Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Administrative Information (Country, Type of Report, Qualification of Reporter) and Clinical Characteristics of the ICI-Associated ICSRs Extracted from VigiBase® and Reporting at Least One irAE Up Until 1 September 2019

irAE population	Value	N
Number of cases	24,079	
Year		24,079
2006	1 (0·0%)	
2008	3 (0·0%)	
2009	13 (0·1%)	
2010	8 (0·0%)	
2011	63 (0·3%)	
2012	295 (1·2%)	
2013	416 (1·7%)	
2014	685 (2·8%)	
2015	1281 (5·3%)	
2016	1870 (7·8%)	
2017	4247 (17·6%)	
2018	7245 (30·1%)	
2019	7952 (33·0%)	
Region		24,079
African	4 (0·0%)	
Americas	8891 (36·9%)	
South-East Asia	39 (0·2%)	
European	8671 (36·0%)	
Eastern Mediterranean	22 (0·1%)	
Western Pacific	6452 (26·8%)	
Type of report		24,079
Spontaneous	16,121 (67·0%)	
Report from study	7725 (32·1%)	
Other	117 (0·5%)	
Not available to sender (unknown)	1 (0·0%)	
Post marketing surveillance/special monitoring	1 (0·0%)	
Missing	114 (0·5%)	
Reporter		24,079
Physician	13,445 (55·8%)	
Pharmacist	1574 (6·5%)	
Other health professional	5318 (22·1%)	
Lawyer	26 (0·1%)	
Consumer or other non-health professional	3065 (12·7%)	
Missing	651 (2·7%)	
Age group		16,384
<45 years	1223 (7·5%)	
45−64 years	6088 (37·2%)	
65−74 years	5779 (35·3%)	

>75 years	3294 (20·1%)	
Female sex	8048 (36·5%)	22,078
Type of cancer		20,556
Brain	56 (0·3%)	
Digestive	651 (3·2%)	
Gynaecological	292 (1·4%)	
Head and neck	416 (2·0%)	
Haematology	417 (2·0%)	
Lung	8455 (41·1%)	
Melanoma	7474 (36·4%)	
Prostate	101 (0·5%)	
Renal	1387 (6·7%)	
Skin	55 (0·3%)	
Urinary	542 (2·6%)	
Not otherwise classified	821 (4·0%)	
ICI		24,079
Anti−PD-1/PD-L1 monotherapy	16,663 (69·2%)	
Anti−CTLA-4 alone	4081 (16·9%)	
Combination therapy	3317 (13·8%)	
Type of initial irAE		24,079
Adrenal	1189 (4·9%)	
Arthritis	1863 (7·7%)	
Colitis	7098 (29·5%)	
Diabetes	756 (3·1%)	
Haematological	360 (1·5%)	
Hepatitis	1917 (8·0%)	
Hypophysitis	1489 (6·2%)	
Mucositis	509 (2·1%)	
Myocarditis	447 (1·9%)	
Myositis	607 (2·5%)	
Nephritis	276 (1·1%)	
Neurological	1667 (6·9%)	
Pancreatitis	451 (1·9%)	
Pneumonitis	5289 (22·0%)	
Skin	633 (2·6%)	
Thyroiditis	2756 (11·4%)	
Uveitis	269 (1·1%)	
Vasculitis	64 (0·3%)	
ICSR with follow-up	10,762 (44·7%)	24,079
Serious initial irAE	20,190 (85·6%)	23,578
Fatal initial irAE	2680 (11·4%)	23,580

CLTA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune-checkpoint inhibitor; ICSR, individual case safety report; irAE, immune-related adverse event; PD-1, programmed-death-1; PD-L1, programmed-death-ligand-1. A case can have multiple initial irAEs and cancer types.

eTable 2. (A) Additional Characteristics of Rechallenged and Non-Rechallenged Cases After an irAE With At Least One ICI AND (B) Additional Factors Associated With the Recurrence of the Same irAE Among Informative Rechallenges

A.						
Initial irAE patients	Rechallenged after irAE	n avail.	No rechallenge after irAE	n avail.		
Number of cases	6123		17,956			
Age group		3597		12,787		
<45 years	255 (7·1%)		968 (7·6%)			
45−64 years	1259 (35·0%)		4829 (37·8%)			
65−74 years	1346 (37·4%)		4433 (34·7%)			
>75 years	737 (20·5%)		2557 (20·0%)			
Female sex	2012 (36·1%)	5572	6036 (36·6%)	16,506		
Updated case	3033 (49·5%)	6123	7729 (43·0%)	17,956		
B.						
	Recurrence after ICI rechallenge	n avail.	No recurrence after ICI rechallenge	n avail.	Odds ratio	95% CI
Age group		100		271		
<45 years	1 (1·0%)		18 (6·6%)		1	Ref
45−64 years	30 (30·0%)		93 (34·3%)		5·81	(0·74−45·34)
65−74 years	49 (49·0%)		106 (39·1%)		8·32	(1·08−64·11)
>75 years	20 (20·0%)		54 (19·9%)		6·67	(0·83−53·25)
Female sex	43 (34·4%)	125	119 (37·0%)	322	0·89	(0·58−1·38)
Updated case	92 (70·8%)	130	203 (63·0%)	322	1·42	(0·91−2·2)
ICI: immune-checkpoint inhibitor; irAE, immune-related adverse event; n avail.: number of cases with available information; Ref: reference						

eTable 3. TTO of the Initial irAEs Associated With At Least One ICI in the Rechallenged (n=6,123) and the Non-Rechallenged ICSR Population (n=17,956)

Type of initial irAE	Rechallenged ICSR population			Non-rechallenged ICSR population			
	n	TTO available	Time to initial irAE onset (days)	n	TTO available	Time to initial irAE onset (days)	p value
Adrenal	374	123 (33%)	108 (67−181)	815	298 (37%)	112 (62−180)	0·78
Arthritis	491	115 (23%)	70 (22−154)	1372	330 (24%)	63 (20−170)	0·56
Colitis	1743	559 (32%)	53 (22−106)	5355	1734 (32%)	51 (24−105)	0·92
Diabetes	245	65 (27%)	130 (53−283)	511	151 (30%)	92 (36−194)	0·06
Haematological	92	26 (28%)	53 (22−143)	268	88 (33%)	57 (26−130)	0·85
Hepatitis	471	139 (30%)	43 (26−96)	1446	503 (35%)	42 (23−86)	0·61
Hypophysitis	353	91 (26%)	84 (48−156)	1136	279 (25%)	77 (45−139)	0·29
Mucositis	134	54 (40%)	70 (29−157)	375	119 (32%)	56 (15−130)	0·47
Myocarditis	102	23 (23%)	28 (18−77)	345	106 (31%)	28 (15−65)	0·78
Myositis	152	38 (25%)	28 (18−42)	455	152 (33%)	28 (18−41)	0·98
Nephritis	78	16 (21%)	70 (47−140)	198	52 (26%)	68 (42−115)	0·60
Neurological	422	83 (20%)	35 (19−76)	1245	351 (28%)	42 (18−89)	0·50
Pancreatitis	118	38 (32%)	94 (58−208)	333	91 (27%)	58 (28−196)	0·16
Pneumonitis	1286	512 (40%)	52 (18−129)	4003	1972 (49%)	46 (16−110)	0·07
Skin	155	45 (29%)	71 (32−233)	478	153 (32%)	57 (23−208)	0·57
Thyroiditis	778	366 (47%)	56 (29−103)	1978	861 (44%)	51 (27−98)	0·09
Uveitis	97	33 (34%)	113 (29−156)	172	72 (42%)	48 (17−101)	0·06
Vasculitis	16	3 (19%)	48 (32−48)	48	10 (21%)	42 (20−65)	0·93

ICI, immune-checkpoint inhibitor; ICSR, individual case safety report; irAE, immune-related adverse event; TTO, time to onset.

eTable 4. Description of the 16,663 ICSRs With Anti−PD-1/PD-L1 Monotherapy Among the irAE Population

	Rechallenged after irAE	n	No rechallenge after irAE	n
Number of cases	4360		12,303	
Age group		2704		8653
<45 years	119 (4·4%)		457 (5·3%)	
45−64 years	909 (33·6%)		3004 (34·7%)	
65−74 years	1058 (39·1%)		3230 (37·3%)	
>75 years	618 (22·9%)		1962 (22·7%)	
Female sex	1388 (34·7%)	3999	4059 (35·4%)	11,471
Type of initial irAE		4360		12,303
Adrenal	275 (6·3%)		504 (4·1%)	
Arthritis	402 (9·2%)		1136 (9·2%)	
Colitis	869 (19·9%)		2496 (20·3%)	
Diabetes	215 (4·9%)		383 (3·1%)	
Haematological	69 (1·6%)		196 (1·6%)	
Hepatitis	278 (6·4%)		838 (6·8%)	
Hypophysitis	136 (3·1%)		281 (2·3%)	
Mucositis	111 (2·5%)		329 (2·7%)	
Myocarditis	73 (1·7%)		270 (2·2%)	
Myositis	113 (2·6%)		365 (3·0%)	
Nephritis	59 (1·4%)		160 (1·3%)	
Neurological	307 (7·0%)		909 (7·4%)	
Pancreatitis	76 (1·7%)		227 (1·8%)	
Pneumonitis	1157 (26·5%)		3622 (29·4%)	
Skin	121 (2·8%)		366 (3·0%)	
Thyroiditis	620 (14·2%)		1535 (12·5%)	
Uveitis	72 (1·7%)		120 (1·0%)	
Vasculitis	11 (0·3%)		36 (0·3%)	
ICSR with follow-up	2277 (52·2%)	4360	5818 (47·3%)	12,303

Serious initial irAE	3779 (86·7%)	4360	10,079 (83·3%)	12,101
Fatal initial irAE	483 (11·1%)	4360	1499 (12·4%)	12,102

ICSR, individual case safety report; irAE, immune-related adverse event; PD-1, programmed-death-1; PD-L1,programmed-death-ligand-1. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 5. Description of the 4081 ICSRs With Anti−CTLA-4 Monotherapy Among the irAE Population

	Rechallenged after irAE	n	No rechallenge after irAE	n
Number of cases	791		3290	
Age group		441		2304
<45 years	65 (14·7%)		283 (12·3%)	
45−64 years	172 (39·0%)		966 (41·9%)	
65−74 years	133 (30·2%)		677 (29·4%)	
>75 years	71 (16·1%)		378 (16·4%)	
Female sex	286 (40·5%)	707	1054 (37·6%)	2806
Type of initial irAE		791		3290
Adrenal	42 (5·3%)		167 (5·1%)	
Arthritis	28 (3·5%)		105 (3·2%)	
Colitis	506 (64·0%)		1925 (58·5%)	
Diabetes	4 (0·5%)		16 (0·5%)	
Haematological	7 (0·9%)		26 (0·8%)	
Hepatitis	43 (5·4%)		261 (7·9%)	
Hypophysitis	123 (15·5%)		626 (19·0%)	
Mucositis	4 (0·5%)		15 (0·5%)	
Myocarditis	2 (0·3%)		15 (0·5%)	
Myositis	2 (0·3%)		16 (0·5%)	
Nephritis	2 (0·3%)		12 (0·4%)	
Neurological	34 (4·3%)		158 (4·8%)	
Pancreatitis	13 (1·6%)		39 (1·2%)	
Pneumonitis	19 (2·4%)		112 (3·4%)	
Skin	16 (2·0%)		66 (2·0%)	
Thyroiditis	29 (3·7%)		147 (4·5%)	
Uveitis	8 (1·0%)		23 (0·7%)	
Vasculitis	0 (0·0%)		7 (0·2%)	
ICSR with follow-up	261 (33·0%)	791	936 (28·4%)	3290
Serious initial irAE	661 (83·6%)	791	2602 (84·5%)	3081
Fatal initial irAE	65 (8·2%)	791	281 (9·1%)	3081

CLTA-4, cytotoxic T-lymphocyte antigen 4; ICSR, individual case safety report; irAE, immune-related adverse event. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 6. Description of the 3317 ICSRs With Combination Therapy Among the irAE Population

	Rechallenged after irAE	**n**	**No rechallenge after irAE**	**n**
Number of cases	972		2345	
Age group		452		1825
<45 years	71 (15·7%)		228 (12·5%)	
45−64 years	178 (39·4%)		859 (47·1%)	
65−74 years	155 (34·3%)		526 (28·8%)	
>75 years	48 (10·6%)		212 (11·6%)	
Female sex	338 (39·0%)	866	921 (41·6%)	2215
Type of initial irAE		972		2345
Adrenal	57 (5·9%)		143 (6·1%)	
Arthritis	61 (6·3%)		129 (5·5%)	
Colitis	370 (38·1%)		930 (39·7%)	
Diabetes	26 (2·7%)		112 (4·8%)	
Haematological	16 (1·6%)		46 (2·0%)	
Hepatitis	152 (15·6%)		340 (14·5%)	
Hypophysitis	94 (9·7%)		229 (9·8%)	
Mucositis	20 (2·1%)		29 (1·2%)	
Myocarditis	27 (2·8%)		59 (2·5%)	
Myositis	37 (3·8%)		72 (3·1%)	
Nephritis	17 (1·7%)		26 (1·1%)	
Neurological	83 (8·5%)		174 (7·4%)	
Pancreatitis	30 (3·1%)		66 (2·8%)	
Pneumonitis	112 (11·5%)		265 (11·3%)	
Skin	18 (1·9%)		45 (1·9%)	
Thyroiditis	130 (13·4%)		293 (12·5%)	
Uveitis	17 (1·7%)		29 (1·2%)	
Vasculitis	5 (0·5%)		5 (0·2%)	
ICSR with follow-up	495 (50·9%)	972	966 (41·2%)	2345
Serious initial irAE	904 (93·0%)	972	2148 (95·3%)	2255
Fatal initial irAE	95 (9·8%)	972	255 (11·3%)	2256

ICSR, individual case safety report; irAE, immune-related adverse event. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 7. Comparison Between Informative and Non-Informative Rechallenges

Non-informative rechallenges refers to cases where the rechallenge effect is unknown.

Rechallenged irAE patients	Informative rechallenges	n	Non-informative rechallenges	n
Number of cases	452		5671	
Age group		371		3226
<45 years	19 (5·1%)		236 (7·3%)	
45−64 years	123 (33·2%)		1136 (35·2%)	
65−74 years	155 (41·8%)		1191 (36·9%)	
>75 years	74 (19·9%)		663 (20·6%)	
Female sex	162 (36·2%)	447	1850 (36·1%)	5125
ICI		452		5671
PD-1/PD-L1 monotherapy	370 (81·9%)		3990 (70·4%)	
CTLA-4 monotherapy	22 (4·9%)		769 (13·6%)	
Combination therapy	60 (13·3%)		912 (16·1%)	
Reaction		452		5671
Adrenal	40 (8·8%)		334 (5·9%)	
Arthritis	29 (6·4%)		462 (8·1%)	
Colitis	125 (27·7%)		1620 (28·6%)	
Diabetes	13 (2·9%)		232 (4·1%)	
Haematological	10 (2·2%)		82 (1·4%)	
Hypophysitis	23 (5·1%)		330 (5·8%)	
Liver	33 (7·3%)		440 (7·8%)	
Mucositis	5 (1·1%)		130 (2·3%)	
Myocarditis	3 (0·7%)		99 (1·7%)	
Myositis	9 (2·0%)		143 (2·5%)	
Nephritis	8 (1·8%)		70 (1·2%)	
Neurological	19 (4·2%)		405 (7·1%)	
Pancreatitis	14 (3·1%)		105 (1·9%)	
Pneumonitis	103 (22·8%)		1185 (20·9%)	
Skin	16 (3·5%)		139 (2·5%)	
Thyroiditis	61 (13·5%)		718 (12·7%)	
Uveitis	11 (2·4%)		86 (1·5%)	
Vasculitis	1 (0·2%)		15 (0·3%)	
ICSR with follow-up	295 (65·3%)	452	2738 (48·3%)	5671
Serious initial irAE	415 (91·8%)	452	4929 (86·9%)	5671
Fatal initial irAE	21 (4·6%)	452	622 (11·0%)	5671

CLTA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune-checkpoint inhibitor; ICSR, individual case safety report; irAE, immune-related adverse event; PD-1,programmed-death-1; PD-L1, programmed-death-ligand-1. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 8. Details About the Occurrence of a Different irAE (Different from the Initial One) After ICI Rechallenge

Type of initial irAE	Total number of different irAEs occurring after ICI rechallenge	Number of different irAEs		
		Anti−PD-1/PD-L1 monotherapy	Anti−CTLA-4 monotherapy	Combination therapy
Adrenal	0	0	0	0
Arthritis	3	1	0	2
Colitis	10	4	0	6
Diabetes	0	0	0	0
Haematological	0	0	0	0
Hepatitis	2	0	0	2
Hypophysitis	0	0	0	0
Mucositis	0	0	0	0
Myocarditis	0	0	0	0
Myositis	0	0	0	0
Nephritis	0	0	0	0
Neurological	1	1	0	0
Pancreatitis	3	2	0	1
Pneumonitis	2	0	0	2
Skin	2	2	0	0
Thyroiditis	3	2	0	1
Uveitis	0	0	0	0
Vasculitis	0	0	0	0

CLTA-4, cytotoxic T-lymphocyte antigen 4; ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event; PD-1, programmed-death-1; PD-L1, programmed-death-ligand-1.

Type of initial irAE	irAE recurrence population			Non-irAE recurrence population			
	n	TTO available	Time to initial irAE onset (days)	n	TTO available	Time to initial irAE onset (days)	p value
Adrenal	5	1 (20%)	109	35	15 (43%)	111 (82−174)	1
Arthritis	13	10 (77%)	83 (48−214)	16	10 (62%)	92 (17−161)	0·6
Colitis	45	29 (64%)	83 (34−174)	78	41 (53%)	58 (27−89)	0·13
Diabetes	0	–	–	13	6 (46%)	52 (40−271)	–
Haematological	3	1 (33%)	103	7	1 (14%)	12	1
Hepatitis	9	4 (44%)	28 (12−48)	22	11 (50%)	71 (42−91)	0·07
Hypophysitis	6	4 (67%)	54 (48−84)	17	4 (24%)	154 (67−227)	0·49
Mucositis	1	1 (100%)	50	3	1 (33%)	1	1
Myocarditis	0	–	–	3	–	–	–
Myositis	2	–	–	7	2 (29%)	40 (40−40)	–
Nephritis	4	2 (50%)	73 (46−100)	4	1 (25%)	183	0·67
Neurological	1	1 (100%)	31 (31−31)	16	6 (38%)	44 (22−68)	1
Pancreatitis	2	1 (50%)	130	11	7 (64%)	105 (64−138)	0·75
Pneumonitis	34	21 (62%)	88 (58−178)	67	36 (54%)	44 (20−90)	0·03
Skin	6	3 (50%)	91 (67−102)	10	6 (60%)	100 (50−260)	0·9
Thyroiditis	10	4 (40%)	107 (76−132)	50	32 (64%)	39 (22−65)	0·08
Uveitis	1	–	–	10	5 (50%)	133 (44−154)	–
Vasculitis	1	1 (100%)	48	0	–	–	–

ICI, immune-checkpoint inhibitor; ICSR, individual case safety report; irAE, immune-related adverse event; TTO, time to onset.

eTable 9. Time to Onset of the Initial irAE in the Recurrence (n=130) and the Non-Recurrence ICSR Populations (n=322) After ICI Rechallenge

eTable 10. Informative Rechallenges With an Anti−PD-1/PD-L1 Monotherapy (n=370)

Rechallenged patients	Recurrence of the initial irAE	n	No recurrence of the initial irAE	n
Number of cases	105		265	
Age group		83		238
<45 years	0 (0·0%)		12 (5·0%)	
45−64 years	25 (30·1%)		76 (31·9%)	
65−74 years	41 (49·4%)		99 (41·6%)	
>75 years	17 (20·5%)		51 (21·4%)	
Female sex	31 (31·0%)	100	94 (35·5%)	265
Type of initial irAE		105		265
Adrenal	5 (4·8%)		31 (11·7%)	
Arthritis	11 (10·5%)		14 (5·3%)	
Colitis	34 (32·4%)		54 (20·4%)	
Diabetes	0 (0·0%)		13 (4·9%)	
Haematological	2 (1·9%)		5 (1·9%)	
Hepatitis	7 (6·7%)		11 (4·2%)	
Hypophysitis	3 (2·9%)		8 (3·0%)	
Mucositis	2 (1·9%)		3 (1·1%)	
Myocarditis	0 (0·0%)		3 (1·1%)	
Myositis	1 (1·0%)		5 (1·9%)	
Nephritis	4 (3·8%)		3 (1·1%)	
Neurological	3 (2·9%)		13 (4·9%)	
Pancreatitis	2 (1·9%)		8 (3·0%)	
Pneumonitis	30 (28·6%)		66 (24·9%)	

Skin	6 (5·7%)		9 (3·4%)	
Thyroiditis	9 (8·6%)		38 (14·3%)	
Uveitis	1 (1·0%)		9 (3·4%)	
Vasculitis	1 (1·0%)		0 (0·0%)	
ICSR with follow-up	76 (72·4%)	105	172 (64·9%)	265
Serious initial irAE	95 (90·5%)	105	245 (92·5%)	265
Fatal initial irAE	7 (6·7%)	105	9 (3·4%)	265

irAE, immune-related adverse event; PD-1, programmed-death-1; PD-L1, programmed-death-ligand-1. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 11. Informative Rechallenges With an Anti−CTLA-4 Monotherapy (n=22)

Rechallenged patients	Recurrence of the initial irAE	n	No recurrence of the initial irAE	n
Number of cases	7		15	
Age group		7		11
<45 years	0 (0·0%)		4 (36·4%)	
45−64 years	1 (14·3%)		4 (36·4%)	
65−74 years	3 (42·9%)		1 (9·1%)	
>75 years	3 (42·9%)		2 (18·2%)	
Female sex	4 (57·1%)	7	7 (46·7%)	15
Type of initial irAE		7		15
Adrenal	0 (0·0%)		2 (13·3%)	
Arthritis	0 (0·0%)		0 (0·0%)	
Colitis	4 (57·1%)		6 (40·0%)	
Diabetes	0 (0·0%)		0 (0·0%)	
Haematological	0 (0·0%)		0 (0·0%)	
Hypophysitis	2 (28·6%)		4 (26·7%)	
Hepatitis	1 (14·3%)		1 (6·7%)	
Mucositis	0 (0·0%)		0 (0·0%)	
Myocarditis	0 (0·0%)		0 (0·0%)	
Myositis	0 (0·0%)		0 (0·0%)	
Nephritis	0 (0·0%)		0 (0·0%)	
Neurological	0 (0·0%)		1 (6·7%)	
Pancreatitis	0 (0·0%)		0 (0·0%)	
Pneumonitis	0 (0·0%)		0 (0·0%)	
Skin	0 (0·0%)		1 (6·7%)	

Thyroiditis	0 (0·0%)		2 (13·3%)	
Uveitis	0 (0·0%)		0 (0·0%)	
Vasculitis	0 (0·0%)		0 (0·0%)	
ICSR with follow-up	3 (42·9%)	7	2 (13·3%)	15
Serious initial irAE	6 (85·7%)	7	11 (73·3%)	15
Fatal initial irAE	0 (0·0%)	7	1 (6·7%)	15

CLTA-4, cytotoxic T-lymphocyte antigen 4; ICSR, individual case safety report; irAE, immune-related adverse event. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 12. Informative Rechallenges With Combination Therapy (n=60)

Rechallenged patients	Recurrence of the initial irAE	n	No recurrence of the initial irAE	n
Number of cases	18		42	
Age group		10		22
<45 years	1 (10·0%)		2 (9·1%)	
45−64 years	4 (40·0%)		13 (59·1%)	
65−74 years	5 (50·0%)		6 (27·3%)	
>75 years	0 (0·0%)		1 (4·5%)	
Female sex	8 (44·4%)	18	18 (42·9%)	42
Type of initial irAE		18		42
Adrenal	0 (0·0%)		2 (4·8%)	
Arthritis	2 (11·1%)		2 (4·8%)	
Colitis	9 (50·0%)		18 (42·9%)	
Diabetes	0 (0·0%)		0 (0·0%)	
Haematological	1 (5·6%)		2 (4·8%)	
Hypophysitis	3 (16·7%)		10 (23·8%)	
Hepatitis	1 (5·6%)		5 (11·9%)	
Mucositis	0 (0·0%)		0 (0·0%)	
Myocarditis	0 (0·0%)		0 (0·0%)	
Myositis	1 (5·6%)		2 (4·8%)	
Nephritis	0 (0·0%)		1 (2·4%)	
Neurological	0 (0·0%)		2 (4·8%)	
Pancreatitis	1 (5·6%)		3 (7·1%)	
Pneumonitis	6 (33·3%)		1 (2·4%)	
Skin	0 (0·0%)		0 (0·0%)	
Thyroiditis	2 (11·1%)		10 (23·8%)	
Uveitis	0 (0·0%)		1 (2·4%)	
Vasculitis	0 (0·0%)		0 (0·0%)	
ICSR with follow-up	13 (72·2%)	18	29 (69·0%)	42
Serious initial irAE	17 (94·4%)	18	41 (97·6%)	42
Fatal initial irAE	1 (5·6%)	18	3 (7·1%)	42

ICSR, individual case safety report; irAE, immune-related adverse event. A case can have multiple initial irAEs (counts of initial irAEs exceed the number of cases).

eTable 13. Details About the ICI Regimen Used (Combination Therapy, Anti−PD-1/PD-L1 monotherapy, anti−CTLA-4 monotherapy) to rechallenge after an irAE Under Combination Therapy Among Informative Rechallenges

Rechallenge regimen	**Any**	**Anti−PD-1/PD-L1**			**Anti−CTLA-4**			**Combination therapy**		
Initial irAE	N	N	Reccurence (same irAE)	Different irAE	N	Reccurence (same irAE)	Different irAE	N	Reccurence (same irAE)	Different irAE
Adrenal	2	0	0	0	1	0	0	1	0	0
Arthritis	4	2	1	0	0	0	0	2	1	2
Colitis	26	10	5	2	3	1	2	13	2	2
Diabetes	0	0	0	0	0	0	0	0	0	0
Haematological	3	2	1	0	0	0	0	1	0	0
Hepatitis	11	3	0	1	2	0	0	6	1	1
Hypophysitis	6	3	1	0	1	0	0	2	0	0
Mucositis	0	0	0	0	0	0	0	0	0	0
Myocarditis	0	0	0	0	0	0	0	0	0	0
Myositis	3	1	1	0	0	0	0	2	0	0
Nephritis	1	0	0	0	0	0	0	1	0	0
Neurological	2	0	0	0	1	0	0	1	0	0
Pancreatitis	4	0	0	0	0	0	0	4	1	1
Pneumonitis	7	3	2	1	0	0	0	4	4	1
Skin	0	0	0	0	0	0	0	0	0	0
Thyroiditis	11	1	0	0	3	1	0	7	0	1
Uveitis	1	0	0	0	0	0	0	1	0	0
Vasculitis	0	0	0	0	0	0	0	0	0	0

CLTA-4, anti-cytotoxic T-lymphocyte antigen 4; ICI, immune-checkpoint inhibitor; ICSR, individual case safety report; irAE, immune-related adverse event; PD-1, programmed-death-1; PD-L1, programmed-death-ligand-1.

eAppendix 1. Medical Dictionary for Regulatory Activities (MedDRA, v21.1) Preferred Terms Used to Identify Immune Related Adverse Events in Vigibase®

Adrenal
Addison's disease
Adrenal insufficiency
Adrenocortical insufficiency acute
Adrenocorticotropic hormone deficiency
Secondary adrenocortical insufficiency
Arthritis
Arthritis
Autoimmune arthritis
Polyarthritis
Rheumatoid arthritis
Colitis
Autoimmune colitis
Colitis microscopic
Diarrhoea
Diarrhoea haemorrhagic
Duodenitis
Enteritis
Enterocolitis
Enterocolitis haemorrhagic
Ulcerative gastritis
Diabetes
Diabetic ketoacidosis
Fulminant type 1 diabetes mellitus
Type 1 diabetes mellitus
Hematological
Autoimmune haemolytic anaemia
Haemolytic anaemia
Haemophagocytic lymphohistiocytosis
Immune thrombocytopenic purpura
Hypophysitis
Hypophysitis
Hypopituitarism
Hypothalamo-pituitary disorder
Lymphocytic hypophysitis
Pituitary enlargement
Liver
Acute hepatic failure
Autoimmune hepatitis
Drug-induced liver injury
Hepatic failure
Hepatitis
Hepatitis acute
Hepatotoxicity

Mucositis
Dry mouth
Mucosal inflammation
Myocarditis
Autoimmune myocarditis
Myocarditis
Myositis
Necrotising myositis
Polymyositis
Rhabdomyolysis
Nephritis
Nephritis
Glomerulonephritis
Neurological
Autoimmune neuropathy
Demyelinating polyneuropathy
Encephalitis
Encephalitis autoimmune
Encephalopathy
Guillain-Barre syndrome
Limbic encephalitis
Meningitis
Meningitis aseptic
Myasthenia gravis
Myasthenia gravis crisis
Myasthenic syndrome
Neuropathy peripheral
Ocular myasthenia
Peripheral motor neuropathy
Peripheral sensorimotor neuropathy
Peripheral sensory neuropathy
Oesophagitis
Eosinophilic oesophagitis
Pancreatitis
Autoimmune pancreatitis
Pancreatitis
Pneumonitis
Interstitial lung disease
Pneumonitis
Organising pneumonia
Skin
Acute febrile neutrophilic dermatosis
Dermatitis
Dermatitis psoriasiform
Drug eruption
Granulomatosis with polyangiitis
Pemphigoid

Skin toxicity
Toxic skin eruption
Thyroiditis
Autoimmune thyroiditis
Hyperthyroidism
Hypothyroidism
Thyroiditis
Uveitis
Autoimmune uveitis
Uveitis
Vasculitis
Vasculitis
Vasculitis necrotising

eAppendix 2. Description of the Vigibase® Extract Case Level Data

The Vigibase® extract case level data is a relational database. It contains a deduplicated version of the dataset. The demographic table includes data on the year of reporting, the patient age and sex, the country of reporting. The outcome table provides information on seriousness and death. The adverse drug reaction table includes data on each adverse drug reaction of ICSRs, coded with MedDRA codes. The medications table includes data on each medication of ICSRs, coded with medicinal product Id (drug name, dose, route of administration, frequency, dechallenge and rechallenge). The time to onset is precalculated for each pair of medication and reaction in ICSRs in a link table. Indication of the medications is provided in an indication table.

eAppendix 3. Statistical Analysis Supplement

The rate of recurrence was calculated as follows:

$$rate\ of\ recurrence = \frac{number\ of\ cases\ experiencing\ reccurence}{number\ of\ informative\ rechallenges} * 100$$

This rate is different of an incidence rate which evaluates the proportion of an adverse event with a drug. The incidence rate cannot be computed in VigiBase® since the denominator (the number of patients exposed to a drug) is not known. Disproportionality analysis was performed to explore the factors associated with the recurrence in a secondary analysis. The common use of disproportionality analysis is evaluating the magnitude of the over-reporting of an adverse event with a drug compared with the other adverse events and the other drugs. Several measurements can be used, including the reporting Odds-Ratio (OR) which is computed as follows

Reporting OR to investigate associations between a drug of interest and an adverse event of interest (common use)			
Exposure	Adverse event	Adverse event of interest	Other adverse events
Drug of interest		a	b
Other drugs		c	d

$$reporting\ OR = \frac{a * d}{b * c}$$

However, in the present study, the disproportionality analysis was used in a different setting, to evaluate to factors associated with the recurrence rather than with the drug.

Reporting OR to investigate factors associated with the recurrence			
Recurrence status	Factors (adverse event, sex…)	Factor is present (e.g. colitis reported in the case)	Factor is absent (e.g. no colitis reported in the case)
Recurrence of irAE		a	b
No recurrence of irAE		c	d

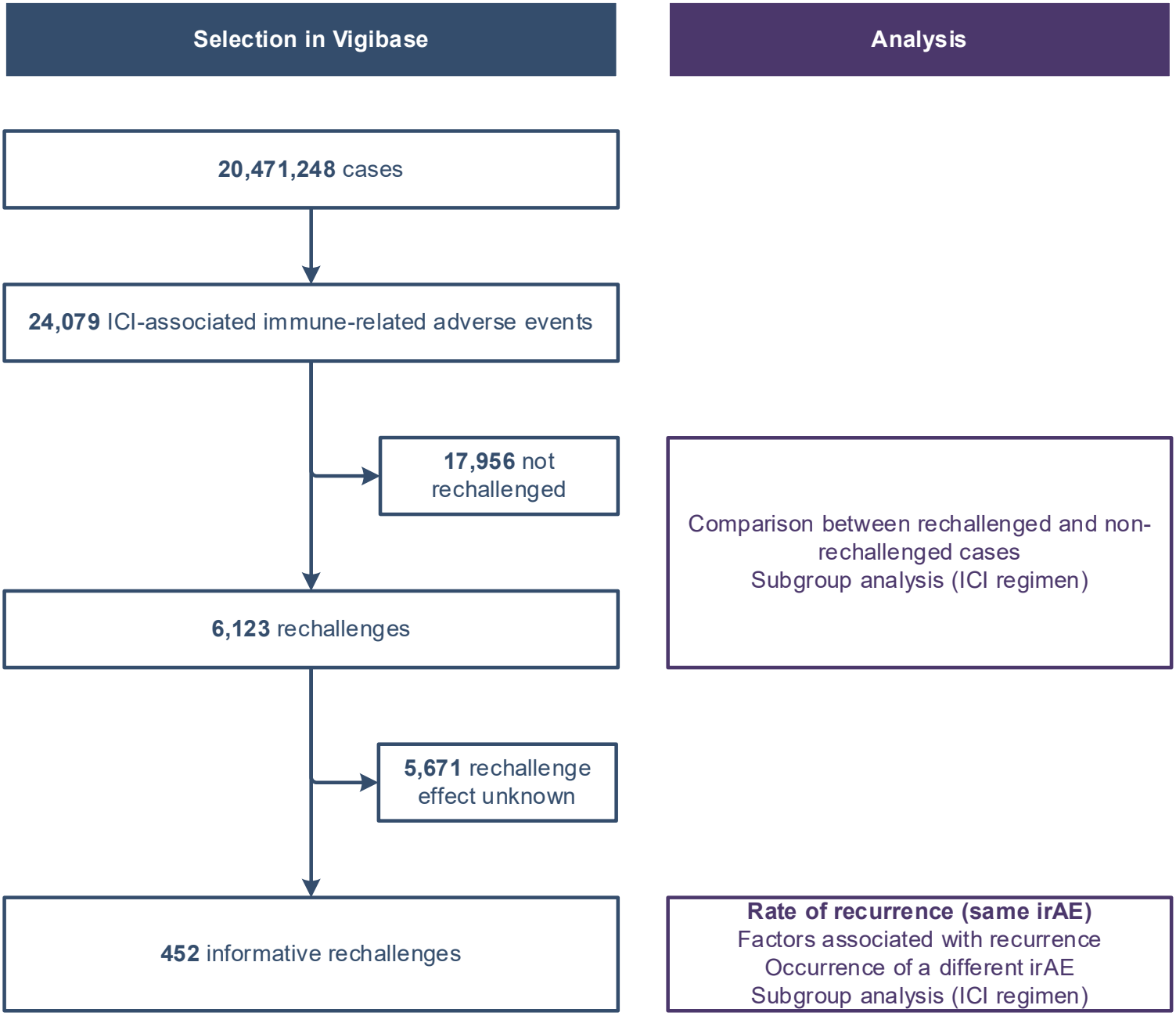
This is formally the chi-square-like contingency table to compute reporting OR. It is also possible to use a logistic regression model using independent and dependent variables to estimate coefficients and OR. The formula would be

$$recurrence\ status \sim factor\ in\ the\ case\ (e.g. colitis\ is\ reported)$$

There can be more than one independent variables in a multivariable logistic regression model, although it requires to access to individual case data. In our study, we computed uni- and multivariable reporting OR to investigate the factors associated with the recurrence. Confidence intervals were computed with the estimates and standard errors of the logistic regression model. A variable selection process was undertaken, as the number of events was insufficient to keep all variables. Stepwise procedure using the Akaike Information Criteria (AIC) was used to identify the most contributive variables to the multivariate logistic regression model.

eFigure 1. Flow Chart of Cases Selection in VigiBase®

ICI, immune-checkpoint inhibitor; irAE, immune-related adverse event



eFigure 2. Rate of Recurrence According to the Initial Immune-Related Adverse Event and the Initial ICI Regimen

Anti-PD-1, anti–programmed-death-1; anti−PD-L1, anti–programmed-death-ligand-1; anti−CTLA-4, anti-cytotoxic T-lymphocyte antigen 4; ICI, immune-checkpoint inhibitor. Only adverse events with ≥10 rechallenges are shown.