

1 Table S1: Recurrence of initial irAE among informative rechallenge cases, with in Grey :
2 recurrence : number of cases with recurrence of irAE after rechallenge, N.avail : number of
3 cases available among cases for recurrence. In Green : No recurrence : number of cases
4 with no recurrence after rechallenge, N avail : number of cases available among cases with
5 no recurrence.
6

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
Number of cases	323		693			
Age, years		263		598		
• <45	13 (4.9%)		49 (8.2%)			
• 45-64	94 (35.7%)		205 (34.3%)		1.73	(0.89-3.34)
• 65-74	116 (44.1%)		234 (39.1%)		1.87	(0.97-3.58)
• >75	40 (15.2%)		110 (18.4%)		1.37	(0.67-2.79)
Sex, female	117 (36.9%)	317	268 (39.1%)	686	0.91	(0.69-1.20)
Cancer						
• Central Nervous system	0 (0.0%)	274	6 (1.1%)	541	•	•
• Digestive	10 (3.6%)	274	20 (3.7%)	541	0.99	(0.46-2.14)
• Head and neck	0 (0.0%)	274	2 (0.4%)	541	•	•
• Hematologic malignancies	1 (0.4%)	274	9 (1.7%)	541	0.22	(0.03-1.72)
• Lung and pleural	97 (35.4%)	274	201 (37.2%)	541	0.93	(0.68-1.25)
• Melanoma	•					
• Skin Non-Melanoma	•					
• Gynecologic	18 (6.6%)	274	40 (7.4%)	541	0.88	(0.49-1.57)
• Prostate	0 (0.0%)	274	4 (0.7%)	541	•	•
• Kidney	40 (14.6%)	274	47 (8.7%)	541	1.80	(1.15-2.82)
• Other genito-urinary	14 (5.1%)	274	53 (9.8%)	541	0.50	(0.27-0.91)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• Thymoma	0 (0.0%)	274	3 (0.6%)	541	•	•
• Not otherwise classified	38 (13.9%)	274	72 (13.3%)	541	1.05	(0.69-1.60)
ICI						
• Anti-PD(L)1 alone	255 (78.9%)	323	584 (84.3%)	693	0.70	(0.50-0.98)
• Anti-CTLA4 alone	7 (2.2%)	323	17 (2.5%)	693	0.88	(0.36-2.15)
• Combination therapy	61 (18.9%)	323	92 (13.3%)	693	1.52	(1.07-2.17)
• Anti-LAG3	•	323		693		
• Anti-TIGIT	1 (0.3%)	323	0 (0.0%)	693	•	•
• Anti-ICOS	•	323		693		
• Anti-DLL1	•	323		693		
Reaction						
• Adrenal	12 (3.7%)	323	64 (9.2%)	693	0.38	(0.20-0.71)
• Arthritis	30 (9.3%)	323	48 (6.9%)	693	1.38	(0.85-2.22)
• Colitis	127 (39.3%)	323	177 (25.5%)	693	1.89	(1.43-2.50)
• Diabetes	2 (0.6%)	323	28 (4.0%)	693	0.15	(0.04-0.63)
• Hematological	4 (1.2%)	323	11 (1.6%)	693	0.78	(0.25-2.46)
• Hypophysitis	10 (3.1%)	323	35 (5.1%)	693	0.60	(0.29-1.23)
• Liver	31 (9.6%)	323	58 (8.4%)	693	1.16	(0.74-1.84)
• Mucositis	9 (2.8%)	323	15 (2.2%)	693	1.30	(0.56-2.99)
• Myocarditis	5 (1.5%)	323	10 (1.4%)	693	1.07	(0.36-3.17)
• Myositis	5 (1.5%)	323	12 (1.7%)	693	0.89	(0.31-2.55)
• Nephritis	7 (2.2%)	323	6 (0.9%)	693	2.54	(0.85-7.61)
• Neurological	11 (3.4%)	323	31 (4.5%)	693	0.75	(0.37-1.52)
• Pancreatitis	8 (2.5%)	323	18 (2.6%)	693	0.95	(0.41-2.21)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• Pneumonitis	59 (18.3%)	323	133 (19.2%)	693	0.94	(0.67-1.32)
• Skin	23 (7.1%)	323	28 (4.0%)	693	1.82	(1.03-3.21)
• Thyroiditis	40 (12.4%)	323	93 (13.4%)	693	0.91	(0.61-1.36)
• Uveitis	4 (1.2%)	323	12 (1.7%)	693	0.71	(0.23-2.22)
• Vasculitis	1 (0.3%)	323	0 (0.0%)	693	•	•
ICSR with follow-up	197 (61.0%)	323	400 (57.7%)	693	1.15	(0.87-1.50)
Seriousness	265 (82.0%)	323	607 (87.6%)	693	0.65	(0.45-0.93)
All-cause death	8 (2.5%)	323	42 (6.1%)	693	0.39	(0.18-0.85)

7
8
9
10

11

12

Table S2: Comparison between rechallenged / not-rechallenged patients

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
Number of cases	18753		29627	
Age, years		13283		21935
• <45	876 (6.6%)		1610 (7.3%)	
• 45-64	4807 (36.2%)		8208 (37.4%)	
• 65-74	4765 (35.9%)		7643 (34.8%)	
• >75	2835 (21.3%)		4474 (20.4%)	
Sex, female	6658 (37.9%)	17572	10895 (39.6%)	27506
Cancer				
• Central Nervous system	81 (0.5%)	14732	203 (0.9%)	22873
• Digestive	632 (4.3%)	14732	900 (3.9%)	22873
• Head and neck	94 (0.6%)	14732	179 (0.8%)	22873
• Hematologic malignancies	192 (1.3%)	14732	362 (1.6%)	22873
• Lung and pleural	5239 (35.6%)	14732	8691 (38.0%)	22873
• Melanoma	•			
• Skin Non-Melanoma	•			
• Gynecologic	925 (6.3%)	14732	1570 (6.9%)	22873
• Prostate	54 (0.4%)	14732	219 (1.0%)	22873
• Kidney	2224 (15.1%)	14732	2254 (9.9%)	22873
• Other genito-urinary	776 (5.3%)	14732	887 (3.9%)	22873
• Thymoma	14 (0.1%)	14732	38 (0.2%)	22873
• Not otherwise classified	2190 (14.9%)	14732	3906 (17.1%)	22873
ICI				
• Anti-PD(L)1 alone	13924 (74.2%)	18753	22647 (76.4%)	29627

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
• Anti-CTLA4 alone	925 (4.9%)	18753	2600 (8.8%)	29627
• Combination therapy	3904 (20.8%)	18753	4380 (14.8%)	29627
• Anti-LAG3	31 (0.2%)	18753	57 (0.2%)	29627
• Anti-TIGIT	1 (0.0%)	18753	10 (0.0%)	29627
• Anti-ICOS	0 (0.0%)	18753	3 (0.0%)	29627
• Anti-DLL1	•	18753		29627
Reaction				
• Adrenal	1033 (5.5%)	18753	1313 (4.4%)	29627
• Arthritis	1709 (9.1%)	18753	2574 (8.7%)	29627
• Colitis	5359 (28.6%)	18753	8497 (28.7%)	29627
• Diabetes	543 (2.9%)	18753	876 (3.0%)	29627
• Hematological	276 (1.5%)	18753	438 (1.5%)	29627
• Hypophysitis	835 (4.5%)	18753	1467 (5.0%)	29627
• Liver	1666 (8.9%)	18753	2626 (8.9%)	29627
• Mucositis	635 (3.4%)	18753	768 (2.6%)	29627
• Myocarditis	577 (3.1%)	18753	896 (3.0%)	29627
• Myositis	510 (2.7%)	18753	773 (2.6%)	29627
• Nephritis	207 (1.1%)	18753	323 (1.1%)	29627
• Neurological	1289 (6.9%)	18753	2418 (8.2%)	29627
• Pancreatitis	269 (1.4%)	18753	531 (1.8%)	29627
• Pneumonitis	3158 (16.8%)	18753	5609 (18.9%)	29627
• Skin	644 (3.4%)	18753	974 (3.3%)	29627
• Thyroiditis	2835 (15.1%)	18753	3534 (11.9%)	29627
• Uveitis	176 (0.9%)	18753	247 (0.8%)	29627
• Vasculitis	42 (0.2%)	18753	102 (0.3%)	29627

13
14
15

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
ICSR with follow-up	11018 (58.8%)	18753	13008 (43.9%)	29627
Seriousness	15214 (81.1%)	18753	24270 (82.4%)	29452
All-cause death	1287 (6.9%)	18753	2408 (8.2%)	29454