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Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events from VigiBase®– Update in 2024

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Key words: Rechallenge – Inhibitor of checkpoint – immune related adverse event

Abstract:

Background: Limited information is available on the safety of a rechallenge with an immune checkpoint inhibitor (ICI) after occurrence of an immune-related adverse event (irAE).

Methods: This is an update of our observational pharmacovigilance cohort study examining individual case safety reports from the World Health Organization database VigiBase. The primary outcome was the recurrence rate (expressed as a percentage with its 95% confidence interval [CI]) of the initial irAE post-rechallenge with the same ICI.

Results: We identified 1,016 irAEs cases from ICI rechallenges. Of these, 323 irAEs recurrences occurred (31.8%, 95%CI 28.1-34.0). The most common post-rechallenge irAEs were nephritis (recurrence rate: 50%, 95%CI 25-75), skin irAEs (44%, 95%CI 31-58), and colitis (39%, 95%CI 33-44).

Conclusions: In this updated, largest cohort study on rechallenge (NCT04696250), we observed a 31.8% recurrence rate of the same irAE post-rechallenge with the same ICI, building upon our previous findings.

Introduction

The advent of immune checkpoint inhibitors (ICIs) has profoundly transformed oncological therapeutics over recent years (1). Sustained therapeutic responses have been documented, such as in metastatic melanoma, where overall survival (OS) at 6.5 years reaches 42% and 49% for nivolumab and the combination of nivolumab and ipilimumab, respectively (2). These substantial clinical benefits at the metastatic stage have led to the broadening implementation of ICIs across the therapeutic spectrum, including in the adjuvant (3) and neoadjuvant settings (4). Now endorsed for the management of all solid cancers, ICIs have indeed been conceded as the contemporary standard of care. This efficacy is paradoxically mediated by the same mechanism that prompts immune-related adverse events (irAEs), stemming from systemic immune activation (5,6) . Up to 80% of patients may encounter any-grade irAEs, with Common Terminology Criteria for Adverse Events (CTCAE) grade 3-5 irAEs affecting 8% (7). Although the majority of irAEs abate upon cessation of ICI therapy and corticosteroid administration, their influence on oncological outcomes remains a subject of ongoing debate (8). For severe or corticoresistant irAEs, the introduction of immunomodulatory agents is recommended, adhering to established guidelines (9). The term 'rechallenge' is frequently utilized to describe the resumption of an ICI following a hiatus required for the irAE resolution (10). With ICIs being introduced earlier in the disease trajectory and concomitant with OS extension, patients frequently face the prospect of multiple exposures to ICIs during their lifetime. Therefore, understanding the safety of rechallenge is critical, in the context of limited alternative treatments. In our princeps cohort (11), we documented a recurrence rate of 28.8% for the original irAE upon rechallenge, noting particularly high recurrence rates for irAEs such as colitis and pneumonitis. Herein, we extend our prior inquiry and provide an updated analysis on irAE recurrence post-rechallenge.

Materials and Methods

Data were sourced from VigiBase®, the World Health Organization (WHO) pharmacovigilance database managed by the Uppsala Monitoring Centre (Sweden).

Incident irAE cases related with at least one ICI administration were systematically collected, until March 1st, 2024. We identified irAEs using Preferred Terms from the Medical Dictionary for Regulatory Activities, version 26.1. ICI therapies included anti-PD-1 antibodies (cemiplimab, dostarlimab, nivolumab, pembrolizumab, retifanlimab), anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab), anti-CTLA-4 antibodies (ipilimumab, tremelimumab), and anti-LAG3 therapy (relatlimab). ICI regimen types were classified as anti-PD(L)-1 monotherapy, anti-CTLA-4 monotherapy, combined anti-PD(L)-1/anti-CTLA-4 therapy, and combined anti-PD(L)-1/anti-LAG3 therapy. For the initial irAE event, a comprehensive collection of administrative, demographic, drug- and irAE-specific data was pursued, encompassing parameters such as patient age, sex, drug indication, rechallenge, irAE type and severity, and irAE-associated mortality. Each irAE was designated as 'serious' or 'non-serious' in accordance with WHO criteria, and cases were discerned as either initial or updated with progressive follow-up details.

The primary outcome was the reported irAE recurrence rate post-rechallenge with the same ICI agent, ascertained among informative rechallenge cases. Exploratory secondary outcomes were factors presumptively associated with irAE recurrence post-rechallenge, which encompassed ICI regimens.

Statistical analyses were consistent with our princeps article (11). Reported recurrence rates were denoted as percentages, dividing the number of irAE recurrence cases by the number of informative rechallenge cases. The 95% Confidence Intervals (CIs) for binomial proportions were estimated applying the Agresti-Coull approach. Qualitative variables were reported as frequencies and percentages, while quantitative variables were reported as medians with interquartile ranges (IQRs). Comparisons between rechallenge and non-rechallenge cohorts

were conducted using the χ^2 test or Fisher's exact test for qualitative data, alongside the unpaired Kruskal-Wallis test for quantitative data. Univariate logistic regression was employed to compute reporting odds ratios (reporting ORs) with 95% CIs. Statistical significance was ascertained through the Wald test, where a p-value less than 0.05 was deemed significant. Statistical computations were performed using the R software for Windows, version 4.3.2 (R Project for Statistical Computing).

The ethics committee at Caen University Hospital deemed formal review and consent procedures unnecessary due to the utilization of anonymized data within this study. The clinical trial registration number is NCT04696250.

Results

The study encompassed 48,380 cases of irAEs associated with ICI administrations, which approximates a twofold increase compared to our inaugural study. A subset of 18,753 cases underwent an ICI rechallenge post-irAE, and 1,016 cases had available data on irAE recurrence. Of these, 323 subjects were notified with a recurrence, equating to a 31.8% recurrence rate (95% CI 28.1-34.0). Within informative cases, 117 (36.0%) were female and the modal age group was 65-74 years (n=116, 44.1%). Factors associated with the recurrence of the initial irAE are detailed in Table 1.

IrAE recurrence was significantly associated with ICI regimens, with a reporting OR of 0.70 (95% CI, 0.50-0.98) for anti-PD(L)1 monotherapy, 0.88 (95%CI, 0.36-2.15) for anti-CTLA-4 monotherapy, and 1.52 (95%CI, 1.07-2.17) for combination therapy.

The three highest recurrence rates were found for nephritis (50%, 95%CI 25-75), skin irAEs (44%, 95%CI 31-58), and colitis (39%, 95%CI 33-44) as shown in Figure 1. Details are provided in Table 2.

Discussion

The safety profile of post-rechallenge ICIs remains a relatively terra incognita within the field. Our study, which includes an expansive cohort of 18,753 rechallenge cases—with 1,016 yielding informative data—substantially enlarges upon the evidence base previously established(11). We observed 31.8% recurrence of the same irAEs post-rechallenge, corroborating both current literature and our antecedent findings(11) .

Reflecting upon retrospective analyses, such as one involving 40 rechallenged patients where 17 (42.5%) experienced a recurrence of the same irAE and 5 (12.5%) manifested a novel irAE (12), our findings are aligned. Moreover, a meta-analysis surveying 789 cases documented incidences of all-grade and high-grade irAEs at 34.2% and 11.7%, respectively(13). Gastrointestinal irAEs were associated with higher high-grade irAEs recurrence, while initial anti-PD(L)-1 correlated with lower recurrence. Despite an augmented incidence of all-grade irAEs post-rechallenge (OR, 3.81; 95% CI, 2.15-6.74; $p < 0.0001$), the incidence of high-grade irAEs was not significantly different ($p > 0.05$), hence the tolerance profile persists as acceptable.

The present inquiry has additionally surfaced novel insights pertaining to nephritis and myocarditis, which were absent from our preceding study(11). The recurrence rate of nephritis was 50%, which overshadows prior estimates documented in the literature(14). Our analysis, comprising 12 cases of rechallenged nephritis, may suffer from insufficient statistical power. Additionally, we were unable to assess the potential influence of the temporal interval between the initial irAE and subsequent rechallenge, a factor that could affect nephritis recurrence risk, thereby constraining our ability to derive conclusive insights on risk modulation of nephritis recurrence. Myocarditis, a relatively infrequent but severe irAE(15), portrayed a 33% recurrence rate post-rechallenge in our cohort, underscoring the necessity for careful consideration when contemplating ICI rechallenge in the context of myocarditis(15). Around one-third of colitis cases exhibited recurrence, although with low mortality rates, potentially allowing for rechallenge when treatment alternatives are absent. Provision of rechallenge necessitates cautious appraisal of the risk-benefit ratio by the clinician, with potential

establishment of augmented surveillance protocols. In the absence of predictive models to forecast patient-specific irAE occurrences and recurrences, retrospective investigations furnish essential guidance for tailoring treatment strategies to individual patient profiles and their unique irAE histories.

Conclusion

The updated dataset of our cohort delineates a global irAE recurrence rate of 31.8% post-ICI rechallenge. This underscores the feasibility of rechallenge in a select patient population, with the stipulation that individualized patient monitoring is imperative, given the observed variability in irAE recurrence and severity.

Adverse drug reaction	No. of cases	Recurrence rate (95%CI), %
Diabetes	30	7 (1-22)
Adrenal	76	16 (9-26)
Hypophysitis	42	17 (8-31)
Neurological	39	21 (11-36)
Thyroiditis	119	22 (15-30)
Mucositis	20	25 (11-47)
Uveitis	16	25 (10-50)
Hematological	15	27 (10-52)
Pancreatitis	25	28 (14-48)
Pneumonitis	187	29 (23-36)
Myositis	17	29 (13-53)
Hepatitis	85	32 (23-42)
Myocarditis	15	33 (15-58)
Arthritis	74	35 (25-47)
Colitis	288	39 (33-44)
Skin	50	44 (31-58)
Nephritis	12	50 (25-75)

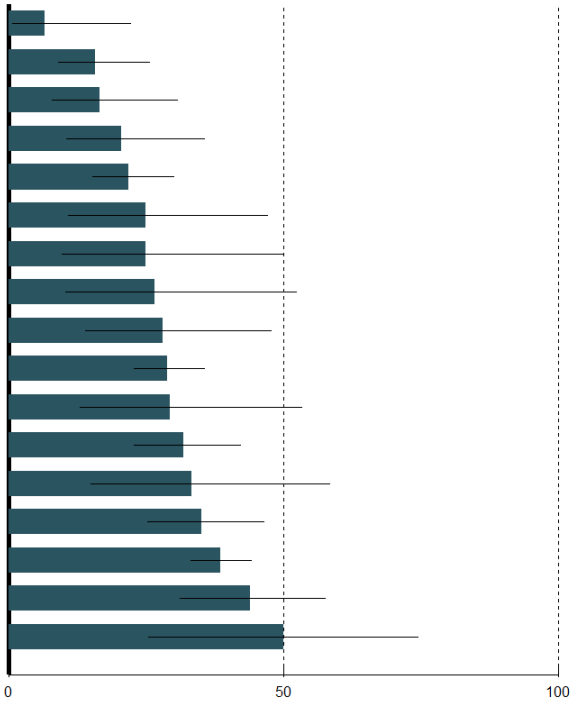

Figure 1: Recurrence rate of irAEs categorized by the initial affected site, updated in March 2024.

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Supplementary materials

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)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• Pancreatitis	8 (2.5%)	323	18 (2.6%)	693	0.95	(0.41-2.21)
• 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)

Table 1: Recurrence of initial irAE among informative rechallenge cases

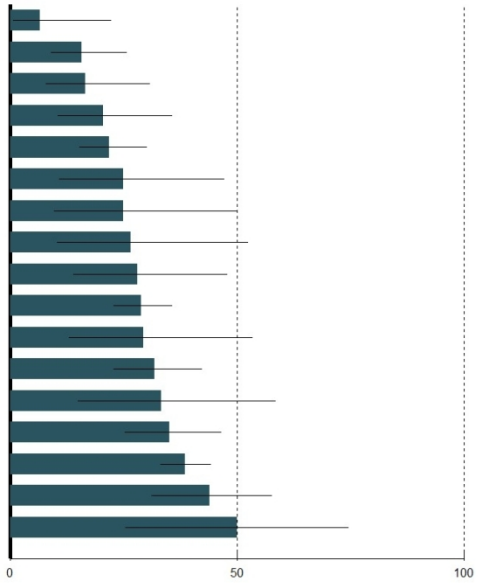
Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
Number of cases	18753		29627	
Age, years		13283		21935
• <45	876 (6.6%)		1610 (7.3%)	
• 45-64	4807 (36.2%)		8208 (37.4%)	
• 65-74	4765 (35.9%)		7643 (34.8%)	
• >75	2835 (21.3%)		4474 (20.4%)	
Sex, female	6658 (37.9%)	17572	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

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
• 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
• 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

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
• 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
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

Table 2: Comparison between rechallenged / not-rechallenged patients

Adverse drug reaction	No. of cases	Recurrence rate (95%CI), %
Diabetes	30	7 (1-22)
Adrenal	76	16 (9-26)
Hypophysitis	42	17 (8-31)
Neurological	39	21 (11-36)
Thyroiditis	119	22 (15-30)
Mucositis	20	25 (11-47)
Uveitis	16	25 (10-50)
Hematological	15	27 (10-52)
Pancreatitis	25	28 (14-48)
Pneumonitis	187	29 (23-36)
Myositis	17	29 (13-53)
Hepatitis	85	32 (23-42)
Myocarditis	15	33 (15-58)
Arthritis	74	35 (25-47)
Colitis	288	39 (33-44)
Skin	50	44 (31-58)
Nephritis	12	50 (25-75)



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Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events : a retrospective study from VigiBase®– Update in 2024 looking for emergent safety signals

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Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events : a retrospective study from VigiBase®– Update in 2024 looking for emergent safety signals

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Contributorship statement
JMLO : Writing, data curation, Revision ; ADS : Writing, data curation ; JC : Writing ; JA : Writing, Design of the study ; CD : Guarantor, Statistics, Writing, Design of the study.

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Strengths and Limitations of this study

- Largest cohort of irAE
- International
- Emergent safety signals
- Restrospective
- No CTCAE grade differentiation

Patient and Public Involvement statement : Not applicable. Patients were not involved in the design, methodology or conduct of this study.

Key words: Rechallenge – Inhibitor of checkpoint – immune related adverse event

Abstract:

Objectives: Limited information is available on the safety of a rechallenge with an immune checkpoint inhibitor (ICI) after occurrence of an immune-related adverse event (irAE). We aim to identify potential emergent safety signals.

Design: This is an update of our observational pharmacovigilance cohort study.

Setting: We exanimated individual case safety reports from the World Health Organization database VigiBase.

Participants: We included all individual case safety reports with ICI and rechallenged ICI.

Interventions: We identified incident irAE cases using MEDRA terms v.26.1 related with at least one ICI administration were systematically collected, until March 1st, 2024.

Primary and secondary outcome measures: The primary outcome was the recurrence rate (expressed as a percentage with its 95% confidence interval [CI]) of the initial irAE post-rechallenge with the same ICI.

Results: We identified 1,016 irAEs cases from ICI rechallenges. Of these, 323 irAEs recurrences occurred (31.8%, 95%CI 28.1-34.0). The most common post-rechallenge irAEs were nephritis (recurrence rate: 50%, 95%CI 25-75), skin irAEs (44%, 95%CI 31-58), and colitis (39%, 95%CI 33-44).

Conclusions: In this updated, largest cohort study on rechallenge (NCT04696250), we observed a 31.8% recurrence rate of the same irAE post-rechallenge with the same ICI, building upon our previous findings.

Data availability statement

Data are available upon reasonable request. Additional data beyond what are provided in the supplement may be made available upon reasonable request to the authors.

Introduction

The advent of immune checkpoint inhibitors (ICIs) has profoundly transformed oncological therapeutics over recent years [1]. Sustained therapeutic responses have been documented, such as in metastatic melanoma, where overall survival (OS) at 6.5 years reaches 42% and 49% for nivolumab and the combination of nivolumab and ipilimumab, respectively [2]. These substantial clinical benefits at the metastatic stage have led to the broadening implementation of ICIs across the therapeutic spectrum, including in the adjuvant [3] and neoadjuvant settings [4]. Now endorsed for the management of all solid cancers, ICIs have indeed been conceded as the contemporary standard of care. This efficacy is paradoxically mediated by the same mechanism that prompts immune-related adverse events (irAEs), stemming from systemic immune activation [5,6] . Up to 80% of patients may encounter any-grade irAEs, with Common Terminology Criteria for Adverse Events (CTCAE) grade 3-5 irAEs affecting 8% [7]. Although the majority of irAEs abate upon cessation of ICI therapy and corticosteroid administration, their influence on oncological outcomes remains a subject of ongoing debate [8]. For severe or corticoresistant irAEs, the introduction of immunomodulatory agents is recommended, adhering to established guidelines [9]. The term 'rechallenge' is frequently utilized to describe the resumption of an ICI following a hiatus required for the irAE resolution [10]. With ICIs being introduced earlier in the disease trajectory and concomitant with OS extension, patients frequently face the prospect of multiple exposures to ICIs during their lifetime. Therefore, understanding the safety of rechallenge is critical, in the context of limited alternative treatments. Our study is an expansive cohort of our initial recruitment [11] in which we documented a recurrence rate of 28.8% for the original irAE upon rechallenge, noting particularly high recurrence rates for irAEs such as colitis and pneumonitis. Herein, we extend our prior inquiry and provide an updated analysis on irAE recurrence post-rechallenge.

Materials and Methods

Data were sourced from VigiBase®, the World Health Organization (WHO) pharmacovigilance database managed by the Uppsala Monitoring Centre (Sweden).

Incident irAE cases related with at least one ICI administration were systematically collected, until March 1st, 2024. We identified irAEs using Preferred Terms from the Medical Dictionary for Regulatory Activities, version 26.1. ICI therapies included anti-PD-1 antibodies (cemiplimab, dostarlimab, nivolumab, pembrolizumab, retifanlimab), anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab), anti-CTLA-4 antibodies (ipilimumab, tremelimumab), and anti-LAG3 therapy (relatlimab). ICI regimen types were classified as anti-PD(L)-1 monotherapy, anti-CTLA-4 monotherapy, combined anti-PD(L)-1/anti-CTLA-4 therapy, and combined anti-PD(L)-1/anti-LAG3 therapy. For the initial irAE event, a comprehensive collection of administrative, demographic, drug- and irAE-specific data was pursued, encompassing parameters such as patient age, sex, drug indication, rechallenge, irAE type and severity, and irAE-associated mortality. Each irAE was designated as 'serious' or 'non-serious' in accordance with WHO criteria, and cases were discerned as either initial or updated with progressive follow-up details.

The primary outcome was the reported irAE recurrence rate post-rechallenge with the same ICI agent, ascertained among informative rechallenge cases. Exploratory secondary outcomes were factors presumptively associated with irAE recurrence post-rechallenge, which encompassed ICI regimens.

Statistical analyses were consistent with our princeps article [11]. Reported recurrence rates were denoted as percentages, dividing the number of irAE recurrence cases by the number of informative rechallenge cases. The 95% Confidence Intervals (CIs) for binomial proportions were estimated applying the Agresti-Coull approach. Qualitative variables were reported as frequencies and percentages, while quantitative variables were reported as medians with interquartile ranges (IQRs). Comparisons between rechallenge and non-rechallenge cohorts

were conducted using the χ^2 test or Fisher's exact test for qualitative data, alongside the unpaired Kruskal-Wallis test for quantitative data. Univariate logistic regression was employed to compute reporting odds ratios (reporting ORs) with 95% CIs. Statistical significance was ascertained through the Wald test, where a p-value less than 0.05 was deemed significant. Statistical computations were performed using the R software for Windows, version 4.3.2 (R Project for Statistical Computing).

The ethics committee at Caen University Hospital deemed formal review and consent procedures unnecessary due to the utilization of anonymized data within this study. The clinical trial registration number is NCT04696250.

Results

The study encompassed 48,380 cases of irAEs associated with ICI administrations, which approximates a twofold increase compared to our inaugural study. A subset of 18,753 cases underwent an ICI rechallenge post-irAE, and 1,016 cases had available data on irAE recurrence. Of these, 323 subjects were notified with a recurrence, equating to a 31.8% recurrence rate (95% CI 28.1-34.0). Within informative cases, 117 (36.0%) were female and the modal age group was 65-74 years (n=116, 44.1%). Factors associated with the recurrence of the initial irAE are detailed in Table S1.

IrAE recurrence was significantly associated with ICI regimens, with a reporting OR of 0.70 (95% CI, 0.50-0.98) for anti-PD(L)1 monotherapy, 0.88 (95%CI, 0.36-2.15) for anti-CTLA-4 monotherapy, and 1.52 (95%CI, 1.07-2.17) for combination therapy.

The three highest recurrence rates were found for nephritis (50%, 95%CI 25-75), skin irAEs (44%, 95%CI 31-58), and colitis (39%, 95%CI 33-44) as shown in Figure 1. Details are provided in Table S2.

Discussion

The safety profile of post-rechallenge ICIs remains a relatively terra incognita within the field. Our study, which includes a cohort of 18,753 rechallenge cases—with 1,016 yielding informative data—substantially enlarges upon the evidence base previously established[11]. We observed 31.8% recurrence of the same irAEs post-rechallenge, corroborating both current literature and our previous findings[11] .

Reflecting upon retrospective analyses, such as one involving 40 rechallenged patients where 17 (42.5%) experienced a recurrence of the same irAE and 5 (12.5%) manifested a novel irAE [12], our findings are aligned. Moreover, a meta-analysis surveying 789 cases documented incidences of all-grade and high-grade irAEs at 34.2% and 11.7%, respectively [13]. Gastrointestinal irAEs were associated with higher high-grade irAEs recurrence, while initial anti-PD(L)-1 correlated with lower recurrence. Despite an augmented incidence of all-grade irAEs post-rechallenge (OR, 3.81; 95% CI, 2.15-6.74; $p < 0.0001$), the incidence of high-grade irAEs was not significantly different ($p > 0.05$), hence the tolerance profile persists as acceptable.

The present inquiry has additionally surfaced novel insights pertaining to nephritis and myocarditis, which were absent from our preceding study[11]. The recurrence rate of nephritis was 50%, which overshadows prior estimates documented in the literature[14]. Our analysis, comprising 12 cases of rechallenged nephritis, may suffer from insufficient statistical power. Additionally, we were unable to assess the potential influence of the temporal interval between the initial irAE and subsequent rechallenge, a factor that could affect nephritis recurrence risk, thereby constraining our ability to derive conclusive insights on risk modulation of nephritis recurrence. Myocarditis, a relatively infrequent but severe irAE[15], portrayed a 33% recurrence rate post-rechallenge in our cohort, underscoring the necessity for careful consideration when contemplating ICI rechallenge in the context of myocarditis[15]. Around one-third of colitis cases exhibited recurrence, although with low mortality rates, potentially allowing for rechallenge when treatment alternatives are absent. Although innovative, our study has certain limitations due to information not available in Vigibase®, as data on

treatments received to manage these initial and recurrent irAE, with impossibility to determine whether there had been a therapeutic escalation from corticosteroids to immunosuppressive agents from the initial to the recurrent irAE. Similarly, clinical outcomes as OS and PFS are not available in this database, to assess whether certain irAE are of predictive interest.

Provision of rechallenge necessitates cautious appraisal of the risk-benefit ratio by the clinician, with potential establishment of augmented surveillance protocols. In the absence of predictive models to forecast patient-specific irAE occurrences and recurrences, retrospective investigations furnish essential guidance for tailoring treatment strategies to individual patient profiles and their unique irAE histories.

Conclusion

The updated dataset of our cohort delineates a global irAE recurrence rate of 31.8% post-ICI rechallenge. This underscores the feasibility of rechallenge in a select patient population, with the stipulation that individualized patient monitoring is imperative, given the observed variability in irAE recurrence and severity.

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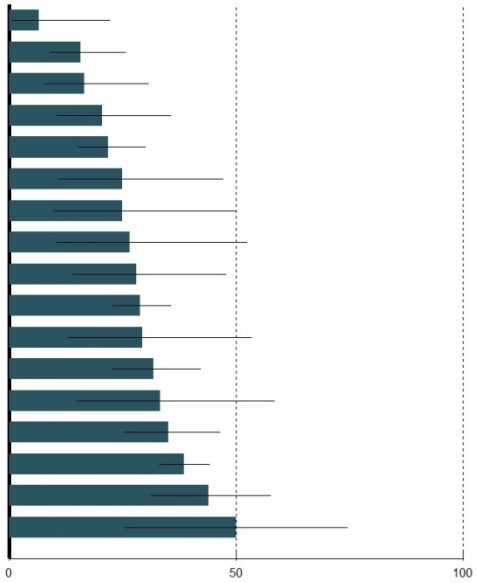
Figure 1: Recurrence rate of irAEs categorized by the initial affected site, updated in March 2024.

Adverse drug reaction	No. of cases	Recurrence rate (95%CI), %
Diabetes	30	7 (1-22)
Adrenal	76	16 (9-26)
Hypophysitis	42	17 (8-31)
Neurological	39	21 (11-36)
Thyroiditis	119	22 (15-30)
Mucositis	20	25 (11-47)
Uveitis	16	25 (10-50)
Hematological	15	27 (10-52)
Pancreatitis	25	28 (14-48)
Pneumonitis	187	29 (23-36)
Myositis	17	29 (13-53)
Hepatitis	85	32 (23-42)
Myocarditis	15	33 (15-58)
Arthritis	74	35 (25-47)
Colitis	288	39 (33-44)
Skin	50	44 (31-58)
Nephritis	12	50 (25-75)



Recurrence rate of irAEs categorized by the initial affected site, updated in March 2024.

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

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)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• Other genito-urinary	14 (5.1%)	274	53 (9.8%)	541	**0.50**	(0.27-0.91)
• 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)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• 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)
• 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)

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

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
• Vasculitis	42 (0.2%)	18753	102 (0.3%)	29627
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

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Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events : a retrospective study from VigiBase®– Update in 2024 looking for emergent safety signals

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Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events : a retrospective study from VigiBase®– Update in 2024 looking for emergent safety signals

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Contributorship statement
JMLO : Writing, data curation, Revision ; ADS : Writing, data curation ; JC : Writing ; JA : Writing, Design of the study ; CD : Guarantor, Statistics, Writing, Design of the study.

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Strengths and Limitations of this study

- Largest cohort of irAE
- International
- Emergent safety signals
- Restrospective
- No CTCAE grade differentiation

Patient and Public Involvement statement : Not applicable. Patients were not involved in the design, methodology or conduct of this study.

Key words: Rechallenge – Inhibitor of checkpoint – immune related adverse event

Abstract:

Objectives: Limited information is available on the safety of a rechallenge with an immune checkpoint inhibitor (ICI) after occurrence of an immune-related adverse event (irAE). We aim to identify potential emergent safety signals.

Design: This is an update of our observational pharmacovigilance cohort study.

Setting: We exanimated individual case safety reports from the World Health Organization database VigiBase.

Participants: We included all individual case safety reports with ICI and rechallenged ICI.

Interventions: We identified incident irAE cases using MEDRA terms v.26.1 related with at least one ICI administration were systematically collected, until March 1st, 2024.

Primary and secondary outcome measures: The primary outcome was the recurrence rate (expressed as a percentage with its 95% confidence interval [CI]) of the initial irAE post-rechallenge with the same ICI.

Results: We identified 1,016 irAEs cases from ICI rechallenges. Of these, 323 irAEs recurrences occurred (31.8%, 95%CI 28.1-34.0). The most common post-rechallenge irAEs were nephritis (recurrence rate: 50%, 95%CI 25-75), skin irAEs (44%, 95%CI 31-58), and colitis (39%, 95%CI 33-44).

Conclusions: In this updated, largest cohort study on rechallenge (NCT04696250), we observed a 31.8% recurrence rate of the same irAE post-rechallenge with the same ICI, building upon our previous findings.

Data availability statement

Data are available upon reasonable request. Additional data beyond what are provided in the supplement may be made available upon reasonable request to the authors.

Introduction

The advent of immune checkpoint inhibitors (ICIs) has profoundly transformed oncological therapeutics over recent years [1]. Sustained therapeutic responses have been documented, such as in metastatic melanoma, where overall survival (OS) at 6.5 years reaches 42% and 49% for nivolumab and the combination of nivolumab and ipilimumab, respectively [2]. These substantial clinical benefits at the metastatic stage have led to the broadening implementation of ICIs across the therapeutic spectrum, including in the adjuvant [3] and neoadjuvant settings [4]. Now endorsed for the management of all solid cancers, ICIs have indeed been conceded as the contemporary standard of care. This efficacy is paradoxically mediated by the same mechanism that prompts immune-related adverse events (irAEs), stemming from systemic immune activation [5,6] . Up to 80% of patients may encounter any-grade irAEs, with Common Terminology Criteria for Adverse Events (CTCAE) grade 3-5 irAEs affecting 8% [7]. Although the majority of irAEs abate upon cessation of ICI therapy and corticosteroid administration, their influence on oncological outcomes remains a subject of ongoing debate [8]. For severe or corticoresistant irAEs, the introduction of immunomodulatory agents is recommended, adhering to established guidelines [9]. The term 'rechallenge' is frequently utilized to describe the resumption of an ICI following a hiatus required for the irAE resolution [10]. With ICIs being introduced earlier in the disease trajectory and concomitant with OS extension, patients frequently face the prospect of multiple exposures to ICIs during their lifetime. Therefore, understanding the safety of rechallenge is critical, in the context of limited alternative treatments. Our study is an expansive cohort of our initial recruitment [11] in which we documented a recurrence rate of 28.8% for the original irAE upon rechallenge, noting particularly high recurrence rates for irAEs such as colitis and pneumonitis. Herein, we extend our prior inquiry and provide an updated analysis on irAE recurrence post-rechallenge.

Materials and Methods

Data were sourced from VigiBase®, the World Health Organization (WHO) pharmacovigilance database managed by the Uppsala Monitoring Centre (Sweden).

Incident irAE cases related with at least one ICI administration were systematically collected, until March 1st, 2024. We identified irAEs using Preferred Terms from the Medical Dictionary for Regulatory Activities, version 26.1. ICI therapies included anti-PD-1 antibodies (cemiplimab, dostarlimab, nivolumab, pembrolizumab, retifanlimab), anti-PD-L1 antibodies (atezolizumab, avelumab, durvalumab), anti-CTLA-4 antibodies (ipilimumab, tremelimumab), and anti-LAG3 therapy (relatlimab). ICI regimen types were classified as anti-PD(L)-1 monotherapy, anti-CTLA-4 monotherapy, combined anti-PD(L)-1/anti-CTLA-4 therapy, and combined anti-PD(L)-1/anti-LAG3 therapy. For the initial irAE event, a comprehensive collection of administrative, demographic, drug- and irAE-specific data was pursued, encompassing parameters such as patient age, sex, drug indication, rechallenge, irAE type and severity, and irAE-associated mortality. Each irAE was designated as 'serious' or 'non-serious' in accordance with WHO criteria, and cases were discerned as either initial or updated with progressive follow-up details.

The primary outcome was the reported irAE recurrence rate post-rechallenge with the same ICI agent, ascertained among informative rechallenge cases. Exploratory secondary outcomes were factors presumptively associated with irAE recurrence post-rechallenge, which encompassed ICI regimens.

Statistical analyses were consistent with our princeps article [11]. Reported recurrence rates were denoted as percentages, dividing the number of irAE recurrence cases by the number of informative rechallenge cases. The 95% Confidence Intervals (CIs) for binomial proportions were estimated applying the Agresti-Coull approach. Qualitative variables were reported as frequencies and percentages, while quantitative variables were reported as medians with interquartile ranges (IQRs). Comparisons between rechallenge and non-rechallenge cohorts

were conducted using the χ^2 test or Fisher's exact test for qualitative data, alongside the unpaired Kruskal-Wallis test for quantitative data. Univariate logistic regression was employed to compute reporting odds ratios (reporting ORs) with 95% CIs. Statistical significance was ascertained through the Wald test, where a p-value less than 0.05 was deemed significant. Statistical computations were performed using the R software for Windows, version 4.3.2 (R Project for Statistical Computing).

The ethics committee at Caen University Hospital deemed formal review and consent procedures unnecessary due to the utilization of anonymized data within this study. The clinical trial registration number is NCT04696250.

Results

The study encompassed 48,380 cases of irAEs associated with ICI administrations, which approximates a twofold increase compared to our inaugural study. A subset of 18,753 cases underwent an ICI rechallenge post-irAE, and 1,016 cases had available data on irAE recurrence. Of these, 323 subjects were notified with a recurrence, equating to a 31.8% recurrence rate (95% CI 28.1-34.0). Within informative cases, 117 (36.0%) were female and the modal age group was 65-74 years (n=116, 44.1%). Factors associated with the recurrence of the initial irAE are detailed in supplementary material.

IrAE recurrence was significantly associated with ICI regimens, with a reporting OR of 0.70 (95% CI, 0.50-0.98) for anti-PD(L)1 monotherapy, 0.88 (95%CI, 0.36-2.15) for anti-CTLA-4 monotherapy, and 1.52 (95%CI, 1.07-2.17) for combination therapy.

The three highest recurrence rates were found for nephritis (50%, 95%CI 25-75), skin irAEs (44%, 95%CI 31-58), and colitis (39%, 95%CI 33-44) as shown in Figure 1. Details are provided in supplementary material.

Discussion

The safety profile of post-rechallenge ICIs remains a relatively terra incognita within the field. Our study, which includes a cohort of 18,753 rechallenge cases—with 1,016 yielding informative data—substantially enlarges upon the evidence base previously established[11]. We observed 31.8% recurrence of the same irAEs post-rechallenge, corroborating both current literature and our previous findings[11] .

Reflecting upon retrospective analyses, such as one involving 40 rechallenged patients where 17 (42.5%) experienced a recurrence of the same irAE and 5 (12.5%) manifested a novel irAE [12], our findings are aligned. Moreover, a meta-analysis surveying 789 cases documented incidences of all-grade and high-grade irAEs at 34.2% and 11.7%, respectively [13]. Gastrointestinal irAEs were associated with higher high-grade irAEs recurrence, while initial anti-PD(L)-1 correlated with lower recurrence. Despite an augmented incidence of all-grade irAEs post-rechallenge (OR, 3.81; 95% CI, 2.15-6.74; $p < 0.0001$), the incidence of high-grade irAEs was not significantly different ($p > 0.05$), hence the tolerance profile persists as acceptable.

The present inquiry has additionally surfaced novel insights pertaining to nephritis and myocarditis, which were absent from our preceding study[11]. The recurrence rate of nephritis was 50%, which overshadows prior estimates documented in the literature[14]. Our analysis, comprising 12 cases of rechallenged nephritis, may suffer from insufficient statistical power. Additionally, we were unable to assess the potential influence of the temporal interval between the initial irAE and subsequent rechallenge, a factor that could affect nephritis recurrence risk, thereby constraining our ability to derive conclusive insights on risk modulation of nephritis recurrence. Myocarditis, a relatively infrequent but severe irAE[15], portrayed a 33% recurrence rate post-rechallenge in our cohort, underscoring the necessity for careful consideration when contemplating ICI rechallenge in the context of myocarditis[15]. Around one-third of colitis cases exhibited recurrence, although with low mortality rates, potentially allowing for rechallenge when treatment alternatives are absent. Although innovative, our study has certain limitations due to information not available in Vigibase®, as data on

treatments received to manage these initial and recurrent irAE, with impossibility to determine whether there had been a therapeutic escalation from corticosteroids to immunosuppressive agents from the initial to the recurrent irAE. Similarly, clinical outcomes as OS and PFS are not available in this database, to assess whether certain irAE are of predictive interest.

Provision of rechallenge necessitates cautious appraisal of the risk-benefit ratio by the clinician, with potential establishment of augmented surveillance protocols. In the absence of predictive models to forecast patient-specific irAE occurrences and recurrences, retrospective investigations furnish essential guidance for tailoring treatment strategies to individual patient profiles and their unique irAE histories.

Conclusion

The updated dataset of our cohort delineates a global irAE recurrence rate of 31.8% post-ICI rechallenge. This underscores the feasibility of rechallenge in a select patient population, with the stipulation that individualized patient monitoring is imperative, given the observed variability in irAE recurrence and severity.

Figure legend

Fig 1. Recurrence rate of irAEs categorized by the initial affected site, updated in March 2024

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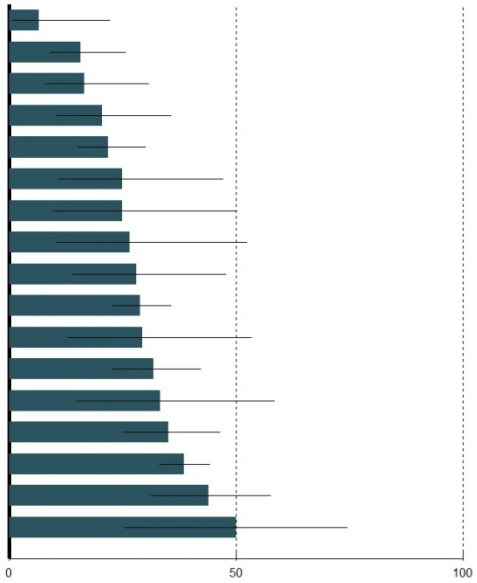
Adverse drug reaction	No. of cases	Recurrence rate (95%CI), %
Diabetes	30	7 (1-22)
Adrenal	76	16 (9-26)
Hypophysitis	42	17 (8-31)
Neurological	39	21 (11-36)
Thyroiditis	119	22 (15-30)
Mucositis	20	25 (11-47)
Uveitis	16	25 (10-50)
Hematological	15	27 (10-52)
Pancreatitis	25	28 (14-48)
Pneumonitis	187	29 (23-36)
Myositis	17	29 (13-53)
Hepatitis	85	32 (23-42)
Myocarditis	15	33 (15-58)
Arthritis	74	35 (25-47)
Colitis	288	39 (33-44)
Skin	50	44 (31-58)
Nephritis	12	50 (25-75)



Recurrence rate of irAEs categorized by the initial affected site, updated in March 2024.

177x127mm (192 x 192 DPI)

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

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)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• Other genito-urinary	14 (5.1%)	274	53 (9.8%)	541	**0.50**	(0.27-0.91)
• 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)

Initial irAE	Recurrence	N avail.	No recurrence	N avail.	Reporting Odds-Ratio	95% Confidence Interval
• 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)
• 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)

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

Initial irAE	Rechallenge after irAE	N avail.	No rechallenge after irAE	N avail.
• Vasculitis	42 (0.2%)	18753	102 (0.3%)	29627
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