Supplemental information (Tables and Figures)

Table S1

Studies, indications, therapy arm description and number of eligible patients (N)

STUDYID	Study Name	Indication	Atezo arm (mono or combo therapy)	Ctrl Arm (Chemotherapy combo)	Line	N (SAFFL)
GO28625	FIR	NSCLC	Atezo	none	1L, 2L	137
GO28754	BIRCH	NSCLC	Atezo	none	1L, 2L, 3L	659
GO28915	OAK	NSCLC	Atezo	Docetaxel	2L	1187
GO29431	IMpower110	NSCLC	Atezo	(Carboplatin/ Cisplatin) + (Pemetrexed/ Gemcitabine)	1L	549
GO29436	IMpower150	NSCLC	Atezo+Carboplatin+Paclitaxel | Atezo+Carboplatin+Paclitaxel+ Bevacizumab	Carboplatin+Placlitaxel+ Bevacizumab	1L	1187
GO29437	IMpower131	NSCLC	Atezo+Carboplatin+Paclitaxel | Atezo+Carboplatin+nab Placlitaxel	Carboplatin+nab-Placlitaxel	1L	1000
GO30081	IMpower133	SCLC	Atezo+Carboplatin+Etoposide	Placebo+Carboplatin+Etoposide	1L	494
GO29537	IMpower130	NSCLC	Atezo+Carboplatin+Paclitaxel	Carboplatin+nab-Placlitaxel	1L	705
GO29438	IMpower132	NSCLC	Atezo+Carbo/Cisplatin+ Pemetrexed	Carbo/Cisplatin+Pemetrexed	1L	727
WO29074	IMmotion150	Advanced Renal Cell Carcinoma	Atezo | Atezo and Bevacizumab	-	1L	204
WO29637	IMmotion151	Advanced Renal Cell Carcinoma	Atezo and Bevacizumab	-	1L	451
WO29522	IMpassion130	TNBC	Atezo	Placebo + Nab Paclitaxel	1L	890
GO29293	IMvigor210	Urothelial Bladder Cancer	Atezo	-	1L	429
GO29294	IMvigor211	Urothelial Bladder Cancer	Atezo	Vinflunine | Paclitaxel | Docetaxel	1L-2L	902

irAEs = immune-related adverse events were reported in all study arms, including Standard of Care without atezolizumab, given the blinded nature of the controlled trials.

Table S2 Incidence proportion and incidence rate of irAEs by indication

a) NSCLC/SCLC

Indication	irAE	IO | C-IO		Chemotherapy	
		nr irAE (%)	irAE per 100 pt-years	nr irAE (%)	irAE per 100 pt-years
NSCLC/SCLC	any irAE	1820 (42.9%)	85.71	602 (25%)	66.4
	Skin	974 (23%)	35.63	341 (14.2%)	33.48
	Hepatitis	604 (14.2%)	18.66	213 (8.9%)	19.13
	Thyroid	471 (11.1%)	14.53	74 (3.1%)	6.35
	Pneumonitis	210 (5%)	5.89	31 (1.3%)	2.6
	Colitis	58 (1.4%)	1.59	6 (0.2%)	0.5
	Adrenal Insufficiency	33 (0.8%)	0.9	5 (0.2%)	0.42
	Pancreatitis	30 (0.7%)	0.82	6 (0.2%)	0.5
	Diabetes Mellitus	23 (0.5%)	0.63	8 (0.3%)	0.67
	Myositis Myositis+Rhabdomyolysis	18 (0.4%)	0.49	3 (0.1%)	0.25
	Meningoencephalitis	21 (0.5%)	0.57	2 (0.1%)	0.17
	Meningitis	15 (0.4%)	0.41	2 (0.1%)	0.17
	Nephritis	13 (0.3%)	0.35	3 (0.1%)	0.25
	Ocular Inflammatory Toxicity	14 (0.3%)	0.38	1 (0%)	0.08
	Vasculitis	12 (0.3%)	0.33	2 (0.1%)	0.17
	Hypophysitis	7 (0.2%)	0.19	0 (0%)	0
	Systemic Immune Activation	2 (0%)	0.05	0 (0%)	0
	Autoimmune Hemolytic Anemia	7 (0.2%)	0.19	1 (0%)	0.08
	Guillain-Barre Syndrome	6 (0.1%)	0.16	0 (0%)	0
	Encephalitis	6 (0.1%)	0.16	0 (0%)	0
	Myocarditis	2 (0%)	0.05	1 (0%)	0.08
	Myasthenia Gravis	0 (0%)	0	1 (0%)	0.08

irAEs = immune-related adverse events were reported in all study arms, including Standard of Care without atezolizumab, given the blinded nature of the controlled trials.

b) Advanced Renal Cell Carcinoma

Indication	irAE	IO | C-IO		Chemotherapy	
		nr irAE (%)	irAE per 100 pt-years	nr irAE (%)	irAE per 100 pt-years
Advanced Renal Cell Carcinoma	any irAE	400 (61.1%)	92.56	-	-
	Skin	233 (35.6%)	35.73	-	-
	Hepatitis	84 (12.8%)	9.76	-	-
	Thyroid	176 (26.9%)	24.93	-	-
	Pneumonitis	14 (2.1%)	1.47	-	-
	Colitis	16 (2.4%)	1.7	-	-
	Adrenal Insufficiency	14 (2.1%)	1.47	-	-
	Pancreatitis	17 (2.6%)	1.8	-	-
	Diabetes Mellitus	9 (1.4%)	0.95	-	-
	Myositis Myositis+Rhabdomyolysis	4 (0.6%)	0.42	-	-
	Meningoencephalitis	4 (0.6%)	0.42	-	-
	Meningitis	4 (0.6%)	0.42	-	-
	Nephritis	6 (0.9%)	0.63	-	-
	Ocular Inflammatory Toxicity	2 (0.3%)	0.21	-	-
	Vasculitis	3 (0.5%)	0.31	-	-
	Hypophysitis	5 (0.8%)	0.52	-	-
	Systemic Immune Activation	4 (0.6%)	0.42	-	-
	Autoimmune Hemolytic Anemia	0 (0%)	0	-	-
	Guillain-Barre Syndrome	0 (0%)	0	-	-
	Encephalitis	0 (0%)	0	-	-
	Myocarditis	2 (0.3%)	0.21	-	-
	Myasthenia Gravis	0 (0%)	0	-	-

irAEs = immune-related adverse events were reported in all study arms, including Standard of Care without atezolizumab, given the blinded nature of the controlled trials.

c) Urothelial Bladder Cancer

Indication	irAE	IO | C-IO		Chemotherapy	
		nr irAE (%)	irAE per 100 pt-years	nr irAE (%)	irAE per 100 pt-years
Urothelial Bladder Cancer	any irAE	288 (32.4%)	78.45	74 (16.7%)	54.2
	Skin	176 (19.8%)	40.33	49 (11.1%)	34.77
	Hepatitis	93 (10.5%)	17.64	26 (5.9%)	17.14
	Thyroid	50 (5.6%)	9.18	0 (0%)	0
	Pneumonitis	19 (2.1%)	3.37	3 (0.7%)	1.92
	Colitis	14 (1.6%)	2.43	1 (0.2%)	0.64
	Adrenal Insufficiency	4 (0.5%)	0.69	1 (0.2%)	0.64
	Pancreatitis	4 (0.5%)	0.69	0 (0%)	0
	Diabetes Mellitus	2 (0.2%)	0.34	0 (0%)	0
	Myositis Myositis+Rhabdomyolysis	8 (0.9%)	1.39	0 (0%)	0
	Meningoencephalitis	0 (0%)	0	1 (0.2%)	0.64
	Meningitis	0 (0%)	0	1 (0.2%)	0.64
	Nephritis	1 (0.1%)	0.17	0 (0%)	0
	Ocular Inflammatory Toxicity	3 (0.3%)	0.52	0 (0%)	0
	Vasculitis	2 (0.2%)	0.34	0 (0%)	0
	Hypophysitis	0 (0%)	0	0 (0%)	0
	Systemic Immune Activation	1 (0.1%)	0.17	0 (0%)	0
	Autoimmune Hemolytic Anemia	0 (0%)	0	0 (0%)	0
	Guillain-Barre Syndrome	0 (0%)	0	0 (0%)	0
	Encephalitis	0 (0%)	0	0 (0%)	0
	Myocarditis	0 (0%)	0	0 (0%)	0
	Myasthenia Gravis	0 (0%)	0	0 (0%)	0

irAEs = immune-related adverse events were reported in all study arms, including Standard of Care without atezolizumab, given the blinded nature of the controlled trials.

d) Triple negative breast cancer

Indication	irAE	IO | C-IO		Chemotherapy	
		nr irAE (%)	irAE per 100 pt-years	nr irAE (%)	irAE per 100 pt-years
TNBC	any irAE	199 (44.7%)	102.7	147 (33%)	78.13
	Skin	93 (20.9%)	39.42	85 (19.1%)	39.59
	Hepatitis	58 (13%)	21.8	57 (12.8%)	23.7
	Thyroid	70 (15.7%)	27	17 (3.8%)	6.75
	Pneumonitis	13 (2.9%)	4.52	2 (0.4%)	0.76
	Colitis	5 (1.1%)	1.71	2 (0.4%)	0.77
	Adrenal Insufficiency	2 (0.4%)	0.69	0 (0%)	0
	Pancreatitis	1 (0.2%)	0.34	0 (0%)	0
	Diabetes Mellitus	1 (0.2%)	0.34	3 (0.7%)	1.14
	Myositis Myositis+Rhabdomyolysis	0 (0%)	0	1 (0.2%)	0.38
	Meningoencephalitis	4 (0.9%)	1.38	1 (0.2%)	0.38
	Meningitis	4 (0.9%)	1.38	1 (0.2%)	0.38
	Nephritis	0 (0%)	0	0 (0%)	0
	Ocular Inflammatory Toxicity	1 (0.2%)	0.34	0 (0%)	0
	Vasculitis	0 (0%)	0	1 (0.2%)	0.38
	Hypophysitis	0 (0%)	0	0 (0%)	0
	Systemic Immune Activation	1 (0.2%)	0.34	0 (0%)	0
	Autoimmune Hemolytic Anemia	0 (0%)	0	0 (0%)	0
	Guillain-Barre Syndrome	0 (0%)	0	0 (0%)	0
	Encephalitis	0 (0%)	0	0 (0%)	0
	Myocarditis	0 (0%)	0	0 (0%)	0
	Myasthenia Gravis	0 (0%)	0	0 (0%)	0

irAEs = immune-related adverse events were reported in all study arms, including Standard of Care without atezolizumab, given the blinded nature of the controlled trials.

Table S3 List of baseline covariates adjusted in the statistical models

Variable	Status	Analysis	Comment
Age	log and scale	Final	used in all irAEs
Sex	Categorical	Final	used in all irAEs
Asian	Categorical	Final	used in all irAEs
Caucasian	Categorical	Final	used in all irAEs
Tumor histology	Categorical	Final	used in all irAEs
Time from initial diagnosis	log and scale	Final	used in all irAEs
Sum of Longest Diameter by Investigator	log and scale	Final	used in all irAEs
Patient with liver metastasis at screening	Categorical	Final	used in all irAEs
Alkaline Phosphatase (U/L)	log and scale	Final	used in all irAEs
SGPT/ALT (U/L)	log and scale	Final	used in all irAEs
SGOT/AST (U/L)	log and scale	Final	used in all irAEs
Chloride (mmol/L)	log and scale	Final	used in all irAEs
Glucose (mmol/L)	log and scale	Final	used in all irAEs
Potassium (mmol/L)	log and scale	Final	used in all irAEs
Erythrocytes (10^12/L)	log and scale	Final	used in all irAEs
Sodium (mmol/L)	log and scale	Final	used in all irAEs
Bilirubin (umol/L)	log and scale	Final	used in all irAEs
Protein, Total (g/L)	log and scale	Final	used in all irAEs
Lactate Dehydrogenase (U/L)	log and scale	Sensitivity analysis	High amount of missing
Thyroid-Stimulating Hormone (mU/L)	log and scale	Final	used in Thyroid only
Weight (kg)	log and scale	Sensitivity analysis	High amount of missing
Baseline ECOG Performance Status	Categorical	Sensitivity analysis	High amount of missing

Table S4 Individual-patient level meta-analysis Hazard Ratio estimates, confidence intervals, p-values for the association of onset of irAE with Overall Survival in patients treated with atezolizumab (alone or in combination) and with chemotherapy.

imAE	Study arm	Tox Grade	HR	Lower*	Upper*	p-value	FDR p-value
Any irAE	TRT: IO or C-IO	G1-2	0.65	0.59	0.71	0.0000	0.0000
	TRT: IO or C-IO	G3-4	1.18	0.96	1.45	0.0616	0.1026
	TRT: C	G1-2	0.81	0.71	0.91	0.0000	0.0001
	TRT: C	G3-4	1.27	0.88	1.83	0.1592	0.2653
Skin	TRT: IO or C-IO	G1-2	0.63	0.56	0.71	0.0000	0.0000
	TRT: IO or C-IO	G3-4	0.78	0.51	1.19	0.2076	0.2596
	TRT: C	G1-2	0.74	0.64	0.87	0.0000	0.0000
	TRT: C	G3-4	0.42	0.14	1.25	0.0521	0.2183
Hepatitis	TRT: IO or C-IO	G1-2	0.94	0.83	1.06	0.2445	0.2934
	TRT: IO or C-IO	G3-4	1.11	0.89	1.4	0.3486	0.3486
	TRT: C	G1-2	0.94	0.8	1.11	0.4471	0.5365
	TRT: C	G3-4	1.24	0.77	1.99	0.3825	0.3825
Pneumonitis	TRT: IO or C-IO	G1-2	0.78	0.62	0.99	0.0208	0.0313
	TRT: IO or C-IO	G3-4	1.71	1.11	2.62	0.0005	0.0019
	TRT: C	G1-2	0.78	0.42	1.47	0.4182	0.5365
	TRT: C	G3-4	1.72	0.84	3.51	0.0873	0.2183
Thyroid	TRT: IO or C-IO	G1-2	0.65	0.56	0.76	0.0000	0.0000
	TRT: C	G1-2	0.85	0.62	1.17	0.2793	0.5365
Colitis	TRT: IO or C-IO	G1-2	0.87	0.5	1.5	0.6191	0.6191
	TRT: IO or C-IO	G3-4	2.14	1.2	3.82	0.0008	0.0019
	TRT: C	G1-2	0.69	0.17	2.83	0.5945	0.5945
	TRT: C	G3-4	0.55	0.17	1.83	0.3075	0.3825

***** Confidence intervals using FDR corrections

irAEs = immune-related adverse events were reported in all study arms, including Standard of Care without atezolizumab, given the blinded nature of the controlled trials.

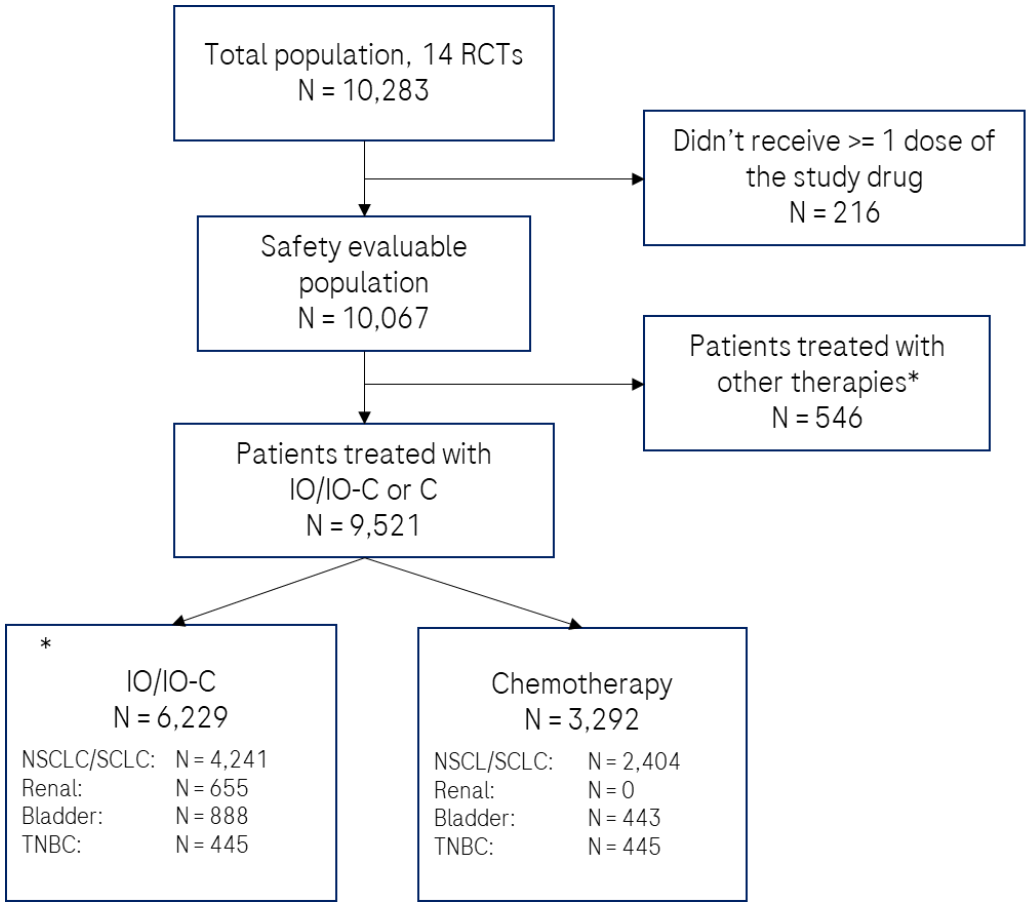
IO = atezolizumab monotherapy, C-IO = atezolizumab in combination with chemotherapy or bevacizumab, chemotherapy = Chemotherapy regime or chemotherapy with bevacizumab.

Skin = immune-related rash, immune-related severe cutaneous reactions.

Hepatitis = immune-related hepatitis (clinical diagnosis), immune-related hepatitis (lab abnormalities).

Thyroid = immune-related hypothyroidism, immune-related hyperthyroidism, immune-related thyroiditis.

Figure S1. Patients disposition



IO = atezolizumab as monotherapy, C-IO = atezolizumab in combination with chemotherapy and/or bevacizumab.

* Other therapies = Sunitinib (advanced renal cell carcinoma studies) .

Figure S2. Proportion of irAEs, by toxicity grade and cancer indication

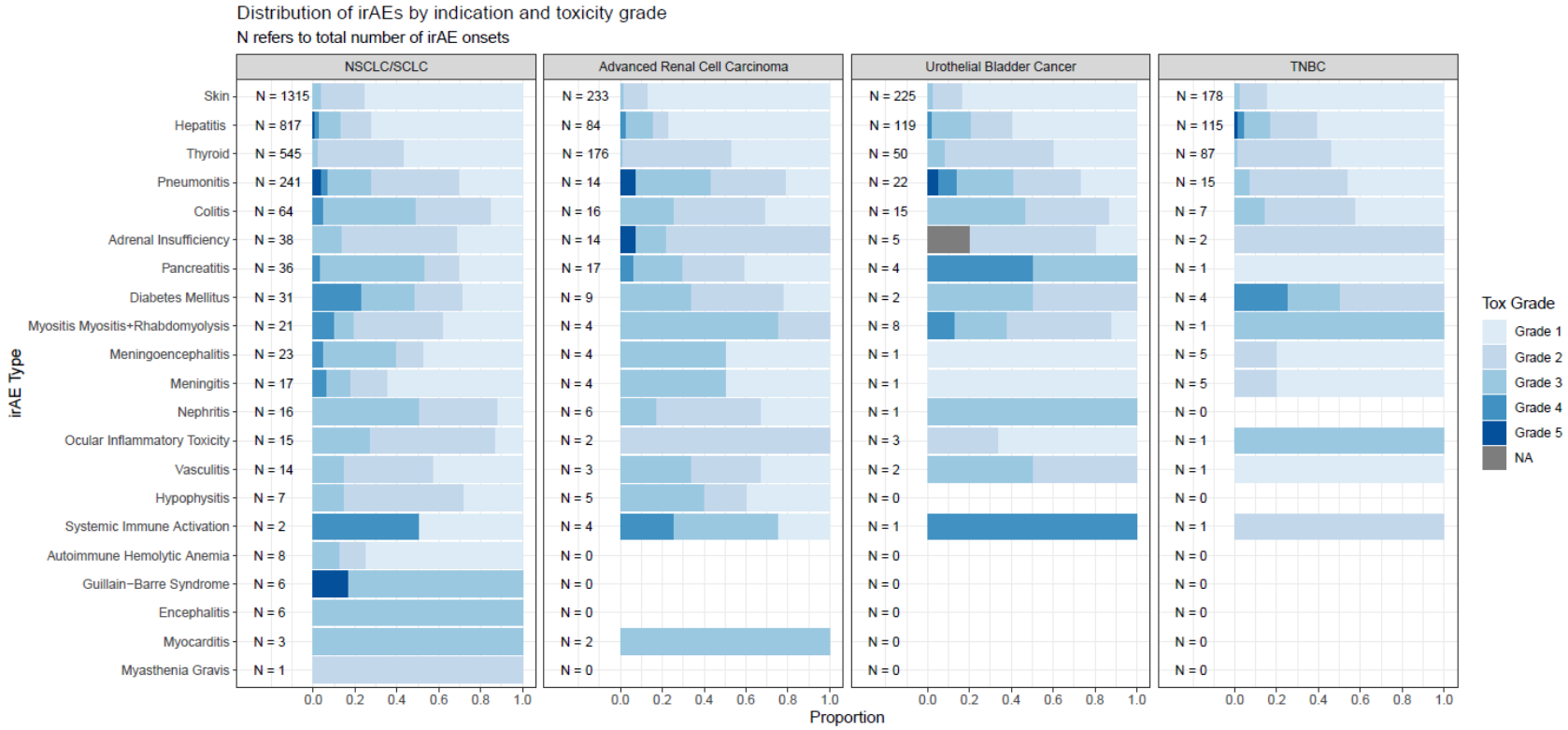


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Figure S3. Incidence rates (incidence densities) of irAE per 100 patients-years at risk

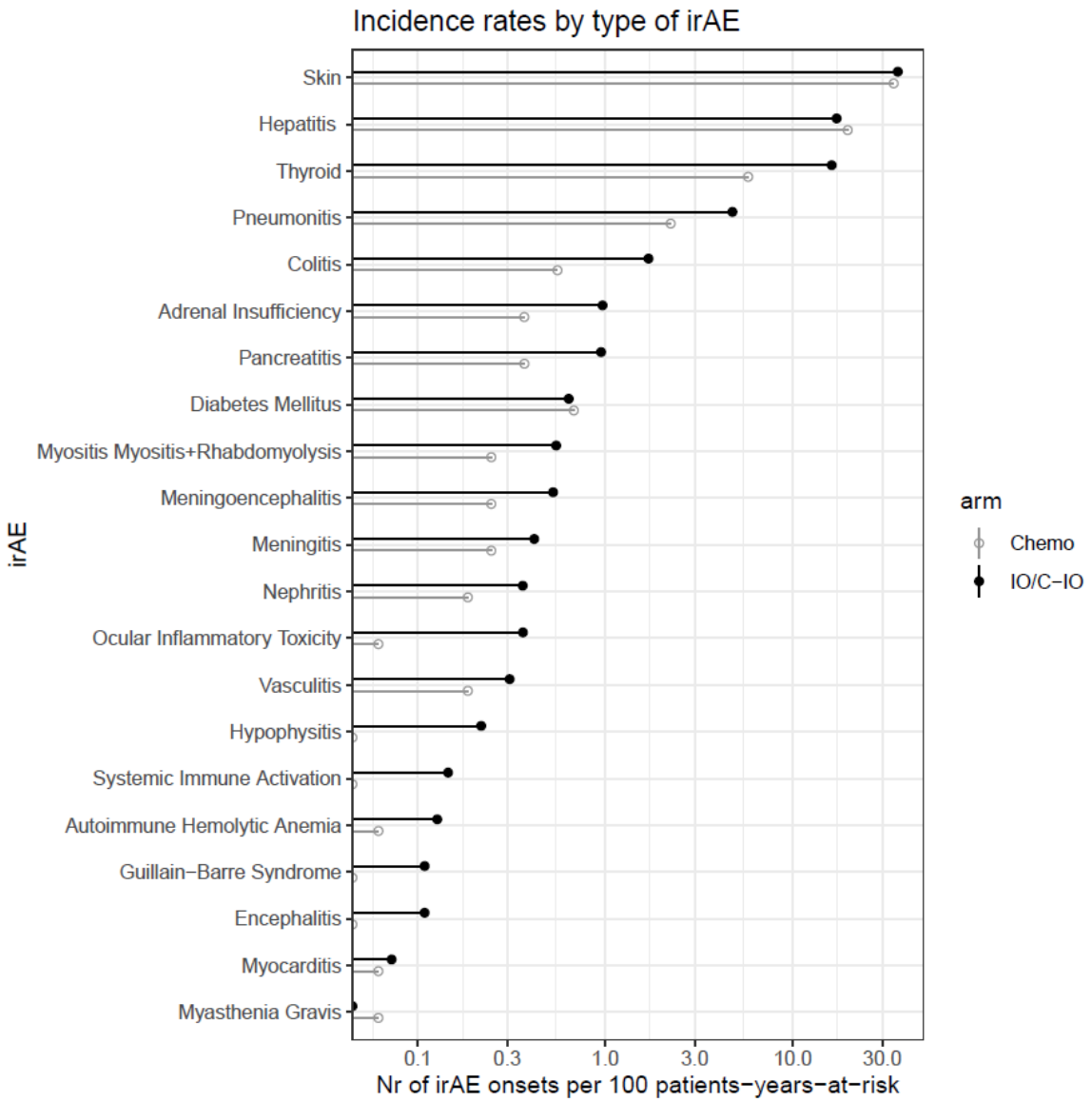

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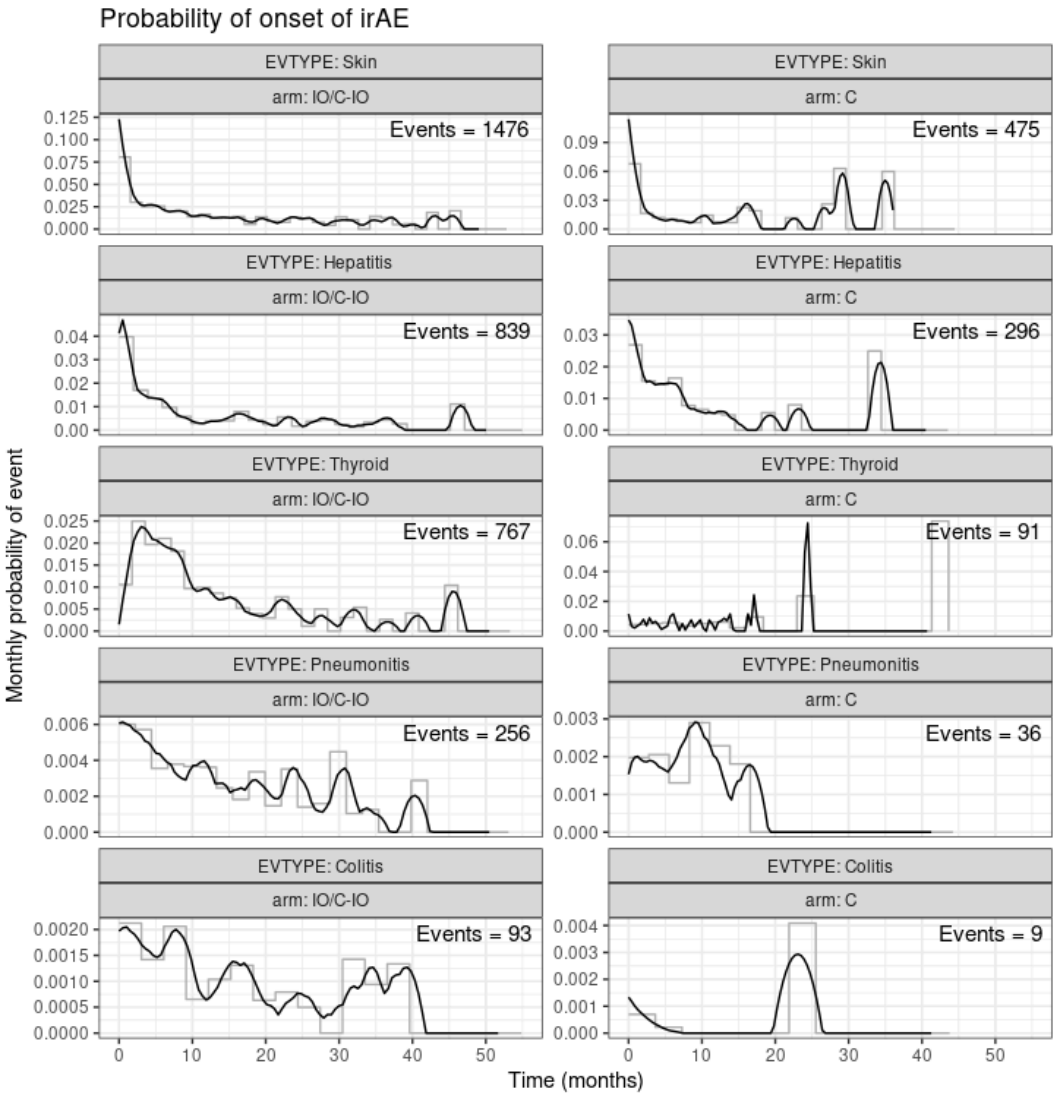
Figure S4

Estimation of the hazard function of the top 5 irAEs for patients treated with IO | C IO and C, using: the piecewise exponential hazard function (gray) and kernel-based methods (black)



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