JAMA Oncology | Original Investigation

Immune Checkpoint Inhibitor Rechallenge After Immune-Related Adverse Events in Patients With Cancer

Charles Dolladille, MD, MSc; Stéphane Ederhy, MD; Marion Sassier, PharmD, MSc; Jennifer Cautela, MD; Franck Thuny, MD, PhD; Ariel A. Cohen, MD, PhD; Sophie Fedrizzi, PharmD, MSc; Basile Chrétien, PharmD, MSc; Angélique Da-Silva, MD; Anne-Flore Plane, MD, MSc; Damien Legallois, MD, MSc; Paul U. Milliez, MD, PhD; Véronique Lelong-Boulouard, PharmD, PhD; Joachim Alexandre, MD, PhD

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

OBJECTIVE To identify the recurrence rate of the same irAE that prompted discontinuation of ICI therapy after an ICI rechallenge in patients with cancer and to identify the clinical features associated with such recurrences.

DESIGN, SETTING, AND PARTICIPANTS This observational, cross-sectional, pharmacovigilance cohort study examined individual case safety reports from the World Health Organization database VigiBase, which contains case reports from more than 130 countries. Case reports were extracted from database inception (1967) to September 1, 2019. All consecutive ICI cases with at least 1 associated irAE were included.

MAIN OUTCOMES AND MEASURES The primary outcome was the rate of recurrence of the initial irAE after an ICI rechallenge. Secondary outcomes included the factors associated with the recurrence after a rechallenge among informative rechallenges, the recurrence rate according to the ICI regimen (anti–programmed cell death 1 or anti–programmed cell death ligand 1 monotherapy, anti–cytotoxic T-lymphocyte antigen-4 monotherapy, or combination therapy), and the rate of occurrence of a different irAE after a rechallenge.

RESULTS A total of 24 079 irAE cases associated with at least 1 ICI were identified. Among the irAEs, 452 of 6123 irAEs associated with ICI rechallenges (7.4%) were informative rechallenges. One hundred thirty recurrences (28.8%; 95% CI, 24.8-33.1) of the initial irAE were observed. In a rechallenge, colitis (reporting odds ratio [OR], 1.77; 95% CI, 1.14-2.75; $P = .01$), hepatitis (reporting OR, 3.38; 95% CI, 1.31-8.74; $P = .01$), and pneumonitis (reporting OR, 2.26; 95% CI, 1.18-4.32; $P = .01$) were associated with a higher recurrence rate, whereas adrenal events were associated with a lower recurrence rate (reporting OR, 0.33; 95% CI, 0.13-0.86; $P = .03$) compared with other irAEs.

CONCLUSIONS AND RELEVANCE This cohort study found a 28.8% recurrence rate of the same irAE associated with the discontinuation of ICI therapy after a rechallenge with the same ICI. Resuming ICI therapy could be considered for select patients, with appropriate monitoring and use of standard treatment algorithms to identify and treat toxic effects.

Author Audio Interview

Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Charles Dolladille, MD, MSc, Normandie University, UNICAEN, CHU de Caen Normandie, PICARO Cardio-oncology Program, Department of Pharmacology, Avenue de la Côte de Nacre, F-14000 Caen, France (Dolladille-c@chu-caen.fr).

JAMA Oncol. doi:10.1001/jamaoncol.2020.0726
Published online April 16, 2020.

Immune checkpoint inhibitors (ICIs) have substantially improved clinical outcomes in many types of cancer and are increasingly being used in early disease settings.[1] Responses to treatment occur in a substantial fraction of patients and are frequently durable and even curative. The number of patients exposed to ICIs has increased in recent years and will continue to grow because indications for this therapy have been extended.[2-4]

Use of ICIs has been associated with immune-related adverse events (irAEs) that are potentially severe or even fatal.[5,6] Immune-related adverse events occur mostly in the colon, liver, lungs, pituitary gland, thyroid, and skin, although uncommon adverse events have involved the heart, nervous system, and other organs.[5]

Most irAEs resolve after discontinuation of the ICI and treatment with steroids. Current oncological guidelines[7-9] recommend permanent discontinuation of ICIs for only the most severe irAEs (Common Terminology Criteria for Adverse Events grade 4). Thus, an ICI rechallenge after temporary discontinuation appears conceivable in many cases, but only limited data are available on the safety of a rechallenge after an irAE. Recent studies of an ICI rechallenge in small cohorts have reported a recurrence rate of an identical irAE ranging from 18% to 42%.[10-14] These results, although precursory, mainly focused on anti-programmed cell death 1 (PD-1) and/or anti-programmed cell death 1 ligand 1 (PD-L1) ICIs or on a specific irAE, such as colitis. Larger cohorts of patients receiving any ICI regimen are mandatory for evaluating the safety of a rechallenge.

In this study, we aimed to identify the recurrence rate of the same irAE that prompted therapy ICI discontinuation after an ICI rechallenge and to further characterize the safety of a rechallenge after a first irAE in patients with cancer. We used VigiBase, the World Health Organization pharmacovigilance database managed by the Uppsala Monitoring Centre in Sweden.

Key Points

Question What is the recurrence rate of an immune-related adverse event after the resumption of immune checkpoint inhibitors (ICIs) in patients with cancer?

Findings In this cohort study of 24 079 immune-related adverse events associated with at least 1 ICI, the recurrence rate of the same immune-related adverse event that prompted discontinuation of ICI therapy was 28.8% after patients received a rechallenge with the same ICI. In a rechallenge, colitis, hepatitis, and pneumonitis had higher recurrence rates compared with other immune-related adverse events.

Meaning Findings of this study suggest that resumption of ICI therapy could be considered for select patients, with appropriate monitoring and use of standard treatment algorithms to identify and treat toxic effects.

Methods

Study Design and Data Sources

This retrospective, cross-sectional, pharmacovigilance cohort study[15] used data from VigiBase, a database that contains more than 20 million individual case safety reports (referred to as *cases* according to the case or noncase methods in pharmacovigilance databases) received from at least 130 member countries of the World Health Organization Programme for International Drug Monitoring. The cases originate from different sources, including health care professionals, patients, and pharmaceutical companies, and the sources are generally notified after ICI marketing. We extracted irAE cases from database inception (1967) to September 1, 2019. The Local Ethics Committee of Caen University Hospital (Comité Local d'Ethique de la Recherche en Santé) determined that this study was exempt from formal institutional review board review and informed consent because it used anonymous data.

Procedures and Description of the Pharmacovigilance Cohort

We included all consecutive irAE cases associated with ICI therapy. The irAEs were identified using the preferred terms of the *Medical Dictionary for Regulatory Activities*, version 21.1 (eAppendix 1 in the Supplement). The ICI drugs were anti–PD-1 antibodies (nivolumab, pembrolizumab, and cemiplimab), anti–PD-L1 antibodies (atezolizumab, avelumab, and durvalumab), and anti–cytotoxic T-lymphocyte antigen-4 (CTLA-4) antibodies (ipilimumab, tremelimumab). We classified ICI regimens as anti–PD-1 or anti–PD-L1 monotherapy, anti–CTLA-4 monotherapy, and the combination of anti–PD-1 or anti–PD-L1 and anti–CTLA-4 therapies.

Regarding the initial irAE, we collected administrative information (country, type of report, and type of reporter), demographic data (age, sex), and drug and irAE data (drug indication, time to irAE onset and rechallenge data, nature and seriousness of the irAE, and mortality associated with the irAE). Each adverse drug reaction was characterized as serious or nonserious according to the World Health Organization definition. A serious reaction was defined as an adverse drug reaction associated with death, life-threatening situation, hospitalization or prolongation of hospitalization, persistent incapacity or disability, and situations judged clinically serious by the physician reporting the case. The Extract Case Level structure of the VigiBase allows the retrieval of rechallenge information, when documented, in cases (eAppendix 2 in the Supplement). Therefore, we identified, among irAEs, the rechallenges (those mentioned in cases) and the informative rechallenges (those with available recurrence status, such as recurrence of the same reaction or no recurrence). The occurrence of a different irAE after an ICI rechallenge was also collected when available; this analysis was only exploratory because the occurrence of a different irAE was not systematically reported in VigiBase. Pharmacovigilance centers can update the cases by adding details on adverse drug reactions. Thus, we classified irAE cases as initial or updated.

Outcomes

The primary outcome was the rate of recurrence of the same irAE after an ICI rechallenge among informative rechal-

lenges. Secondary outcomes included rechallenge and nonrechallenge cases, the factors associated with the recurrence after a rechallenge among informative rechallenges, the ICI regimen (anti–PD-1 or anti–PD-L1 monotherapy, anti–CTLA-4 monotherapy, or combination therapy), and the rate of occurrence of a different irAE after an ICI rechallenge (among informative rechallenges).

Statistical Analysis

The recurrence rate was obtained by dividing the number of cases with an irAE recurrence by the number of informative rechallenges and was expressed as a percentage. The recurrence rate differed from an incidence rate; the recurrence rate calculation did not use the total number of patients treated with a drug. The 95% CI for binomial proportion was estimated with the Agresti-Coull method. Qualitative variables were reported as frequency (percentage), and quantitative variables were reported as a median with interquartile range (IQR). The rechallenge and nonrechallenge cases were compared using the χ^2 test or Fisher exact test for qualitative variables and the unpaired Kruskal-Wallis test for quantitative variables. A disproportionality analysis was performed to identify the factors associated with the recurrence among informative rechallenges. Disproportionality was not used to identify the associations between the ICI and irAEs (eAppendix 3 in the Supplement).

Univariate and multivariate reporting odds ratios (reporting ORs) with 95% CIs were computed using a logistic regression model. *P* values were computed using an unpaired, 2-tailed Wald test. The threshold for statistical significance was set at a 2-sided $P < .05$. Independent variables were selected with a stepwise procedure in the multivariate model. Statistical analyses and data management were performed from November 21, 2019, to December 10, 2019, using R for Windows, version 3.5.3 (R Project for Statistical Computing).

Results

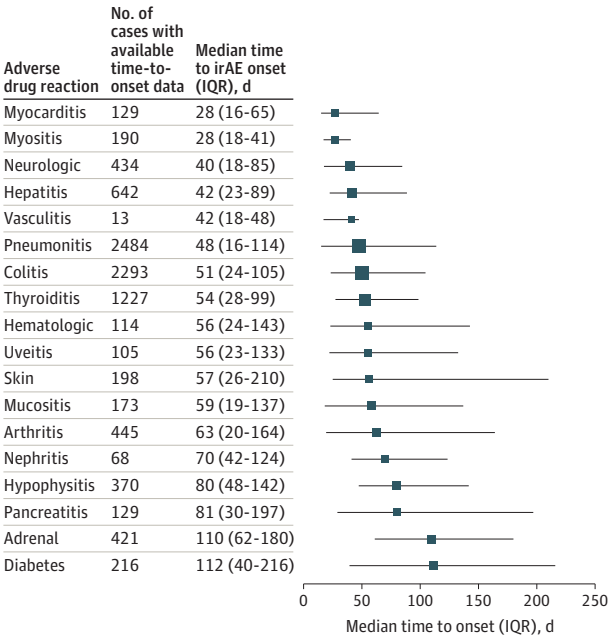
Immune-Related Adverse Events

Of the 20 471 248 total cases identified in VigiBase, 24 079 (0.1%) were irAEs associated with at least 1 ICI (eFigure 1 in the Supplement). The first irAE case associated with ICI therapy was registered in VigiBase in 2006 (irAE cases are described in eTable 1 in the Supplement). Median (IQR) time to onset of initial irAE ranged from 28 (16-65) days for myocarditis to 112 (40-216) days for diabetes (**Figure 1**). Most irAEs were deemed serious (n = 20 190 [85.6%] of 23 578 with available data), and 2680 (11.4% of 23 580 with available data) were fatal.

ICI Rechallenges

Among the 24 079 irAEs, 6123 (25.4%) were associated with an ICI rechallenge (**Table 1**); eTable 2 in the Supplement shows the clinical characteristics of the initial irAEs associated with at least 1 ICI in the rechallenge and the nonrechallenge cases. For patients initially treated with combination therapy (n = 972 [15.9%]), a rechallenge was administered with either anti–PD-1 or anti–PD-L1 monotherapy (n = 504 [51.9%]), anti–CTLA-4 monotherapy (n = 52 [5.3%]), or combination therapy (n = 416 [42.8%]).

Figure 1. Time to Onset of Initial Immune-Related Adverse Events



Squares represent the median and whiskers represent the interquartile range (IQR) of time to immune-related adverse event (irAE) onset. Square size is log-proportional to the number of cases.

Rechallenge was more frequently administered in patients with head and neck (rechallenge cases: n = 132 [2.4%] vs nonrechallenge cases: n = 284 [1.9%]), kidney (538 [10.0%] vs 849 [5.6%]), and urinary tract (208 [3.9%] vs 334 [2.2%]) cancers and less frequently in those with gynecological (47 [0.9%] vs 245 [1.6%]), lung (2099 [38.9%] vs 6356 [41.9%]), and prostate (8 [0.1%] vs 93 [0.6%]) cancers. In addition, rechallenge more frequently occurred after endocrine irAEs (adrenal rechallenge cases: n = 374 [6.1%] vs nonrechallenge cases: n = 815 [4.5%], diabetes: 245 [4.0%] vs 511 [2.8%], thyroiditis: 779 [12.7%] vs 1977 [11.0%], and uveitis: 97 [1.6%] vs 172 [1.0%]) and was less commonly reported after pneumonitis (1288 [21.0%] vs 4001 [22.3%]). The irAEs associated with high mortality rates in the literature[6] (ie, myocarditis and neurological irAEs) were equally represented in the rechallenge (myocarditis: 102 [1.7%]; neurological: 424 [6.9%]) and nonrechallenge (myocarditis: 345 [1.9%]; neurological: 1243 [6.9%]) cases in this study. Median (IQR) time to onset for each type of initial irAE was similar among the rechallenge and nonrechallenge cases (eTable 3 in the Supplement).

Rechallenge with anti–PD-1 or anti–PD-L1 monotherapy (rechallenge cases: n = 4360 [71.2%] vs nonrechallenge cases: n = 12 303 [68.5%]) and combination therapy (972 [15.9%] vs 2345 [13.1%]) was administered more frequently than rechallenge with anti–CTLA-4 monotherapy alone (791 [12.9%] vs 3290 [18.3%]) (Table 1). Details about the 24 079 irAE cases stratified by the ICI regimen are provided in eTables 4 to 6 in the Supplement. Rechallenge cases compared with nonrechallenge cases involved more serious irAEs (5344 [87.3%] vs 14 846

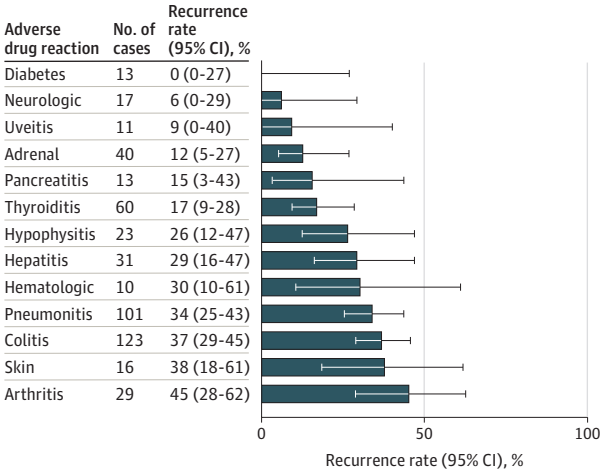
Table 1. Comparison Between Rechallenge and Nonrechallenge Cases After an Immune-Related Adverse Event With at Least 1 Immune Checkpoint Inhibitor (n = 24 079)

Initial irAE	No. (%)	
	Rechallenge after irAE (n = 6123)	No rechallenge after irAE (n = 17 956)
ICI		
Anti-PD-1 or anti-PD-L1 alone	4360 (71.2)	12 321 (68.6)
Anti-CTLA-4 alone	791 (12.9)	3290 (18.3)
Combination therapy	972 (15.9)	2345 (13.1)
Type of initial irAE[a]		
Adrenal	374 (6.1)	815 (4.5)
Arthritis	491 (8.0)	1372 (7.6)
Colitis	1745 (28.5)	5353 (29.8)
Diabetes	245 (4.0)	511 (2.8)
Hematological	92 (1.5)	268 (1.5)
Hepatitis	473 (7.7)	1444 (8.0)
Hypophysitis	353 (5.8)	1136 (6.3)
Mucositis	135 (2.2)	374 (2.1)
Myocarditis	102 (1.7)	345 (1.9)
Myositis	152 (2.5)	455 (2.5)
Nephritis	78 (1.3)	198 (1.1)
Neurological	424 (6.9)	1243 (6.9)
Pancreatitis	119 (1.9)	332 (1.8)
Pneumonitis	1288 (21.0)	4001 (22.3)
Skin	155 (2.5)	478 (2.7)
Thyroiditis	779 (12.7)	1977 (11.0)
Uveitis	97 (1.6)	172 (1.0)
Vasculitis	16 (0.3)	48 (0.3)
Initial irAE		
Serious	5344 (87.3)	14 846 (85.1)
Fatal	643 (10.5)	2037 (11.7)

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

[a] A case can have multiple initial irAEs; counts of initial irAEs exceeded the number of cases.

Figure 2. Rate of Recurrence According to the Initial Immune-Related Adverse Event



[85.1%]) according to the pharmacological definition and fewer deaths (643 [10.5%] vs 2037 [11.7%]). The proportion of updated cases was higher in the rechallenge compared with nonrechallenge cases.

Rate of irAE Recurrence After ICI Rechallenge

Among the 6123 irAEs associated with ICI rechallenges, 452 (7.4%) were informative rechallenges (eTable 7 in the Supplement compares the characteristics of informative and noninformative rechallenges). Among the informative rechallenges, 130 (28.8%; 95% CI, 24.8-33.1) were a recurrence of the initial irAE. The rates of recurrence stratified by the organs involved in the initial irAE are shown in **Figure 2**. Myocarditis recurred in 0 of 3 patients, and neurological irAEs recurred in 3 of 19 patients. The 1 case with vasculitis (0.8%) as the initial irAE had a recurrence of vasculitis after a rechallenge (**Table 2**). The recurrence rate was 28.6% (n = 105; 95% CI, 24.0%-33.2%) after anti-PD-1 or anti-PD-L1 monotherapy resumption, 47.4% (n = 7; 95% CI, 24.8%-69.9%) after anti-CTLA-4 monotherapy resumption, and 43.5% (n = 18; 95% CI, 29.1%57.8%) after combination therapy resumption.

Among informative rechallenges, the occurrence of a different irAE after a rechallenge was reported in 20 cases (4.4%). Colitis was the most frequent irAE reported in 10 cases (50.0%) (eTable 8 in the Supplement).

Factors Associated With Recurrence Among Informative Rechallenges

Table 2 shows the factors associated with recurrence after informative rechallenges. In the univariate analysis, age, sex, and ICI regimen were not associated with recurrence. In the rechallenge, colitis was associated with a higher recurrence rate (reporting OR, 1.77; 95% CI, 1.14-2.75; $P = .01$), whereas adrenal irAEs were associated with a lower recurrence rate (reporting OR, 0.33; 95% CI, 0.13-0.86; $P = .03$) compared with other irAEs. In the multivariate analysis, after adjusting for age, sex, ICI regimen, follow-up status, and irAE types, the following variables were associated with a higher irAE recurrence rate: anti–CTLA-4 regimen (reporting OR, 3.5; 95% CI, 1.05-11.64; $P = .04$), age, colitis (reporting OR, 2.99; 95% CI, 1.6-5.59; $P < .001$), hepatitis (reporting OR, 3.38; 95% CI, 1.31-8.74; $P = .01$), and pneumonitis (reporting OR, 2.26; 95% CI, 1.18-4.32; $P = .01$).

Median (IQR) times to initial irAE onset were comparable between recurring and nonrecurring irAEs except for initial pneumonitis, which appeared to occur later in recurring vs nonrecurring irAEs (88 [58-178] days vs 44 [20-90] days) (eTable 9 in the Supplement). In a subgroup analysis stratified by ICI regimen (eFigure 2 and eTables 10 to 12 in the Supplement), we extracted 60 informative rechallenges after combination therapy. Among these cases, 29 (48.3%) were rechallenges with an anti–PD-1 or anti–PD-L1 monotherapy, 7 (11.7%) with an anti–CTLA-4 monotherapy, and 24 (40.0%) with the same combination therapy. Pneumonitis recurred after combination therapy in 85.7% of cases (4 out of 4 patients after combination therapy rechallenge, and 2 out of 3 patients after anti–PD-1

Table 2. Factors Associated With the Recurrence of the Same Immune-Related Adverse Event

Initial irAE	No. (%)		Reporting OR (95% CI)	
	Recurrence after ICI rechallenge (n = 130)	No recurrence after ICI rechallenge (n = 322)	Univariate analysis	Multivariate analysis
ICI				
Anti–PD-1 or anti–PD-L1 alone	105 (80.8)	265 (82.3)	0.9 (0.54-1.52)	NA
Anti–CTLA-4 alone	7 (5.4)	15 (4.7)	1.16 (0.46-2.93)	3.5 (1.05-11.64)
Combination therapy	18 (13.8)	42 (13.0)	1.07 (0.59-1.94)	NA
Type of initial irAE[a]				
Adrenal	5 (3.8)	35 (10.9)	0.33 (0.13-0.86)	NA
Arthritis	13 (10.0)	16 (5.0)	2.12 (0.99-4.55)	NA
Colitis	47 (36.2)	78 (24.2)	1.77 (1.14-2.75)	2.99 (1.60-5.59)
Diabetes	0	13 (4.0)	NA	NA
Hematological	3 (2.3)	7 (2.2)	1.06 (0.27-4.18)	NA
Hepatitis	11 (8.5)	22 (6.8)	1.26 (0.59-2.68)	3.38 (1.31-8.74)
Hypophysitis	6 (4.6)	17 (5.3)	0.87 (0.33-2.25)	NA
Mucositis	2 (1.5)	3 (0.9)	1.66 (0.27-10.06)	NA
Myocarditis	0	3 (0.9)	NA	
Myositis	2 (1.5)	7 (2.2)	0.7 (0.14-3.43)	NA
Nephritis	4 (3.1)	4 (1.2)	2.52 (0.62-10.25)	4.92 (0.94-25.64)
Neurological	3 (2.3)	16 (5.0)	0.45 (0.13-1.58)	NA
Pancreatitis	3 (2.3)	11 (3.4)	0.67 (0.18-2.43)	NA
Pneumonitis	36 (27.7)	67 (20.8)	1.46 (0.91-2.33)	2.26 (1.18-4.32)
Skin	6 (4.6)	10 (3.1)	1.51 (0.54-4.24)	3.21 (0.81-12.75)
Thyroiditis	11 (8.5)	50 (15.5)	0.5 (0.25-1.00)	0.37 (0.12-1.16)
Uveitis	1 (0.8)	10 (3.1)	0.24 (0.03-1.91)	NA
Vasculitis	1 (0.8)	0	NA	NA
Initial irAE				
Serious	118 (90.8)	297 (92.2)	0.83 (0.40-1.70)	NA
Fatal	8 (6.2)	13 (4.0)	1.56 (0.63-3.85)	NA

Abbreviations: CTLA-4, cytotoxic T-lymphocyte antigen-4; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; NA, not applicable; OR, odds ratio; PD-1, programmed cell death 1; PD-L1, programmed cell death 1 ligand 1.

[a] A case can have multiple initial irAEs; counts of initial irAEs exceeded the number of cases. Adjustment variables were age, sex, ICI regimen, type of initial irAE, case seriousness, and follow-up status.

or anti–PD-L1 monotherapy rechallenge) (eTable 13 in the Supplement).

Discussion

To our knowledge, this study reports on the most extensive characterization of a rechallenge with the same ICI therapy after a first irAE using cases from VigiBase. Despite the retrospective design and the absence of Common Terminology Criteria for Adverse Events grading data, the study has a number of strengths, such as the inclusion of a broad spectrum of all ICI regimens labeled to date (anti–PD-1 or anti–PD-L1 monotherapy, anti–CTLA-4 monotherapy, or combination therapy), whereas previous studies focused on anti–PD-1 or anti–PD-L1 alone[14]; all types of cancer; or all irAEs, including those associated with high mortality rates (ie, myocarditis and neurological irAEs). This study also identified 452 informative ICI rechallenges, which, to our knowledge, represent the largest collection to date.

Overall, we found that about one-quarter to one-third of patients who discontinued ICI therapy after a first irAE had a recurrence of the same irAE after rechallenge with the same ICI; a different irAE occurred in 4.4% of patients. These recurrence rates were similar to those found in case series,[10-14] although several factors played a role in our estimations. First, pharmacovigilance notifications are usually performed shortly after the adverse event, so irAEs with a delayed recurrence may be missed. Second, VigiBase can retrieve rechallenge information only for the same adverse event associated with the same drug, and the occurrence of other adverse events (different from the initial event) after drug rechallenge is not systematically reported.

In the present study, the total rate of irAE occurrence after an ICI rechallenge was approximately one-third of cases. Pollack et al[12] retrospectively examined 80 patients who had a rechallenge with an anti–PD-1 alone after several initial irAEs. Over a median follow-up period of 14.3 months, the same irAE occurred in 18%, and any type of irAE occurred in 39% of the patients after the ICI rechallenge. Santini et al[13] retrospectively identified 68 patients with advanced non-small cell lung cancer who were treated with anti–PD-1 or anti–PD-L1 either as monotherapy or in combination with anti–CTLA-4. Of these patients, 38 (55.9%) received a rechallenge with an anti–PD-1 or anti–PD-L1 therapy alone. Over a median follow-up of 14.3 months, the same irAE occurred in 26% of the patients, and any type of irAE occurred in 52% of the patients after the ICI rechallenge. Abu-Sbeih et al[11] also retrospectively analyzed 167

patients who resumed an ICI regimen (19.2% anti–CTLA-4 alone and 80.8% anti–PD-1 or anti–PD-L1 alone) after improvement of colitis and diarrhea irAEs. Colitis and diarrhea recurred in 57 patients (34%). In the retrospective cohort study by Simonaggio et al,[14] of the 93 patients who experienced an initial irAE with an anti–PD-1 or anti–PD-L1 drug, 40 (43%) received a rechallenge with the same drug. Over a median follow-up of 14 months, the same irAE occurred in 42% of the patients, and any irAE type occurred in 55% of the cohort.

We described additional characteristics of recurrence in this study, which complement the traits published in previous case series.[11-14] The recurrence rates for colitis, hepatitis, and pneumonitis were higher after rechallenge compared with other irAEs, whereas the recurrence rate for adrenal irAEs was lower than that for other irAEs. A possible explanation for this latter finding is that the administration of a steroid replacement therapy precludes the relapse of the disease. Another explanation is the absence of reversibility of adrenal irAEs. In the subgroup analysis, the irAE recurrence rate differed according to the irAE type and the ICI regimen. After combination therapy, recurrence occurred most frequently after pneumonitis (85.7% of the cases, or in 4 of 4 patients after combination therapy rechallenge and 2 of 3 patients after anti–PD-1 or anti–PD-L1 monotherapy rechallenge). These findings are consistent with those in previous reports,[12,16] which highlighted that ICIs did not exhibit similar toxic effect profiles and risk of recurrence. In this study, initial irAEs that are considered to be the most life-threatening,[6] including myocarditis and neurological irAEs, did not appear to be associated with higher recurrence rates compared with other initial irAEs; myocarditis recurred in 0 of 3 patients and neurological irAEs recurred in 3 of 19 patients.

With regard to the safety of resuming combination therapy after a first irAE, available information is scarce. Pollack et al[12] demonstrated that a rechallenge with anti-PD-1 therapy after an irAE during a combination treatment with anti–CTLA-4 and anti–PD-1 drugs for metastatic melanoma was associated with recurrence of the same irAE in 18% of patients and with the occurrence of a different irAE in 21% of patients. In the present study, 60 informative rechallenges after combination therapy were extracted. Among the 24 patients who received the rechallenge with the same combination therapy, 4 of 4 cases of pneumonitis recurred, suggesting that clinicians must be cautious in such cases (eTable 13 in the Supplement).

The question of whether to administer ICI rechallenge is crucial. Practical guidelines for irAE management are based on clinical observations and expert consensus, but they do not discuss the possibility of a rechallenge.[8,9,17] Randomized studies have shown that patients with irAEs may have favorable clinical outcomes after ICI discontinuation.[18,19] Thus, many patients with ongoing stable or responding disease may not need an ICI rechallenge as maintenance therapy, although assessment of long-term data are needed to examine this issue. Patients who progress after the discontinuation of an ICI for irAE occurrence may find an ICI rechallenge to be beneficial. In the absence of specific recommendations, the decision to rechallenge must be discussed in each case and may be considered for select patients. In this context, a multidisciplinary review board may be valuable, along with appropriate monitoring and standard treatment algorithms for identifying and treating the toxic effects of this therapy.

Limitations

This study has several limitations. First, it evaluated only cases that involved a rechallenge with the same ICI drug after a first irAE and only the recurrence of the same irAE. Occurrence of a different irAE after a rechallenge could be assessed only in an exploratory manner owing to the limited available information in VigiBase. Moreover, data on the seriousness and fatality of the recurrent irAEs were not available in the database. Although some data regarding life-threatening initial irAEs (ie, myocarditis and neurological irAEs) were included in this study, clinicians should use their critical judgment and extreme caution in administering an ICI rechallenge to patients with such irAEs. Ninety-two percent of the rechallenge cases in the database were not informative as they did not provide the rechallenge outcome; therefore, most of the numerical results presented here are indicative of general patterns. Recurrence rates may be higher in updated cases (reporting bias). However, information regarding the management of the initial irAE is lacking; in particular, extracting data on the use of corticosteroids or any immunosuppressive drugs is not possible; these drugs can be reported in the cases, but it is not possible to distinguish whether they were prescribed for irAE management or introduced a long time before and independent of the irAE. Moreover, data on the delay between ICI discontinuation and rechallenge were not available.

In addition, pharmacovigilance databases have some bias, such as underreported and missing data. All cases in VigiBase are self-reported using the *Medical Dictionary for Regulatory Activities* terms; therefore, additional clinical data regarding irAE severity, particularly Common Terminology Criteria for Adverse Events classification and toxic effect management, are not reported. Moreover, although the Extract Case Level structure differs from the standard database in VigiBase in that it includes information on drug rechallenge, it does not contain any information on the severity and management of the second adverse event. Pharmacovigilance analyses allow for signal detection and generate hypotheses that need to be replicated, ideally in prospective clinical studies.

Conclusions

To our knowledge, this is the largest cohort study to assess the safety of resuming the same ICI drug (anti–PD-1 or anti–PD-L1 monotherapy, anti–CTLA-4 monotherapy, and combination therapy) after an initial irAE. Overall, ICI rechallenge was associated with a recurrence of the same irAE in one-quarter to one-third of the cases. In a rechallenge, colitis, hepatitis, and pneumonitis had a higher recurrence rate compared with other irAEs. Rechallenge conditions require further investigation in a prospective clinical trial.

ARTICLE INFORMATION

Accepted for Publication: February 24, 2020.

Published Online: April 16, 2020. doi:10.1001/jamaoncol.2020.0726

Author Affiliations: Normandie University, University of Caen Normandy, Centre Hospitalier Universitaire (CHU) de Caen Normandie, PICARO Cardio-oncology Program, Department of Pharmacology, EA 4650, Signalisation, Électrophysiologie et Imagerie des Lésions d'Ischémie-Reperfusion Myocardique, Caen, France (Dolladille, Alexandre); Hôpitaux Universitaires Paris-Est, Assistance Publique-Hôpitaux de Paris, Hôpital Saint Antoine, Service de Cardiologie, Unico, Unité de Cardio-Oncologie APHP.6, GRC Groupe de Recherche Clinique en Cardio Oncologie, Inserm 856, Université Pierre et Marie Curie, Paris, France (Ederhy, Cohen); CHU de Caen Normandie, Department of Pharmacology, Caen, France (Sassier, Fedrizzi, Chrétien, Da-Silva, Lelong-Boulouard); Aix-Marseille Mediterranean University, Assistance Publique-Hôpitaux de Marseille, Marseille, France (Cautela, Thuny); Cardio-Oncology Center, Unit of Heart Failure and Valvular Heart Diseases, Department of Cardiology, Hôpital Nord, Marseille, France (Cautela, Thuny); Centre de Recherche Cardiovasculaire et Nutrition, Inserm 1263, Inra, Marseille, France (Cautela, Thuny); Groupe Méditerranéen de Cardio-Oncologie, Marseille, France (Cautela, Thuny); Oncosafety Network of the Early Phases Cancer Trials Center, Marseille, France (Cautela, Thuny); Centre Francois Baclesse Centre de Lutte Contre le Cancer (Cancer Centre), Caen, France (Da-Silva); CHU de Caen Normandie, PICARO Cardio-oncology Program, Department of Cardiology, Caen, France (Plane); Normandie University, UNICAEN, CHU de Caen Normandie, PICARO Cardio-oncology Program, Department of Cardiology, EA 4650, Signalisation, Électrophysiologie et Imagerie des Lésions d'Ischémie-Reperfusion Myocardique, Caen, France (Legallois, Milliez).

Author Contributions: Dr Dolladille had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Dolladille, Sassier, Cautela, Plane, Milliez, Lelong-Boulouard, Alexandre.
Acquisition, analysis, or interpretation of data: Dolladille, Ederhy, Cautela, Thuny, Cohen, Fedrizzi, Chrétien, Da-Silva, Legallois, Milliez.
Drafting of the manuscript: Dolladille, Milliez, Alexandre.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Dolladille, Fedrizzi.
Administrative, technical, or material support: Thuny, Alexandre.
Supervision: Dolladille, Ederhy, Cautela, Milliez, Lelong-Boulouard, Alexandre.

Conflict of Interest Disclosures: Dr Plane reported receiving consultant and lecture fees from Novartis. No other disclosures were reported.

Funding/Support: This study was funded by CHU Caen Normandie and Université de Caen Normandie.

Role of the Funder/Sponsor: The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The information presented in this study does not represent the opinion of the Uppsala Monitoring Centre or the World Health Organization.

Additional Contributions: Sophie Rushton-Smith, PhD, MedLink Healthcare Communications, provided editing assistance on the final version of this article and received compensation from the authors. The research team at the Uppsala Monitoring Centre (Uppsala, Sweden) undertook customized searches and provided case-level data from VigiBase, the World Health Organization global database of individual case safety reports; without this team, this study would not have been possible. Members of this team received no additional compensation, outside of their usual salary, for their contributions.

REFERENCES

1. Postow MA, Callahan MK, Wolchok JD. Immune checkpoint blockade in cancer therapy. *J Clin Oncol*. 2015;33(17):1974-1982. doi:10.1200/JCO.2014.59.4358

2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2017;377(14):1345-1356. doi:10.1056/NEJMoa1709684

3. Motzer RJ, Tannir NM, McDermott DF, et al; CheckMate 214 Investigators. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med*. 2018;378(14):1277-1290. doi:10.1056/NEJMoa1712126

4. Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. *Lancet Oncol*. 2016;17(7):883-895. doi:10.1016/S1470-2045(16)30098-5

5. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. *N Engl J Med*. 2018;378(2):158-168. doi:10.1056/NEJMra1703481

6. Wang DY, Salem J-E, Cohen JV, et al. Fatal toxic effects associated with immune checkpoint inhibitors: a systematic review and meta-analysis. *JAMA Oncol*. 2018;4(12):1721-1728. doi:10.1001/jamaoncol.2018.3923

7. Champiat S, Lambotte O, Barreau E, et al. Management of immune checkpoint blockade dysimmune toxicities: a collaborative position paper. *Ann Oncol*. 2016;27(4):559-574. doi:10.1093/annonc/mdv623

8. Brahmer JR, Lacchetti C, Schneider BJ, et al; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol*. 2018;36(17):1714-1768. doi:10.1200/JCO.2017.77.6385

9. Haanen JBAG, Carbonnel F, Robert C, et al; ESMO Guidelines Committee. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(suppl 4):iv119-iv142. doi:10.1093/annonc/mdx225

10. Nakajima EC, Lipson EJ, Brahmer JR. Challenge of rechallenge: when to resume immunotherapy following an immune-related adverse event. *J Clin Oncol*. 2019;37(30):2714-2718. doi:10.1200/JCO.19.01623

11. Abu-Sbeih H, Ali FS, Naqash AR, et al. Resumption of immune checkpoint inhibitor therapy after immune-mediated colitis. *J Clin Oncol*. 2019;37(30):2738-2745. doi:10.1200/JCO.19.00320

12. Pollack MH, Betof A, Dearden H, et al. Safety of resuming anti-PD-1 in patients with immune-related adverse events (irAEs) during combined anti-CTLA-4 and anti-PD1 in metastatic melanoma. *Ann Oncol*. 2018;29(1):250-255. doi:10.1093/annonc/mdx642

13. Santini FC, Rizvi H, Plodkowski AJ, et al. Safety and efficacy of re-treating with immunotherapy after immune-related adverse events in patients with NSCLC. *Cancer Immunol Res*. 2018;6(9):1093-1099. doi:10.1158/2326-6066.CIR-17-0755

14. Simonaggio A, Michot JM, Voisin AL, et al. Evaluation of readministration of immune checkpoint inhibitors after immune-related adverse events in patients with cancer. *JAMA Oncol*. 2019;5(9):1310-1317. doi:10.1001/jamaoncol.2019.1022

15. Salem J-E, Manouchehri A, Moey M, et al. Cardiovascular toxicities associated with immune checkpoint inhibitors: an observational, retrospective, pharmacovigilance study. *Lancet Oncol*. 2018;19(12):1579-1589. doi:10.1016/S1470-2045(18)30608-9

16. Menzies AM, Johnson DB, Ramanujam S, et al. Anti-PD-1 therapy in patients with advanced melanoma and preexisting autoimmune disorders or major toxicity with ipilimumab. *Ann Oncol*. 2017;28(2):368-376. doi:10.1093/annonc/mdw443

17. Puzanov I, Diab A, Abdallah K, et al; Society for Immunotherapy of Cancer Toxicity Management Working Group. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. *J Immunother Cancer*. 2017;5(1):95. doi:10.1186/s40425-017-0300-z

18. Postow MA, Chesney J, Pavlick AC, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. *N Engl J Med*. 2015;372(21):2006-2017. doi:10.1056/NEJMoa1414428

19. Larkin J, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med*. 2015;373(13):1270-1271. doi:10.1056/NEJMc1509660