	0	0	0	0	0	0	0
Fatigue	17 (16.7%)	7 (6.9%)	0	0	8 (14.8%)	3 (5.6%)	0	0	2 (18.2%)	1 (9.1%)	0	0
Nervous system disorders	2 (2.0%)	1 (1.0%)	1 (1.0%)	0	2 (3.7%)	1 (1.9%)	1 (1.9%)	0	0	0	0	0

Suppl. Table 4: Characteristics of patients with malignant melanoma included in the survival analysis

Patient characteristics		rs2910164 genotype	
		GG (n=47)	CC (n=8)
Median age in years (range)		66 (27-86)	68 (63-87)
Male/Female		64% / 36%	63% / 37%
ECOG status	0	40 (85.1%)	8 (100%)
	1	6 (12.8%)	0 (0%)
	2	1 (2.1%)	0 (0%)
UICC stage	IIIC	4 (8.5%)	2 (25.2%)
	IV	42 (89.4%)	6 (75.0%)
	unknown	1 (2.1%)	0 (0%)
Metastasis site	visceral	28 (59.6%)	6 (75.0%)
	liver	12 (25.5%)	4 (50.0%)
	bone	13 (27.7%)	3 (37.5%)
	cerebral	11 (23.4%)	2 (25.0%)
	skin / tissue	16 (34.0%)	5 (62.5%)
Prior line(s) of therapy	0	36 (76.6%)	6 (75.0%)
	1	6 (12.8%)	1 (12.5%)
	2	3 (6.4%)	1 (12.5%)
	3+	2 (4.2%)	0 (0%)
Prior immune checkpoint inhibitor therapy		8 (17.0%)	2 (25.0%)
Prior interferon therapy		10 (21.3%)	2 (25.0%)
Prior tyrosine kinase inhibitor therapy		4 (8.5%)	0 (0%)
Immune checkpoint inhibitor	Nivolumab	3 (6.4%)	1 (12.5%)
	median no. of cycles (range)	52 (8-54)	20
	Pembrolizumab	44 (93.6%)	7 (87.5%)
	median no. of cycles (range)	16 (1-34)	5 (2-25)
Corticosteroids for treatment of side effects	none	39 (83.0%)	4 (50.0%)
	low dose (< 1 mg/kg/day)	2 (4.3%)	2 (25.0%)
	high dose (≥ 1 mg/kg/day)	6 (12.8%)	2 (25.0%)
Reason for end of treatment	disease progression	28 (59.6%)	7 (87.5%)
	drug toxicity	2 (4.3%)	0 (0%)
	withdrawal by subject	1 (2.1%)	0 (0%)
	lost to follow-up	2 (4.3%)	1 (12.5%)
	end of follow-up time	14 (29.8%)	0 (0%)

No., number.

Suppl. Table 5: Characteristics of patients with lung cancer included in the survival analysis

Patient characteristics		rs2910164 genotype	
		GG (n=41)	CC (n=4)
Median Age		67 years (30-83)	61.5 years (56-82)
Male/Female		68% / 32%	75% / 25%
ECOG status	0	27 (65.9%)	4 (100%)
	1	12 (29.3%)	0 (0%)
	2	2 (4.9%)	0 (0%)
Diagnosis	adenocarcinoma	23 (56.1%)	4 (100%)
	squamous cell carcinoma	12 (29.3%)	0 (0%)
	other lung cancer[A]	6 (24.6%)	0 (0%)
UICC stage	IIIC	1 (2.4%)	0 (0%)
	IV	38 (92.7%)	4 (100.0%)
	unknown	2 (4.9%)	0 (0%)
Metastasis site	visceral	29 (70.7%)	2 (50.0%)
	liver	5 (12.2%)	0 (0%)
	bone	15 (36.6%)	3 (75.0%)
	cerebral	11 (26.8%)	1 (25.0%)
	skin / tissue	4 (9.8%)	0 (0%)
Molecular aberration	EGFR	3 (7.3%)	0 (0%)
	KRAS	1 (2.4%)	0 (0%)
	ALK	1 (2.4%)	0 (0%)
	no target mutation	29 (70.7%)	4 (100.0%)
	missing	7 (17.1%)	0 (0%)
Prior line(s) of therapy	0	3 (7.3%)	1 (25.0%)
	1	17 (41.5%)	2 (50.0%)
	2	15 (36.6%)	1 (25.0%)
	3+	6 (14.6%)	0 (0%)
Prior tyrosine kinase inhibitor therapy		4 (9.8%)	0 (0%)
Immune checkpoint inhibitor	Nivolumab	33 (80.5%)	2 (50.0%)
	median no. of cycles (range)	12.0 (1-54)	7.5 (7-8)
	Pembrolizumab	5 (12.2%)	1 (25.0%)
	median no. of cycles (range)	7.0 (2-30)	3
	Atezolizumab	3 (7.3%)	1 (25.0%)
	median no. of cycles (range)	14 (8-17)	1
Corticosteroids for treatment of side effects	none	27 (65.9%)	2 (50.0%)
	low dose (< 1 mg/kg/day)	2 (4.9%)	0 (0%)
	high dose (≥ 1 mg/kg/day)	12 (29.2%)	2 (50.0%)
Reason for end of treatment	disease progression	28 (68.3%)	4 (100.0%)
	drug toxicity	3 (7.3%)	0 (0%)
	lost to follow-up	3 (7.3%)	0 (0%)
	end of follow-up time	7 (17.1%)	0 (0%)

[A] poorly differentiated NSCLC (3), SCLC (1), atypical carcinoid (1), Adenosquamous carcinoma (1)
No., number.

Suppl. Table 6: Monoclonal antibodies used for flow cytometry

Antibody	Clone	Supplier
anti-CD4	GK1.5	BioLegend
anti-CD8a	53-6.7	BioLegend
anti-CD11b	M1/70	BioLegend
anti-CD11c	N418	BioLegend
anti-CD44	IM7	BioLegend
anti-CD45	104	ThermoFisher
anti-CD62L	MEL-14	BioLegend
anti-CD69	H1.2F3	ThermoFisher
anti-IFNγ	XMG1.2	BioLegend
anti-Ly6C	HK1.4	BioLegend
anti-Ly6G	1A8	BioLegend
anti-perforin	eBioOMAK-D	ThermoFisher